No one with HIV should die from tuberculosis

Published Online
October 26, 2015
http://dx.doi.org/10.1016/S0140-6736(15)00319-0

See Series pages 2324, 2334, 2344, and 2354

Tuberculosis is the leading cause of mortality among individuals infected with HIV, killing more than 1000 people every day.[1] Even if they receive treatment for tuberculosis, people with HIV are more likely to die from tuberculosis than people without HIV,[2] especially if they are not receiving antiretroviral therapy or if they have multidrug-resistant tuberculosis.[3,4] They do not die because we cannot treat HIV or cure tuberculosis. They die because of substantial gaps in the delivery of care and innovation, despite decades of knowledge about the synergy between tuberculosis and HIV, about how to stop the spread of tuberculosis, and how to optimise HIV treatment.[5]

In 2008, WHO endorsed the Three I's strategy[6]—intensified case-finding, isoniazid prophylaxis therapy, and infection control—to address the crisis of tuberculosis deaths among people with HIV. Intensified case-finding and isoniazid prophylaxis therapy save both lives and resources, given the number of tuberculosis cases prevented.[7] A "fourth I", representing integrated care at the facility level for individuals co-infected with HIV and tuberculosis, has also been shown to improve treatment outcomes for both tuberculosis and HIV.[8,9] Despite endorsement of these almost decade-old strategies, people with HIV continue to die from tuberculosis at an alarming rate because not enough is being done to ensure optimum prevention, detection, and treatment.

How do we change this dynamic? The Stop TB Partnership's Global TB Plan 2016–2020, now under development, calls for mass scale-up of tuberculosis screening, diagnosis, and treatment for people living with HIV—with coverage targets of at least 90%.[10] But much more is needed than just ambitious targets.

First, and at a minimum, known strategies for stopping the spread of tuberculosis have to be prioritised, implemented, and scaled up in low-income and middle-income settings for both adults and children. As the papers in the *Lancet* Series on tuberculosis[11–14] show, these strategies include active case-finding, rapid diagnosis, post-exposure treatment (both isoniazid prophylaxis therapy and treatment for drug-resistant strains), and early initiation of optimum treatment for all strains of tuberculosis. These strategies have driven rates of tuberculosis down substantially among vulnerable patients in settings such as New York City and Baltimore in the USA, and Rio de Janeiro in Brazil.[15–17]

Second, innovative approaches must be adopted to halt the deadly toll of tuberculosis in people with HIV. For example, initiation of antiretroviral therapy needs to become an urgent priority among all people living with HIV, including in areas of high tuberculosis and HIV co-infection, to prevent tuberculosis incidence, progression, and mortality.[18–21] An overwhelming evidence base now clarifies the need for any patient with HIV, irrespective of CD4 count, to be started on antiretroviral therapy as soon as possible after diagnosis.[22–25] Some in the medical and public health communities have added immediate initiation of antiretroviral therapy as the "fifth I" in the strategy to halt tuberculosis mortality. There is also a need for better ways to treat tuberculosis in patients with HIV, which will involve evaluating innovative treatment strategies and improving the science of tuberculosis clinical trials. Furthermore, there should be greater inclusion of people with HIV in tuberculosis drug trials, since this population is often excluded from such research. These exclusions mean there are limited indications for the use of new tuberculosis drugs in HIV-infected individuals—those with the highest rates of mortality—and there is little information about drug–drug interactions with antiretroviral therapy.

Third, better screening and diagnostic strategies are needed to detect tuberculosis in people with HIV

Dieter Telemans/Panos

co-infection. A simple symptom screen, if correctly implemented, could identify many people with tuberculosis for diagnostic referral;[26] by contrast, sputum-based diagnostic methods miss most cases of tuberculosis among those with active disease and HIV.[27] There are now point-of-care tests available for the measurement of HIV viral load, but no such test is available for tuberculosis.[28]

Fourth, countries will continue to need technical and financial support to overcome the barriers to the implementation of comprehensive tuberculosis strategies. It is noteworthy, however, that in many settings, these barriers have been successfully addressed in the provision of HIV care in general, but not when it comes to tuberculosis care in the HIV-infected population.[29,30] A better understanding of the reasons for these differences in the provision of care would help target resources more effectively and improve tuberculosis prevention and treatment. So too would broader application of proven HIV strategies to tuberculosis, including community-based care, treatment as prevention, adaptive adherence support strategies, engagement with survivors, and a human rights driven approach.

Deaths from tuberculosis will be halted only if the tuberculosis community can emulate the ambitious scientific and advocacy agenda set by those working in HIV—where, in the span of 40 years, HIV went from being an unrecognised deadly pathogen to an easily diagnosed chronic condition with many prevention and treatment options. During that same period, there has been far too little innovation in tuberculosis prevention, diagnosis, and treatment. There is some cause for optimism from the recent introduction of molecular diagnostics and the approval of the first two new tuberculosis drugs, bedaquiline and delamanid,[31] in almost half a century, but transformative science for tuberculosis still has a long way to go. In the meantime, tuberculosis can be tackled by scaling up existing effective interventions.

The global expansion of comprehensive high-quality treatment for HIV has set a moral and human rights benchmark for other global health initiatives.[3] Preventable deaths from tuberculosis among people living with HIV are an unconscionable stain on this accomplishment. Well proven epidemic-control strategies for tuberculosis and the use of antiretroviral therapy have stopped deaths from tuberculosis in people with HIV in many settings. It is well past time to make this a reality for all people living with HIV and to expand the high levels of human and financial capital invested in HIV to the disease responsible for killing so many infected individuals.

Jennifer Furin, Paula Akugizibwe, Lucica Ditiu, Glenda Gray, Domingo Palmero, Sarah Zaidi
Tuberculosis Research Unit, Case Western Reserve University, Cleveland, OH 44106, USA (JF); Clinton Health Access Initiative, Boston, MA, USA (PA); Stop TB Partnership Secretariat, World Health Organization, Geneva, Switzerland (LD); South African Medical Research Council and Perinatal HIV Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (GG); Hospital de Infecciosas Dr F J Muñiz, Buenos Aires, Argentina (DP); and Bangkok, Thailand (SZ)
jjf38@case.edu

We declare no competing interests. We thank Mark Harrington for the important comments he contributed during the drafting of this Comment, and Carly Rodriguez for coordination and research assistance in the preparation of this Comment.

1 WHO. Global tuberculosis report 2014. Geneva: World Health Organization, 2014.
2 Straetemans M, Glaziou P, Bierrenbach AL, Sismanidis C, van der Werf MJ. Assessing tuberculosis case fatality ratio: a meta-analysis. *PLoS One* 2011; **6:** e20755.
3 Odone A, Amadasi S, White RG, Cohen TC, Grant AD, Houben MGJ. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *PLoS One* 2014; **9:** e112017.
4 Isaakidis P, Casas EC, Das M, Tseretopoulou X, Ntzani EE, Ford N. Treatment outcomes for HIV and MDR-TB co-infected adults and children: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2015; **19:** 969–78.
5 Harries AD, Zachariah R, Corbett EL, et al. The HIV-associated tuberculosis epidemic—when will we act? *Lancet* 2010; **375:** 1906–19.
6 WHO. Report of a joint WHO HIV/AIDS and TB Department meeting, 2008. Three I's meeting. Geneva: World Health Organization, 2008. http://www.who.int/hiv/pub/meetingreports/WHO_3Is_meeting_report.pdf (accessed Aug 18, 2015).
7 Gupta S, Abimbola T, Date A, et al. Cost-effectiveness of the Three I's for HIV/TB and ART to prevent TB among people living with HIV. *Int J Tuberc Lung Dis* 2014; **18:** 1159–65.
8 Hermans SM, Castelnuovo B, Katabira C, et al. Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART initiation in a large urban HIV clinic in Uganda. *J Acquir Immune Defic Syndr* 2012; **60:** e29–35.
9 Durovni B, Saraceni V, Moulton LH, et al. Effect of improved tuberculosis screening and isoniazid preventive therapy on incidence of tuberculosis and death in patients with HIV in clinics in Rio de Janeiro, Brazil: a stepped wedge, cluster-randomised trial. *Lancet Infect Dis* 2013; **13:** 852–58.
10 Stop TB Partnership. The global plan to stop TB 2016–2020. 2015. http://www.stoptb.org/global/plan/plan2/ (accessed Sept 11, 2015).
11 Theron G, Jenkins HE, Cobelens F, et al. Data for action: collection and use of local data to end tuberculosis. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00321-9.
12 Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00322-0.
13 Rangaka MX, Cavalcante SC, Marais BJ, et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00323-2.

14 Ortblad KF, Salomon JA, Bärnighausen T, Atun R. Stopping tuberculosis: a biosocial model for sustainable development. *Lancet* 2015; published online Oct 26. http://dx.doi.org/10.1016/S0140-6736(15)00324-4.

15 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. *N Engl J Med* 1995; **333:** 229–33.

16 Graham NM, Galai N, Nelson KE, et al. Effect of isoniazid chemoprophylaxis on HIV-related mycobacterial disease. *Arch Intern Med* 1996; **156:** 889–94.

17 Cavalcante SC, Durovni B, Barnes GL, et al. Community-randomized trial of enhanced DOTS for tuberculosis control in Rio de Janeiro, Brazil. *Int J Tuberc Lung Dis* 2010; **14:** 203–09.

18 Lawn SD, Wood R, De Cock KM, Kranzer K, Lewis JJ, Churchyard GJ. Antiretrovirals and isoniazid preventive therapy in the prevention of HIV-associated tuberculosis in settings with limited health-care resources. *Lancet Infect Dis* 2010; **10:** 489–98.

19 INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015; **373:** 795–807.

20 Gandhi NR, Andrews JR, Brust JC, et al. Risk factors for mortality among MDR- and XDR-TB patients in a high HIV prevalence setting. *Int J Tuberc Lung Dis* 2012; **16:** 90–97.

21 Abdool Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med* 2010; **362:** 697–706.

22 Suthar AB, Lawn SD, del Amo J, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Med* 2012; **9:** e1001270.

23 Havlir D, Kendall M, Ive P, et al. Timing of antiretroviral therapy for HIV-1 and tuberculosis. *N Engl J Med* 2011; **365:** 1482–91.

24 The TEMPRANO ANRS 12136 Study Group. A trial of early antiretrovirals and isoniazid preventive therapy in Africa. *N Engl J Med* 2015; **373:** 808–22.

25 Cohen M, Chen Y, McCauley M, et al. Final results of the HPTN 052 randomized controlled trial: antiretroviral therapy prevents HIV transmission. 8th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention; July 19–22, 2015. Program number MOAC0106LB, track C.

26 Van't Hoog AH, Meme HK, Laserson KF, et al. Screening strategies for tuberculosis prevalence surveys: the value of chest radiography and symptoms. *PLoS One* 2012; **7:** e38691.

27 Swindells S, Komarow L, Tripathy S, et al. Screening for pulmonary tuberculosis in HIV-infected individuals: AIDS Clinical Trials Group Protocol A5253. *Int J Tuberc Lung Dis* 2013; **17:** 532–39.

28 Ritchie AV, Ushiro-Lumb I, Edmaga D, et al. SAMBA HIV semiquantitative test, a new point-of-care viral-load-monitoring assay for resource-limited settings. *J Clin Microbiol* 2014; **52:** 3377–83.

29 Gupta S, Granich R, Date A, et al. Review of policy and status of implementation of collaborative HIV-TB activities in 23 high-burden countries. *Int J Tuberc Lung Dis* 2014; **18:** 1149–58.

30 Clinton Health Access Initiative. Survey on barriers to TB-HIV integration in 14 high-burden countries. Boston, MA: Clinton Health Access Initiative, 2014.

31 Zumla AI, Gillespie SH, Hoelscher M, et al. New antituberculosis drugs, regimens, and adjunct therapies: needs, advances, and future prospects. *Lancet Infect Dis* 2014; **14:** 327–40.