

Editorial

Paradigm shift to address drug resistant tuberculosis in people living with HIV needed, and needed now

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People living with HIV have a higher risk of multi-drug resistant (MDR) (Wells *et al.* 2007; Dubrovina *et al.* 2008; WHO 2008b) and extensively drug resistant (XDR) tuberculosis (Gandhi *et al.* 2006) with increased mortality, and greatly reduced survival time. Only 6% (less than 30,000) of the half million estimated incident MDR cases were diagnosed and notified globally by the end of 2007. Fifty-four countries had reported at least one case of XDR-TB (WHO 2009a,b). Data on the HIV prevalence among these notified cases and the extent of the problem in children are not available. In the latest global anti-tuberculosis drug resistance survey of WHO, only seven countries, none of which have a generalized HIV epidemic, reported tuberculosis (TB) drug resistance stratified by HIV status (WHO 2008a). However, people living with HIV are particularly vulnerable to the impact of drug resistant TB due to the difficulties and delays in the diagnosis (Wells *et al.* 2007), complications of concomitant treatment with TB and antiretroviral therapy (ART) (Havlir *et al.* 2008) and poor TB infection control measures in many HIV care settings (Gandhi *et al.* 2006; Kawai *et al.* 2006).

Diagnosis of drug resistant TB requires sophisticated infrastructure and expertise, which at the moment is scarcely available in most resource constrained and HIV prevalent settings. The emergence of XDR TB, and its fatal association with HIV, has exposed the failures of implementing the measures recommended in the Stop TB Strategy of WHO (Raviglione & Smith 2007). It is encouraging to note that a global momentum is building towards accelerated nationwide implementation of collaborative TB/HIV activities (WHO 2004) and the scaling-up of the management of MDR-TB (WHO 2008b), critical components of the Stop TB Strategy (WHO 2009a). In this editorial, we argue that not enough attention has yet been

given to the interface between MDR and XDR with HIV and a framework of priority actions is needed to address the problem and consolidate synergy between TB and HIV stakeholders at all levels.

The first step is to understand the extent of the problem systematically and promptly. Although current global surveillance activities identified countries in the former Soviet Union and regions of China as having a high proportion of MDR TB cases, and nearly half of the estimated MDR cases reside in China and India (WHO 2008a) the extent of the MDR problem in people living with HIV, including children, has not been properly documented. Furthermore, the situation in sub-Saharan Africa is largely unknown (Ben Amor *et al.* 2008; Zager & McNerney 2008) due mainly to lack of laboratory infrastructure. However, the XDR-TB outbreaks affecting primarily people living with HIV in KwaZulu Natal (Gandhi *et al.* 2006) and other provinces of South Africa (O'Donnell *et al.* 2009) give cause for serious concern. New HIV infections are on the rise in those countries with higher proportions of MDR TB cases including China, the Russian Federation and Ukraine (UNAIDS 2008). Data on the risk of MDR TB among HIV positive TB patients is available from just two places in the former Soviet Union, Donetsk, Ukraine, and Latvia which showed TB patients living with HIV are almost nearly twice as likely to have MDR-TB as patients without HIV (Dubrovina *et al.* 2008; WHO 2008a). Therefore, an urgent and systematic review of the extent and magnitude of the convergence of the HIV and drug resistant TB epidemics is needed, particularly in Africa and Eastern Europe. High quality anti-TB drug resistance surveys are needed which include HIV testing as an essential component, and synergistic opportunities between the expansion of global HIV

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(Bennett *et al.* 2008) and anti-TB (WHO 2008a) drug resistance surveillance should be sought. Whenever possible, TB and HIV resistance surveys should be conducted together within a common infrastructure platform to harmonize resources and expertise.

Second, harmonization of the increasing and ongoing global efforts to strengthen laboratory services (FIND 2007; World Bank 2008; WHO 2009b) and HIV (PEPFAR 2009), particularly in HIV prevalent settings, is needed with enhanced global coordination and national leadership of TB and HIV programmes and other relevant stakeholders. The similar infrastructure needs for the expansion of molecular TB and HIV diagnostics (such as polymerase chain reaction, PCR) offer an excellent opportunity of synergy for resources and expertise. This can be achieved through enhancing the active involvement of HIV stakeholders into the Global Laboratory Initiative (WHO 2008b, 2009b), which is working towards universal access to quality-assured TB diagnostic services by 2015 and providing strategic direction to guide the massive scale-up of laboratory services to effectively address the diagnostic challenges of TB, notably HIV-associated and drug-resistant TB. Other innovative approaches using the HIV channel need to be sought to synergise resources and expertise.

Third, given the serious threat that MDR and XDR TB pose to people living with HIV, much greater emphasis needs to be given to the prevention, early diagnosis, and treatment of TB, including drug resistant TB, for people living with HIV. Effective TB infection control measures are essential in all HIV care and treatment settings. Mechanisms to enhance intensified and prompt TB case finding, particularly among people living with HIV, and the expanded use of all available laboratory investigations to facilitate the diagnosis of drug susceptible and resistant strains (culture technologies and molecular tests) need to be prioritized. In those people living with HIV with no evidence of active TB disease, TB preventive treatment should be provided as part of their routine standard of care. In general, meaningful involvement of HIV stakeholders in the design and delivery of quality basic TB prevention, diagnosis and treatment services for people living with HIV is long overdue and crucially needed, including the expansion of drug susceptibility testing and management of drug resistant TB. Similarly the expansion of HIV testing by all TB service providers to all TB patients, including those who are presenting with signs and symptoms of TB, should be scaled up as a standard practice. TB stakeholders need to mainstream HIV prevention and treatment services into their routine activities. By 2007, data from eight countries that contributed nearly one-fifth of the global burden of HIV-associated TB

showed that, on average, there are up to five decentralized TB treatment facilities for every ART facility (WHO 2009a). This offers an excellent opportunity to expand ART facilities and enhance the access of TB patients, including those with MDR and XDR for HIV treatment.

Fourth, management of drug-drug interactions with ART and anti-TB drugs is a major challenge, and it is likely that the frequency and severity of toxicities and adverse events with second line TB drugs and ART will be severe. More research is urgently needed to answer the questions about when to start ART in a patient with drug resistant TB, and with what medicines, to identify the likely drug interactions of second line TB drugs and ART, and identify other events in the clinical response to combined treatment (Scano *et al.* 2008). People living with HIV, including children, need to be included in clinical trials involving new TB drugs in the development pipeline. In the meantime, patients should be provided quality assured second line drugs based on their clinical characteristics and susceptibility pattern. Access to quality assured second line anti-TB drugs should be enhanced from its current level and access has to be ensured also for people living with HIV. Optimal patient-centred treatment has to be expanded including community based care. The role and engagement of community groups and people living with the diseases in the design and implementation of prevention and treatment services has to be supported as a routine programme activity. Expanding TB infection control measures and promoting sound clinical practice in all health facilities and congregate settings such as prisons and drug rehabilitation centres is also vital to prevent the higher rate of nosocomial transmission and mortality of MDR and XDR TB among people living with HIV. This is particularly important with the expansion of delivery of TB services by HIV stakeholders who must, from now on, ensure that minimum standards of quality TB control are met so as to prevent transmission of both susceptible and resistant TB to people living with HIV who are attending the settings for their routine care.

Fifth, establishing a standard monitoring and evaluation system aligned to existing national systems for use by all stakeholders to effectively document and monitor the implementation of activities related to the diagnosis and treatment of drug resistant TB among people living with HIV and particularly outcomes from treatment is an essential step as it will help to inform the performance of programmes. Development of region and country-specific comprehensive responses, inline with existing national TB and AIDS control strategies, to enhance the quality of management of both drug susceptible and drug resistant TB among people living with HIV as early as possible and providing them with treatment for both diseases is essential.

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Finally, it is imperative that this message reaches out in a timely fashion to the Ministers of Health of the 27 high MDR TB burden countries (of which 12 are also high burden for HIV related TB) as they meet in Beijing, China to discuss national responses to MDR and XDR TB. If a meaningful paradigm shift does not happen now regarding drug resistant TB in people living with HIV, the implications and cost, particularly in those high MDR burden countries with increasing new HIV infections, would be grave and of historic proportions.

References

- Ben Amor Y, Nemser B, Sutherland D *et al.* (2008) Underreported threat of multidrug-resistant tuberculosis in Africa. *Emerging Infectious Diseases* **14**, 1345–1352.
- Bennett DE, Bertagnolio S (2008) The World Health Organization's global strategy for prevention and assessment of HIV drug resistance. *Antiviral Therapy* **13**(Suppl. 2), 1–13.
- Dubrovina I, Miskinis K, Gilks C *et al.* (2008) Drug-resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics? *International Journal of Tuberculosis and Lung Disease* **12**, 756–762.
- FIND (2007) *FIND and the Government of Lesotho Sign an Agreement for an Effective Response to XDR-TB in the Southern african region*. Press release, Foundation for Innovative and New Diagnostics. Available at: http://www.finddiagnostics.org/news/press/lesotho_mar07.shtml (accessed on 4 February 2009).
- Gandhi NR, Moll A, Sturm AW *et al.* (2006) Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* **368**, 1575–1580.
- Havlir DV, Getahun H, Sanne I, Nunn P (2008) Opportunities and challenges for HIV care in overlapping HIV and TB epidemics. *JAMA* **300**, 423–430.
- Kawai V, Soto G, Gilman RH *et al.* (2006) Tuberculosis mortality, drug resistance, and infectiousness in patients with and without HIV infection in Peru. *American Journal of Tropical Medicine and Hygiene* **75**, 1027–1033.
- O'Donnell M, Master I, Osburn G & Horsburgh R (2009) *Improved Survival for Patients with Extensively Drug Resistant TB in South Africa*. 16th Conference on Retroviruses and Opportunistic Infections. February 8–11, 2009, Montreal, Canada.
- PEPFAR (2009) *New Public-Private Partnership to Strengthen Laboratory Systems*. Press release. US President's Emergency Plan for AIDS Relief. Available at: <http://www.pepfar.gov/press/94448.htm> (accessed on 4 February 2009).
- Raviglione MC & Smith MI (2007) XDR tuberculosis – implications for global public health. *New England Journal of Medicine* **356**, 656–659.
- Scano F, Vitoria M, Bumnan W *et al.* (2008) Management of HIV-infected patients with MDR- and XDR-TB in resource-limited settings. *International Journal of Tuberculosis and Lung Disease* **12**, 1370–1375.
- UNAIDS (2008) *Report on the Global AIDS Epidemic*. Joint United Nations Programme on HIV/AIDS, 2008.
- Wells CD, Cegielski JP, Nelson LJ *et al.* (2007) HIV infection and multidrug-resistant tuberculosis: the perfect storm. *Journal of Infectious Diseases* **196**(Suppl. 1), S86–S107.
- WHO (2004) *Interim Policy on Collaborative TB/HIV Activities*. World Health Organisation, Geneva. WHO/HTM/TB/2004.330 WHO/HTM/HIV/2004.1.
- WHO (2008a) *Anti-Tuberculosis Drug Resistance in the World. Fourth Global Report*. WHO, Geneva. WHO/HTM/TB/2008.394.
- WHO (2008b) *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*. WHO, Geneva. WHO/HTM/TB/2008.402.
- WHO (2009a) *Global Tuberculosis Control : Surveillance, Planning, Financing*. WHO report, Geneva.
- WHO (2009b) *The WHO Global Laboratory Initiative*. <http://www.who.int/tb/dots/laboratory/gli/en/index.html> (accessed on 4 February 2009).
- WorldBank (2008) *World Bank Statement for World TB Day, March 24, 2008*. Available at: <http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTHEALTHNUTRITIONANDPOPULATION/EXTTC/0,,contentMDK:21688686~menuPK:384175~pagePK:64020865~piPK:149114~theSitePK:384139,00.html> (accessed on 7 February 2009).
- Zager EM & McNerney R (2008) Multidrug-resistant tuberculosis. *BMC Infectious Diseases* **8**, 10.

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