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Multidrug-resistant and extensively drug-resistant tuberculosis: consequences for the global HIV community

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Abstract

Purpose of review—Physicians, researchers and policy makers must understand the myriad consequences of multidrug and extensively drug-resistant tuberculosis (TB) within the HIV community in order to guide clinical care, research and resource allocation.

Recent findings—Extensively drug-resistant TB can no longer be considered as occurring in isolated outbreaks as it has been reported in 45 countries from all regions of the world. HIV has been associated as an independent risk factor for infection with drug-resistant TB. HIV patients appear more likely to suffer from primary, transmitted resistance as opposed to developing acquired resistance during the course of treatment for TB. New rapid diagnostics offer promise of providing clinically useful first-line drug susceptibility information but require validation in HIV patients and smear negative individuals. Demonstration projects of community-based treatment of drug-resistant TB and integration of TB and HIV care provide opportunities to decentralize management of drug-resistant TB.

Summary—Multidrug-resistant and extensively drug-resistant TB disproportionately affect HIV patients and result in increased morbidity and mortality. In this study, we address these challenging issues and offer some short-term and longer term strategies for their alleviation.

Keywords

drug-resistant tuberculosis; extensively drug-resistant tuberculosis; multidrug-resistant tuberculosis; South Africa; tuberculosis/HIV coinfection

Introduction

Much scientific, clinical and public health work remains to be done in the field of the interaction of drug-resistant tuberculosis (TB) and HIV. Drug-resistant TB diagnosis and treatment will ultimately benefit from basic science research; however, in the face of the current convergent epidemics, study of implementation strategies and coordination of

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available resources are immediately vital. This review will encompass recent changes in the epidemiology of TB and HIV, new evidence for acquisition and progression of drug-resistant TB in HIV patients, diagnostic opportunities, and novel treatment and management strategies.

Epidemiology

The HIV epidemic has cost the world more than 25 million lives. Despite significant progress made with respect to diagnosis and treatment with antiretrovirals (ARVs), 2 million people died in 2007, and 33 million people are living with HIV/AIDS globally [1]. Meanwhile, areas of the world such as the Russian Federation, the Caribbean, Indonesia and Viet Nam are experiencing a rise in new infections [1].

Mycobacterium tuberculosis

(*M. tuberculosis*) infection is present in an estimated one-third of the world's population. In the last year, 9.2 million new cases of TB were estimated to have occurred and 1.7 million died of TB. TB and HIV/AIDS are the leading independent causes of mortality from communicable diseases worldwide, and now an estimated 12–14 million people are coinfected with HIV and *M. tuberculosis* [2]. Among HIV patients, TB is the most common opportunistic infection [3]. HIV results in increased susceptibility to TB, reactivation of latent TB and acceleration of active TB.

HIV and drug-resistant TB

The worldwide emergence of drug-resistant TB has blunted and may reverse the benefits from the historic rollout of ARVs [4]. Multidrug-resistant TB (MDR TB), defined as resistance to the two most potent first-line TB drugs, isoniazid and rifampin, was identified decades ago but the prevalence was underestimated and the consequences underappreciated. During 2006, an estimated 500 000 cases of MDR TB occurred globally according to the most recent WHO global surveillance [5•]. Extensively drug-resistant (XDR TB), defined as MDR TB and resistance to the fluoroquinolones and one of the three injectable second-line agents (amikacin, kanamycin or capreomycin), now poses an even graver threat. Initially reported in 2006, XDR TB has now been detected in more than 45 countries [5•,6•] (see Fig. 1). Although case series of XDR TB have been reported from Europe, Asia and South America, the largest cluster of cases remains in KwaZulu Natal, South Africa among predominantly HIV-infected patients [7•]. In the study from the rural hospital in Tugela Ferry, KwaZulu Natal, among 544 patients with culture positive TB, 41% were found to have MDR TB, yet a startling 24% of those MDR patients were found to have XDR TB. All of the patients tested were HIV positive, with a median CD4 cell count of 63 cells/μl, and 98% died [7•]. Overall, TB cases in KwaZulu Natal are growing at a frightening rate, with approximately 255 000 cases diagnosed from 2005 to 2007, but XDR TB cases have increased dramatically as well. During the same time period, 996 cases of XDR TB cases were reported in South Africa, while 656 came from KwaZulu Natal [Gandhi N, Moll AP, personal communication]. In Tugela Ferry alone, more than 90% of drug-resistant TB cases are coinfected with HIV and the mortality from XDR TB remains above 85% and is more than 60% from MDR TB (Gandhi N and Moll AP, personal communication) [8].

Although it had been suspected, recent information suggests an increased independent risk of drug-resistant TB among patients coinfected with HIV. Among more than 5200 patients in Latvia, HIV infection was associated with a 2.1 odds ratio of drug-resistant TB (1.4–3.0, $P<0.01$) [5•]. In Ukraine, among 1496 patients with culture positive pulmonary TB, the rate of MDR was 23.8% among HIV negative as compared to 31.6% among HIV positive patients, odds ratio (OR) 1.3 (1.1–1.5) [9••]. Notably, the relationship was significant among

new cases but not among previously treated TB cases, supporting the premise that HIV patients are at higher risk for primary drug resistance: infection with a drug-resistant isolate during their first episode of TB. There are little data to assess the relationship between HIV and XDR TB. In the Ukraine study, too few MDR TB specimens were evaluated for second-line drug (SLD) testing, and in KwaZulu Natal, the high coinfection rate has yet to allow for statistical comparison between HIV positive and negative patients.

Diagnostic opportunities

The inability to rapidly confirm TB diagnosis and determine subsequent drug susceptibility remains one of the greatest hindrances to successful TB control. While awaiting diagnostic confirmation, patients suffer from inadequate therapy and continue to spread drug-resistant TB to others. In regions of the world harboring the vast majority of coinfection, diagnosis of active TB still relies on sputum microscopy alone. Most resource-limited settings need basic mycobacterial culture and drug susceptibility testing (DST), the standard of care in industrialized countries [10]. Sputum microscopy detects only 50% of pulmonary TB cases compared with standard culture under ideal conditions and is even less sensitive in immunocompromised hosts [11]. Furthermore, diagnosis of drug-resistant TB by solid or liquid culture and indirect DST by the proportional method still may require 2–3 months. As the devastating epidemic in rural South Africa has demonstrated, most patients with XDR TB will die before standard culture results and DST are available. The global impact of drug-resistant TB has catalyzed recent effort on the perfection of rapid diagnostic tests that can also reliably perform DST. However, of all the promising rapid diagnostics, most require validation in HIV coinfected populations and though successful in diagnosing MDR TB, none detects XDR TB.

Molecular testing for TB and drug resistance is faster but less sensitive than culture. It requires sophisticated laboratory infrastructure and training. PCR amplifications of common resistance mutations to isoniazid (*katG and inhA*) and rifampin (*rpoB*) are used in the Hain MTBDR-plus assay (Hain Lifescience, Nehren, Germany) and compared to automated liquid culture reached 98% sensitivity and 100% specificity in smear positive patients in a cohort from a reference laboratory in South Africa [12•]. The technique has not been perfected among smear negative patients. The INNO-LiPA RifTB line probe assay (Innogenetics, Ghent, Belgium) performs with similar sensitivity to the Hain test in smear positive specimens for detection of rifampin resistance that in most cases represents concurrent isoniazid resistance and thus MDR TB [13]. If genotypic testing continues to perform poorly in smear negative patients, then a combination of rapid genotypic testing for first-line DST and augmented phenotypic testing may be necessary for populations with HIV disease and a high proportion of drug-resistant TB.

Microscopic observation and drug susceptibility (MODS) is one such phenotypic assay and a promising low-cost and nonproprietary technique that requires little laboratory infrastructure [14–16]. MODS utilizes an inverted light microscope to identify characteristic cord formation of *M. tuberculosis* in liquid media. It can also reliably detect isoniazid and rifampin drug susceptibility and does so in an average of 7 days, compared with 22 days for automated liquid media (BacT/Alert3D system) and 68 days for solid media (Lowenstein–Jensen media) [14]. Validation of the MODS technique in a highly endemic HIV population is currently underway in sub-Saharan Africa. Colorimetric testing is another novel method that uses *M. tuberculosis* metabolic byproducts to produce color change in standard culture media and with different concentrations of anti-TB medications can predict drug susceptibility [17,18]. Colorimetric tests appear to be limited in use to smear positive sputum samples but have the advantage to be easily augmented to most existing laboratories already performing standard culture [17–20].

Treatment of coinfected patients

The outcomes for MDR and XDR TB are poor compared with that for drug-susceptible TB. The necessary SLDs are less potent, more toxic and more expensive. Many SLDs are not available in resource-limited settings, and treatment regimens for drug-resistant TB with or without HIV coinfection are based on case series and expert consensus. Although, well below the expected treatment success with drug-susceptible TB, notably positive outcomes have been reported in predominately HIV negative populations with both MDR and XDR TB. In Latvia, a directly observed therapy short-course (DOTS)-plus strategy for MDR TB patients utilizing known regional resistance patterns or individualized DST led to cure or treatment completion in 66% of HIV negative patients [21]. In Peru, a comprehensive program for HIV negative patients with MDR TB resulted in 83% cure [22]. Although reports of XDR TB patients from South Korea, Russia and Peru demonstrate survival rates of 55, 48 and 60%, respectively, these are all among largely HIV negative populations [23•, 24•,25••]. In one of the few case series in a population of majority HIV coinfected patients on ARVs, a 52% survival rate from XDR TB at 6 months was reported from a South African specialty TB hospital [26]. However, survivor bias heavily confounds the study as the majority of patients with XDR TB will have died before referral to the specialty hospital [27•].

Specific medication regimens for the treatment of MDR and XDR TB should be tailored based on DST results, if available. However, in most settings, DST is not accessible for individual patients and standard regimens are used, preferably from population-based DST data. If MDR or XDR TB is suspected while awaiting DST, empiric therapy may be initiated with four or five oral SLDs usually including a fluoroquinolone and an injectable agent, though embarking on a second-line regimen without prior proof of drug resistance may not be possible in most settings [28,29]. The addition of a single injectable agent, such as streptomycin, to a failing first-line regimen should be strictly avoided. Oral SLDs include ethionomide, prothionomide, cycloserine, terizidone, para-aminosalicylic acid (PAS) and the fluoroquinolones. Despite significant heterogeneity among reported treatment trials for MDR TB, a recent meta-analysis suggests three characteristics associated with clinical success: regimens including five or more drugs, a longer duration of treatment (at least 18–24 months) and employment of the DOTS-plus strategy (Orenstein EW, Basu S, Shah NS *et al.*, unpublished data). XDR TB treatment regimens may employ third-line agents in which little more than in-vitro efficacy exists. Additionally, surgical resection can be beneficial in a carefully selected population of patients with pulmonary drug-resistant TB but the adjunctive procedure is of unclear benefit in HIV positive patients who are more likely to have primary drug resistance and harbor disseminated disease [30•,31].

HIV antiretroviral therapy and second-line TB medications

ARVs are critically important for treatment of drug-resistant TB in coinfected patients. The restoration of immune function is necessary for a successful therapeutic response. Thus, HIV voluntary counseling and testing (VCT) to identify HIV coinfection in patients with drug-resistant TB represents a crucial first step. Yet, sobering world estimates from 2006 suggest that only 12% of all reported TB patients received HIV testing and while that percentage may be increasing, it is likely far short of universal VCT [29]. Less than half of those tested and eligible were started on ARVs [29].

Studies need to clarify the suspected additive toxicities of SLDs and ARV therapy and the cumulative toxicities of SLDs administered over extended treatment durations, as well as define the specific drug–drug interactions in coinfected patients. As rifampin is by definition not used for the treatment of drug-resistant TB, the most problematic drug interactions with

nonnucleoside reverse transcriptase inhibitors and protease inhibitors are not relevant. However, the toxicities of concern include peripheral neuropathy with nucleoside reverse transcriptase inhibitors and aminoglycosides, neuropsychiatric toxicity with efavirenz and cycloserine and gastrointestinal intolerance with many ARV and SLDs (see Table 1) [32,33].

Strategies to reduce the epidemic of HIV and drug-resistant TB

The disastrous collision of HIV and drug-resistant TB requires both immediate short-term interventions and the development of durable and sustainable strategies. While awaiting chemotherapeutic advances for TB treatment, massive infusions of resources are needed to strengthen TB control programs.

Effects of MDR/XDR TB on the HIV epidemic are listed as follows (adapted from [34]):

1. increased risk of drug-resistant TB compared with HIV-uninfected individuals
2. increased mortality among HIV patients coinfected with drug-resistant TB
3. potential morbidity from drug toxicities of second-line TB drugs and ARVs
4. nosocomial transmission of drug-resistant TB to HIV patients in hospitals and clinics
5. risk to healthcare workers caring for HIV patients
6. strain on national TB control programs and DOTS programs
7. unmet demand for laboratory services and specialized treatment referral
8. rivalry for resources between HIV and TB programs
9. growing stigma of TB and HIV coinfected patients comparable to early HIV epidemic
10. overall reversal of gains from historic ARV rollouts.

Intensified case finding

Early identification of cases of drug-resistant TB could result in greater treatment success and also reduce patients' duration of infectivity. Investigation of all the contacts of patients with drug-resistant TB should be performed with rapid diagnostics and if symptoms of active disease exist, therapy based on the index patient's DST pattern should be initiated while awaiting the contact's own DST [29]. Public health authorities should pursue active screening for TB in HIV clinics and other healthcare locations where suspicion for TB may be high as well as in community congregate settings.

Infection control

The strong evidence for nosocomial transmission of MDR and XDR TB in rural South Africa emphasizes the need for airborne infection control measures [7•,35••]. The structure of infection control can be categorized in three ways: administrative measures such as policies that reduce the reliance on hospitalization; environmental measures such as promotion of natural ventilation; and personal measures such as respirator mask use and HIV testing for staff [36,37••,38•]. A recent mathematical model demonstrated that 28% of XDR TB cases in Tugela Ferry could be avoided over 5 years by consistent use of respirator masks and a reduction in length of hospital stay, and 48% of all expected XDR TB cases could be averted by also employing rapid DST, practicing thorough VCT and HIV treatment, isolating patients into groups of five and improving natural ventilation [39•].

These simple measures are available in most resource-limited settings. Additionally, all staff caring for TB patients should be offered confidential HIV counseling and testing and for those who are positive, administrators should encourage discreet transfer to a low TB risk area as well as provide ARV therapy [39•,40]. The mathematical model above calculated that mask use and VCT could reduce staff acquisition of XDR TB by 75%.

Community-based treatment

In poor regions of the world, HIV and TB have created a cruel competition for human and technological resources. The unusual strain on overburdened specialty hospitals has prompted a push for decentralized care for patients with drug-resistant TB as a promising new model of treatment delivery [41•]. Many patients with MDR and XDR TB in KwaZulu Natal, for instance, never reach a referral hospital for treatment [42]. For those who are able to access care, the challenges of treatment completion are enormous. Alternatively, lessons learned from established HIV programs teach that improved treatment adherence and better patient outcomes can be achieved with a decentralized model in which patients may be admitted to specialized centers for shorter durations for treatment initiation but are then transitioned to local step-down facilities or home-based programs for the extended course of care [43]. In the community-based strategy of treatment for HIV negative XDR TB in Peru, patients were also provided thorough adverse event monitoring, nutritional and psychological support and, if necessary, surgical resection [25••]. While demonstrating the feasibility of outpatient therapy for drug-resistant TB, the strategy requires validation among HIV-infected patients who may suffer more drug interactions and have an overall poorer prognosis. Community-based injection teams for treatment of MDR TB patients in their homes are currently operating in rural KwaZulu Natal, and a prospective study of this decentralized approach is underway [44]. One concern of community-based therapy is transmission to household contacts; however, in KwaZulu Natal, the Department of Health's contact tracing program has demonstrated that household based transmission remains low (1–2%) [45].

Integration of HIV and TB care

Integration of TB and HIV clinical care improves outcomes of coinfected patients [46–48,49•]. Indeed, preliminary results from the first randomized control trial of integrated TB/HIV treatment suggest a reduction of mortality by 55% in coinfected patients based on the timing of ARV initiation [50••]. Much more can be accomplished if databases and registries that often operate in parallel for HIV and TB patients can be merged and be accessible to decentralized providers. Finally, it is important to mention that drug-resistant TB and HIV can create a compounded stigma among coinfected patients. Ethical dilemmas have arisen regarding the protection of the public health and personal liberty and the allocation of scarce resources. Although abuses have already been documented in South Africa after the involuntary incarceration of coinfected patients, clinicians and policy makers can navigate this historic pitfall by the humane provision of education in treatment literacy for patients and families, training of community health workers, building of infrastructure for community-based care and increasing access to currently available diagnostics and therapeutics [42].

Conclusion

MDR and XDR TB threaten to erode the fragile progress made by the provision of ARV medications for the global HIV community. HIV patients are disproportionately affected by drug-resistant TB; thus, new diagnostics need to incorporate rapid DST and be able to perform well in HIV patients whereas treatment trials must include patients on ARVs and SLDs for drug-resistant TB. Current human, technological and financial levels are unable to

meet the needs of both epidemics, thus necessitating immediate infusion of resources as well as simple and low-cost interventions to integrate drug-susceptible and resistant TB with HIV care.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 93).

1. Joint United Nations Programme on HIV/AIDS (UNAIDS). Report on the global HIV/AIDS epidemic. 2008. UNAIDS/08.25E / JC1510E
2. World Health Organization. Global burden of disease and risk factors. 2004. Update
3. World Health Organization. The Stop TB Strategy. 2006. WHO/HTM/TB/2006.368. www.stoptb.org
4. Wells CG, Cegielski P, Nelson LJ, et al. HIV infection and multidrug resistant tuberculosis: the perfect storm. J Infect Dis. 2007; 196:S86–S107. [PubMed: 17624830]
5. World Health Organization. Anti-tuberculosis drug resistance in the world. Fourth Global Report. WHO/HTM/TB/2008.394 This is a summary of the latest global surveillance for MDR and XDR TB.
6. Shah NS, Wright A, Bai G-H, et al. Worldwide emergence of extensively drugresistant tuberculosis. Emerg Infect Dis. 2007; 13:380–387. [PubMed: 17552090] This is a survey of Supernational Reference Laboratories defining MDR and XDR trends from 48 countries.
7. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients coinfected with tuberculosis and HIV in a rural area of South Africa. Lancet. 2006; 368:1575–1580. [PubMed: 17084757] This report describes the initial and still the largest cluster of cases of XDR TB globally.
8. Moll, A.; Gandhi, NR.; Andrews, J., et al. Extensively drug-resistant (XDR) TB more common than MDR TB in Tugela Ferry, South Africa with evidence for resistance amplification over time; 38th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; Cape Town. 2007.
9. Dubrovina I, Miskinis K, Lyepshina S, et al. Drug-resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics? Int J Tuberc Lung Dis. 2008; 12:756–762. [PubMed: 18544200] The study establishes an independent relationship between HIV and drug-resistant TB.
10. World Health Organization. Global tuberculosis control: surveillance, planning, financing. 2008. WHO/HTM/TB/2008.393
11. Elliott AM, Namaambof K, Allent BW, et al. Negative sputum smear results in HIV positive patients with pulmonary tuberculosis in Lusaka, Zambia. Int J Tuberc Lung Dis. 1993; 74:191–194.
12. Barnard M, Albert H, Coetzee G, et al. Rapid molecular screening for multidrug-resistant tuberculosis in a high-volume public health laboratory in South Africa. Am J Respi Critical Care Med. 2008; 177:787–792. This is a study of rapid molecular testing for common resistant mutations in urban South Africa.

13. Tortoli E, Marcelli F. Use of the INNO LiPA Rif. TB for detection of *Mycobacterium tuberculosis* DNA directly in clinical specimens and for simultaneous determination of rifampin susceptibility. Eur J Clin Microbiol Infect Dis. 2007; 26:51–55. [PubMed: 17180347]
14. Moore DAJ, Evans CAW, Gilman RH, et al. Microscopic-observation drug-susceptibility assay for the diagnosis of TB. N Engl J Med. 2006; 355:1539–1550. [PubMed: 17035648]
15. Arias M, Mello FCQ, Pavon A, et al. Clinical evaluation of the microscopic-observation drug-susceptibility assay for detection of tuberculosis. Clin Infect Dis. 2007; 44:674–680. [PubMed: 17278058]
16. Ejigu GS, Woldeamanuel Y, Shah NS, et al. Microscopic-observation drug susceptibility assay provides rapid and reliable identification of MDR-TB. Int J Tuberc Lung Dis. 2008; 12:332–337. [PubMed: 18284841]
17. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis. 2007; 196(Suppl 1):15–27. [PubMed: 17538878]
18. Palomino JC, Martin A, Portaels F. Rapid drug resistance detection in *Mycobacterium tuberculosis*: a review of colorimetric methods. Clin Microbiol Infect. 2007; 13:754–762. [PubMed: 17378933]
19. Affolabi D, Odoun M, Sanoussi N, et al. Rapid and inexpensive detection of multidrug resistant tuberculosis with the nitrate reductase assay using liquid medium and applied directly to sputum samples. J Clin Microbiol. 2008; 46:3243–3245. [PubMed: 18753346]
20. Musa HR, Ambroggi M, Souto A, Angeby KA. Drug susceptibility testing of *Mycobacterium tuberculosis* by a nitrate reductase assay applied directly on microscopypositive sputum samples. J Clin Microbiol. 2005; 43:3159–3161. [PubMed: 16000429]
21. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet. 2005; 365:318–326. [PubMed: 15664227]
22. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med. 2003; 348:119–128. [PubMed: 12519922]
23. Kim H, Hwang SS, Kim HJ, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV infected patients with multidrug-resistant tuberculosis. Clin Infect Dis. 2007; 45:1290–1295. [PubMed: 17968823] The study describes outcomes of HIV negative XDR TB patients from South Korea.
24. Keshavjee S, Gelmanova IY, Farmer PE, et al. Treatment of extensively drug resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet. 2008; 372:1403–1409. [PubMed: 18723218] The study describes outcomes of HIV negative XDR TB patients from Russia.
25. Mitnick CD, Shin SS, Seung KJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med. 2008; 359:563–574. [PubMed: 18687637] This is an important article reviewing community-based treatment of XDR TB among HIV negative patients, which lends strategies to be replicated in HIV-burdened areas.
26. O'Donnell, MR.; Pym, A.; Master, I., et al. Clinical treatment outcomes and epidemiologic risk factors for extensively drug resistant tuberculosis patients on treatment in KwaZulu-Natal, South Africa; 38th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; Cape Town. 2007.
27. Andrews JR, Gandhi NR, Moll AP, et al. High mortality among patients with multidrug and extensively drug-resistant tuberculosis in rural South Africa. 200738th World Conference on Lung Health of the International Union Against Tuberculosis and Lung DiseaseCape Town This review describes outcomes of MDR and XDR TB patients and stratification by CD4 cell count.
28. Partners in Health. The PIH guide to medical management of multidrug resistant tuberculosis. 2003. http://www.pih.org/inforesources/pihguide-dotstb.html
29. World Health Organization. Guidelines for the Programmatic Management of Drug Resistant Tuberculosis. 2006. WHO/HTM/TB/2006.361
30. Törün T, Tahaoglu K, Özmen I, et al. The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2007; 11:979–985. [PubMed: 17705975] The study offers promise for adjunctive nonmedical therapy in MDR TB.

31. Park S-K, Kim JH, Kang H, et al. Pulmonary resection combined with isoniazid- and rifampin-based drug therapy for patients with multidrug-resistant and extensively drug-resistant tuberculosis. Int J Infect Dis. 2008 [Epub ahead of print].
32. Friedland G. Tuberculosis, drug resistance, and HIV/AIDS: a triple threat. Curr Infect Dis Rep. 2007; 9:252–261. [PubMed: 17430708]
33. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents. 2006.
34. Andrews J, Shah NS, Moll AP, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. J Infect Dis. 2007; 196:S482–S490. [PubMed: 18181698]
35. Andrews J, Gandhi NR, Moodley P, et al. Exogenous re-infection as a cause of multidrug- and extensively drug-resistant tuberculosis in rural South Africa. J Infect Dis. 2008; 198:1582–1589. [PubMed: 18847372] The study emphasizes the transmission of distinct drug-resistant isolates among hospitalized patients, furthering the role of primary transmission of drug-resistant TB in HIV patients.
36. World Health Organization. Tuberculosis infection control in the era of expanding HIV care and treatment. Addendum to WHO Guidelines for the Prevention of Tuberculosis in Healthcare Facilities in Resource-Limited Settings. 2007. WHO/TB/99.269/2007
37. Bock NN, Jensen PA, Miller B, Nardell E. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. J Infect Dis. 2007; 196:S108–S113. [PubMed: 17624819] The article describes the administrative, environmental and personal protective measures required for TB control in healthcare facilities.
38. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med. 2007; 4:e68. [PubMed: 17326709] The study quantitatively delineates the effect of natural ventilation in healthcare facilities.
39. Basu S, Andrews JR, Poolman EM, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: a modeling study. Lancet. 2007; 370:1500–1507. [PubMed: 17964351] The mathematical model not only describes combinations of infection control measures that can prevent XDR TB, but also cautions an otherwise rise in new cases, if left unchecked.
40. Harries AD, Zachariah R, Bergström K, et al. Human resources for control of tuberculosis and HIV-associated tuberculosis. Int J Tuberc Lung Dis. 2005; 9:128–137. [PubMed: 15732730]
41. Padayatchi N, Friedland G. Decentralised management of drug-resistant tuberculosis (MDR- and XDR-TB) in South Africa: an alternative model of care. Int J Tuberc Lung Dis. 2008; 12:978–980. [PubMed: 18647461] The commentary discusses the value of decentralized care and making patients and families a key part of the treatment team.
42. Moodley, P.; Moll, AP.; Shah, NS., et al. Multi and extensively drug resistant *Mycobacterium tuberculosis* in KwaZulu Natal; 38th World Conference on Lung Health of the International Union Against TB and Lung Disease; Cape Town. 2007.
43. Gandhi, N.; Moll, AP.; Pawinski, R., et al. Favorable outcomes of integration of TB and HIV treatment in a rural South Africa: The Sizonqoba study [abstract]; 16th International AIDS Conference; 13–18 August 2006; Toronto, Canada. 2006.
44. Brust, JCM.; Scott, M.; Moll, AP., et al. Community based treatment for multidrug resistant (MDR) tuberculosis in HIV population from rural South Africa. Mexico City: International AIDS Society; 2008.
45. Moll, A. Results of Contact Investigations for XDR and MDR TB patients in rural sub-district of KwaZulu Natal, South Africa: yield and barriers to implementation; 39th World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease; Paris. 2008.
46. Coetzee D, Hilderbrand K, Goemaere E, et al. Integrating tuberculosis and HIV care in the primary care setting in South Africa. Trop Med Int Health. 2004; 9:a11–a15. [PubMed: 15189469]
47. Friedland G, Karim SA, Karim QA, et al. Utility of tuberculosis directly observed therapy programs as sites for access to and provision of antiretroviral therapy in resource-limited countries. Clin Infect Dis. 2004; 38(Suppl 5):421–428.

48. Jack C, Lalloo U, Karim QA, et al. A pilot study of once-daily antiretroviral therapy integrated with tuberculosis directly observed therapy in a resource-limited setting. J Acquir Immune Defic Synd. 2004; 36:929–934.

49. Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. J Infect Dis. 2007; 196(Suppl 1):114–123. The discussion presents various cases of integration and the associated barriers and outcomes.

50. HIV treatment at same time as TB treatment halves death rate in South African study. The SAPIT study (Starting Antiretroviral therapy at three Points In Tuberculosis therapy). 2008 Aug 15.HIV and AIDS Treatment and PracticePress release This will be an important study to review in entirety as it promises to demonstrate mortality benefit from early initiation of ARVs in TB coinfected patients compared with sequential therapy. The study may serve as an example for the needed rigorous clinical investigation in coinfected patients.

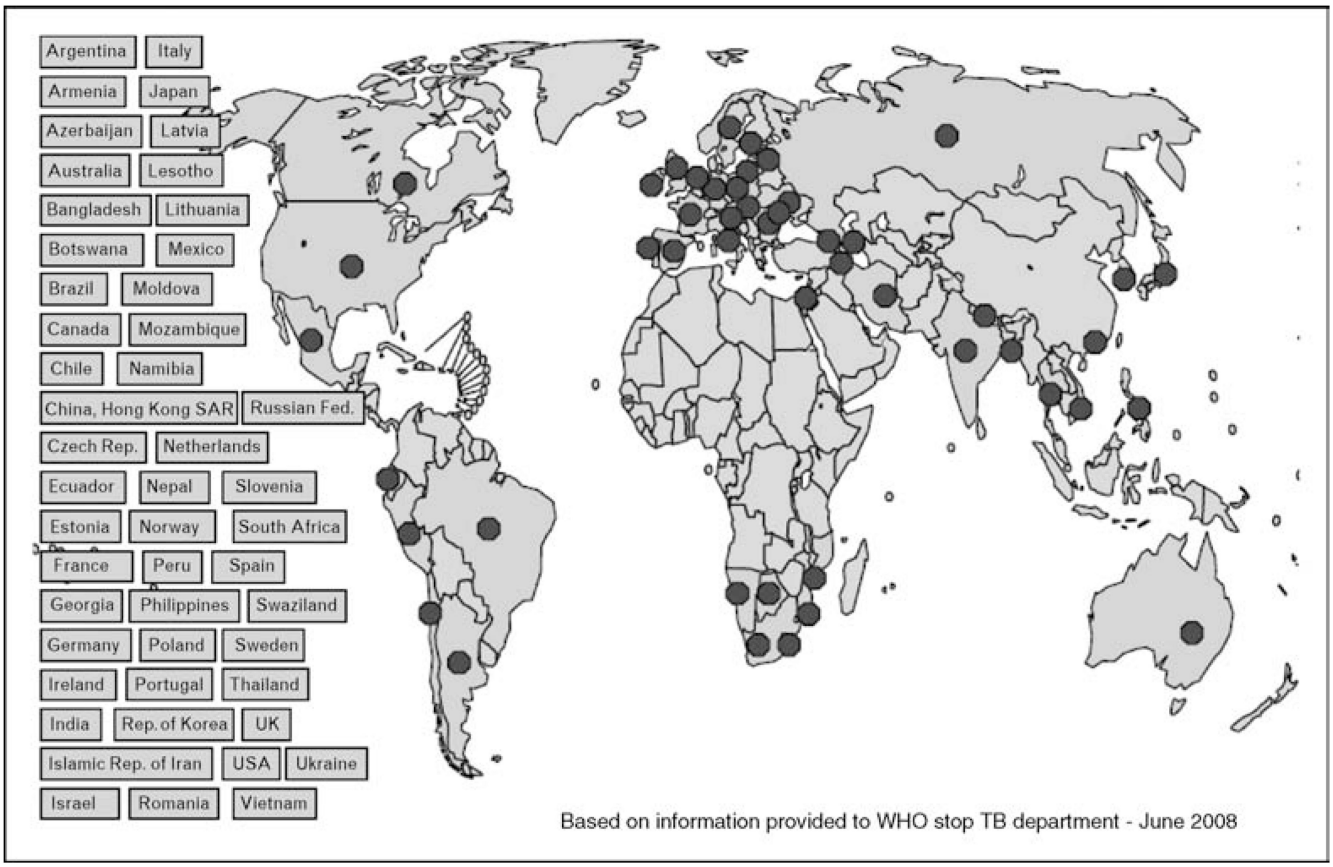

Figure 1. Countries with extensively drug-resistant TB cases as of June 2008

All regions of the world are represented. The largest cluster remains in the province of KwaZulu Natal, South Africa. Note that areas of the world with the greatest TB burdens (Africa, Southeast Asia and China) are underrepresented – the result of limited laboratory infrastructure needed for XDR TB diagnosis. Refer to http://www.who.int/tb/challenges/xdr/xdr_map_june08.pdf. Reproduced from [5•] with permission from the WHO.

Table 1

Common side effects shared by antiretrovirals and antituberculosis medications

Hepatitis	**Nevirapine**, **ritonavir-boosted protease inhibitors**, *isoniazid*, *rifampin*[a], *pyrazinamide*
Gastrointestinal distress	**All antiretrovirals** (less common with lamivudine and emtricitabine), *fluoroquinolones, ethionamide* (associated with taste alteration), *para-aminosalicylic acid*
Nephrotoxicity	**Tenofovir** (renal tubular dysfunction), **idinavir–ritonavir**, *streptomycin*, *aminoglycosides* (nephrotoxic TB agents carry particular risk of potentiating lactic acidosis common to the NRTIs used in antiretroviral rollout regimens)
Neuropsychiatric disorders	**Efavirenz** (insomnia, drowsiness, vivid dreams), *cycloserine* (headaches, tremor, seizure), *terizidone* (mainly headache and seizures)
Peripheral neuropathy	**Stavudine**, **didanosine**, *cycloserine*, *streptomycin*, *aminoglycosides*, *isoniazid* (overcome with pyridoxine administration)

Antiretrovirals are in bold. Antituberculosis medications are in italics. Stavudine, didanosine, tenofovir, lamivudine and emtricitabine are NRTIs. Nevirapine and efavirenz are NNRTIs. Idinavir and ritonovir are protease inhibitors. Common global rollout antiretroviral regimens: (stavudine or zidovidine)+(lamivudine or emtricitabine)+(nevirapine or efavirenz) or (tenofovir or abacavir)+(lamivudine or emtricitabine)+(nevirapine or efavirenz). MDR, multidrug-resistant; NNRTIs, nonnuceloside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; TB, tuberculosis; XDR, extensively drug-resistant.

[a]Rifampin induction of cytochrome P450 reduces serum levels of NNRTIs and protease inhibitors but is not therapeutically relevant for MDR/XDR TB and HIV coinfection.Adapted from [32,33].