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Extensively Drug-Resistant Tuberculosis: A New Face to an Old Pathogen

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Abstract

The presence and consequences of resistance to drugs used for the treatment of tuberculosis have long been neglected. The recent detection and recognition of widespread multiple-drug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis have raised interest and concern among clinicians and public health authorities globally. In this article, we describe the current global status of drug-resistant tuberculosis. We discuss the development of resistance, current management, and strategies for control.

Keywords

XDR TB; multiple-drug-resistant tuberculosis (MDR TB); TB/HIV coinfection; Tugela Ferry; South Africa

EPIDEMIOLOGY

One third of the world's population is infected with *Mycobacterium tuberculosis* or has active tuberculosis (TB), making it the second leading cause of infectious death globally. In 2006, 9.2 million incident cases were reported and 1.2 million people died as a result of TB (1). Although the global incidence rate appears to be slowing, the absolute number of new cases is increasing because of worldwide population growth. Countries in Southeast Asia, Africa, and the former Soviet Union are regions of particular concern as the surge of cases in these regions threatens global TB control. The breakdown of the health care infrastructure after the dissolution of the Soviet Union has resulted in poorly functioning TB control programs, and there is evidence of increasing HIV infection contributing to the TB epidemic (2,3). In Asia and Africa, the increase in TB directly corresponds to the worsening of the HIV epidemic over the past two decades. Globally, the incidence rate of TB is 139/100,000; at the extremes, the World Health Organization (WHO) African Region incidence rate is 363/100,000 and the United States case rate is 4.4/100,000 (1,4).

DRUG RESISTANCE

Rising rates of TB drug resistance must now be added to the volatile global TB scene. Though not a new phenomenon, the growth of drug resistance is of great clinical and public health concern. In 1945, the first anti-TB drug, streptomycin, was developed; by 1947, resistance to this drug was already noted and the utility of multiple-drug regimens to treat

DISCLOSURE STATEMENT
The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

TB was recognized (5,6). The classical mechanism of resistance is that of acquired resistance, whereby *M. tuberculosis* develops mutations under pressure of inadequate drug therapy. These mutations provide advantage by altering or overproducing the drug target protein, making the bacteria inaccessible to the anti-TB agent or attenuating its effect (7). Recently, however, primary drug resistance—the result of transmission of drug-resistant organisms—has received much more attention, particularly in the setting of high HIV prevalence and rapid TB spread.

THE ALARM BELL

In January 2005, researchers and clinicians were working at a provincial district hospital in Tugela Ferry in rural KwaZulu Natal, South Africa to demonstrate the efficacy of concurrent and coordinated management of HIV/AIDS and TB. Results looked promising as patients treated concurrently achieved undetectable viral loads, rising CD4 counts, and improved TB outcomes (8). Despite this, several unanticipated deaths were noted, resulting from drug-resistant TB. Further surveillance with culture and drug susceptibility testing (DST) over the next year revealed widespread drug resistance, including resistance to all six drugs available for DST (isoniazid, rifampin, ethambutol, streptomycin, ciprofloxacin, and kanamycin). Among 542 patients with culture-positive TB, 221 (39%) had multiple-drug-resistant (MDR) TB, and of these, 53 (24%) had resistance to all six drugs tested (9). A joint WHO and Centers for Disease Control and Prevention (CDC) Task Force subsequently defined extensively drug-resistant (XDR) TB as resistance to isoniazid and rifampin plus resistance to any fluoroquinolone and one of the injectables: amikacin, kanamycin, or capreomycin (9,10). The detection of XDR TB garnered much attention, and for the first time in decades, international resources are being directed toward drug-resistant TB.

Since January 2005, >300 cases of XDR TB have been diagnosed in Tugela Ferry (A.P. Moll, personal communication), and 996 cases were documented in South Africa through December 2007 (11). Few data are available from the remainder of the African continent. Reports of widespread drug resistance among data from 14 supranational laboratories worldwide included XDR TB in 2% of specimens when the CDC and WHO conducted intensive global surveillance (12), and WHO's newly released fourth Global Drug Resistance Surveillance Report revealed that the proportion of MDR TB among new cases has nearly tripled overall to 2.9% since the last report in 2004, with extremes of up to 22% in former Soviet republics. Among retreatment cases, the proportion of MDR TB cases was 15.3%, with extremes of up to 60% in the former Soviet republics of Azerbaijan and Uzbekistan (11). Overall, nearly half a million cases of MDR TB were estimated to have occurred in 2006, representing ~4.6% of all TB cases. Half of the global MDR TB burden is in China and India; Russia carries another 7%.

As of February 2008, XDR TB has been reported in 45 countries. The countries of the former Soviet Union represent an area of great concern because of their heavy TB burden. In this area, 10% of all the MDR cases were XDR with extremes of up to 24% in Estonia, 15% in Donetsk Oblast of Ukraine, and 12.8% in Azerbaijan. Even developed countries such as Japan reported 30% XDR among MDR cases, although this represents a relatively low number of cases given the low burden of MDR TB in this region.

DEVELOPMENT OF XDR TB

Often, blame for the development of drug resistance is quick to fall on patients' poor adherence to medications. However, poor medication adherence seldom reflects an individual's desire to obviate treatment; multiple factors related to the patient, provider, and health care system are often responsible for therapeutic failure and acquired resistance (13–16). Factors attributable to clinicians or providers involve prescribing errors, suboptimal

dosing, insufficient monitoring of therapy, and drug interactions between anti-TB agents and agents for comorbidities. Health care system factors include poorly functioning TB control programs, medication stock-outs, lack of staff, and inadequate access for patients because of distance or lack of transportation to medical facilities. Also extremely important to the development of drug resistance are global and national policies that rely only on smear to diagnose TB disease and do not promote the use of culture with DST, recommending it only for patients who fail therapy or relapse. This policy allows patients with drug resistance, including MDR/XDR TB, to remain unrecognized, receiving inadequate therapy for months while continuing to transmit TB to others. Since 1995, WHO has promoted the strategy of DOTS (directly observed therapy, short course) to ensure treatment adherence and completion. This strategy, which utilizes sputum AFB smear as the sole laboratory diagnostic test, was seen as the only effective strategy to combat TB. However, we have now learned that DOTS alone is not sufficient, that culture with DST is essential to make an accurate diagnosis, and that resource-limited settings (RLS) cannot be exempt from standards of care but in fact should be the center of development of TB control strategies.

HIV AND MDR/XDR TB

The HIV/AIDS epidemic has been the primary cause of the surge in TB cases over the past few decades. Global studies of the two conditions reveal clear parallels. HIV infection facilitates reactivation of *M. tuberculosis* (10% per year compared with 5%–10% lifetime risk in HIV-negative patients) and results in more rapid progression from infection to active disease. The nature of the relationship between HIV and TB drug resistance is less straightforward; several studies express differing conclusions regarding an independent association (17). However, HIV has been associated with rifampin resistance (18–20). Furthermore, malabsorption of anti-TB medications has been demonstrated in HIV-infected patients (21–23).

Although all the XDR TB patients tested for HIV in the Tugela Ferry cluster were HIV-positive (9) and most of the cases of XDR TB have been reported among HIV-infected patients in South Africa, there have been reports of XDR TB among HIV-negative patients (24). Recently, investigators in South Korea reported a cohort of patients with XDR TB, none of whom were HIV-infected (25). Indeed, the last national survey in South Africa did not demonstrate an association between HIV status and drug-resistant TB, although this study only incorporated data from 2001–2002 (26). However, two further studies show a significant relationship. A survey from Latvia (2001–2005) showed that HIV is an independent predictor of any TB drug resistance ($p < 0.05$) as well as MDR TB (OR = 2.1, $p < 0.01$) (11). Another study from Donetsk Oblast, Ukraine demonstrated that HIV was a significant risk factor for any TB drug resistance ($p < 0.05$) and MDR TB (OR = 1.5, $p < 0.05$) (27).

RISK FACTORS FOR DRUG-RESISTANT TB

The clinician has few tools with which to gauge drug resistance when evaluating a patient presenting with symptoms typical of TB. There are no studies currently to demonstrate that tuberculin skin tests, radiology studies, laboratory studies, or smear status can be useful in predicting drug resistance. Several studies have identified historical factors (Table 1) that may increase the likelihood of drug resistance; however, studies to validate these findings are lacking, especially in HIV-coinfected patients. Furthermore, these factors are absent in many patients, and their utility in determining initial drug treatment of tuberculosis has not been studied. In the initial Tugela Ferry cluster, the majority of patients with XDR TB had not previously received TB therapy (9). In another study in Tugela Ferry, only 38% had been hospitalized within the past two years, and only 28% had had previous anti-TB

therapy, supporting the view that primary transmission had occurred (29). The absence of clear clinical diagnostic features for drug resistance underscores the need for rapid diagnosis and DST.

DIAGNOSIS

During the past century, there have been few advances in TB diagnosis, which in most parts of the world is still reliant on sputum smear positivity. This test is at best <60% sensitive in normal hosts and significantly less in those who are immunocompromised. When utilized, culture necessitates 6–8 weeks on solid media and 2–3 weeks on automated liquid media [Bactec, Mycobacterial Growth Indicator Tube (MGIT)]. Developed nations have benefited from the use of nucleic acid amplification tests performed directly on sputum specimens; however, this technology has been plagued by low sensitivity and is beyond the reach of most RLS, which carry most of the burden of global TB.

Several assays under investigation seem promising. The microscopic observation drug susceptibility (MODS) technique is a low-cost, low-tech method with excellent correlation to culture, and it permits diagnostic results and susceptibility to isoniazid and rifampin within a median of 7 days (30). It has great potential for RLS and is currently being validated in settings with high HIV prevalence. Loop-mediated isothermal amplification (LAMP), a new molecular method developed by Eiken, requires little molecular training but still necessitates some specimen processing. Currently, operational and maintenance costs make LAMP less feasible for RLS (31). Frequent barriers to use of molecular tools include specimen processing and DNA extraction. The GeneXpert® assay, developed by Cepheid, is a promising technology that automates the process completely, requiring little input from laboratory workers and modest infrastructure (31). Studies to include detection of molecular beacons for rifampin resistance within hours are in progress. Biotec Laboratories, Ltd. has developed a phage-based assay (FastPlaqueTB®) with results potentially available within two days, although currently the sensitivity lags, and significant laboratory infrastructure is still required (31).

Other methods focused on DST include molecular assays, such as the Foundation for Innovative New Diagnostics (FIND)–supported Genotype MTBDR® assay by HAIN Life-Science and the INNO-Lipa Rif.TB® assay by Innogenetics. These involve PCR amplification of known rpoB and katG mutations, and hybridization to oligonucleotide probes on nitrocellulose strips (32). Susceptibility results are available within 1–2 days. A recent study in South Africa of the HAIN product among 536 sputum-smear-positive specimens, including PCR amplification of inhA mutations (Genotype MTBDRplus®), revealed excellent sensitivity (98.9%, 94.2%, 98.8%) and specificity (99.4%, 99.7%, 100%), as well as positive predictive value and negative predictive value for rifampin monoresistance, isoniazid monoresistance, and MDR TB (33). Though less useful for smear-negative specimens, the assay's price may be negotiable to less than that of standard culture and DST, making it feasible for implementation in RLS. The abovementioned GeneXpert® system targets similar mutations but, with a completely automated process, places less emphasis on skilled laboratory workers and infrastructure, making it more accessible to RLS (31).

MANAGEMENT

As the foundation of public health strategy for global TB control, DOTS has accomplished cure rates approaching 90% in many countries (1), although reliance on DOTS without culture/DST has contributed to the development of drug resistance. The Stop TB strategy (34) was established in 2000 to widen the scope of the TB control efforts. The goals of Stop TB are to promote strengthening of health systems, strategies for combating drug-resistant

TB and HIV/TB coinfection, expansion of DOTS, patient empowerment, and endorsement of research (http://www.stoptb.org). Treatment for drug-susceptible TB should result in a >95% cure rate when well executed. However, such success rates are not obtainable in the presence of drug resistance. Treatment for patients with drug-resistant TB is more costly, more complex, more toxic, and less effective. These factors contribute to decreased cure and completion rates and increased mortality.

With regard to specific treatment agents and regimens, there are no randomized clinical trial data, and the choice of agents largely depends on results of DST or standardized regimens based on knowledge of the DST profile of the specific geographic region. Empiric initiation of therapy with 4–5 oral drugs and intramuscular aminoglycoside or capreomycin is common, with the injectable agent utilized for at least 6 months after sputum conversion (13,15). Once DST results are known, the most toxic and/or least potent drugs can be discontinued (Table 2). Treatment for MDR TB continues for at least 24 months; the use of quinolones seems to improve outcomes (35–38). Because XDR TB is still quite a new phenomenon, data on treatment duration required for cure are limited, although one study reported a median of 43 months among HIV-negative patients (25) while another, also among HIV-negative patients, reported a median of 24.9 months (39). Notably, this latter study continued the injectable agent for a median of 15 months, and frequently utilized later-generation fluoroquinolones (levofloxacin and moxifloxacin). Adjunctive surgical debulking of pulmonary lesions has been shown to be of some benefit in patients with broad drug resistance, particularly in those with focal disease and in those who remain AFB-smear-positive despite 4–6 months of appropriate treatment (38–40). Surgical intervention does not obviate the need for extended pharmacological treatment.

In Latvia, a DOTS-plus strategy was associated with 66% cure of 204 patients with MDR TB (new and retreatment) (35). In a retrospective review of MDR TB patients at a U.S. TB specialty hospital, 75% experienced favorable outcomes and 12% died of TB or surgery (the remaining patients were lost to follow-up or had insufficient microbiologic data) (36). XDR TB patients show poorer outcomes—a South Korean study of XDR TB in HIV-negative patients demonstrated treatment success in 53.5% while 14% died, 4.7% relapsed (new positive cultures within six months of completing treatment), and 25.6% were treatment failures (positive sputum cultures at the end of treatment) (25). A recently published, retrospective study of HIV-negative patients with XDR TB from Peru, initially enrolled in 1999–2002, demonstrated that strict monitoring and management could achieve cure rates of 60% (39). Not surprisingly, coinfection with HIV worsens outcomes. In the initial Tugela Ferry cluster, the mortality rate was 98% among patients with XDR TB; all patients tested were HIV-positive (9). A subsequent study in Tugela Ferry showed six-month mortality rates of 32% among non-MDR TB patients, 69% among MDR TB patients, and 79% among XDR TB patients (41). Twelve-month mortality rates were 42%, 73%, and 85%, respectively. All patients were HIV-positive, and CD4 levels among survivors (109 cells/mm^3) were significantly ($p < 0.01$) higher than levels in those who succumbed to XDR TB (52 cells/mm^3). Among 65 patients with XDR TB from New York City, only 33.8% completed therapy, and survival differed according to HIV status (75% mortality among HIV-positive versus 30% among HIV-negative patients) (42). A TB referral hospital in Durban, South Africa reported 52% survival at six months among 62 patients with XDR TB, although this may be misleading, since patients able to access treatment in this setting were likely those with better prognoses. For lack of alternatives, agents such as amoxicillin-clavulanate, clarithromycin, and clofazamine were utilized in these patients' regimens as well as in the above-mentioned Peru study (39), although no clear data support their clinical anti-TB activity (43). For XDR TB, low albumin, underlying chronic disease, and bilateral cavitary disease have been found to be predictors of poor outcome (25).

Among the largest cluster of patients with XDR TB from Tugela Ferry (9), the majority had not received prior treatment for TB; most had been previously hospitalized; TB isolate genotypes were similar in 85%; and health care workers (HCWs) became infected, all of which strongly suggests nosocomial transmission. Given these observations and the lack of beds in TB specialty hospitals in high-prevalence areas, avoidance of hospitalization and reduction of inpatient stays have been suggested as prevention strategies. Ambulatory treatment programs for drug-resistant TB have been developed, although few have been evaluated. Two community-based treatment studies among HIV-negative patients in Lima, Peru demonstrated 83% probable cures among 75 patients with MDR TB (44) and 60% cure among 48 patients with XDR TB (39). Another recent study in the rural Guangxi province of China reported a decentralized model of TB care, moving care from county dispensaries to township hospitals, and reported improved completion and cure rates (45); HIV status was not reported in this study. A decentralized strategy (46) has the potential to unburden health care facilities, reduce nosocomial transmission of drug-resistant TB, and permit patients to return to their homes and families much more quickly (or spend the end of their lives at home instead of in a health care facility). However, validation of this approach is needed, particularly in settings of high HIV prevalence.

Many patients coinfected with HIV and TB experience severe and frequent adverse effects and are more dependent on nursing care (47). These patients require compassionate care, extensive psychological and social support, and sometimes economic relief. Staff should be informed and trained regarding the needs of patients with drug-resistant TB and coinfection with HIV, particularly in the realm of palliative care. Given their poor prognosis, patients with MDR/XDR TB should receive education regarding drug-resistant TB and be treated empathetically, not forcibly detained. A comprehensive, multidisciplinary, patient-centered approach can persuade patients to seek care earlier without fear of abandoning their families, will decrease defaulting, and will optimize care of dying patients (48,49).

In most settings, patients coinfected with HIV and TB receive their care from different providers, often standing in long queues in different clinics. Although HIV increases vulnerability to TB, and TB disease promotes viremia and HIV progression, distinct providers remain focused on their own specialty. Drug interactions between regimens from different providers increase toxicities, mortality, and defaulting. Integrating TB and HIV care has recently been promoted to improve diagnosis, treatment, and outcome of coinfected patients (50–53). Pilot projects have demonstrated feasibility and efficacy (8,54,55), and integration is now among the WHO international recommended policy priorities (56) to improve care (http://www.stoptb.org/wg/tbhiv/).

STRATEGIES FOR CONTROL

The current global status of TB control is inadequate, and the potential impact on successful antiretroviral (ARV) rollout programs worldwide is of great concern. Already, national health care systems are feeling the strain of draining resources, and at the community level the progress with HIV is being thwarted by another new, lethal, “untreatable” illness disproportionately affecting RLS. The global threat is being recognized, however, and steps are being taken on multiple fronts, discussed below.

Infection Control

Control of airborne infection is a crucial part of the strategy to control TB. Although guidelines have been developed, they have received little attention (57). There are three components to airborne infection control (58): administrative measures, environmental measures, and measures to reduce personal risk.

Administrative measures include protocols for staff education, enhanced communication between hospital departments, decreased hospital admissions and durations of stay, and development and use of laboratory methods to identify TB and drug resistance rapidly, with the intention of isolating patients with suspected or proven TB. Given concerns about nosocomial transmission, transitioning patients to or initiating new patients in outpatient community-based care programs is being evaluated in trials.

Recently, environmental measures, such as natural ventilation that relies on airflow through doors and windows, have received considerable attention and support. A study in Peru (59) demonstrated that natural ventilation can achieve sufficient air exchange to decrease risk of TB transmission. Utilizing the classic Wells-Riley model of airborne infection transmission, risk was 39% with mechanical ventilation versus 11% with all windows and doors open. Certainly a simpler, cheaper, and more effective intervention could not be devised, although its utility is limited to warm climates. Bacteriocidal UV light and high-efficiency particulate filters are alternative techniques recommended to decrease nosocomial infection, although the former relies on electricity, which is precious and unreliable in many areas, and the latter is expensive to install and maintain (57,58).

Efforts to reduce personal risk involve cough hygiene education for all staff and patients, as well as use of N95 respirators, particularly in high-risk areas of health care facilities (i.e., TB wards, ARV clinics). Respirator use is more problematic because of the resources required to purchase and maintain a steady supply of masks, and the staff's long-standing aversion to wearing them.

An essential part of infection control involves protection of HCWs, a precious resource in most developing countries (57,58). In Tugela Ferry, significant strides have been made: HCWs undergo formal education and instruction regarding infection control practices, including use of masks (A.P. Moll, personal communication). HCW deaths from drug-resistant TB have made the staff at this institution much more aware of the risk and likely to comply. In Tugela Ferry, two HCWs were among the 53 patients with XDR TB, and since 2005, eight HCWs, all with suspected or confirmed HIV, have died of MDR or XDR TB (9,60). Confidential voluntary counseling and testing for HIV should be offered to all HCWs, and those who test positive should be offered (*a*) a discreet transfer to a less high-risk post within the facility (58) and (*b*) ARV treatment at higher CD4 cell thresholds than national eligibility criteria would normally permit (60).

Although these infection control measures seem logical, it is difficult to quantify their effect. However, a recent study utilizing mathematical modeling confirms their utility (61). Voluntary counseling and testing for HIV by HCWs alone would decrease TB infections among HCWs by one third. Developing a comprehensive action plan with multiple infection-control interventions can have an enormous impact—48% of cases of XDR TB over the next five years could be averted using a combination of approaches (Figure 1): staff use of N95 respirators; decreases in hospital admissions and duration of inpatient stay; increased natural ventilation; rapid DST; isolation of patients into smaller groups of no more than five; and voluntary counseling and testing for HIV by staff and patients, with appropriate provision of ARVs (61).

Laboratory Capacity and Surveillance

It is imperative to incorporate methods for rapid diagnosis of TB and DST into routine clinical care, particularly in settings of highly prevalent drug resistance. Every person suspected of TB should have sputum smear, culture, and DST for both first- and second-line drugs so that the appropriate diagnosis and treatment regimen are determined at the outset. This will decrease interim morbidity and mortality resulting from diagnostic delay and

inappropriate treatment and further spread of drug-resistant TB. The local threshold of "high prevalence" at which to obtain DST on every sputum culture will vary significantly by region, even within a country. In order to accomplish culture and DST on all patients suspected of TB disease, global laboratory capacity must be strengthened. Testing technologies must utilize methods feasible for RLS. Currently, not only the technological capacity and infrastructure but also the human resources are lacking. Skilled HCWs to staff these laboratories must become a priority of national TB control strategies.

Furthermore, the need for surveillance of culture and DST with second-line drug testing is of utmost importance (62). A study from South Africa (63), using specimens collected over the past decade, demonstrated the accumulation of mutations that led to the development of XDR TB. If appropriate surveillance measures had been in place, the XDR phenomenon would have been identified earlier and perhaps with less loss of life.

HIV and Antiretroviral Therapy

Although HIV testing among TB patients has increased substantially over recent years, only 12% of TB patients globally and 32% of South African TB patients received HIV testing in 2006 (1). These numbers highlight the need for stronger collaboration between HIV clinicians and TB programs. HIV testing allows access not only to ARVs but also to preventive care. Cotrimoxazole therapy has been demonstrated to decrease morbidity and mortality (64) among HIV/TB coinfected patients. Thus far, ARVs have only been demonstrated to decrease mortality in drug-susceptible TB (8,65) and to decrease TB incidence (66). However, this benefit is expected to apply to drug-resistant TB as well. Encouragingly, in 2006, 78% of TB patients worldwide who tested positive for HIV received cotrimoxazole prophylaxis, although only 41% received ARVs (1).

Latent TB and Contact Tracing

Strategies to reduce TB among HIV patients include use of isoniazid for preventive therapy (IPT) (34). In low-HIV-prevalence settings, all HIV-positive patients should have tuberculin skin testing and initiate isoniazid for latent infection once active disease is excluded. However, controversy exists with regard to benefit of IPT in settings of high HIV prevalence and TB drug resistance. Concern that IPT may facilitate drug resistance has delayed its widespread adoption. Studies are under way to clarify this question.

Investigation of contacts of TB patients has been recommended but rarely instituted, most commonly owing to lack of resources. Calls for increased case finding through contact tracing have been reemphasized because of the extraordinary mortality associated with MDR/XDR TB. Resources should be allocated for this endeavor; ideally, contacts of MDR/XDR TB patients with active TB disease would undergo rapid diagnostic testing to optimize therapy from the start. However, in contacts with latent TB infection, there are no current data to support treatment, given the toxicities of first-line (besides isoniazid and rifampin) and second-line drugs, and the possibility of infection with an isolate that differs from that of the index patient (15). Contacts should be followed for at least two years for development of active disease. In HIV patients with exposure to MDR/XDR TB, initiation of ARVs may be a consideration. With any signs or symptoms of active TB disease, a specimen should be sent for culture/DST and an MDR TB treatment regimen should be initiated (15).

Improved Drug Access and Drug Development

Access to second-line drugs to treat drug-resistant TB should be a priority of national programs. The Green Light Committee of WHO was established to address access to inexpensive drugs. The need still far outweighs the demand: As of December 2007, only 30,000 patients in 52 countries, representing <5% of the global burden of drug-resistant TB,

were approved to receive second-line drugs through the Green Light Committee (1). Until recently, the pharmaceutical pipeline has not been encouraging; no new TB drugs have been developed in 30 years. Several promising new agents are in development and clinical trials, but it will likely take 3–5 years before a new drug is available for patients. Efforts toward novel drug design and accelerated approval are needed, as well as clinical trials to optimize regimens (34,67).

SUMMARY POINTS

1. Drug-resistant TB has emerged as a threat to global TB control and successful ARV rollout programs.
2. Both primary and acquired drug resistance contribute to MDR/XDR TB.
3. HIV coinfection increases the risk of MDR/XDR TB, facilitates progression to active disease, delays diagnosis, complicates treatment, and worsens prognosis.
4. Strengthening laboratory capacity, including DST for second-line drugs and regular surveillance efforts, is essential to successful management and prevention of drug-resistant TB.
5. Measures to control airborne infection, including natural ventilation, personal protective equipment, isolation, HIV testing of HCWs, and reduction of hospitalizations, are crucial to TB control and can have significant preventive impact.
6. Earlier identification of active TB patients, increased HIV testing of TB patients, and utilization of Cotrimoxazole and ARVs in coinfected patients can improve outcomes and prevent future infections.

FUTURE ISSUES

1. Evaluating transmission using genetic fingerprinting of TB isolates responsible for MDR/XDR TB and developing novel approaches to prevention.
2. Establishing the feasibility and efficacy of community-based treatment for drug-resistant TB.
3. Improving the pharmacological pipeline and clinical trials to determine the best agents and regimens for drug-resistant TB, particularly in the setting of HIV coinfection.
4. Establishing the best approach to contacts of MDR/XDR TB patients, particularly among HIV-positive and pediatric populations.

Abbreviations

Acquired drug resistance	accrual of mutations that inactivate an anti-TB agent as selection pressure is exerted by the drug during inadequate treatment
Primary drug resistance	transmission of *M. tuberculosis* isolates that already demonstrate resistance
DST	drug susceptibility testing

multiple-drug-resistant tuberculosis (MDR TB)	tuberculosis with laboratory-demonstrated resistance to isoniazid and rifampin
Extensively drug-resistant tuberculosis (XDR TB)	tuberculosis with laboratory-demonstrated resistance to isoniazid and rifampin *and* any fluoroquinolone *and* one of the following: amikacin, kanamycin, or capreomycin
AFB	acid fast bacilli
DOTS	directly observed therapy, short course
RLS	resource-limited settings
HCW	health care worker
ARV	antiretroviral therapy

LITERATURE CITED

1. World Health Organization. Global tuberculosis control—surveillance, planning, financing: WHO report 2008. 2008. WHO/HTM/TB/2008.393 http://www.who.int/tb/publications/2008/en/
2. Kazionny B, Wells CB, Kluge H, et al. Implications of the growing HIV-1 epidemic for tuberculosis control in Russia. Lancet 2001;358:1513–1514. [PubMed: 11705567]
3. Morozova I, Riekstina V, Sture G, et al. Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia. Int. J. Tuberc. Lung Dis 2003;7(9):903–906. [PubMed: 12971677]
4. Centers for Disease Control and Prevention. Trends in tuberculosis—United States, 2007. MMWR 2008;57(11):281–285. [PubMed: 18354371]
5. Pyle M. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. Proc. Staff Meet. Mayo Clin 1947;22(21):465–472.
6. British Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. Br. Med. J 1948;2:769–782. [PubMed: 18890300]
7. Rattan A, Kalia A, Ahmad N. Multidrug-resistant mycobacterium tuberculosis: molecular perspectives. Emerg. Infect. Dis 1998;4(2):195–210. [PubMed: 9621190]
8. Gandhi, N.; Moll, A.; Pawinski, R., et al. Favorable outcomes of integration of TB and HIV treatment in rural South Africa: the Sizonqoba study; Presented at Int. AIDS Conf., 16th; Toronto. 2006.
9. 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]
10. Centers for Disease Control and Prevention. Revised definition of extensively drug-resistant tuberculosis. MMWR 2006;55:1176.
11. World Health Organization. Antituberculosis drug resistance in the world: fourth global report. 2008. WHO/HTM/TB/2008.394 http://www.who.int/tb/publications/2008/en/
12. Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR 2006;55:301–305. [PubMed: 16557213]
13. Partners in Health. The PIH guide to medical management of multidrug-resistant tuberculosis. 2003. http://www.pih.org/inforesources/pihguide-dotstb.html
14. Rich, ML. Diagnosis and treatment of multidrug-resistant tuberculosis. In: Raviglione, MC., editor. Reichman & Hershfield's Tuberculosis: A Comprehensive, International Approach. 3rd ed.. New York: Informa Healthcare; 2006.
15. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. 2006. WHO/HTM/TB/2006.361 http://www.who.int/tb/publications/2006/en/index.html

16. Friedland G. Tuberculosis, drug resistance and HIV/AIDS: triple threat. Curr. Infect. Dis. Rep 2007;9:252–261. [PubMed: 17430708]
17. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis—the perfect storm. J. Infect. Dis 2007;196 Suppl.:86–107.
18. Lutfey M, Della-Latta P, Kapur V, et al. Independent origin of mono-rifampin-resistant *Mycobacterium tuberculosis* in patients with AIDS. Am. J. Respir. Crit. Care Med 1996;153(2): 837–840. [PubMed: 8564140]
19. Ridzon R, Whitney CG, McKenna MT, et al. Risk factors for rifampin mono-resistant tuberculosis. Am. J. Respir. Crit. Care Med 1998;157:1881–1884. [PubMed: 9620922]
20. Munsiff SS, Joseph S, Ebrahimzadeh A. Rifampin-monoresistant tuberculosis in New York City, 1993–1994. Clin. Infect. Dis 1997;25:1465–1467. [PubMed: 9431396]
21. Peloquin CA, Nitta AT, Burman WJ, et al. Low antituberculosis drug concentrations in patients with AIDS. Ann. Pharmacother 1996;30:919–925. [PubMed: 8876848]
22. Tappero JW, Bradford WZ, Agerton TB. Serum concentrations of antimycobacterial drugs in patients with pulmonary tuberculosis in Botswana. Clin. Infect. Dis 2005;41:461–469. [PubMed: 16028152]
23. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced human immunodeficiency virus disease. Antimicrob. Agents Chemother 2004;48:4473–4475. [PubMed: 15504887]
24. Moodley, P.; Moll, A.; Shah, NS., et al. Multi- and extensively drug-resistant *Mycobacterium tuberculosis* in KwaZulu Natal. Presented at Intersci; Conf. Antimicrobial Agents and Chemotherapy, 47th; Chicago. 2007.
25. 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]
26. Weyer, K.; Lancaster, J.; Brand, J. Survey of Tuberculosis Drug Resistance in South Africa 2001–2002. South African Medical Research Council. 2004. http://www.sahealthinfo.org/tb/tbsurvey.htm
27. Lyepshina, S. Association between multidrug-resistant tuberculosis and HIV status in the civilian and penitentiary sectors of Donetsk Oblast, Ukraine; Presented at Union World Conf. Lung Health, 38th ; Cape Town, South Africa. 2007.
28. Jeon CY, Hwang SH, Min JH, et al. Extensively drug resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital. Clin. Infect. Dis 2008;46:42–49. [PubMed: 18171212]
29. Andrews, JR.; Gandhi, NR.; Moll, AP., et al. Clinical predictors of multidrug and extensively drug-resistant tuberculosis in Tugela Ferry, South Africa; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.
30. 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]
31. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J. Infect. Dis 2007;196 Suppl.:15–27. [PubMed: 17538878]
32. O'Brien, R. New diagnostics for MDR and XDR-TB: What is in the pipeline?; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.
33. 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. Respir. Crit. Care Med 2008;177:787–792. [PubMed: 18202343]
34. World Health Organization. The Stop TB strategy. 2006. WHO/HTM/TB/2006.368 http://www.whqlibdoc.who.int/hq/2006/WHO_HTM_STB_2006.368_eng.pdf
35. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualised treatment of multidrugresistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318–326. [PubMed: 15664227]
36. Chan ED, Laurel V, Strand MJ. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am. J. Respir. Crit. Care Med 2004;169:1103–1109. [PubMed: 14742301]

37. Yew WW, Chan CK, Chau CH. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000;117(3):744–751. [PubMed: 10713001]
38. Törün T, Tahaoglu K, Özmen I. The role of surgery and fluoroquinolones in the treatment of multidrug-resistant tuberculosis. Int. J. Tuberc. Lung Dis 11 Sep;:979–985.
39. Mitnick CD, Shin SS, Seung KW, et al. Comprehensive management of extensively drug resistant tuberculosis. N. Engl. J. Med 2008;359(6):563–574. [PubMed: 18687637]
40. Lalloo UG, Naidoo R, Ambaram A, et al. Recent advances in the medical and surgical treatment of multi-drug resistant tuberculosis. Curr. Opin. Pulm. Med 2006;12:179–185. [PubMed: 16582672]
41. Andrews, JR.; Gandhi, NR.; Moll, AP., et al. High mortality among patients with multidrug and extensively drug-resistant tuberculosis in rural South Africa; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.
42. Ahuja, SD.; Munsiff, SS.; Sharma, S., et al. Clinical outcomes of extensively drug resistant tuberculosis patients in New York City; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.
43. O'Donnell, MR.; Pym, A.; Master, I., et al. Clinical treatment outcomes and epidemiologic risk factors for extensive drug resistant tuberculosis patients on treatment in KwaZulu-Natal, South Africa; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.
44. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N. Engl. J. Med 348:119–128. [PubMed: 12519922]
45. Wei X, Liang X, Walley J. Decentralising tuberculosis services from county tuberculosis dispensaries to township hospitals in China: an intervention study. Int. J. Tuberc. Dis 2008;12(5): 538–547.
46. Padayatchi N, Friedland G. Controlled decentralised management of multiple and extensively drug resistant tuberculosis (MDR & XDR TB): an alternate model of care. Int. J. Tuberc. Lung Dis 2008;12(8):978–980. [PubMed: 18647461]
47. McIlleron H, Meintjes G, Burman WJ, et al. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. J. Infect. Dis 2007;196 Suppl.:63–75.
48. Singh JA, Upshur R, Padayatchi N. XDR-TB in South Africa: no time for denial or complacency. PLoS Med 2007;4(1):e50. [PubMed: 17253901]
49. Padayatchi N, Friedland G. Managing multiple and extensively drug-resistant tuberculosis and HIV. Expert Opin. Pharmacother 2007;8(8):1035–1037. [PubMed: 17516869]
50. Farmer P, Léandre F, Mukherjee J, et al. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). Bull. World Health Organ 2001;79(12):1145–1151. [PubMed: 11799447]
51. Miti S. Integration of tuberculosis treatment in a community-based home care programme for persons living with HIV/AIDS in Ndola, Zambia. Int. J. Tuberc. Lung Dis 2003;7 Suppl.:92–98.
52. 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(6):a11–a15. [PubMed: 15189469]
53. 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.:421–428.
54. 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. Syndr 2004;36:929–934. [PubMed: 15220699]
55. Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. J. Infect. Dis (Suppl.) 2007;196:114–123.
56. World Health Organization & Stop TB Partnership. The global plan to stop TB 2006–2015. 2006. http://www.stoptb.org/globalplan/
57. 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 health care facilities in resource-limited settings. 2007. WHO/TB/99.269/2007 http://www.who.int/tb/publications/2007/en/index.html

58. Bock NN, Jensen PA, Miller B, et al. Tuberculosis infection control in resource-limited settings in the era of expanding HIV care and treatment. J. Infect. Dis 2007;196 Suppl:108–113.

59. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med 2007;4(2):e68. [PubMed: 17326709]

60. Moll, A. Treatment of HIV-associated XDR TB patients; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.

61. 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]

62. Sturm, AW. The role and value of molecular characterization of XDR-TB strains; Presented at Union World Conf. Lung Health, 38th; Cape Town, South Africa. 2007.

63. Pillay M, Sturm AW. Evolution of the extensively drug-resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in KwaZulu-Natal, South Africa. Clin. Infect. Dis 2007;45:1409–1414. [PubMed: 17990220]

64. Onyebujoh PC, Ribeiro I, Whalen CC. Treatment options for HIV-associated tuberculosis. J. Infect. Dis 2007;196 Suppl.:35–45.

65. Manosuthi W, Chottanapand S, Thongyen S, et al. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. J. Acquir. Immune Defic. Syndr 2006;43:42–46. [PubMed: 16885778]

66. Lawn SD, Myer L, Bekker LG, et al. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on treatment outcomes and implications for tuberculosis control. AIDS 2006;20(12):1605–1612. [PubMed: 16868441]

67. Mitnick CD, Castro KG, Harrington M, et al. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. PLoS Med 2007;4(11):e292. [PubMed: 17988168]

68. Nunn P, Kibuga D, Gathua S, et al. Thiacetazone commonly causes cutaneous hypersensitivity reactions in HIV positive patients treated for tuberculosis. Lancet 1991;337:627–630. [PubMed: 1705647]

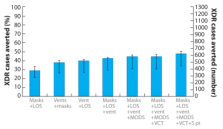

Figure 1.

Efficacy of rapidly available combinations of strategies to reduce nosocomial transmission of XDR TB. Mask: both staff N95 respirators and patient masks with adherence enforcement. LOS: reducing average length of stay to 5 days. Vent: improvements in natural ventilation. MODS: microscopic observed drug susceptibility assay. VCT: voluntary counseling and testing in admitted patients, with subsequent antiretroviral therapy to those who qualify. 5 pt: isolating patients in groups of five patients. Reprinted from Reference 61 with permission from Elsevier.

Table 1

Risk factors for drug-resistant TB (14–16,27,28)

- Residence in region with known high MDR/XDR TB prevalence
- Known exposure to MDR/XDR TB patient
- HIV/AIDS
- History of:
  - previous TB therapy, especially within the past year
  - relapse or recurrence after previous successful treatment
  - hospitalization within the past two years
  - nonadherence or default
  - incarceration
  - substance abuse or attendance of addiction treatment facilities
  - kanamycin resistance
  - malabsorption
  - medications known to cause drug interactions with concurrent TB therapy

Table 2

Antituberculosis agents (13–15,47,68)

First-line agents	Metabolism	Side effects
isoniazid	hepatic acetylated	hepatitis, peripheral neuropathy (prevented with pyridoxine 25 or 50 mg daily)
rifampin/rifabutin, rifapetine	hepatic	hepatitis, orange body fluids
pyrazinamide	hepatic; renal excretion	hepatic; renal excretion
ethambutol	renal excretion	retrobulbar neuritis in renal failure
streptomycin	renal excretion	ototoxicity, nephrotoxicity, peripheral neuropathy, pain at injection site, vestibular toxicity
Second-line agents		
ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin, gatifloxacin	renal excretion	mild GI distress, psychosis, seizure (mainly in elderly),QT interval prolongation, dysglycemia
kanamycin, amikacin, capreomycin	renal excretion	ototoxicity, nephrotoxicity, peripheral neuropathy, pain at injection site, vestibular toxicity
ethionamide/prothionamide	hepatic; renal excretion	frequent GI distress, metallic taste, hypothyroidism especially with PAS
cycloserine	renal excretion	neurologic/psychiatric: irritability, aggression, headaches, tremors; uncommon: psychosis, neuropathy, seizures
terizidone	renal excretion	GI distress, headache, seizures, dysarthria
para-aminosalicylic acid (PAS)	hepatic; renal excretion	frequent GI distress, hypothyroidism especially with ETO; uncommon: hepatitis
thiacetazone	GI excretion	GI distress, vertigo, conjunctivitis, hypersensitivity reactions including TEN, SJS especially in HIV infection
Third-line agents (limited data)		
linezolid	renal excretion	lowers seizure threshold, myelosuppression if duration >2 weeks, peripheral neuropathy; serotonin syndrome
clofazimine	GI excretion	GI distress; reddish brown discoloration of skin, which slowly resolves after discontinuation of drug
amoxicillin/clavulanate	hepatic; renal excretion	rash, GI distress
clarithromycin	hepatic	GI distress, headache; rare: hepatic failure

Abbreviations: GI, gastrointestinal; ETO, ethionamide; TEN, toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome.