HIV Coinfection in Multidrug- and Extensively Drug-Resistant Tuberculosis Results in High Early Mortality

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Rationale: The multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) epidemics are rapidly expanding in South Africa. Our initial report of HIV-associated XDR TB in South Africa revealed rapid and near complete mortality. Lower mortality has been described in the literature, but few of these patients have been HIV coinfected.

Objectives: To characterize mortality from MDR and XDR TB in a setting with high HIV-coinfection rates.

Methods: We conducted a retrospective observational study among 654 MDR and XDR TB cases diagnosed in Tugela Ferry, South Africa, from 2005 to 2007. Demographics and HIV status were abstracted from available medical records.

Measurements and Main Results: Survival was determined from the date of sputum collection until October 2008 and correlated with year of diagnosis and drug-susceptibility test results. From 2005 to 2007, 272 MDR TB and 382 XDR TB cases were diagnosed; HIV-coinfection rates were 90 and 98%, respectively. One-year mortality was 71% for MDR and 83% for XDR TB patients; 40% of MDR TB and 51% of XDR TB cases died within 30 days of sputum collection. One-year mortality among both MDR and XDR TB patients improved from 2005 to 2007; however, the majority of deaths still occurred within the first 30 days. One-year and 30-day mortality rates were worse with greater degree of drug resistance ($P < 0.001$).

Conclusions: Mortality from MDR and XDR TB in this high HIV-prevalence region is extraordinarily high, particularly within the first 30 days. Efforts to reduce mortality must focus on earlier diagnosis and early initiation of second-line TB and antiretroviral therapy.

Keywords: *Mycobacterium tuberculosis*; AIDS; multiple antibacterial drug-resistance; survival; South Africa

Drug-resistant tuberculosis (TB) has emerged as a significant global epidemic and poses a serious threat to HIV-infected persons (1–3). In 2006, there were an estimated 489,000 new

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Patients with MDR and XDR TB have achieved treatment success rates of 60 to 80% and 44 to 60%, respectively, in low HIV–prevalence settings.

What This Study Adds to the Field

Patients with MDR and XDR TB and HIV coinfection have markedly higher mortality rates than those previously reported in low HIV–prevalence settings.

cases of multidrug-resistant (MDR) TB—which is TB that is resistant to at least isoniazid and rifampin—and 116,000 estimated deaths (1). Reports of extensively drug-resistant (XDR) TB, defined as MDR TB with additional resistance to any fluoroquinolone and at least one injectable second-line TB drug (amikacin, kanamycin, or capreomycin), first emerged in 2005 and has since been identified in 55 countries worldwide (1, 4). XDR TB is associated with poorer outcomes than MDR TB (5–7) and has extremely high mortality among HIV-infected persons (8). Until recently, drug-resistant TB control efforts have not focused on sub-Saharan Africa where rates of MDR and XDR TB have been low or underreported (9). The convergence of the massive and maturing HIV epidemic with faltering TB programs in this region has now created conditions for a "perfect storm" of drug-resistant TB (3).

Studies from low- and middle-income settings demonstrate that patients with MDR TB can achieve treatment success rates of 60 to 80% in effective TB program settings (10). Despite severely limited treatment options, reasonable treatment success rates of 44 to 60% have also been reported in patients with XDR TB who are not coinfected with HIV (5, 6, 11–14). In contrast, the mortality rate was 98% among the initial cohort of patients with XDR TB from a high HIV prevalence setting in rural KwaZulu-Natal, South Africa (8). All patients tested for HIV in that study were HIV-infected.

One possible explanation for this marked difference in treatment outcomes is the influence of HIV coinfection. HIV has been associated with increased mortality in drug-susceptible and drug-resistant TB disease (15–19), and HIV coinfection rates in South Africa exceed 70% among both MDR and XDR TB cases (20). Another possible explanation is that our cohort is derived from a district health facility, rather than a tertiary referral center, thereby avoiding survival bias (21, 22). Our findings may be a consequence of capturing mortality among

patients who died early, before they had the opportunity to receive TB culture results and be referred for treatment at the tertiary MDR or XDR TB care center.

Given the differences in mortality between our initial report and other published cohorts, we sought to further characterize mortality among 654 cases of MDR and XDR TB diagnosed at our study site in Tugela Ferry, South Africa, since 2005. We also examined the relationship between mortality and the extent of drug resistance and described temporal changes in mortality and drug resistance patterns. Preliminary results from this study have been previously reported in the form of an abstract (23).

METHODS

Setting

Tugela Ferry is a resource-poor, 2,000 square-kilometer rural area in KwaZulu-Natal province, South Africa, which is home to 200,000 Zulu people. The vast majority of homes lack electricity or running water, and the unemployment rate is over 85% (24). HIV prevalence among women receiving antenatal care is 37%. The incidence of TB is approximately 1,100 per 100,000 population, and more than 80% of TB cases are HIV coinfected (25). A 355-bed government district hospital provides primary and secondary healthcare in this rural area.

Patients presenting to the district hospital with signs and symptoms of TB were evaluated clinically and with sputum microscopy, culture, and drug-susceptibility testing (DST). Detailed methodology regarding sputum collection, culture, and DST has been described previously (8). Briefly, mycobacterial culture was performed using both liquid (BACTEC mycobacterial growth indicator tube [MGIT]-960 system [BD, Franklin Lakes, NJ] and solid medium (Middlebrook 7H10; Difco Laboratories, Detroit, MI). DST for isoniazid (H), rifampicin (R), ethambutol (E), streptomycin (S), ciprofloxacin (Cx), and kanamycin (Km) was performed on all positive mycobacterial cultures by the standard 1% proportional method on Middlebrook 7H10 agar. Pyrazinamide is not included in the standard DST panel, even though it is included in the standard first-line TB treatment regimen.

Patients with a diagnosis of TB were given standard first-line TB therapy while awaiting results of culture and DST (typically 6–8 wk). Patients with confirmed MDR or XDR TB were referred to the provincial TB specialty hospital in Durban, where MDR TB patients were treated with a standardized regimen of kanamycin, ciprofloxacin, ethionamide, ethambutol (if susceptible), pyrizinamide (if susceptible), and terizidone or cycloserine (if ethambutol resistant) for 6 months (intensive phase) and continued on this regimen, without kanamycin, for an additional 18 months. XDR TB cases were treated similarly, except ciprofloxacin and kanamycin were replaced by para-amino salicylic acid (PAS) and capreomycin (only available since early 2007). Third-line TB drugs and surgical treatment were not routinely used.

Patients diagnosed with active TB were routinely offered HIV testing and, if HIV-infected, referred to a comprehensive HIV program, which provided free antiretroviral therapy. Newly diagnosed patients with HIV and with CD4 counts less than 200 cells/mm³ were typically started on antiretroviral therapy 1 to 2 months after initiating TB therapy.

Study Population and Drug-Resistance Classification

We performed a retrospective, observational study to examine all-cause mortality among patients diagnosed with MDR or XDR TB. All patients (both outpatient and inpatient) diagnosed with MDR or XDR TB from Tugela Ferry from January 2005 to December 2007 were included in this analysis. Data regarding the date of sputum collection, culture, and DST results, vital status, date of death (if applicable), and current treatment status for all MDR and XDR TB patients were abstracted from the drug-resistant TB register maintained by the TB treatment program in Tugela Ferry. This register has been validated by the KZN province Department of Health and has been found to be highly complete. Patients were classified as having MDR or XDR TB

using standard definitions (26). Patients were further subdivided and grouped according to the specific drugs to which their isolate was resistant (e.g., if resistant to isoniazid [H], rifampicin [R] and streptomycin [S], the patient was classified as HRS). The outcome of interest was all-cause mortality within the first year following MDR or XDR TB diagnosis.

Medical Record Review

We performed a medical record review in a convenience sample of MDR TB (n = 123) and XDR TB (n = 139) patients for whom medical records were available. We characterized patient demographics, HIV history (HIV status, CD4 count within 90 d before or after MDR/XDR TB diagnosis, and antiretroviral use), TB treatment history, and hospitalization history (before and during MDR/XDR TB episode).

Statistical Analysis

We calculated simple frequencies and proportions of patients in each drug-resistance category. We used the Cochran-Armitage test for linear trend over calendar years for each category. Patients' demographic and clinical characteristics were described in terms of percents, medians, and interquartile ranges (IQR). The primary outcome was the time to death from date of sputum collection. Patients were censored at the time of last patient contact.

Applying product limit estimation, we estimated survival rates in each resistance group and used Kaplan-Meier survival curves for graphic displays. Median survival times, along with 95% confidence intervals, were estimated based on the product-limit estimates for the MDR and XDR TB groups overall, by calendar year, and by drug-resistance pattern. For comparison of survival rates, we applied the log-rank test. Due to small numbers, certain resistance groups were combined for survival analysis: HRE, HRS, HRES were combined into "other MDR TB group"; and HRCxKm, HRECxKm, and HRSCxKm into "other XDR TB group." Significance was declared at a two-sided α level of 0.05 and all statistical analyses were conducted using SAS, version 9.1 (Cary, NC).

The study protocol was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, the Committee on Clinical Investigations of Albert Einstein College of Medicine, and the Human Investigations Committee of Yale University.

RESULTS

There were 272 MDR TB and 382 XDR TB patients diagnosed from January 2005 to December 2007. The most common resistance pattern among MDR TB patients was resistance to isoniazid, rifampicin, and streptomycin (HRS; n = 183, 67%; Table 1). The most common XDR TB pattern was resistance to all first-line and second-line TB drugs tested: isoniazid, rifampicin, ethambutol, streptomycin, ciprofloxacin, and kanamycin (HRESCxKm; n = 276, 72%; Table 1). The distribution of resistance patterns among MDR TB cases did not change from 2005 to 2007 (*P* for trend = 0.34). However, the proportion of XDR TB cases resistant to all tested drugs (HRESCxKm) increased significantly (*P* for trend < 0.001) during this period.

Medical records were reviewed in a subset of 123 patients with MDR TB and 139 patients with XDR TB (Table 2). They did not differ significantly, in terms of age, sex, or survival time, from the larger cohort (data not shown). Forty-three percent of patients with MDR TB and 56% of patients with XDR TB were women. Among those ever tested for HIV, 90% of patients with MDR TB and 98% of patients with XDR TB were coinfected with HIV. The median CD4 cell count at TB diagnosis was 87 (IQR, 41–217) and 66 (IQR, 24–169) cells/mm³, respectively. Only 15 and 22% of patients with MDR and XDR TB, respectively, were receiving antiretroviral therapy before their drug-resistant TB diagnosis. Nearly three-quarters (75% of patients with MDR TB and 69% of patients with XDR TB) were previously treated for TB, the majority of whom were

TABLE 1. DISTRIBUTION OF DRUG-SUSCEPTIBILITY PATTERNS BY CALENDAR YEAR AMONG PATIENTS WITH MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

	Total	2005	2006	2007
Total	654	180	237	237
MDR TB	272	62	118	92
HR	48 (18)	12 (19)	21 (18)	15 (16)
HRE	3 (1)	2 (3)	0 (0)	1 (1)
HRS	183 (67)	36 (58)	85 (72)	62 (67)
HRES	38 (14)	12 (19)	12 (10)	14 (15)
XDR TB	382	118	119	145
HRCxKm	63 (16)	47 (40)	12 (10)	4 (3)
HRECxKm	7 (2)	6 (5)	1 (1)	0 (0)
HRSCxKm	36 (9)	11 (11)	22 (18)	3 (2)
HRESCxKm	276 (72)	54 (46)*	84 (71)*	138 (95)*

Definition of abbreviations: Cx = Ciprofloxacin; E = Ethambutol; H = Isoniazid; Km = Kanamycin; MDR = multidrug-resistant; R = Rifampin; S = Streptomycin; TB = tuberculosis; XDR = extensively drug-resistant.

Values are n or n (%).

* *P* for trend < 0.001.

treated in the past year. More than half (51% of patients with MDR TB and 57% of patients with XDR TB) were hospitalized within the past 2 years.

Thirty-seven percent of patients with MDR TB and 25% of those with XDR TB were referred for treatment with second-line TB drugs (Table 2). The median time from sputum collection to referral for drug-resistant TB therapy was 69 days (IQR, 53–95 d) and 66 days (IQR, 52–84 d), respectively.

Overall Mortality

Among the full cohort of 654 patients, vital status was available for 265 of 272 (97%) patients with MDR TB and 374 of 382 (98%) patients with XDR TB. Overall, 188 of 265 (71%) patients with MDR TB, and 310 of 374 (83%) patients with XDR TB, died (*P* < 0.001). Survival time and dates of death were available for 214 of 265 (81%) patients with MDR TB and 294 of 374 (79%) patients with XDR TB. The median follow-up time among patients who survived was 413 days (IQR, 209–721 d).

Mortality was highest in the 30 days after sputum collection, with 40% of patients with MDR TB and 51% of patients with XDR TB dying during this time (Figure 1). The mortality rate was also greatest in the first 30 days (633 and 956 deaths per 100 patient-years, respectively) and decreased thereafter (67 and 139 deaths per 100 patient-years, respectively). The median survival time from sputum collection among patients with MDR TB was 60 days (95% CI, 39–174 d) and 28.5 days (95% CI, 20–34 d) among patients with XDR TB (*P* < 0.0001).

Among patients with MDR and XDR TB who survived more than 6 weeks, the typical time to receipt of conventional culture and DST result, survival was markedly better: 60% (76 of 127) of patients with MDR TB and 43% (59 of 136) of patients with XDR TB were alive at last follow-up.

Mortality by Drug-Susceptibility Pattern

Survival time diminished in a stepwise fashion with increasing drug resistance (Figure 2; *P* < 0.0001). Median survival was best (182 d [95% CI, 31–395 d]) for patients with resistance to only isoniazid and rifampin (HR) and worsened substantially to 27 days (95% CI, 20–38 d) among patients with resistance to all tested first-line and second-line drugs (HRESCxKm). The proportion of patients who died within 1 year also increased stepwise from 61% in the HR group to 90% in the HRESCxKm group (*P* < 0.0001). In all resistance groups, the majority of deaths occurred within the first 30 days after sputum collection (Figure 2).

Mortality by Calendar Year

In patients with MDR and XDR TB, mortality improved based on year of sputum collection from 2005 to 2007. In 2005, 76% of MDR TB patients died within 1 year of sputum collection compared with 60% in 2006 and 55% in 2007 (*P* = 0.02; Figure 3A). Among patients with XDR TB, 85% died within 1 year in 2005 compared with 84% in 2006 and 75% in 2007 (*P* = 0.01; Figure 3B).

Although 30-day mortality also improved from 2005 to 2007, the majority of deaths continued to occur within the first 30 days. Thirty-day mortality was 54% in 2005, 35% in 2006, and 34% in 2007 among patients with MDR TB (*P* = 0.003) and 57, 56, and 42%, respectively, for patients with XDR TB (*P* = 0.001).

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF PATIENTS WITH MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS

	MDR TB	XDR TB
Total with available medical records, n	123	139
Female sex, n (%)	53 (43)	78 (56)
Age, years, median (IQR)	34 (29–43)	34 (29–42)
Tested for HIV, n (%)	94 (76)	117 (84)
HIV positive, n (% tested)	85 (90)	115 (98)
CD4 measured at TB diagnosis, n (% of HIV+)	41 (48)	36 (31)
Median (IQR)	87 (41–217)	66 (24–169)
VL measured at TB diagnosis, n (% of HIV+)	12 (14)	18 (16)
Median	160,000	135,500
(IQR)	(81,500–1,010,000)	(180–410,000)
Receiving antiretroviral therapy at time of TB diagnosis, n (% of HIV+)	13 (15)	25 (22)
Positive sputum smear, n (%)	77 (63)	84 (61)
Presence of extrapulmonary TB, n (%)	34 (28)	41 (30)
Previous TB Treatment		
Any, n (%)	92 (75)	96 (69)
Past year, n (%)	67 (55)	78 (56)
Previous hospitalization within past 2 years, n (%)	63 (51)	79 (57)
Referred for second line TB therapy: n (%)	46 (37)	35 (25)
Time to referral: median days (IQR)	69 (53–95)	66 (52–84)

Definition of abbreviations: IQR = interquartile range; MDR = multidrug-resistant; TB = tuberculosis; VL = HIV viral load; XDR = extensively drug-resistant.
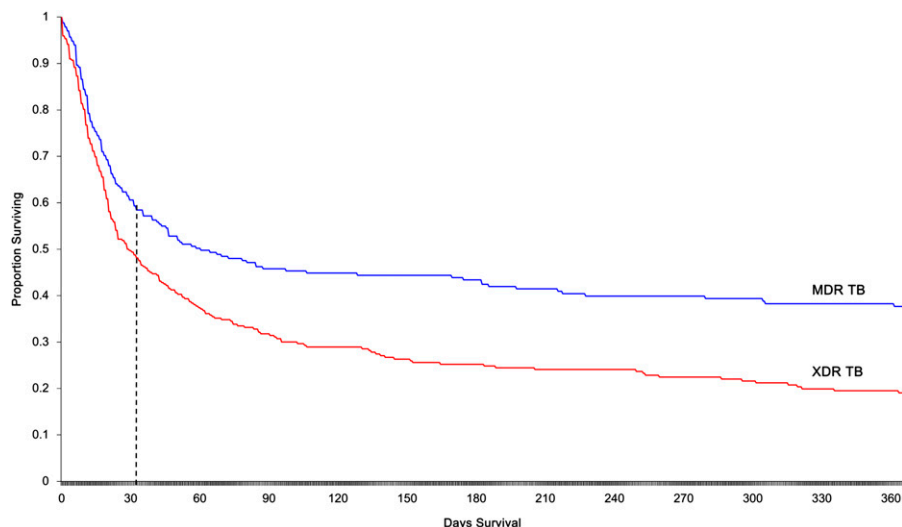
Figure 1. Kaplan-Meier survival plot among multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) patients, 2005 to 2007 (log-rank, $P < 0.0001$).

DISCUSSION

We report on survival among patients with drug-resistant TB from a high HIV-prevalence setting in rural KwaZulu-Natal, South Africa. This study is the largest cohort of XDR TB cases reported to date worldwide. Mortality among patients with XDR TB has remained extremely high. A unique and disturbing finding is the high mortality seen in the MDR TB cohort as well. The majority of the deaths among both MDR and XDR TB cases occurred within 30 days after sputum collection, a period shorter than the typical 6 to 8 weeks required to diagnose drug-resistant TB by conventional culture and drug-susceptibility testing methods.

The high early mortality in this study reinforces our previous finding that the majority of patients do not survive long enough to receive their drug-resistant TB diagnosis and to initiate treatment. We demonstrate that this occurs not only among cases with XDR TB, but also among cases with MDR TB in this high HIV-prevalence setting. These patients likely received only ineffective first-line TB treatment without the opportunity to be referred for second-line TB therapy at specialized tertiary centers. Indeed, among patients with MDR and XDR TB who survived at least 6 weeks and potentially started second-line TB drugs, survival rates were 60 and 43%, proportions similar to

those seen in other low- and middle-income settings (5, 10–14). This rapid mortality suggests that efforts to improve survival in this setting must focus on improved case detection, more rapid diagnosis, and early initiation of second-line TB therapy.

Awareness of the drug-resistant TB epidemic in South Africa has increased substantially since 2005. Healthcare professionals are now more vigilant in suspecting MDR and XDR TB, and greater resources have been allocated to expand laboratory capacity and strengthen TB treatment programs. These changes appear to have translated into improvements in survival from 2005 to 2007 among both MDR and XDR TB cases. Despite the overall improvement in survival, however, the majority of deaths in all years consistently occurred within 30 days after sputum collection and before drug-resistant TB was diagnosed.

It is critical to understand why the mortality rates in our setting are far greater than those reported from other MDR and XDR TB cohorts worldwide where similar delays in diagnosis of drug-resistant TB are likely to occur. First, most reports have been from low HIV–prevalence settings where few if any patients with MDR or XDR TB were coinfected with HIV. In contrast, more than 90% of patients with MDR and XDR TB in our setting were coinfected with HIV. HIV is well-known to complicate TB disease, and coinfection increases mortality in all
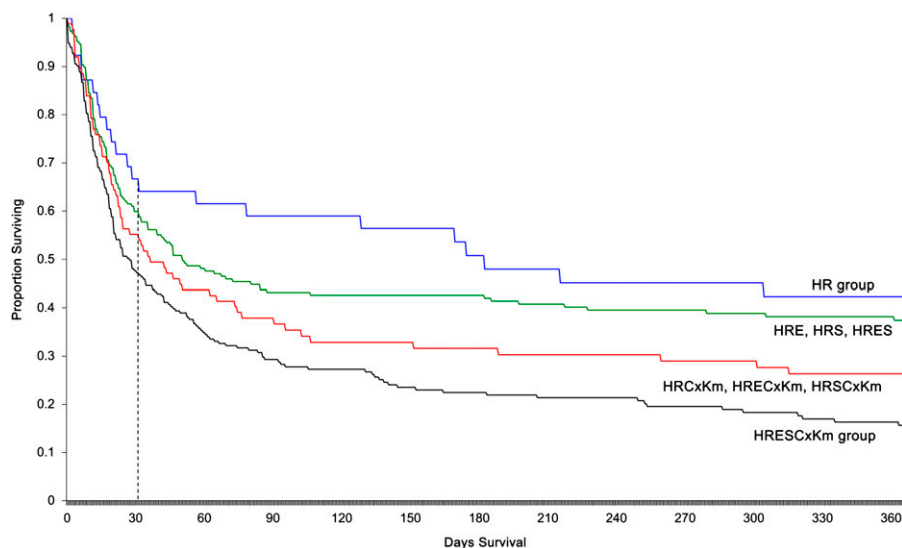

Figure 2. Kaplan-Meier survival plot by drug resistance pattern among patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB), 2005 to 2007 (log-rank, $P < 0.0001$). Letters indicate drugs to which isolate was resistant: H, Isoniazid; R, Rifampin; E, Ethambutol; S, Streptomycin; Cx, Ciprofloxacin; Km, Kanamycin. Median survival was 182 days (95% CI, 31–395 d) for patients with MDR TB and resistance to only HR; 50 days (95% CI, 35–106 d) for patients with MDR TB and resistance to HRE, HRS, or HRES; 36 days (95% CI, 23–74 d) for patients with XDR TB and resistance to HRCxKm, HRECxKm, or HRSCxKm; and 27 days (95% CI, 20–38 d) for patients with XDR TB and resistance to HRESCxKm.
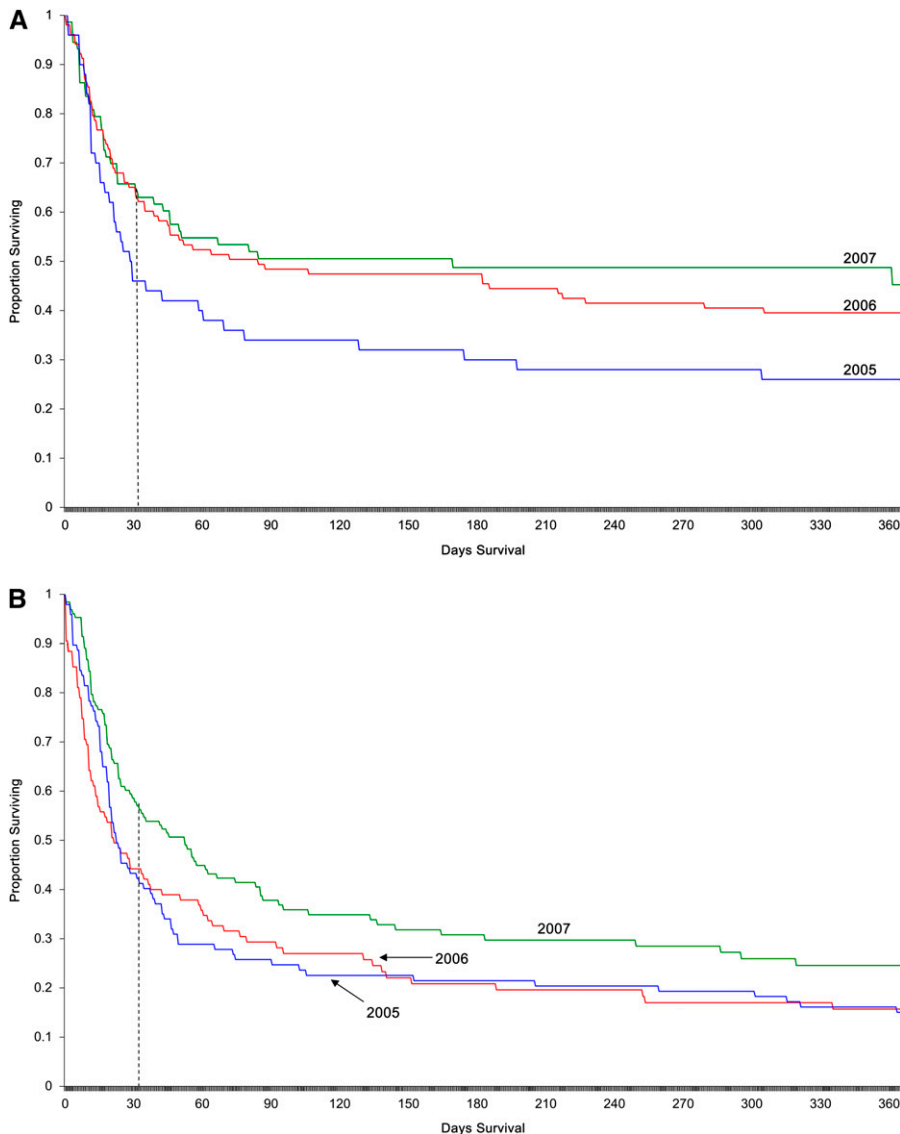
Figure 3. (*A*) Kaplan-Meier survival plot among patients with multidrug-resistant (MDR) tuberculosis (TB) by calendar year of sputum collection, 2005 to 2007 (log rank, $P = 0.02$). (*B*) Kaplan-Meier survival plot among patients with extensively drug-resistant (XDR) TB by calendar year of sputum collection, 2005 to 2007 (log rank, $P = 0.01$).

forms of TB (15–19). During the MDR TB outbreaks that occurred in industrialized countries in the 1990s, HIV coinfection rates also exceeded 90%, and mortality was similar to our setting: 72 to 98% of patients died, and the median survival from presentation to death was 4 to 16 weeks (3). Second, most other studies report results from patients referred to a tertiary drug-resistant TB treatment program, and, therefore, may have introduced a survival bias (22). Considering that conventional TB culture and DST takes 6 to 8 weeks, and additional delays exist related to referrals, patients must survive well beyond 30 days to receive treatment for drug-resistant TB. Because the majority of deaths in our study occurred in this time frame, these patients would have been systematically excluded from a tertiary referral program cohort, creating a bias toward improved treatment outcomes. Our findings may better represent outcomes in patients with MDR and XDR TB in high HIV–prevalence settings in sub-Saharan Africa, insofar as they include even those who never reached the point of referral for treatment.

Efforts to improve treatment outcomes in HIV coinfected patients with MDR or XDR TB must begin with improved TB case detection. At present, the policy in most resource-limited settings is to reserve mycobacterial culture and DST for patients who have failed treatment (i.e., inadequate response after 3 mo of first-line therapy) or for recurrent cases of TB. This policy results in delays in diagnosis beyond the 6 to 8 weeks it takes for conventional culture and DST results. Our data suggest that most patients with MDR and XDR TB would have died even before having their sputum sent for culture and DST. Thus, not only is the number of drug-resistant TB cases likely an underestimate, but also, the role of early mortality due to drug-resistant TB is likely under-appreciated. Universal culture and DST for all TB suspects must be considered as the first step in tackling this epidemic.

Further strategies must focus on diagnosing drug-resistant TB and initiating second-line TB treatment within days of presentation. A low-cost, rapid point-of-care test that is sensitive in HIV-infected patients and can be used at the peripheral health center level is urgently needed. The recent development of several new rapid drug-resistant TB assays provides hope for earlier diagnosis (27–29); however, further efforts are needed to develop tests that are sensitive in smear-negative TB cases and can be used in resource-poor settings.

Currently, in most developing countries, the availability of second-line TB therapy is limited to centralized drug-resistant TB programs. Although limiting access is important to guard

against further development of TB drug-resistance, it introduces additional delays in initiating second-line TB therapy. Consideration should be given for the use of empiric second-line TB therapy in patients at high-risk for drug-resistant TB who are awaiting DST results. Early evidence suggests that such an approach may improve survival (11, 30–32). With adequate training and support, decentralization of MDR TB therapy to community settings provides a practical, patient-centered approach to delivering care that can reduce the time to treatment initiation.

Finally, greater efforts to prevent the development of MDR and XDR TB, especially in high HIV prevalence settings, are important. TB programs should be strengthened to prevent amplification of drug resistance, and widespread infection control programs to prevent transmission of drug-resistant TB strains should be implemented. Further, earlier diagnosis and treatment of HIV must be a priority. Although our data cannot directly address this, antiretroviral therapy has been shown to substantially improve TB incidence and survival (17, 33), and is likely to do so for drug-resistant TB as well. All of the above measures, taken together, are essential to preventing new infection with drug-resistant TB strains, preventing the development of active disease following infection, and reducing overall mortality.

Our study has several limitations. Our data are derived from a drug-resistant TB register that does not contain full clinical or treatment details; thus, we are unable to provide details about the timing of DST results and the initiation of second-line TB therapy for every patient. Nonetheless, we performed a chart review on a representative subset of patients and confirmed that a significant delay for referral existed (while awaiting DST results) and that only a small proportion of patients survived long enough to be referred for second-line therapy. Second, we are not able to estimate delays between the onset of symptoms and presentation for care (i.e., delayed presentation) that contributed to the early mortality we observed. However, based on observations of patients in other studies at our site, all who were receiving frequent clinical follow-up, rapid mortality from MDR or XDR TB occurred within weeks from the onset of patients' symptoms (34, 35). Thus, the contribution of delayed presentation to the rapid mortality observed is uncertain. Additional studies examining the virulence of these MDR and XDR TB strains and host factors in HIV-coinfected patients must be performed to determine the cause of this rapid mortality.

The drug-resistant TB epidemic in South Africa has been rapidly expanding over the past 5 years, fueled by the maturation of the world's worst HIV epidemic. The collision of these two epidemics has resulted in extraordinary rates of mortality, the majority of which occurs before a diagnosis is made. Without early diagnosis and initiation of treatment, a similar tragedy may unfold in other parts of Africa and Eastern Europe, where these two epidemics are converging. Immediate, intensive efforts to combat this dual epidemic are critical for averting its further expansion and its associated high mortality.

References

1. World Health Organization. Anti-tuberculosis drug resistance in the world: fourth global report. 2008.
2. Dubrovina I, Miskinis K, Lyepshina S, Yann Y, Hoffmann H, Zaleskis R, Nunn P, Zignol M. Drug-resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics? *Int J Tuberc Lung Dis* 2008;12:756–762.
3. Wells C, Cegielski JP, Nelson L, Laserson K, Holtz T, Finlay A, Castro K, Weyer K. HIV infection and multidrug resistant tuberculosis – the perfect storm. *J Infect Dis* 2007;196:S86–S107.
4. Shah NS, Wright A, Bai GH, Barrera L, Boulahbal F, Martin-Casabona N, Drobniewski F, Gilpin C, Havelkova M, Lepe R, *et al.* Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg Infect Dis* 2007;13:380–387.
5. Migliori GB, Besozzi G, Girardi E, Kliiman K, Lange C, Toungoussova OS, Ferrara G, Cirillo DM, Gori A, Matteelli A, *et al.* Clinical and operational value of the extensively drug-resistant tuberculosis definition. *Eur Respir J* 2007;30:623–626.
6. Shah NS, Pratt R, Armstrong L, Robison V, Castro KG, Cegielski JP. Extensively drug-resistant tuberculosis in the United States, 1993–2007. *JAMA* 2008;300:2153–2160.
7. Chan ED, Strand MJ, Iseman MD. Treatment outcomes in extensively resistant tuberculosis. *N Engl J Med* 2008;359:657–659.
8. Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, Zeller K, Andrews J, Friedland G. 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* 2006;368:1575–1580.
9. Ben Amor Y, Nemser B, Singh A, Sankin A, Schluger N. Underreported threat of multidrug-resistant tuberculosis in Africa. *Emerg Infect Dis* 2008;14:1345–1352.
10. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvani AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:153–161.
11. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, Fitzmaurice GM, Cantara Viru FA, Appleton SC, Bayona JN, *et al.* Comprehensive treatment of extensively drug-resistant tuberculosis. *N Engl J Med* 2008;359:563–574.
12. Kim HR, Hwang SS, Kim HJ, Lee SM, Yoo CG, Kim YW, Han SK, Shim YS, Yim JJ. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. *Clin Infect Dis* 2007;45:1290–1295.
13. Eker B, Ortmann J, Migliori GB, Sotgiu G, Muetterlein R, Centis R, Hoffmann H, Kirsten D, Schaberg T, Ruesch-Gerdes S, *et al.* Multidrug- and extensively drug-resistant tuberculosis, Germany. *Emerg Infect Dis* 2008;14:1700–1706.
14. Keshavjee S, Gelmanova IY, Farmer PE, Mishustin SP, Strelis AK, Andreev YG, Pasechnikov AD, Atwood S, Mukherjee JS, Rich ML, *et al.* Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. *Lancet* 2008;372:1403–1409.
15. Quy HT, Cobelens FG, Lan NT, Buu TN, Lambregts CS, Borgdorff MW. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. *Int J Tuberc Lung Dis* 2006;10:45–51.
16. Connolly C, Davies GR, Wilkinson D. Impact of the human immunodeficiency virus epidemic on mortality among adults with tuberculosis in rural South Africa, 1991–1995. *Int J Tuberc Lung Dis* 1998;2:919–925.
17. Lawn SD, Myer L, Bekker LG, Wood R. Burden of tuberculosis in an antiretroviral treatment programme in sub-Saharan Africa: impact on

treatment outcomes and implications for tuberculosis control. *AIDS* 2006;20:1605–1612.

18. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS* 2001;15: 143–152.

19. Harries AD, Nyangulu DS, Kang'ombe C, Ndalama D, Glynn JR, Banda H, Wirima JJ, Salaniponi FM, Liomba G, Maher D, *et al.* Treatment outcome of an unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba Hospital, Malawi. *Trans R Soc Trop Med Hyg* 1998;92:343–347.

20. Andrews J, Gandhi NR, Moll A, Shah NS, Sturm AW, Lalloo U, Moodley P, Friedland G. clinical predictors of multidrug and extensively drug-resistant tuberculosis—Tugela Ferry, South Africa. 38th Union World Conference on Lung Health. 2007.

21. O'Donnell M, Padayatchi N, Master I, Osburn G, Horsburgh CR. Improved early results for patients with extensively drug resistant tuberculosis and HIV in South Africa. *Int J Tuberc Lung Dis* 2009;13:855–861.

22. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol* 2005;162:1016–1023.

23. Gandhi NR, Shah NS, Andrews J, Vella V, Moll A, Scott M, Babaria P, Marra C, Lalloo U, Friedland G. High early mortality among HIV-infected patients with multidrug-resistant (MDR) or extensively drug-resistant tuberculosis (XDR TB) in Rural South Africa. 16th Conference on Retroviruses and Opportunistic Infections. 2009. 2-10-2009.

24. Umzinyathi District Management. Tuberculosis MDR/XDR: the Msinga experience 2005–2009. 2009. South Africa.

25. Buthelezi SSS. Situational analysis of TB drug resistance in KwaZulu-Natal province: Republic of South Africa. 2nd Meeting of the Global XDR TB Task Force. 4-9-2008.

26. Centers for Disease Control and Prevention (CDC). Notice to readers: revised definition of extensively drug-resistant tuberculosis. *MMWR Morb Mortal Wkly Rep* 2006;55:1176.

27. Moore DA, Evans CA, Gilman RH, Caviedes L, Coronel J, Vivar A, Sanchez E, Pinedo Y, Saravia JC, Salazar C, *et al.* Microscopic-observation drug-susceptibility assay for the diagnosis of TB. *N Engl J Med* 2006;355:1539–1550.

28. Hillemann D, Weizenegger M, Kubica T, Richter E, Niemann S. Use of the genotype MTBDR assay for rapid detection of rifampin and isoniazid resistance in *Mycobacterium tuberculosis* complex isolates. *J Clin Microbiol* 2005;43:3699–3703.

29. Barnard M, Albert H, Coetzee G, O'Brien R, Bosman ME. 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.

30. Raviglione MC. Facing extensively drug-resistant tuberculosis–a hope and a challenge. *N Engl J Med* 2008;359:636–638.

31. Scano F, Vitoria M, Burman W, Harries AD, Gilks CF, Havlir D. Management of HIV-infected patients with MDR- and XDR-TB in resource-limited settings. *Int J Tuberc Lung Dis* 2008;12:1370–1375.

32. Dowdy DW, Chaisson RE, Maartens G, Corbett EL, Dorman SE. Impact of enhanced tuberculosis diagnosis in South Africa: a mathematical model of expanded culture and drug susceptibility testing. *Proc Natl Acad Sci USA* 2008;105:11293–11298.

33. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. *AIDS* 2008;22:1897–1908.

34. Gandhi NR, Moll AP, Lalloo U, Pawinski R, Zeller K, Moodley P, Meyer E, Friedland G. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study. *J Acquir Immune Defic Syndr* 2009;50:37–43.

35. Andrews JR, Gandhi NR, Moodley P, Shah NS, Bohlken L, Moll AP, Pillay M, Friedland G, Sturm AW. Exogenous reinfection as a cause of multidrug-resistant and extensively drug-resistant tuberculosis in rural South Africa. *J Infect Dis* 2008;198:1582–1589.