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Xpert MTB/RIF Use Is Associated With Earlier Treatment Initiation and Culture Conversion Among Patients With Sputum Smear-Negative Multidrug-Resistant Tuberculosis

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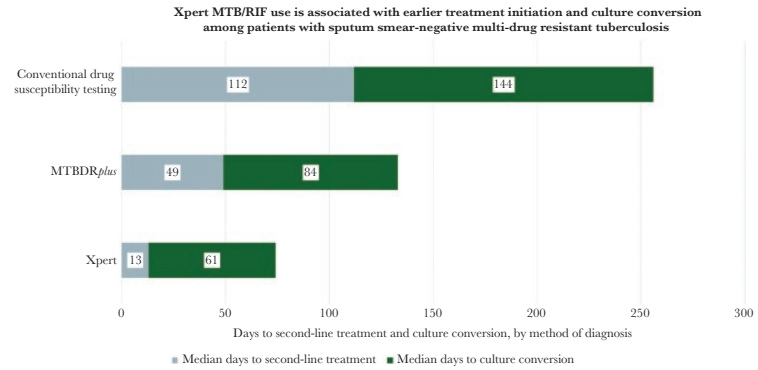
Background. Although rapid molecular diagnostic tests for tuberculosis (TB) have decreased detection time of *Mycobacterium tuberculosis* and drug resistance, whether their use improves clinical care and outcomes is uncertain. To address these knowledge gaps, we evaluated whether use of the Xpert MTB/RIF assay impacts treatment and clinical outcome metrics among patients treated for sputum smear-negative multidrug-resistant (MDR)-TB.

Methods. We conducted a retrospective cohort study of adult patients initiating treatment for sputum smear-negative MDR-TB at the National Center for Tuberculosis and Lung Diseases in Tbilisi, Georgia from 2011 to 2016. The Xpert MTB/RIF was introduced in Georgia in 2010 and implemented into programmatic use in 2014. Exposure was availability of an Xpert result at time of diagnosis. Time to second-line treatment initiation, sputum culture conversion, and end-of-treatment outcomes were determined. Time to event was compared using a Cox proportional hazards model.

Results. Among 151 patients treated for sputum smear-negative MDR-TB (96% culture positive), the Xpert was utilized in the clinical management of 78 (52%) patients and not used in 73 (48%). An adjusted analysis controlling for potential confounders found that patients in the Xpert group had shorter median time to second-line treatment (13 vs 56 days; adjusted hazard ratio [aHR], 10.21; $P < .0001$) and culture conversion (61 vs 93 days; aHR, 1.93; $P < .001$). There was no difference in treatment outcomes.

Conclusions. Use of the Xpert in the management of sputum smear-negative MDR-TB decreases time to second-line therapy and sputum culture conversion, providing evidence of its clinical impact and supporting its programmatic utility.

Graphical Abstract



Keywords. culture conversion; drug-resistant TB; molecular diagnostics; Xpert MTB/RIF.

Tuberculosis (TB) remains a major global health problem, and before the coronavirus disease 2019 pandemic it was the leading cause of infectious disease-related mortality in the world [1]. The emergence of rifampicin-resistant or multidrug-resistant TB (RR/MDR-TB) is a substantial barrier to meeting the World Health Organization END TB Strategy goal of eliminating TB by 2035 [2]. The implementation of new and repurposed drugs, including bedaquiline and linezolid, has been a major breakthrough and led to shorter treatment regimens and improved

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outcomes for patients with drug-resistant disease; however, detection of drug resistance remains a major obstacle to providing optimal care for patients with RR/MDR-TB [3–5]. Among the estimated 465 000 incident cases of RR/MDR-TB in 2019, only 206 000 were confirmed cases, highlighting a substantial gap in drug-resistance detection [1].

The introduction of rapid molecular diagnostic tests has shortened the time to detection of *Mycobacterium tuberculosis* and associated drug resistance from months to a few hours. Although several such tests have been endorsed by the World Health Organization (WHO) and implemented in a variety of settings, data on their impact on clinical outcomes are limited with most studies focusing on drug-susceptible disease [6–8]. It is expected that earlier diagnosis of TB and identification of drug resistance will lead to improved treatment outcomes, but evaluating whether and in which settings this is true will allow national TB programs (NTP) to prioritize allocation of limited resources. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA) is an automated molecular test that simultaneously detects *M tuberculosis* and rifampicin resistance in less than 2 hours with high sensitivity and specificity; it was implemented into routine clinical care in the Georgian NTP in 2014 [9].

The country of Georgia has a high burden of drug-resistant TB; from 2011 to 2013, 9%–11% of newly diagnosed TB cases and 31%–38% of retreatment cases were MDR-TB. Our retrospective cohort study evaluated the impact of implementation of the Xpert MTB/RIF assay on clinical outcomes among adults treated for sputum smear-negative MDR-TB. We hypothesized that time to second-line therapy and time to culture conversion are decreased among patients for whom the Xpert assay was used in clinical management.

METHODS

Study Design/Setting

We conducted a retrospective cohort study at the National Center for Tuberculosis and Lung Diseases (NCTLD) in Tbilisi, Georgia. The NCTLD implements the National TB Program of the country along with the National Center for Disease Control. The NCTLD campus contains the National TB Reference Laboratory (NRL), a 100-bed MDR-TB inpatient treatment facility and outpatient directly observed therapy (DOT) clinics. All diagnostic testing for patients with suspected TB and treatment for patients diagnosed with TB including MDR disease are provided free of charge by the Georgian NTP with support of the Global Fund to Fight AIDS, Tuberculosis and Malaria. We included adults (≥18 years) treated for pulmonary sputum smear-negative MDR-TB who initiated treatment at the NCTLD between February 2011 and October 2016.

Patient Consent Statement

Approval for this project was obtained from the NCTLD ethics committee and the Emory University institutional review board. Given that this was a retrospective study with low risk, informed consent was waived.

Laboratory

All patients with suspected pulmonary TB had sputum samples sent for solid and mycobacteria growth indicator tube (MGIT) liquid cultures with first-line phenotypic drug-susceptibility testing (DST) performed on all *M tuberculosis* isolates. If any resistance was detected, second-line phenotypic DST was performed as previously described [10]. The Xpert MTB/RIF assay was introduced in the Georgian NTP for operational research in 2010 and implemented into routine clinical care and decision making in 2014. Xpert results performed during the operational research period were performed at the NRL and were not sent to health centers or available to treating physicians. During the study period, the Xpert MTB/RIF assay was utilized according to a diagnostic algorithm in parallel to microscopy on sputum samples for patients with presumptive TB. For patients without an Xpert result or with an Xpert result of rifampicin-susceptible, the MTBDR*plus* assay was performed on the positive diagnostic culture for additional molecular testing of first-line drugs pending phenotypic DST results [6]. A portion of each sputum specimen was used for both molecular testing and culture at the NRL.

Treatment

Treatment regimens for drug-resistant TB in Georgia during the study period were individualized based on DST results when available and guided by WHO recommendations for the treatment of MDR-TB [11]. Pending phenotypic DTS results, initial empiric treatment was guided by Xpert and/or MTBDR*plus* results when available and/or history of MDR treatment or contact to an MDR case. All regimens were recommended to include a fluoroquinolone and injectable agent. All treatment regimens were reviewed and decided upon by the NCTLD Drug Resistance Committee. Newer drugs including bedaquiline, delamanid, linezolid, and clofazimine were not implemented into programmatic use until the end of our study period in 2015. Per NTP guidelines, patients treated for MDR-TB were recommended to be hospitalized for initiation of second-line drug treatment and discharged to outpatient care when tolerability to treatment and improvement were achieved. The standard of care for treatment duration during the study period was a minimum of 20 months. All treatment was administered via DOT.

Data Management

Demographic characteristics, TB information, laboratory results, and clinical outcomes were abstracted from medical charts and national TB databases. Our main exposure was defined as the use of Xpert for initial diagnostic work up of pulmonary TB. Patients with Xpert performed on a diagnostic sample and with an available result were included in the Xpert group, and

others were included in the non-Xpert group. The non-Xpert group included patients managed using MTBDR*plus*, conventional DST, or with history of MDR-TBor, a known MDR-TB contact. The time to MDR-TB treatment initiation was defined as days from initial sputum collection to start of second-line treatment. The time to culture conversion was defined as days from initial diagnostic sputum culture collection to the date of the first of 2 consecutive negative sputum cultures performed at least 1 month apart. Participants were censored due to death, loss to follow up, or end of the study period. All data were collected onto standardized data collection forms and entered into an online REDCap database [12].

Statistical Analysis

Categorical variables were evaluated using either the χ^2 or Fisher exact tests, and continuous variables were evaluated with the Wilcoxon rank-sum test. A 2-sided $P < .05$ was considered statistically significant. Unadjusted associations with time to event were assessed using Kaplan-Meier curves and the log-rank test. A Cox proportional hazards model was used to compare the time to second-line treatment initiation, time to culture conversion, and time as an outpatient on first-line treatment. The proportional hazards assumption was assessed by ensuring that log-log survival curves were parallel and interaction terms included in a time-dependent model were not significant. Cox model building and covariate selection was based on the purposeful selection of patient-level factors [13]. Bivariate logistic regression was used to estimate the impact of Xpert use on the final treatment outcome. Analyses were conducted using SAS software, version 9.4.

RESULTS

Among 151 patients initiating treatment for sputum smear-negative MDR-TB at the NCTLD during the study period, the Xpert assay was used in the management of 78 (51.7%) patients and not used in 73 (48.3%). Among the 73 patients in the non-Xpert group, treatment decisions were based on the MTBDR*plus* assay in 49 patients, conventional DST in 20 patients, history of MDR-TB in 2 patients, and known MDR-TB contact in 2 patients. Almost all patients (96%) had culture-positive TB disease; a total of 6 patients (3 in each group) had negative diagnostic sputum cultures including 2 patients with a positive sputum Xpert result. Among the 78 patients in the Xpert group, 2 had a negative Xpert result but positive culture, and another culture-positive patient had a positive Xpert for *M tuberculosis* but indicated rifampin susceptibility. The groups were similar in terms of sex, age, tobacco use, alcohol use, incarceration history, human immunodeficiency virus, and previous treatment for MDR-TB (Table 1). Only 2 patients (1.3%) in the Xpert group received bedaquiline, linezolid, or clofazimine in the first 30 days. Proportions of patients receiving these drugs at any point during treatment were similar between groups except for linezolid; there more patients receiving linezolid in the Xpert (18%) group than in the non-Xpert (5.6%) group. When used, newer drugs were initiated late in therapy, including at a mean of 138 days for linezolid and 126 days for bedaquiline.

Treatment Outcomes

Conventional treatment outcomes were similar between groups, with favorable outcomes in 48 patients (61.5%) in the Xpert group compared to 41 (56.2%) in the non-Xpert group, and death in 2 (2.6%) and 3 (4.1%) patients, respectively (Table 2). A total of 47 patients (31.1%) were lost to follow up by the end of the study period: 23 (29.5%) in the Xpert group and 24 (32.9%) in the non-Xpert group. Logistic regression analysis found no association between Xpert use and favorable treatment outcomes (odds ratio 1.25; 95% confidence interval [CI], 0.65–2.39) or death (odds ratio 0.84; 95% CI, 0.47–1.50). Treatment initiation as a hospital inpatient was more common in the Xpert group, with 67 patients (85.9%) being hospitalized for initial treatment compared to 33 (45.2%) in the non-Xpert group.

Time to Event Analysis

Time to second-line treatment was shorter for patients managed with Xpert, as demonstrated by Kaplan-Meier curves and the log-rank test (Figure 1). Overall, second-line treatment was started at a median of 28 days (interquartile range [IQR], 12–56) (Table 2). Among those managed with Xpert, time to second-line treatment was significantly shorter at 13 days (IQR, 8–21) compared to 56 days (IQR, 40–92) among those managed without Xpert ($P < .0001$). Time to any treatment initiation was similar between groups. In a subset of patients whose MDR-TB treatment was started as an outpatient (n = 51), time to second-line treatment was also decreased in the Xpert group at 13 days (IQR, 7–20) compared to 63.5 (IQR, 42–99) days ($P < .0001$).

Among 139 patients with a positive diagnostic sputum culture and at least 1 follow-up culture, culture conversion was achieved in 119 patients (85.6%) at a median of 71 days (IQR, 54–111). Time to culture conversion was decreased for patients managed with Xpert by Kaplan-Meier curves and the log-rank test (Figure 1). Among those managed with Xpert, the median time to sputum culture conversion was 61 days (IQR, 42–85) compared to 92.5 days (IQR, 70–141) in those managed without Xpert ($P < .0001$). After adjusting for age, sex, history of imprisonment, tobacco use, alcohol use, and cavitary disease, adjusted hazard ratios were 10.2 (95% CI, 8.3–23.5) for second-line treatment initiation and 1.9 (95% CI, 1.3–2.8) for culture conversion (Table 4).

Xpert Versus Other Diagnostic Methods Informing Treatment Decisions

Varying times to treatment initiation and culture were found when comparing groups categorized by use of Xpert, MTBR*plus*,

Table 1. Characteristics of Patients Treated for Smear-Negative MDR-TB, by Use of Xpert MTB/RIF Assay at Diagnosis

Characteristic	Total N = 151 (%)	Xpert MTB/RIF Used N = 78 (%)	Xpert MTB/RIF Not Used N = 73 (%)	*P* Value[a]
Age (median, IQR)	36.6 (26.3–48.2)	34.1 (27.7–47.3)	39.0 (26.0–49.7)	.73[b]
Body mass index (kg/m^2)	19.9 (18.2–21.7)	20.0 (18.3–21.8)	19.9 (18.1–21.4)	.63[b]
Female	37 (24.5)	21 (26.9)	16 (21.9)	.48
Current tobacco use	77 (51.0)	43 (55.1)	34 (46.6)	.37[c]
Current alcohol use	67 (44.4)	34 (43.6)	33 (45.2)	.80[c]
Diabetes mellitus	5 (3.3)	2 (2.6)	3 (4.1)	.67[c]
Hepatitis C virus antibody positive	46 (30.5)	27 (34.6)	19 (26.0)	.25
HIV infection	13 (8.6)	6 (7.7)	7 (9.6)	.79
History of imprisonment	42 (27.8)	23 (29.5)	19 (26.0)	.63
Previous TB diagnosis	67 (44.4)	29 (37.2)	38 (52.1)	.07
Previous MDR-TB treatment	21 (13.9)	10 (12.8)	11 (15.1)	.11
Disease Location				
Pulmonary only	139 (92.1)	73 (93.6)	66 (90.4)	.47
Pulmonary and extrapulmonary	12 (7.9)	5 (6.4)	7(9.6)	
Cavitary disease	10 (6.6)	2 (2.6)	8 (11.0)	.05
Current case definition				
New	84 (55.6)	49 (62.9)	35 (48.0)	.03
Relapse	11 (7.3)	8 (10.3)	3 (4.1)	
Treatment after default	27 (17.9)	13 (16.7)	14 (19.2)	
Treatment after failure	1 (0.7)	-	1 (1.4)	
Treatment after unknown[d]	28 (18.5)	8 (10.3)	20 (27.4)	
Diagnostic Culture Result				
Positive	145 (96.0)	75 (96.1)	70 (95.9)	1.0[c]
Negative	6 (4.0)	3 (3.9)	3 (4.1)	
Drugs Received Within 30 Days of Diagnostic Sputum Collection				
Isoniazid	58 (38.4)	17 (21.8)	41 (56.2)	<.0001
Rifampin	52 (34.4)	10 (12.8)	42 (57.5)	<.0001
Pyrazinamide	102 (67.6)	58 (74.4)	44 (60.3)	.06
Ethambutol	91 (60.3)	47 (60.2)	44 (60.3)	.99
Prothionamide	64 (42.4)	56 (71.8)	8 (11.0)	<.0001
Kanamycin	24 (15.9)	19 (24.4)	5 (6.9)	.003
Capreomycin	55 (36.4)	50 (64.1)	5 (6.9)	<.0001
Levofloxacin	56 (37.1)	46 (59.0)	10 (13.7)	<.0001
Moxifloxacin	26 (17.2)	25 (32.1)	1 (1.4)	<.0001
Cycloserine	70 (46.4)	62 (79.5)	8 (11.0)	<.0001
Para-aminosalicylic acid	69 (45.7)	60 (76.9)	9 (12.3)	<.0001
Clofazimine	2 (1.3)	2 (2.6)	-	.50[c]
Bedaquiline	2 (1.3)	2 (2.6)	-	.50[c]
Linezolid	2 (1.3)	2 (2.6)	-	.50[c]
Imipenem/cilastatin	2 (1.3)	2 (2.6)	-	.50[c]
Drugs Ever Received During Treatment				
Isoniazid	61 (40.4)	17 (21.8)	44 (60.3)	<.001
Rifampin	54 (35.8)	10 (12.8)	44 (60.3)	<.001
Kanamycin	74 (49.0)	23 (29.5)	51 (69.9)	<.001
Capreomycin	96 (63.6)	62 (79.5)	34 (46.6)	<.001
Levofloxacin	119 (78.8)	49 (62.8)	70 (95.9)	<.001
Moxifloxacin	51 (33.8)	35 (44.9)	16 (21.9)	.003
Cycloserine	143 (94.7)	73 (93.6)	70 (95.9)	.53
Para-aminosalicylic acid	137 (90.7)	66 (84.6)	71 (97.3)	.007
Clofazimine	17 (11.3)	8 (10.3)	9 (12.3)	.69
Bedaquiline	12 (8.0)	8 (10.3)	4 (5.6)	.29
Linezolid	18 (12.0)	14 (18.0)	4 (5.6)	.02
Imipenem/cilastatin	5 (3.3)	3 (3.9)	2 (2.8)	1.0[c]
TB-related adjunctive surgery	20 (13.3)	12 (15.4)	8 (11.0)	.42

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; NCTLD, National Center for Tuberculosis and Lung Diseases.

[a]χ^2 test unless noted.

[b]Wilcoxon rank-sum test.

[c]Fisher's exact test.

[d]Treatment after unknown outcome of previous treatment course.

Table 2. Clinical Outcomes of Patients Treated for Smear-Negative MDR-TB, by Use of Xpert MTB/RIF Assay at Diagnosis

Characteristic	Total Population N = 151 (%)	Xpert MTB/RIF[a] Used N = 78 (%)	Xpert MTB/RIF Not Used N = 73 (%)	*P* Value[b]
Treatment				
Initial treatment inpatient	100 (66.2)	67 (85.9)	33 (45.2)	<.0001
Days to any treatment (median IQR)	10 (3–25)	10 (6–19)	7 (0–49)	.8977[c]
Days to second-line treatment (median IQR)	28 (12–56)	13 (8–21)	56 (40–92)	<.0001[c]
Days as outpatient on first-line treatment (n = 51) (median IQR)	50 (22–92)	13 (7–20)	63.5 (42–99)	<.0001[c]
Days as inpatient on drug-susceptible ward (mean SD)	3.1 (12.2)	1.4 (6.3)	5.3 (16.6)	.08[d]
Outcomes				
Favorable outcome	89 (58.9)	48 (61.5)	41 (56.2)	.50
Death	5 (3.3)	2 (2.6)	3 (4.1)	.67[e]
Lost to follow up	47 (31.1)	23 (29.5)	24 (32.9)	.65
Days to culture conversion (median IQR)	71 (54–111)	61 (42–85)	92.5 (70–141)	<.0001[c]

Abbreviations: IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; NCTLD, National Center for Tuberculosis and Lung Diseases; SD, standard deviation.

[a]Includes 2 patients with negative Xpert result and another with positive Xpert for *Mycobacterium tuberculosis* but indicating rifampin susceptibility.

[b]χ^2 test unless noted.

[c]Wilcoxon rank-sum test.

[d]*t* test.

[e]Fisher's exact test.

and conventional DST (Table 3). Time to second-line treatment was decreased for the Xpert group (median 13 days; IQR, 7.5–21) versus the MTBDR*plus* group (49 days; IQR, 36–66) and the conventional DST group (112 days; IQR, 88–132) ($P < .0001$). Time to culture conversion was also decreased among patients in the Xpert group (61 days; IQR, 42–85) compared with MTBDR*plus* (83.5 days; IQR, 66–108) and conventional DST (143.5 days; IQR, 111–190) ($P < .0001$). Few patients were treated based on previous MDR-TB treatment (n = 2) or known MDR-TB contact (n = 2).

DISCUSSION

During the last decade, a "diagnostic revolution" has led to novel molecular TB tests being developed and subsequently endorsed by the WHO for clinical use based on their high-performance characteristics. In the recently released WHO rapid diagnostic consolidated guidelines, the Xpert MTB/RIF assay is currently recommended as the initial diagnostic test for all persons with suspected pulmonary TB [14]. However, this recommendation was predominantly based on the diagnostic and therapeutic impact of the Xpert, and the need for more research on the impact of molecular tests on patient outcomes was requested. Our retrospective cohort study thus adds important impact data with the use of the Xpert to the available scarce literature. We found that implementation of the Xpert into clinical use had therapeutic and patient outcome impact among patients treated for smear-negative MDR-TB as represented by a decreased time to second-line treatment and sputum culture conversion, respectively [15]. Despite not showing an impact on overall patient outcomes, our findings demonstrate the utility of the Xpert among a hard-to-diagnose group of smear-negative MDR patients and provide important data supporting its use in populations with a high burden of drug-resistant disease.

Our finding of a substantially decreased time to second-line treatment of 13 versus 56 days with the use of the Xpert highlights the large therapeutic impact of rapid molecular tests on initiation of appropriate treatment, particularly for RR-TB, and is line with other studies. Studies from additional high-burden MDR-TB countries in the region, including Latvia and Russia, have also demonstrated a similar reduction in time to second-line treatment initiation of approximately 1 month among MDR-TB patients with the use of the Xpert compared with culture and phenotypic DST [16, 17]. Studies in South Africa also found a decreased time to MDR-TB treatment initiation with use of Xpert, including a reduction of 25 days with Xpert use compared with an algorithm utilizing the MTBDR*plus* line probe assay in an urban setting [18]. In another study conducted in a rural setting, the median time to second-line treatment initiation was 18 days with Xpert, 29 days with a line probe assay, and 64 days with culture and DST [19]. A major difference of our study was that our population consisted solely of patients with smear-negative MDR-TB disease, whereas the above studies were conducted predominantly among persons with smear-positive disease. Prior studies demonstrating that smear-negative TB patients are responsible for 13%–16% of disease transmission highlights the importance of early diagnosis and in the case of MDR disease, detection of drug resistance to ensure initiation of early and appropriate second-line treatment [20, 21]. Our results

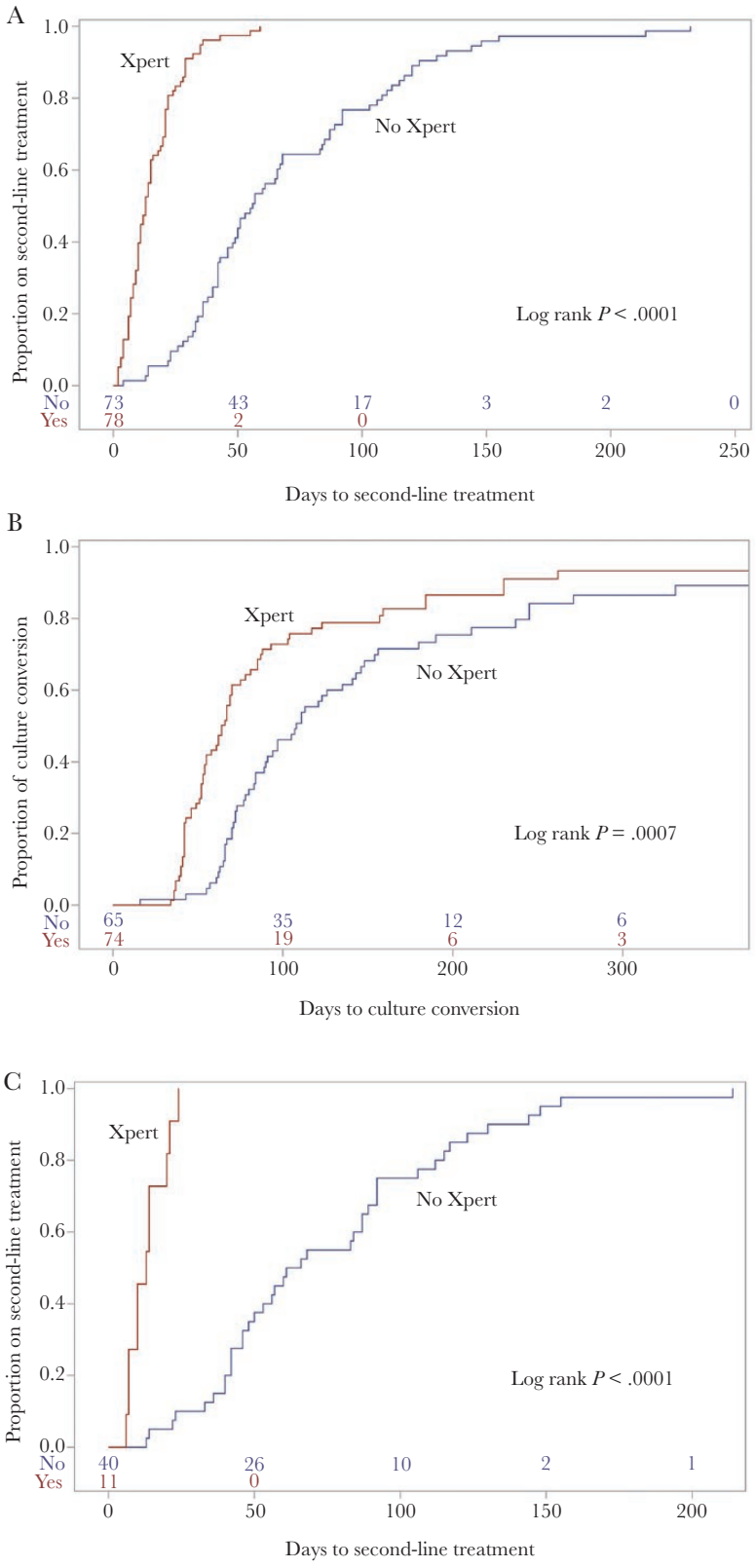

Figure 1. Kaplan-Meier curves showing time to outcomes among patients treated for smear-negative multidrug-resistant tuberculosis at the National Center for Tuberculosis and Lung Diseases from February 2011 to October 2016, by use of Xpert MTB/RIF assay at diagnosis. (A) Cumulative proportion of patients initiating second-line treatment. (B) Cumulative proportion of sputum culture conversion. (C) Cumulative proportion receiving second-line treatment among 51 patients initiating therapy as an outpatient.

Table 3. Treatment Outcomes of Patients Treated for Smear-Negative MDR-TB at the NCTLD From February 2011 to October 2016, by Method Informing Treatment Decision

Characteristic	Xpert MTB/RIF N = 78 (%)	MTBDR*plus* N = 49 (%)	Conventional DST N = 20 (%)	Previous MDR-TB Treatment N = 2 (%)	Known MDR-TB Contact N = 2 (%)	*P* Value[a]
Inpatient treatment	67 (85.9)	24 (49.0)	7 (35.0)	1 (50.0)	1 (50.0)	<.0001
Favorable outcome	48 (61.5)	29 (59.2)	10 (50.0)	1 (50.0)	1 (50.0)	.89
Death	2 (2.6)	2 (4.1)	1 (5.0)	0	0	.73
Lost to follow up	23 (29.5)	14 (28.6)	9 (45.0)	0	1 (50.0)	.47
Days to second-line treatment (median IQR)	13 (7.5–21)	49 (36–66)	112 (88–132)	28 (14–42)	8.5 (4–13)	<.0001[b]
Days to culture conversion (median IQR)	61 (42–85)	83.5 (66–108)	143.5 (111–190)	77	–	<.0001[b]
Days as outpatient on first-line treatment (n = 51) (median IQR)	13 (7–20)	50 (42–87)	115 (84–130)	14	13	<.0001[b]

Abbreviations: DST, drug-susceptibility testing; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; NCTLD, National Center for Tuberculosis and Lung Diseases.

[a]Fisher's exact test unless noted.

[b]Kruskal-Wallis test.

showing that smear-negative MDR patients diagnosed via the Xpert spent much less time in the community receiving first-line therapy (13 vs 64 days, $P < .0001$) and less days on an inpatient drug-susceptible TB ward (1.4 vs 5.3 days, $P = .08$) alludes to the potential of molecular testing to decrease the risk of MDR disease transmission in both the community and healthcare settings. The Xpert and other molecular assays are essential to implement treatment as prevention strategies for MDR disease [22].

Regarding patient outcomes, our findings demonstrate meaningful differences in time to sputum culture conversion. Among patients diagnosed with the Xpert, the time to sputum culture version was approximately 1 month faster (61 vs 93 days, $P < .0001$), which likely reflects the earlier initiation of second-line treatment. These results add to the scant literature on the impact of the Xpert assay on outcomes including a China study of 50 patients with RR-TB (sputum smear status not reported), which found that Xpert use assay was associated with a substantially reduced time to sputum culture conversion versus culture and phenotypic DST (63 vs 197 days, $P < .001$) [7]. In addition, when comparing our cohort by use of Xpert, MTBDR*plus*, and culture-based detection of *M tuberculosis* and associated drug resistance, we found a stepwise increase in time to sputum culture conversion among the 3 groups (culture + phenotypic DST > culture + MTBDR*plus* > Xpert). This novel finding provides important data that can help programs choose and determine the potential impact of various diagnostic strategies.

We did not find a difference in the proportion of favorable versus unfavorable outcomes or death between groups or an association between Xpert use and these outcomes in regression analysis. This is consistent with the literature, where few studies have identified an impact of Xpert on TB outcomes or mortality, including an individual patient data meta-analysis and a larger systemic review and meta-analysis [23, 24]. The majority of patients from these meta-analyses and included studies had drug-susceptible TB, and there is much more limited data on the impact of the Xpert assay among patients with drug-resistant TB—a population that stands to benefit more from rapid diagnosis. Similar to our results, studies in Russia and South Africa found nonsignificant trends towards improved treatment outcomes with the use of Xpert assay [17, 25]. In contrast, a large study of 952 MDR-TB patients in Kazakhstan found that the use of the Xpert versus culture-based methods was associated with a much higher rate of favorable outcomes (74 vs 49%, $P < .0001$) [26]. An important point to note is that our study and those mentioned above were carried out before the full implementation of new drug regimens for drug-resistant TB, which are shorter and more effective than prior second-line

Table 4. Time to Event Analysis Among Patients Treated for Smear-Negative MDR-TB Initiating Therapy at the NCTLD From February 2011 to October 2016

Outcome	Proportion (N %)	Days (Median, IQR)	cHR (95% CI)	aHR[a] (95% CI)
Second-line treatment initiation	151/151 (100)	28 (12–56)		
Xpert	78/78	13 (8–21)	9.17 (5.89–14.25)	10.21 (6.35–16.42)
No Xpert	73/73	56 (40–92)	Ref	Ref
Culture conversion	119/139 (85.6)	71 (54–111)		
Xpert	65/74 (87.8)	61 (42–85)	1.83 (1.27–2.64)	1.93 (1.31–2.83)
No Xpert	54/65 (83.1)	92.5 (70–141)	Ref	Ref

Abbreviations: aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval; IQR, interquartile range; MDR-TB, multidrug-resistant tuberculosis; NCTLD, National Center for Tuberculosis and Lung Diseases; Ref, .

[a]Adjusted for age, sex, history of imprisonment, tobacco use, alcohol use, and cavitary disease.

treatment regimens and may help realize the full impact of molecular tests among patients with drug resistance disease [8, 27]. Studies using standard methodologies are needed to measure the outcome impact of rapid molecular tests in settings with high rates of drug-resistant TB [15].

Limitations of our study included a focus on a relatively small and targeted population of persons with smear-negative RR-TB. We did not have data on the total number of smear-negative TB suspects tested during our study period to assess the number needed to test to detect a case of smear-negative RR-TB, which would be important information for diagnostic strategy planning. Given the retrospective nature of the study, we were unable to collect information on additional reasons for treatment delay that may have impacted time to treatment initiation and may have helped to explain why even with the use of the Xpert second-line treatment, initiation still averaged close to 2 weeks. Given the retrospective nature of the study, there may be unmeasured confounders that could have impacted treatment decisions and could not measure other important outcomes including acquired drug resistance, morbidity, and quality of life. However, our findings among a well characterized cohort provide important real-world data, including accounting for cases of misclassification by test result (2 culture-positive patients in the Xpert group who had a negative Xpert result), and provide findings that can help guide the management of a hard-to-diagnose group of TB patients.

CONCLUSIONS

In conclusion, we found that use of the Xpert MTB/RIF assay in the management of smear-negative MDR-TB led to important and clinically relevant decreases in the time to second-line treatment and sputum culture conversion, and we provided evidence that supports its programmatic utility. Further prospective and larger studies will help confirm our findings and allow for the evaluation of other important patient outcomes.

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