Adherence in the Treatment of Patients With Extensively Drug-Resistant Tuberculosis and HIV in South Africa: A Prospective Cohort Study

Max R. O'Donnell, MD, MPH,†‡ Allison Wolf, MPH,* Lise Werner, MSc,‡ C. Robert Horsburgh, MD, MUS,§ and Nesri Padayatchi, MBChB, MSc‡||*

Objective: Extensively drug-resistant tuberculosis (XDR-TB)/HIV coinfection is difficult to treat with frequent adverse drug reactions and associated with high mortality. Adherence to antiretroviral therapy (ARV) and second-line TB medications may reduce mortality, prevent amplification of drug resistance, and improve outcomes.

Methods: Prospective cohort study of XDR-TB patients on treatment in KwaZulu-Natal, South Africa. Adherence to ARV and TB medications was assessed separately at baseline and monthly. Knowledge, attitudes, and beliefs were assessed at baseline. Optimal adherence was defined as self-report of taking all pills in the previous 7 days; missing any pills was defined as suboptimal adherence. Primary outcome was optimal adherence 6 months after initiation of XDR-TB treatment to TB medications, ARV, and both ("dual adherence").

Results: One hundred four XDR-TB patients (79.8% HIV coinfected, 84.3% on ARV at enrollment) were enrolled and followed monthly (median 8 visits; interquartile range: 4–12). Six-month optimal adherence was higher for ARV (88.2%) than TB medications (67.7%) ($P < 0.001$). Low educational attainment, male gender, and year of enrollment were independently associated with dual suboptimal adherence. At baseline, participants indicated that XDR-TB was curable (76.0%), HIV and TB were linked (81.7%), and ARV improves TB outcomes (72.1%). Baseline knowledge, attitudes, and beliefs did not predict subsequent adherence.

Conclusions: Medication adherence was significantly higher for ARV than for TB medications in this cohort. Short-course treatment regimens for drug-resistant TB with lower pill burden may increase adherence and improve outcomes in XDR-TB/HIV. Programmatic support for dual adherence is critical in the treatment of drug-resistant TB and HIV.

Key Words: extensively drug-resistant tuberculosis, HIV/AIDS, adherence, knowledge, attitudes and beliefs

(*J Acquir Immune Defic Syndr* 2014;67:22–29)

INTRODUCTION

Extensively drug-resistant tuberculosis (XDR-TB), the most resistant form of tuberculosis (TB),[1] is difficult to treat[2] and is associated with substantial mortality[3,4] and poor treatment outcomes.[5,6] Globally, the majority of reported cases of XDR-TB are from South Africa.[7,8] XDR-TB in South Africa is characterized by a high percentage of HIV coinfection, early mortality, and poor 24-month treatment outcomes.[9–11] XDR-TB–HIV treatment involves complex medication regimens with potential drug interactions and adverse drug reactions.[12] A recent prospective study of XDR-TB treatment in South Africa described ongoing community spread of drug-resistant TB strains and low rates of TB culture conversion with frequent reversion.[13] However, medication adherence was not measured in this study.

Medication adherence is critical for both HIV and TB outcomes, and suboptimal adherence mediates the development of antimycobacterial and antiretroviral drug resistance on treatment.[14–16] Early studies have shown that approximately 95% adherence to antiretroviral therapy (ARV) is needed to ensure HIV viral suppression.[17,18] Later studies using more potent and durable regimens have demonstrated viral suppression with lower adherence.[19,20] Clinical trials of drug-susceptible TB treatment have shown that 95% of patients are capable of successful outcome with direct observation and support by study personnel.[21] Under operational conditions many patients default their TB treatment and successful outcomes range from 55% to 95%.[22,23] Medication adherence in patients with drug-resistant TB and HIV is understudied; to our knowledge, there are no published reports in this group.

Patient adherence in HIV and TB treatment has been recently reviewed.[24,25] A "gold standard" for measuring

Received for publication February 17, 2014; accepted May 5, 2014.

From the *Division of Pulmonary, Allergy and Critical Care Medicine, Columbia University Medical Center, New York, NY; †Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; ‡Centre for Aids Program of Research in South Africa (CAPRISA), University of KwaZulu-Natal, Durban, South Africa; §Department of Epidemiology, Boston University School of Public Health, Boston, MA; and ||University of KwaZulu-Natal, Durban, South Africa.

M.R.O. was supported by the National Institutes of Health, National Institute of Allergy and Infectious Diseases (5K23AI098479), Albert Einstein Center for Global Health & Clinical and Translational Research Institute, and Stony-Wold Herbert Fund. M.R.O. and N.P. were supported by the Centre for AIDS Programme of Research in South Africa (CAPRISA).

The authors have no conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.jaids.com).

Correspondence to: Max R. O'Donnell, MD, MPH, Division of Pulmonary, Allergy and Critical Care Medicine, Columbia University College of Physicians and Surgeons, PH-8 East, Room 101, 622 West 168th Street, New York, NY 10032 (e-mail: mo2130@columbia.edu).

medication adherence in either field is controversial and each method has strengths and weaknesses.[26] Patient-reported recall is widely used in measuring HIV medication adherence and has been shown to correlate with ARV pill count and HIV viral load suppression.[27] There are no validated instruments to measure medication adherence in the treatment of drug-resistant TB.

Adherence to both TB medications and ARV may be affected by patient's knowledge, attitudes, and beliefs (KAB).[28,29] Factors associated with KAB include poverty, gender, education, perceived stigma around HIV or TB or both, and other social, structural, and cultural factors.[24,30–32] To understand factors associated with treatment outcomes and survival in XDR-TB–HIV, we initiated a prospective study of XDR-TB treatment (PROX Study) in KwaZulu-Natal, South Africa. Our primary aim was to measure adherence to ARV and TB medication and understand factors associated with suboptimal adherence. A secondary aim was to understand the effect of baseline KAB on early self-reported adherence to TB treatment and ARV. Our hypothesis was that baseline knowledge of the connection between HIV and TB would be associated with improved adherence to ARV and second-line TB treatment among XDR-TB- and HIV-coinfected patients.[33]

METHODS

We prospectively enrolled consecutive patients with culture-confirmed XDR-TB admitted for initiation of XDR-TB treatment at a public TB specialist hospital in KwaZulu-Natal, South Africa, from August 2009 through July 2011. Patients were eligible for enrollment if they were 18 years or older, diagnosed with active TB disease according to national TB program guidelines, had culture-proven XDR-TB according to a standard case definition, had not been previously treated for XDR-TB, agreed to start treatment for XDR-TB, and had capacity to give informed consent in either English or isiZulu. Prisoners and patients previously treated for XDR-TB were excluded. Patients received usual care for XDR-TB (ie, individualized therapy based on drug susceptibility pattern), HIV, and other diseases.

All participants gave written informed consent, and the study protocol was approved by the ethical review committees of the University of KwaZulu-Natal and the Albert Einstein College of Medicine.

Adherence was measured by separate 7-day recall for ARV and second-line TB medications ("TB medications") in a questionnaire administered by study staff fluent in both English and isiZulu at study intake and monthly, as previously described[34] (see **Supplemental Text Box 1, Supplemental Digital Content,** http://links.lww.com/QAI/A536). For the purposes of analysis, a cumulative 6-month adherence variable (for TB and separately for ARV) was used, which included responses given at baseline and at the monthly visits.[18] Participants were considered "optimally adherent" at each monthly visit only if they stated that they had taken all of their doses and missed none. If participants stated that they had not taken all or missed some of the medications, they were considered "suboptimally adherent" for that class of medications (either ARV or TB medication).[14] For the purposes of analysis, a cumulative 6-month adherence variable was used for TB and separately for ARV, which included responses given at baseline and at the 1- to 6-month time points. The participants were considered optimally adherent for the cumulative 6-month adherence for ARV, XDR-TB medications, or both ARV and XDR-TB medications ("dual adherence") only if they were optimally adherent for all time points.

KAB around TB and HIV were assessed through a questionnaire administered at baseline before XDR-TB treatment initiation. A study staff person fluent in English and isiZulu administered the KAB questionnaire, adherence questions, and recorded clinical and demographic data.

Hospitalized patients were cared for in open wards by nursing staff with approximately 20 patients per health care

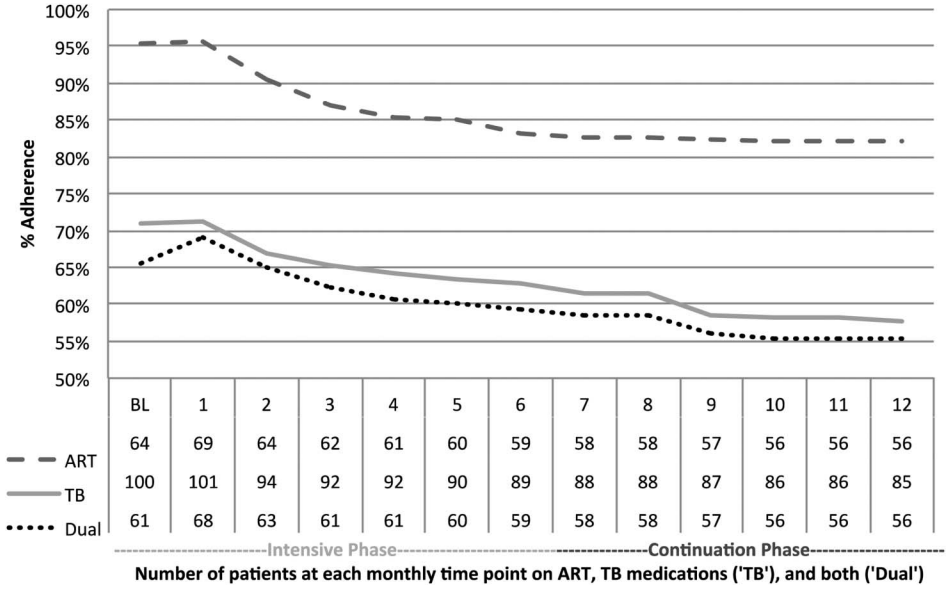

FIGURE 1. Percentage of patients with BL and monthly cumulative optimal treatment adherence to ARV, TB medications. Numbers reporting adherence data for ARV, TB medications (TB), or both (dual) at each monthly visit in the table below. Data censored at time of death (N = 19/104). BL, baseline.

worker. Although all medications are given to patients, the ward nurse does not directly observe them taking their medications. In addition, patients may refuse a specific pill or injection. As outpatients, patients are enrolled in the public, provincial directly observed therapy (DOTS) program that relies on a community or household DOTS supporter to provide patient support and attest through signature that the medications are being taken correctly and on schedule. Physicians check DOTS support cards at monthly visits.

During the second and third years of the study, a patient support and education initiative was started to enhance adherence and improve patient care. This consisted of 2 staff members meeting with small groups of XDR-TB patients on a weekly basis. The purpose was to develop patient peer support and to encourage adherence and provide patient-oriented information around topics associated with drug-resistant TB and HIV.

Descriptive statistics were calculated using standard methods. Associations were tested with Fisher exact test; paired values were tested using McNemar test. To identify factors associated with incomplete adherence to ARV or TB medications, we first identified factors in bivariate analysis and then constructed multiple logistic regression models including variables that were statistically significant and/or associated with >10% change in effect measure. Interaction between terms was assessed for significant change of the risk estimate. Test for trend was performed using Cochran–Armitage test. Statistical analysis was performed using SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

During the study period, 110 consecutive patients aged 18 years or older with culture-confirmed XDR-TB and without previous treatment for XDR-TB presented to the study site. Of these, 5 patients either refused to participate or lacked capacity to consent. One XDR-TB patient was a prisoner and therefore ineligible to enroll by study protocol. The remaining 104 XDR-TB patients were eligible, gave written informed consent, and were prospectively enrolled in the study within 2 weeks of initiation of XDR-TB treatment. The majority of participants were female (52%), young (median age: 35 years, range: 18–60 years), and HIV coinfected (79.8%). Among HIV-coinfected patients, 84.3% were on ARV and median CD4 count at baseline was 267 cells per cubic millimeter [interquartile range (IQR): 135–452 cells/mm^3]. Of these patients, 70 (85%) of 82 were on ARV at the time of admission and an additional 9% (7/82) were started subsequently (median time to ARV initiation 136 days). These patients reported relatively high levels of educational attainment (32% completed secondary) and monthly income (median $296; IQR: $185–$588). The majority of patients had been previously treated for drug-sensitive TB (92.3%) and for multi-drug-resistant TB (57.7%) (Table 1).

XDR-TB treatment was based on drug susceptibility testing to 6 antimycobacterial drugs (isoniazid, rifampicin, ofloxacin, streptomycin, kanamycin, and ethambutol) and consisted of on average 7 (range: 4–9) antimycobacterial drugs. The majority of patients were on an initial TB treatment regimen, including capreomycin, moxifloxacin, para-amino salicylic acid, ethionamide (98.1%), terizidone, and pyrazinamide (96.2%). XDR-TB patients were started on a median 7 (range: 4–9) TB medications and 3 ARV (range: 3–5). Patients were treated with ARV regimens that included nonnucleotide reverse transcriptase inhibitors (efavirenz, N = 68; neviripine, N = 3; not recorded, N = 6) and nucleotide reverse transcriptase inhibitors. During the study period, 2 patients were changed to protease inhibitor-containing regimens after clinically failing treatment. Overall median time of

TABLE 1. Demographic Characteristics of XDR-TB Patients Initiated on XDR-TB Therapy During Study Period

Baseline Characteristic	XDR-TB Patients, N (%)
Sex	
Male	50 (48.1)
Female	54 (51.9)
Age (yr)	
18–25	21 (20.2)
26–35	32 (30.8)
36–50	42 (40.4)
>50	9 (8.9)
Median age (IQR)	35 (27–43)
Completed primary school	
Yes	81 (79.4)
No	21 (20.6)
Missing	2
Household income (US$/mo)*, median (IQR)	$296 ($185–588)
HIV status†	
Positive	83 (79.8)
Negative	21 (20.2)
CD4 T-cell count‡ (cells/mm^3)	
Known	74 (89)
Unknown	9 (11)
Median CD4 count (IQR)	267 (135–452)
HIV positive on ARV§	
Yes	77 (92.7)
No	6 (7.3)
TB medications, n (range)	7 (4–9)
ARV medications, n (range)	3 (2–5)
Previous TB history	
Yes	96 (92.3)
No	8 (7.7)
Previous MDR-TB history	
Yes	60 (57.7)
No	44 (42.3)
History of being a health care worker	
Yes	5 (4.8)
No	99 (95.2)

*Calculated from South African Rand at exchange rates from July 2011. Income data missing for 8 patients.

†HIV infected includes known HIV infected on admission (82) and diagnosed as HIV infected subsequently (1).

‡Among HIV-infected patients; patients with known CD4 T-cell counts who had at least 1 count during the study period.

§On ARV includes ARV on admission (70) and ARV initiated subsequently (7).

follow-up for all XDR-TB patients on treatment was 9 months (IQR: 2–19 months). Median inpatient time was 144 days (IQR: 77–189 days).

Adherence Data

We obtained self-reported TB medication adherence data for all 104 XDR-TB patients and adherence data for 68 (88%) of 77 patients on ARV. On average, each patient had 8 monthly visits (IQR: 3–14) during which adherence to ARV and TB medications was assessed by self-reported 7-day recall. Among all XDR-TB patients on treatment, 67.3% reported optimal 6-month adherence to TB medications, whereas among XDR-TB- and HIV-coinfected patients on ARV, 88.2% reported optimal adherence to ARV (Table 2). Among XDR-TB- and HIV-coinfected patients on both XDR-TB medications and ARV, optimal 6-month adherence to ARV was 88.2% and optimal 6-month adherence to TB medications was 67.7% ($P < 0.001$). In total, 64.3% reported optimal 6-month adherence to both TB medications and ARV ("dual adherence"). Optimal adherence to ARV was significantly associated with optimal adherence to TB medications [odds ratio (OR): 21.0; 95% confidence interval (CI): 2.38 to 184.89, $P = 0.006$]. The largest subset (15/25) of patients nonadherent to either ARV or second-line TB medications reported optimal adherence to ARV but not to TB medications (Table 3).

On longitudinal analysis, initially 95% of patients reported optimal adherence to ARV and 71% reported optimal adherence to TB medications, and among patients on ARV and TB medications, 67% reported optimal adherence to both. At month 4, cumulative optimal adherence to ART (87%), TB medications (67%), and both (64%) were lower and continued to slowly decline through the first 12 months of treatment (Fig. 1). However, there was not a significant decline in adherence after the end of the intensive phase, which included nurse-administered injectable agents for the majority of patients (92%).

Among the patients who reported suboptimal adherence to TB medications, 13 (59%) of 22 reported they took "most" or "missed few" of their medications, 7 (32%) of 22 reported taking few or often missing their TB medications, and 2 (9%) of 22 reported always missing or never taking their TB medications. Among patients on ARV who reported suboptimal adherence, 7 (88%) of 8 reported that they took "most" or "missed few" of their ARV and 1 (12%) of 8 reported always missing or never taking his ARV. Among XDR-TB–HIV patients with at least 6 consecutive monthly visits, 57.6% report 6 visits with optimal ARV adherence as compared with 37.5% reporting optimal TB medication adherence on 6 consecutive visits. Number of monthly study visits with self-reported optimal adherence to TB medications was correlated with TB culture conversion over the course of XDR-TB treatment. TB culture conversion was defined as 2 consecutive negative cultures taken ≥30 days apart (see **Figure S1, Supplemental Digital Content,** http://links.lww.com/QAI/A536).

XDR-TB- and HIV-coinfected patients were less adherent to TB medications (65.1%) than HIV-negative XDR-TB patients (76.2%) ($P = 0.33$). For XDR-TB patients not on ARV at baseline, optimal TB medication adherence was 63.6%, not significantly different compared with TB medication adherence in XDR-TB patients on ARV (65.7%) ($P = 1.00$). Patients seemed to be less adherent to their overall XDR-TB medication regimens if they included cycloserine (33.3%), but this difference was not statistically significant ($P = 0.09$) (see **Figure S2, Supplemental Digital Content,** http://links.lww.com/QAI/A536).

On multivariate analysis, higher educational attainment was associated with optimal dual adherence at 6 months (OR: 5.39; 95% CI: 1.03 to 28.25). Women were more likely to report being optimally adherent (OR: 4.68; 95% CI: 1.11 to 19.68) as were younger patients, although this association was not statistically significant (OR: 2.95; 95% CI: 0.65 to 13.42). In addition, there was significantly lower dual optimal adherence among patients who enrolled earlier, in 2009, compared with patients who enrolled later, in 2011 (test for trend, $P < 0.001$). The variable "adverse drug reaction" was not included in the multivariate analysis because including the variable did not change estimates of effect and many participants had missing data (N = 20) (Table 4).

In the baseline KAB questionnaire, participants were optimistic regarding adhering to XDR-TB treatment for >2 years (80.8%), being cured of XDR-TB (76.0%), and successfully completing treatment (96.2%). Participants identified linkages between TB and HIV (81.7%), ARV and XDR-TB treatment (72.1%), and modes of TB transmission (97.1%). About half of all patients (48.1%) incorrectly identified sharing a cup as a possible mode of transmission. Answers to these KAB questions were not significantly associated with increased percentages of optimal adherence to TB medications or to both TB medications and ARV at 6 months (Table 5).

TABLE 2. Cumulative 6-Month Optimal Adherence to ARV and TB Medications in All XDR-TB Patients (N = 104)

TB Medication Adherence	ARV Adherence*	Dual Adherent†
70/104 (67.3)	60/68 (88.2)	45/68 (66.2)

*Seventy-five patients reported being on ARV at 6 months; 68 provided adherence data.

†Calculated among HIV-infected individuals on ARV with adherence data. Count includes individuals who are dual adherent to both ARV and TB medications. One patient provided ARV adherence data but not TB adherence data.

TABLE 3. Cumulative 6-Month Optimal Adherence in XDR-TB- and HIV-coinfected Patients on Both ARV and TB Medications (N = 68)

	ARV Adherence	
XDR-TB Medication Adherence	Optimal Adherence	Suboptimal Adherence
Optimal adherence	45	1
Suboptimal adherence	15	7
Sometimes nonadherent	9 (60.0)	4 (57.1)
Often nonadherent	4 (26.7)	3 (42.9)
Always nonadherent	2 (13.3)	0
XDR-TB medication adherence	46/68 (67.7%)	
ARV adherence	60/68 (88.2%)	$P < 0.001$

TABLE 4. Univariate and Multivariate Analysis of Factors Associated With Optimal Adherence to TB Medications, ARV, and Both (Dual) at 6 Months

	TB Medication Adherence N = 104 (%)*	ARV Adherence N = 70 (%)†	Dual Adherence N = 68 (%)‡	Dual Adherence Univariate OR (95% CI)	Dual Adherence Multivariate OR (95% CI)
Gender					
Male	29/50 (58.0)	25/31 (80.7)	16/29 (55.2)	1.00 (ref)	1.00 (ref)
Female	41/54 (75.9)	35/39 (89.7)	29/39 (74.4)	2.72 (0.99 to 7.44)	4.68 (1.11 to 19.68)
Age (yr)					
<35	35/49 (71.4)	24/28 (85.7)	18/28 (64.3)	1.00 (ref)	2.95 (0.65 to 13.42)
≥35	35/55 (63.6)	36/42 (85.7)	27/40 (67.5)	1.00 (0.37 to 2.71)	1.00 (ref)
Completed primary school					
No	8/21 (38.1)	10/16 (62.5)	5/16 (31.3)	1.00 (ref)	1.00 (ref)
Yes	60/81 (74.1)	48/52 (92.3)	38/52 (73.1)	5.97 (1.76 to 20.26)	5.39 (1.03 to 28.25)
Previous XDR-TB History					
No	24/44 (54.6)	24/29 (82.8)	16/29 (55.2)	1.00 (ref)	1.00 (ref)
Yes	46/60 (76.7)	36/41 (87.8)	29/41 (70.7)	1.96 (0.73 to 5.31)	0.78 (0.19 to 3.15)
Income (ZAR)					
<R2010	32/48 (66.7)	31/38 (81.6)	23/38 (60.5)	1.00 (ref)	1.00 (ref)
≥R2010	32/48 (66.7)	27/30 (90.0)	20/30 (66.7)	1.30 (0.48 to 3.54)	1.96 (0.44 to 8.66)
Year enrolled					
2011	38/42 (90.5)	27/30 (90.0)	26/30 (86.7)	1.00 (ref)	1.00 (ref)
2010	28/42 (66.7)	26/29 (89.7)	18/29 (62.1)	0.25 (0.07 to 0.92)	0.41 (0.09 to 1.78)
2009	4/20 (20.0)	7/11 (63.6)	1/11 (9.1)	0.02 (0.00 to 0.15)	0.01 (0.00 to 0.13)
Adverse events on treatment§					
No	13/24 (54.2)	11/15 (73.3)	7/15 (46.7)	1.00 (ref)	
Yes	30/51 (58.8)	28/33 (84.9)	17/33 (51.5)	1.21 (0.36 to 4.12)	

ZAR, South African Rand.
*Calculation based on individuals with adherence data (N = 104) within the first 6 months of follow-up.
†Calculation based on individuals with ARV adherence data (N = 70) within the first 6 months of follow-up.
‡Analysis includes patients with ARV and TB adherence data (N = 68).
§Within the first 6 months of follow-up.

DISCUSSION

To our knowledge, this is the first prospective study of adherence in the integrated treatment of drug-resistant TB and HIV. Our main finding is that patients being treated for XDR-TB and HIV coinfection are significantly more likely to report complete adherence to ARV compared with TB medications through the first 6 months of their XDR-TB treatment. It is probable that these self-reported adherence figures are an overestimate because patients may be hesitant to report the extent of their nonadherence to study staff.[35,36] In our cohort, KAB including knowledge of the relationship between TB and HIV, attitudes around XDR-TB and HIV stigma, and beliefs regarding adherence did not predict subsequent self-reported adherence at 6 months.

Adherence in the treatment of drug-resistant TB–HIV is critically important because adherence mediates treatment outcomes, the development of drug resistance on treatment, the infectivity of the patients on treatment, and is therefore associated with transmission of TB infection in the community. Improved adherence to ARV is associated with improved survival in XDR-TB–HIV patients.[10] However, ARV does not seem to be associated with improved rates of TB culture conversion in drug-susceptible or drug-resistant TB.[5,10,37] Therefore, if XDR-TB patients are adherent to ARV but poorly adherent to TB medications, the concern is that they will survive to spread drug-resistant TB strains in the hospital and in the community and be more likely to develop amplification of drug resistance on treatment.

Risk factors for incomplete adherence at 6 months included male gender and low educational attainment, which is consistent with some, but not all, previous studies.[30,35,38,39] Year of admission was also associated with complete adherence, which may be due to improved patient education after our patient support intervention, differential reporting bias, or other factors.[33,40] We have identified risk groups (ie, men and lower educated patients) who may be amenable to specific interventions to improve adherence. In addition, the finding that the majority of TB suboptimal adherent patients do report optimal ARV adherence is helpful. It suggests that these patients are not intrinsically nonadherent and that with enhanced patient support, education, and most importantly more tolerable TB drug regimens, it may be possible to improve adherence for these patients.

The 6-month adherence data predominantly represent in-hospital adherence because patients were hospitalized for

TABLE 5. Baseline KAB With Overall Stratified by Percent Adherent to TB Medications in all XDR-TB Patients (n = 104) and Both TB Medications and ARV Adherent ("Dual") in XDR-TB–HIV Patients (N = 68)

KAB Question		Overall, N (%)	TB Medication Adherent, n/N (%)	Dual Adherent, n/N (%)
Is XDR-TB curable?	No	7 (6.7)	4/7 (57.1)	2/5 (40.0)
	Yes	79 (76.0)	55/79 (69.6)	38/56 (67.9)
	Don't know	18 (17.3)	11/18 (61.1)	5/7 (71.4)
	P		0.66	0.43
Is XDR-TB treatment >2 yrs?	No	4 (3.8)	1/4 (25.0)	1/1 (100.0)
	Yes	84 (80.8)	59/84 (70.2)	40/60 (66.7)
	Don't know	16 (15.4)	10/16 (62.5)	4/7 (57.1)
	P		0.15	0.79
Not taking medications every day will likely make my XDR-TB worse?	No	1 (1.0)	0/1 (0.0)	0/1 (0.0)
	Yes	95 (91.3)	64/95 (67.4)	44/65 (6.7)
	Don't know	8 (7.7)	6/8 (75.0)	1/2 (50.0)
	P		0.40	0.41
I think I will complete XDR-TB treatment successfully?	No	0 (0.0)	—	—
	Yes	100 (96.2)	67/100 (67.0)	44/66 (66.7)
	Don't know	4 (3.8)	3/4 (75.0)	1/2 (50.0)
	P		1.00	1.00
Is there a link between TB and HIV?	No	7 (6.7)	4/7 (57.1)	0/1 (0.0)
	Yes	85 (81.7)	58/85 (68.2)	40/58 (69.0)
	Don't know	12 (11.5)	8/12 (66.7)	5/9 (55.6)
	P		0.85	0.32
ARV for my HIV helps to fight XDR-TB?	No	5 (4.8)	3/5 (60.0)	2/4 (50.0)
	Yes	75 (72.1)	55/75 (73.3)	38/53 (71.7)
	Don't know	24 (23.1)	12/24 (50.0)	5/11 (45.5)
	P		0.10	0.17
XDR-TB transmitted by air when XDR-TB patient coughs?	No	1 (1.0)	1/1 (100.0)	1/1 (100.0)
	Yes	101 (97.1)	68/101 (67.3)	44/66 (66.7)
	Don't know	2 (1.9)	1/2 (50.0)	0/1 (0.0)
	P		1.00	0.57
XDR-TB transmitted by sharing a cup?	No	41 (39.4)	27/41 (65.9)	17/27 (63.0)
	Yes	50 (48.1)	37/50 (74.0)	25/35 (71.4)
	Don't know	13 (12.5)	6/13 (46.2)	3/6 (50.0)
	P		0.17	0.51
Enough information about XDR-TB?	No	63 (60.6)	44/63 (69.8)	27/39 (69.2)
	Yes	34 (32.7)	20/34 (58.8)	15/25 (60.0)
	Don't know	7 (6.7)	6/7 (85.7)	3/4 (75.0)
	P		0.37	0.77
XDR-TB patients treated respectfully?	No	7 (7.1)	6/7 (85.7)	3/3 (100.0)
	Yes	86 (86.9)	56/86 (65.1)	36/56 (64.3)
	Don't know	6 (6.1)	4/6 (66.7)	3/5 (60.0)
	Missing	5		
	P		0.58	0.78
Told family and friends about XDR-TB?	No	10 (9.6)	6/10 (60.0)	3/6 (50.0)
	Yes	93 (89.4)	63/93 (67.7)	41/61 (67.2)
	Don't know	1 (1.0)	1/1 (100.0)	1/1 (100.0)
	P		0.82	0.61
Family/friends treat differently with XDR-TB?	No	87 (85.3)	60/87 (69.0)	41/59 (69.5)
	Yes	9 (8.8)	4/9 (44.4)	1/5 (20.0)
	Don't know	6 (5.9)	5/6 (83.3)	2/3 (66.7)
	Missing	2		
	P		0.26	0.11
Should treat XDR-TB at patient's community level?	No	1 (1.0)	0/1 (0.0)	0/1 (0.0)
	Yes	99 (95.2)	67/99 (67.7)	44/65 (67.7)
	Don't know	4 (3.8)	3/4 (75.0)	1/2 (50.0)
	P		0.53	0.41

a median of 4.7 months. Given high patient-to-nurse ratios, therapy in hospital is seldom directly observed. Self-reported 7-day adherence to ARV and XDR-TB medications decreased significantly during the first 12 months on treatment and may represent in part the transition from inpatient to outpatient care. On discharge from hospital to outpatient care, patients are enrolled in the local DOTS program. This program is underresourced and relies on family members and friends to provide patient support. It is likely that the reported limitations of DOTS for drug-susceptible TB lead to even less effective adherence in the treatment of drug-resistant TB–HIV.

A major limitation of our study is the reliance on self-reported 7-day recall for adherence. Self-reported 7-day recall was the only means of measuring adherence in this study. Seven-day recall has been used extensively in ARV adherence studies where it has been shown to correlate with percentage of patients with undetectable HIV RNA viral load.[31,36] Seven-day recall has not been validated as a measure of adherence in the treatment of drug-resistant TB.[14,34] Self-reported adherence based on recall may lead to overestimation or less likely underestimation of actual adherence due to reporting or recall bias. It is unlikely that there was differential error with respect to ARV and TB medications and therefore it is likely that XDR-TB patients in this cohort do have lower rates of adherence to TB medications than ARV. Other limitations include relatively short duration of follow-up, which limits our ability to comment on implications for treatment outcome or mortality. Another limitation is that we lack precise data on how changes in medications or adverse drug reactions during treatment affect adherence.

The potential implication of our main finding is that XDR-TB–HIV patients in KwaZulu-Natal, South Africa, may have reduced mortality with higher adherence to ARV and yet have decreased TB culture conversion due to poor adherence to XDR-TB medications. Incomplete TB adherence with prolonged survival may also result prolonged transmission of infectious strains in the community and in amplification of TB drug resistance on treatment, which is consistent with the epidemiology of drug-resistant TB in KwaZulu-Natal province.[41] To address these findings, shorter duration regimens for treatment of drug-resistant TB are needed. As such TB regimens are introduced, it will be important to introduce programs for patient and adherence support, including ongoing monitoring and evaluation. Additional resources need to be devoted to enhancing adherence for drug-resistant TB–HIV within the context of TB–HIV control programs.

ACKNOWLEDGMENTS

The authors acknowledge Ms. Nokwanda Depargo for her efforts in recruiting and enrolling patients. The authors also sincerely appreciate the physicians and nurses of King Dinizulu Hospital.

REFERENCES

1. WHO. *Global Tuberculosis Report 2013. WHO/HTM/TB/2013.15*. Geneva, Switzerland: World Health Organization, 2013.
2. Kliiman K, Altraja A. Predictors of poor treatment outcome in multi- and extensively drug-resistant pulmonary TB. *Eur Respir J*. 2009;33:1085–1094.
3. Gandhi NR, Moll A, Sturm AW, et al. 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.
4. Dheda K, Shean K, Zumla A, et al. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. *Lancet*. 2010;375:1798–1807.
5. O'Donnell MR, Padayatchi N, Master I, et al. Improved early results for patients with extensively drug-resistant tuberculosis and HIV in South Africa. *Int J Tuberc Lung Dis*. 2009;13:855–861.
6. Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA*. 2000;283:2537–2545.
7. WHO. *Multidrug and Extensively Drug-Resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. WHO/HTM/TB/2010.3*. Geneva: WHO; 2010.
8. Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012;9:e1001300.
9. Abdool-Karim Q, Abdool-Karim SS. The evolving HIV epidemic in South Africa. *Int J Epidemiol*. 2002;31:37–40.
10. O'Donnell MR, Padayatchi N, Kvasnovsky C, et al. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis*. 2013;19:413–424.
11. Gandhi NR, Shah NS, Andrews JR, et al. HIV coinfection in multidrug- and extensively drug-resistant tuberculosis results in high early mortality. *Am J Respir Crit Care Med*. 2010;181:80–86.
12. Shean K, Streicher E, Pieterson E, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *PLoS One*. 2013;8:e63057.
13. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet*. 2014;383:1230–1239.
14. O'Connor JL, Gardner EM, Mannheimer SB, et al. Factors associated with adherence amongst 5295 people receiving antiretroviral therapy as part of an international trial. *J Infect Dis*. 2013;208:40–49.
15. Gardner EM, Sharma S, Peng G, et al. Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. *AIDS*. 2008;22:75–82.
16. Kulkarni P, Akarte S, Mankeshwar R, et al. Non-adherence of new pulmonary tuberculosis patients to anti-tuberculosis treatment. *Ann Med Health Sci Res*. 2013;3:67–74.
17. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21–30.
18. Stephenson J. AIDS researchers target poor adherence. *JAMA*. 1999;281:1069.
19. Bangsberg DR. Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression. *Clin Infect Dis*. 2006;43:939–941.
20. Glass TR, Rotger M, Telenti A, et al. Determinants of sustained viral suppression in HIV-infected patients with self-reported poor adherence to antiretroviral therapy. *PLoS One*. 2012;7:e29186.
21. Elzinga G, Raviglione MC, Maher D. Scale up: meeting targets in global tuberculosis control. *Lancet*. 2004;363:814–819.
22. Nunn AJ, Phillips PP, Gillespie SH. Design issues in pivotal drug trials for drug sensitive tuberculosis (TB). *Tuberculosis*. 2008;88(suppl 1):S85–S92.
23. Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: systematic review. *BMJ*. 2008;336:484–487.
24. Munro SA, Lewin SA, Smith HJ, et al. Patient adherence to tuberculosis treatment: a systematic review of qualitative research. *PLoS Med*. 2007;4:e238.
25. Ortego C, Huedo-Medina TB, Llorca J, et al. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. *AIDS Behavior*. 2011;15:1381–1396.
26. Williams AB, Amico KR, Bova C, et al. A proposal for quality standards for measuring medication adherence in research. *AIDS Behavior*. 2013;17:284–297.

27. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behavior.* 2006;10:227–245.
28. Potchoo Y, Tchamdja K, Balogou A, et al. Knowledge and adherence to antiretroviral therapy among adult people living with HIV/AIDS treated in the health care centers of the association "Espoir Vie Togo" in Togo, West Africa. *BMC Clin Pharmacol.* 2010;10:11.
29. Xu W, Lu W, Zhou Y, et al. Adherence to anti-tuberculosis treatment among pulmonary tuberculosis patients: a qualitative and quantitative study. *BMC Health Serv Res.* 2009;9:169.
30. Naidoo P, Peltzer K, Louw J, et al. Predictors of tuberculosis (TB) and antiretroviral (ARV) medication non-adherence in public primary care patients in South Africa: a cross sectional study. *BMC Public Health.* 2013;13:396.
31. Finlay A, Lancaster J, Holtz TH, et al. Patient- and provider-level risk factors associated with default from tuberculosis treatment, South Africa, 2002: a case-control study. *BMC Public Health.* 2012;12:56.
32. Rowe KA, Makhubele B, Hargreaves JR, et al. Adherence to TB preventive therapy for HIV-positive patients in rural South Africa: implications for antiretroviral delivery in resource-poor settings? *Int J Tuberc Lung Dis.* 2005;9:263–269.
33. Gebremariam MK, Bjune GA, Frich JC. Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study. *BMC Public Health.* 2010;10:651.
34. Mannheimer S, Friedland G, Matts J, et al. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for human immunodeficiency virus-infected persons in clinical trials. *Clin Infect Dis.* 2002;34:1115–1121.
35. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care.* 2000;12:255–266.
36. Balikuddembe R, Kayiwa J, Musoke D, et al. Plasma drug level validates self-reported adherence but predicts limited specificity for nonadherence to antiretroviral therapy. *ISRN Pharmacol.* 2012;2012:274978.
37. Brust JC, Lygizos M, Chaiyachati K, et al. Culture conversion among HIV co-infected multidrug-resistant tuberculosis patients in Tugela Ferry, South Africa. *PLoS One*. 2011;6:e15841.
38. Kyser M, Buchacz K, Bush TJ, et al. Factors associated with non-adherence to antiretroviral therapy in the SUN study. *AIDS Care.* 2011;23:601–611.
39. Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. *Int J Tuberc Lung Dis.* 2010;14:454–463.
40. Mindachew M, Deribew A, Tessema F, et al. Predictors of adherence to isoniazid preventive therapy among HIV positive adults in Addis Ababa, Ethiopia. *BMC Public Health.* 2011;11:916.
41. Klopper M, Warren RM, Hayes C, et al. Emergence and spread of extensively and totally drug-resistant tuberculosis, South Africa. *Emerg Infect Dis.* 2013;19:449–455.