The Influence of Mining and Human Immunodeficiency Virus Infection among Patients Admitted for Retreatment of Tuberculosis in Northern Tanzania

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Abstract. In tuberculosis (TB)–prevalent settings, patients admitted for retreatment of TB may account for a high burden of poor treatment outcome. We performed a retrospective cohort study to characterize retreatment patients and outcomes at a TB referral hospital in northern Tanzania. From 2009 to 2013, 185 patients began a retreatment regimen, the majority for relapse after prior treatment completion. Men accounted for an unexpected majority (88%), 36 (20%) were human immunodeficiency virus (HIV) infected and for 45 (24%) mining was their primary occupation. A poor outcome (death, default, or persistent smear positivity after 7 months of treatment) was found in 37 (23%). HIV infection was the only significant predictor of poor outcome (adjusted odds ratio [aOR] = 2.50, 95% confidence interval [CI] = 1.07–5.83, $P = 0.034$). Interventions to minimize need for retreatment or improve retreatment success may be regionally specific. In our setting, community-based diagnosis and management among at-risk subpopulations such as miners and those HIV infected appear of highest yield.

In Tanzania, like many tuberculosis (TB) endemic countries, patients categorized as undergoing retreatment for TB account for proportionally the highest rates of death, treatment failure, and default among all TB patients excluding those with known drug resistance.¹ The national estimate for treatment success rate in human immunodeficiency virus (HIV)–negative patients without prior treatment was 90%, but was 80% in patients with a history of TB treatment.¹ Patients undergoing retreatment are often prescribed the World Health Organization (WHO) Category II regimen of extended total duration, which contains the daily intramuscular injection of streptomycin, a medication with considerable cumulative side effects including ototoxicity and vestibular toxicity that may further compromise treatment completion.²

Kibong'oto Infectious Diseases Hospital (KIDH) is a regional referral hospital for retreatment TB cases, and the national referral hospital for multidrug-resistant (MDR) TB. The Mererani region includes numerous small-scale mining operations, principally involved in the mining of the precious gemstone tanzanite. The mines are run with low-level mechanization, use roughly 8,000 transient workers, and are situated in a community of approximately 200,000 people with interdependence on the mining industry.³ The mining occupation in other TB-endemic settings has been associated with high rates of HIV coinfection, comorbid lung disease such as silicosis and risk of TB reinfection.⁴ Perception suggests that miners account for a considerable number of patients admitted to KIDH for retreatment and may account for a greater proportion of those with poor retreatment outcome.

We therefore sought to perform a retrospective cohort study of all patients admitted to KIDH for a retreatment regimen over the past 5 years to define the local burden of retreatment, clinical characteristics among retreatment patients, and predictors of retreatment outcome.

The hospital initiative was designed and undertaken by the KIDH administration and approval for analysis was additionally granted by the institutional review board of the Univer-

sity of Virginia. All charts from patients admitted to KIDH from January 1, 2009 to December 31, 2013 were screened. KIDH practice was to treat all patients with a prior history of TB with a WHO Category II regimen excluding those with known drug-resistant TB. Thus, a case was defined as “retreatment,” if prescribed a Category II regimen after having failed a prior drug susceptible TB treatment course, relapsed within 18 months after having completed treatment, or defaulted treatment but remained sputum smear positive. Patients that were treated with a WHO Category II regimen for another reason were labeled as “other,” including smear-negative patients with TB signs and symptoms that had failed an empiric course of antibacterial treatment. Specifically, the regimen was daily injectable streptomycin, oral rifampin, isoniazid, ethambutol, and pyrazinamide given for 2 months, then all oral drugs given for 1 month, followed by 5 months of rifampin and isoniazid.⁵ Chart review included demographics, comorbidities, HIV status, and among the HIV infected, CD4 cells/mm³ and antiretroviral use at admission. Per hospital protocol, an acid-fast bacilli (AFB) sputum smear was performed on admission for all pulmonary TB patients, again at 2 months after treatment, and monthly thereafter until 7 months after treatment. Similarly, a baseline weight (in kilograms) was recorded and repeated monthly after the second month of treatment. Although MDR-TB treatment began in Tanzania at KIDH in 2009, initially drug susceptibility testing was not routinely performed on retreatment patients given logistical constraints and specimen turnaround at the reference laboratory.⁶ After 2013, molecular testing with either the Xpert MTB/RIF (Cepheid, Sunnyvale, CA) or the MTBDRplus (Hain Lifescience, Nehren, Germany) has been performed onsite.

During the study period and excluding those with known MDR-TB, total 2,140 patients were admitted for TB treatment, of which 185 (8.6%) received a retreatment regimen (by year of admission: in 2009, 46 [10% of total from that year]; in 2010, 38 [9%]; in 2011, 37 [9%]; in 2012, 36 [8%]; in 2013, 28 [6%]). The majority were men (87.6%) and 36 (19.5%) were HIV infected (Table 1). Among HIV infected, the median CD4 count was 136.5 cells/mm³ (interquartile range [IQR] = 29.7–248.0), and 17 (47.2%) were on antiretrovirals at admission. Although 45 (24.3%) had documentation of mining as their

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TABLE 1

Clinical characteristics among patients admitted for retreatment, *N* = 185

Characteristic	Result
Age, mean years $\pm$ SD	42.4 $\pm$ 12.8 (minimum 22, maximum 85)
Gender, male (% <i>N</i>)	162 (87.6)
Baseline weight, mean kg $\pm$ SD	50.9 $\pm$ 7.9 (minimum 30, maximum 79)
HIV positive (% <i>N</i>)	36 (19.5)
CD4 count, mean cells/mm ³	167.4 $\pm$ 142.3 (minimum 2, maximum 658)
ART at admission (% HIV positive)	17 (47.2)
Diabetes (% <i>N</i>)	3 (1.6)
Pneumoconiosis (% <i>N</i>)	3 (1.6)
Mining as primary occupation (% <i>N</i>)	45 (24.3)
Known smoking (% <i>N</i>)*	6 (3.2)
Known alcohol use (% <i>N</i>)*	13 (7)
Current treatment episode†	
Second	143 (81.7)
Third or more	32 (18.3)
Reason for retreatment‡	
Relapse	121 (65.8)
Return after default	18 (9.8)
Failure	8 (4.3)
Other	37 (20.1)

ART = antiretroviral therapy; HIV = human immunodeficiency virus; SD = standard deviation.
 *Smoking and alcohol use were considered underreported.

†Available in 175 patients.

‡Available in 184 patients.

primary occupation, only 3 (1.6%) were labeled as having pneumoconiosis. Unexpectedly, among miners only four (8.9%) were HIV infected, which was a smaller proportion than in the non-miners (22.9%).

Baseline sputum AFB smear microscopy found 36 patients (19.5%) were smear negative, 11 (5.9%) were scanty, 18 (9.7%) were 1+, 35 (18.9%) were 2+, 79 (42.7%) were 3+, and 6 patients had a missing result. Among patients with positive baseline sputum smear and excluding those with early death, default or transfer out of care, the median time of sputum smear conversion to negative was 2 months (IQR = 2–3 months). Time to sputum culture conversion did not vary by HIV status (Mann–Whitney *U*, *P* = 0.13).

TABLE 2

Predictors of retreatment outcome (*N* = 161)

Characteristic	Cured/treatment complete (<i>N</i> = 124)	Death/default/smear positive (<i>N</i> = 37)	<i>P</i> value
Age, mean years $\pm$ SD	41.9 $\pm$ 12.4	45.2 $\pm$ 14.8	0.18
Gender			0.37
Male (% <i>N</i>)	110 (88.7%)	35 (94.6%)	
Female (% <i>N</i>)	14 (11.3%)	2 (5.4%)	
HIV			0.04
Negative (% <i>N</i>)	103 (83.1%)	25 (67.6%)	
Positive (% <i>N</i>)	21 (16.9%)	12 (32.4%)	
Mining			0.82
No (% <i>N</i>)	95 (76.6%)	29 (78.4%)	
Yes (% <i>N</i>)	29 (23.4%)	8 (21.6%)	
Baseline smear negative			0.12
No/unknown (% <i>N</i>)	102 (82.3%)	26 (70.3%)	
Yes (% <i>N</i>)	22 (17.7%)	11 (29.7%)	
Reason for retreatment			0.19
Relapse/failure	91 (73.4%)	23 (62.2%)	
Other	33 (26.6%)	14 (37.8%)	
Year of treatment			0.58
2009–2010	60 (48.4%)	16 (43.2%)	
2011–2013	64 (51.6%)	21 (56.8%)	

HIV = human immunodeficiency virus; SD = standard deviation.

Twenty-four patients transferred out to another facility and 161 had evaluable outcomes: 124 (77.0%) were cured/treatment complete, 21 (13.0%) died, 12 (7.5%) defaulted, and 4 (1.9%) remained smear positive (three of which were ultimately treated for MDR-TB). Hence 37 patients (23.0% of those evaluable) had a poor outcome (Table 2). Controlling for age, reason for retreatment, and baseline smear status in multivariate logistic regression analysis, HIV infection remained the only significant predictor of poor outcome (odds ratio [OR] = 2.44, 95% confidence interval [CI] = 1.04–5.73, *P* = 0.04). As 24 patients did not have evaluable outcomes, a modified sensitivity analysis was performed imputing all transferred patients had one of either outcome: no other additional predictor was significant but the OR for HIV infection ranged from 1.62 (imputing all transfers had poor outcome) to 2.53 (imputing all had good outcome). Interestingly, among the HIV infected, 7 (46.7%) of those on antiretrovirals at baseline had a poor outcome compared with only 5 (27.8%) that were not on antiretrovirals (*P* = 0.22). Yet of the patients that died, 12 (57%) were within the first 2 months of treatment, of whom seven were HIV infected with a median CD4 count of 30 cells/mm³ (IQR = 7–130) that was lower than those without early death, median CD4 count of 178 cells/mm³ (IQR = 90–248) (*P* = 0.09). Alternatively, among those evaluable beyond the second month of treatment, the median weight gain in patients with a favorable outcome was 4.0 kg (IQR = 1.98–5.85) compared with 2.0 kg (IQR = 0.75–3.0) in patients with poor outcome (*P* = 0.01).

In summary, the majority of patients prescribed a retreatment regimen were admitted for relapse after recent TB treatment, and while nearly 25% had a history of mining as their primary occupation, miners were less likely to be HIV infected and appeared not at increased risk of poor outcome from retreatment. Nevertheless, retreatment outcomes were complicated by a considerable number of patients with death, default, or treatment failure as manifested by persistent sputum smear positivity. Similar to other cohorts from sub-Saharan Africa, HIV infection remained the strongest predictor of poor outcome,⁷ and patients with the lowest CD4 count on admission frequently suffered from early inpatient death.

Relapse of TB can occur for a number of reasons including suboptimal initial treatment that fails to eradicate the bulk of the infecting mycobacterial population, amplified drug resistance of residual bacilli or host factors that compromise the immune response. Previously we have found plasma drug concentrations of isoniazid and rifampin to be below the expected range in patients treated for pulmonary TB at KIDH.^{8,9} Such findings may explain why the degree of weight gain as a marker of malabsorption appeared an important predictor of cure/treatment completion as similarly found in other cohorts,¹⁰ and calls for more specific study of weight trajectory and its association with nutrient and medication malabsorption.¹¹

Furthermore, empiric dose adjustment or therapeutic drug monitoring of anti-TB drugs may prevent early death or further relapse and we believe warrants controlled study in our setting.¹² Such an approach may be particularly important for the HIV infected patients presenting with significant immunosuppression (as manifest by low CD4 count) that were frequently observed to suffer early death in this cohort.¹³ Other HIV-prevalent settings have found early TB death in the form of sepsis and/or mycobacteremia,^{14,15} and have suggested that more aggressive anti-TB management should be

trialed. Although it was common practice to prescribe antiretrovirals between 2 weeks and 2 months after TB treatment initiation in the antiretroviral naive per international consensus recommendations,¹⁶ four of the seven patients with early death were on antiretrovirals prior to admission. As the duration of antiretroviral therapy was not obtained, the contribution of an unmasking immune reconstitution inflammatory syndrome (IRIS) could not be assessed.

As routine culture, susceptibility testing, and *Mycobacterium tuberculosis* genotyping were not performed on patients initially admitted for retreatment, patients may have been misclassified as relapsed when instead they had drug-resistant TB, reinfected with a new *M. tuberculosis* strain or non-TB mycobacteria. In a similarly treatment experienced population referred to KIDH for MDR-TB treatment, non-TB mycobacteria were found in ~5% of patients.⁶ Indeed, the patients that remained persistently smear positive in this current retreatment cohort and whose sputa were ultimately cultured and found to have MDR-TB may have already had amplified drug resistance on admission for retreatment.¹³ Our findings emphasize the importance of rapid drug susceptibility testing in retreatment patients and caution against the reliance on sputum smear conversion as a proxy for effective treatment.

As patients with mining as their primary occupation accounted for nearly 25% of all those admitted for retreatment, we believe this represents an important subpopulation in our setting for increased community-based interventions.¹⁷ Similarly, although gender did not predict poor outcome, nearly 90% of all patients admitted for retreatment were men, a far larger proportion of the typical 60–65% men in the general TB population at KIDH, and raises concern about gender-based behaviors or occupations that may predispose to relapse or reinfection. For example, the small-scale mines of tanzanite in Mererani are worked largely by young men transiently migrating from other parts of Tanzania or neighboring countries in east Africa. Such workers suffer from poor health access, lack of knowledge of the local medical systems, and fear that declaration of illness may risk losing their job. Aside from the environmental conditions inside the mines themselves with silica dust exposure and poorly ventilated areas leading to increased TB transmission,^{18,19} as has been observed elsewhere, mining sites such as Mererani may serve as a high burden center for increasing TB transmission to other lower burden settings as the infected worker returns home.^{20,21}

There are limitations to this study inherent in the retrospective design. For instance, although HIV status was reported in all TB patients per hospital protocol, chart review undoubtedly limited the reporting of such conditions as pneumoconiosis and tobacco smoking that were dependent on physician documentation and patient recall. Similarly, the occupation reflected the patient's current employment, and thus a prior history of mining may have been underreported, and could account for the lack of difference in retreatment outcome between miners and "non-miners." Nonetheless, these findings highlight the need for TB control strategies that emphasize community-based interventions at high burden settings, such as mining sites, and enhance treatment methods to minimize relapse in at-risk patients and among those ultimately admitted with relapse, to assure retreatment success.

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