Severe Adverse Events in Outpatient Drug-Resistant TB Treatment in South Africa

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BACKGROUND

South Africa adopted a policy of decentralization of drug-resistant TB treatment to satellite and outpatient sites in 2011. Outcomes of treatment at these new sites are not yet known.

We report on the occurrence of adverse events (AE) to treatment at two outpatient, decentralized, drug-resistant tuberculosis (DR-TB) treatment sites in Johannesburg, South Africa.

METHODS

Combined retrospective and prospective medical record review of the six-month intensive phase of treatment for patients (>18 years old) with DR-TB registered between May 2012 to December 2013. Patients who transferred out or were lost to follow-up during the study period were excluded.

A standardized regimen of kanamycin, moxifloxacin, ethionamide, terizidone, and pyrazinamide was used according to the South African national DR-TB guidelines.

Adverse events were graded as mild (grade I), moderate (grade II), severe (grade 3), potentially life-threatening (grade 4), or fatal (grade 5) according to the AIDS Clinical Trials Group grading system .

MAIN FINDINGS

•All 217 patients had resistance to rifampicin; 41 (20%) were also resistant to isoniazid (MDR-TB).
•179 (82%) of patients were co-infected with HIV with a median CD4 count of 114 cells/µl. (Table 1)
•240 AEs were recorded in 118 (54%) patients (Figure 1)
-hearing loss (28% of patients)
-hypokalemia (5%),
-acute kidney injury (4%)
-peripheral neuropathy (6%) and
-vomiting (4%)



•Severe AEs (grade 3 to 5) accounted for 73 (30%) of AEs and were reported in 38 (18%) patients.
•Severe AEs were more likely to occur in those 50 years or older [Odds ratio: 5.9, 95%CI: 1.5 – 23.4], in HIV co-infected with CD4 < 100 cells/µl [2.3, CI: 1.2-4.4] and in those diagnosed with DR-TB in an inpatient setting ([1.9, CI 1.1-3.4].
•Acute kidney injury was more likely to occur in men [2.3, CI 0.9-5.6] and those diagnosed in inpatient settings [2.8, CI 1.1-7.2].
•Death occurred in 22 (10%) patients during the intensive phase of treatment.
•No statistically significant differences were detected in AE incidence or severity according to HIV status [0.7, CI 0.3-1.5 and 1.6, CI 0.6-0.4].

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RESULTS

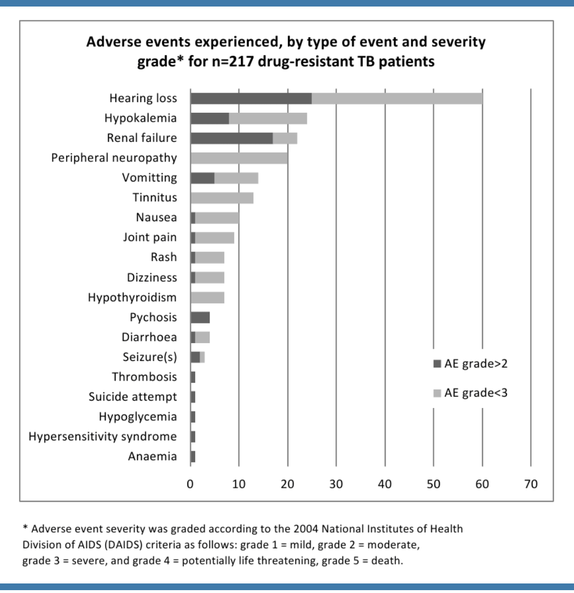
Table 1. Characteristics of patients at two decentralized drug-resistant TB treatment sites in Johannesburg, South Africa

Description	Count	Median	% Or IQR
All patients	217		
Male	109		50.2%
Age		36	30 - 42.9
Older (age 50+)	10		4.9%
HIV infection	179		82.5%
Baseline CD4		114	61 - 247
Low baseline CD4 (≤ 100)	64		29.5%
Diagnosed as inpatient	65		32.2%

Table 2 Risk of developing adverse events

	Odds ratio	95% confidence interval
Any adverse event		
Male	0.75	0.47 – 1.20
Older (age 50+)	0.94	0.29 – 3.09
HIV infection	0.66	0.29 – 1.49
Low baseline CD4 (≤100)	1.28	0.70 – 2.33
Diagnosed as inpatient	0.93	0.56 – 1.55
Any severe adverse event		
Male	1.47	0.85 – 2.55
Older	**5.87**	**1.47 – 23.4**
HIV infection	1.57	0.64 – 3.83
Low baseline CD4	**2.32**	**1.21 – 4.44**
Diagnosed as inpatient	**1.92**	**1.09 – 3.40**
Hearing loss		
Male	1.25	0.72 – 2.17
Older	1.57	0.43 – 5.75
HIV infection	1.57	0.65 – 3.83
Low baseline CD4	1.29	0.68 – 2.42
Diagnosed as inpatient	1.06	0.60 – 1.89
Renal failure		
Male	2.27	0.91 – 5.62
Older	1.20	0.14 – 10.02
HIV infection	1.40	0.31 – 6.37
Low baseline CD4	2.65	0.88 - 7.96
Diagnosed as inpatient	**2.80**	**1.10 – 7.15**

Figure 1: Number of adverse events experienced, by type of event and severity grade* for n=217 drug-resistant TB patients



* Adverse event severity was graded according to the 2004 National Institutes of Health Division of AIDS (DAIDS) criteria as follows: grade 1 = mild, grade 2 = moderate, grade 3 = severe, and grade 4 = potentially life threatening, grade 5 = death.

CONCLUSION

- Severe adverse events are being experienced by one-fifth of patients managed at outpatient DR-TB treatment sites.
- Adverse events are more likely to occur in those diagnosed with DR-TB as inpatients, people older than 50 years, and HIV infected patients with low baseline CD4.
- The most common toxicities: hearing loss, hypokalemia, and renal failure, are all related to aminoglycoside treatment.
- There is an urgent need for better tolerated, aminoglycoside-free regimens for the treatment of drug-resistant TB