Original research

TREATMENT OUTCOMES AND ADVERSE REACTIONS IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS MANAGED BY AMBULATORY OR HOSPITALIZED CARE FROM 2010-2011 IN TASHKENT, UZBEKISTAN

Lola Kalandarova,1 Mirzagaleb Tillashaikhov,2 Nargiza Parpieva,3 Shoiba Saidova,1 Jamshid Gadoev,4 Natavan Alikhanova,5 Rony Zachariah,6 Davron Mukhtarov,7 Sarvar Alidjanov,7 Anthony D Harries8

1 City TB dispensary, Tashkent, Uzbekistan
2 Republican Specialized Scientific and Practical Centre of Phthisiology and Pulmonology, Tashkent, Uzbekistan
3 Tashkent Medical Academy, Department of Phthisiology, Uzbekistan
4 WHO Representative Office, Tashkent, Uzbekistan
5 Scientific Research Institute of Lung Diseases, NTP, Monitoring and Evaluation Department, Baku, Azerbaijan
6 Medecins Sans Frontieres, Brussels Operational Centre, City of Luxembourg, Luxembourg
7 Postgraduate Medical Education, Tashkent, Uzbekistan
8 International Union Against Tuberculosis and Lung Disease, Paris, France

Corresponding author: Lola Kalandarova (email: lola_nur69@mail.ru)

ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB) is a growing threat to global TB control. Uzbekistan is one of the 15 high-burden MDR-TB countries in the World Health Organization (WHO) European Region. According to national policy, all patients should receive a 6-month intensive phase of treatment through hospitalized inpatient care. However, between January and December 2011, owing to physical reconstruction of the hospital for MDR-TB patients in Uzbekistan, all patients started and continued treatment on a fully ambulatory outpatient basis. A retrospective cohort study was therefore carried out to compare final treatment outcomes and reported adverse drug reactions among patients with MDR-TB who completed the intensive phase of treatment through inpatient care (2010) with those who completed the intensive phase on an ambulatory basis (2011) in Tashkent, Uzbekistan. A total of 129 MDR-TB patients received hospitalized intensive-phase treatment and 82 received ambulatory intensive-phase treatment. There were no significant differences between the two groups with respect to sociodemographic characteristics, clinical features or co-morbidities. Treatment outcomes were similar between the two groups, with a tendency to more favourable outcomes in those on ambulatory therapy (treatment success: 63%, ambulatory care; 53%, hospitalized care). Reported adverse reactions were significantly higher in those on hospitalized therapy (86%) compared with ambulatory therapy (55%), for reasons that are not clear, with most adverse outcomes reported in the third, fourth or fifth month for hospitalized patients and in the first month for ambulatory patients. In conclusion, the National TB Programme needs to reconsider its current policy for the model of inpatient MDR-TB care in favour of ambulatory treatment, in line with WHO recommendations.

Keywords: AMBULATORY CARE, CENTRAL ASIA, MULTIDRUG-RESISTANT TUBERCULOSIS, NATIONAL TUBERCULOSIS PROGRAMME (NTP), OPERATIONAL RESEARCH, SORT IT, TUBERCULOSIS

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB – disease caused by organisms that are resistant to at least rifampicin and isoniazid) is a growing threat to global TB control. In 2013, MDR-TB accounted for 3.5% of new TB cases worldwide and 20.5% of previously treated TB cases, translating into approximately 480 000 cases per
year (1). Only 97 000 (20%) started specific treatment, usually for 24 months, among whom the treatment success rate was less than 50% (1).

Globally, many countries rely on hospital-based care during the intensive phase for the treatment of MDR-TB. As this treatment phase lasts for at least 6 months, this long period of hospitalization often leads to the problem of lack of bed capacity; introduces the risk of nosocomial reinfection with a different strain of *Mycobacterium tuberculosis*; and is not patient friendly (2). This is of particular concern as case detection and drug-susceptibility testing continue to improve with the scale-up of rapid molecular diagnostic assays such as the Xpert MTB/RIF assay (which simultaneously detects *Mycobacterium tuberculosis* complex and resistance to rifampicin in under 2 h), and an increasing number of cases are being detected through these methods (1). One of the high-priority global targets for MDR-TB is to ensure that all patients diagnosed with MDR-TB are initiated and then continued on MDR-TB treatment without delay (3).

Traditionally, national TB programmes have instituted policies for hospital-based care for patients with MDR-TB, because it is thought that inpatient care allows better monitoring of adverse drug reactions and it is known that such reactions, if badly managed, can decrease patient compliance and adherence to medication, which in turn is likely to influence treatment efficacy (4, 5).

Current World Health Organization (WHO) guidelines on MDR-TB conditionally recommend ambulatory rather than hospital-based models of care (6, 7). The recommendation is conditional, owing to limited evidence comparing outcomes of patients treated under ambulatory versus hospitalized conditions. This is also compounded by the fact that there have been no randomized clinical controlled trials to demonstrate evidence in favour of one method over the other. A recent systematic review and meta-analysis of observational studies, however, found that there is no difference in the treatment outcomes of patients treated through either an ambulatory outpatient system or hospitalization (2).

Uzbekistan, a central Asian country, has a high burden of TB and is one of the 15 high-burden MDR-TB countries in the WHO European Region (8). The formal and systematic detection of MDR-TB started in 2006 in the capital city, Tashkent, with assistance from the Global Fund Against AIDS, Tuberculosis and Malaria (GFATM) and the Supranational Reference Laboratory in Gauting, Germany. Specialized beds for the treatment of patients with diagnosed MDR-TB were opened in the Phthisiology and Pulmonology Republican Specialized Scientific and Practical Centre, Tashkent. According to the National Protocol, all patients receive the intensive phase of treatment through hospitalized inpatient care (9, 10). However, between January and December 2011, owing to physical reconstruction of the health-care facility, patients with MDR-TB could not be hospitalized and had to start and continue on treatment on a fully ambulatory basis. This has allowed an opportunity to historically compare the management and reporting of adverse drug reactions and final treatment outcomes of patients with MDR-TB managed on an inpatient basis and on an ambulatory basis.

The aim of the study was therefore to compare the characteristics, adverse drug reactions and treatment outcomes of patients diagnosed with MDR-TB managed either as hospitalized inpatients or as ambulatory patients during the intensive phase of treatment. Specific objectives were to compare the following in patients managed by ambulatory care between January and December 2011 and patients managed through hospitalized care between January and December 2010: (i) baseline characteristics; (ii) final treatment outcomes; and (iii) the frequency, type and reporting of adverse drug reactions.

**METHODS**

**STUDY DESIGN**

This was a retrospective cohort study comparing final MDR-TB treatment outcomes among all included patients with MDR-TB who started treatment at the Republican TB Centre and completed the full course of the intensive phase of treatment through inpatient care followed by outpatient treatment in the continuation phase of treatment, with those who completed the full course of treatment on an ambulatory basis from the beginning of the treatment.

**STUDY SETTING**

**General setting**

Uzbekistan is a central Asian country with an estimated population of approximately 30 million. Uzbekistan
comprises 12 provinces (oblasts), one autonomous republic (Republic of Karakalpakstan) and the capital city, Tashkent, which has a population of nearly 2.5 million.

**TB control**
The Republican Specialized Scientific-Practical Medical Centre of Tuberculosis and Pulmonology (RSPMCTP) under the National TB Programme (NTP) coordinates all TB control activities across the country and reports to the Ministry of Health of the Republic of Uzbekistan.

In Tashkent, TB work is carried out by six TB dispensaries. The Tashkent City TB Dispensary carries out the detection, treatment and follow-up of patients with TB, as well as providing TB organizational and methodological assistance to city hospitals and clinics. In addition, the City TB Dispensary collects paper-based quarterly and annual reports on patients with MDR-TB from other TB dispensaries and primary health-care facilities located in Tashkent. Cases with sensitive TB strains are recorded on an electronic TB register; however, drug-resistant cases are recorded on paper-based forms. A panel of TB doctors (consilium) at the City TB Dispensary evaluates each detected TB case, assigns a treatment regimen, conducts follow-up during the treatment, and adjusts the treatment regimen if necessary. Examination and treatment of all patients with TB is free. In accordance with the legislation of the Republic of Uzbekistan, all patients start treatment in the intensive phase through inpatient care (9, 10).

Until 2006, only first-line medicines were available in the country for the treatment of patients with TB. Since 2006, a pilot project of MDR-TB treatment was started in Tashkent City within the framework of a GFATM grant. Specialized inpatient units were organized for this group of patients in the RSPMCTP. As previously described, between January and December 2011, owing to the reconstruction of the RSPMCTP that included the MDR-TB unit, conditions were created under which the treatment of patients with MDR-TB was started, continued and finished on an ambulatory and outpatient basis. The MDR-TB treatment regimen administered during the study period is shown in Box 1. Monitoring and evaluation of the treatment of patients with MDR-TB is conducted by the City TB Dispensary, which maintains an electronic database, and keeps outpatient cards for all patients. Final TB treatment outcomes are assessed for each patient and are defined in Box 1.

**STUDY POPULATION**
The study included all patients with MDR-TB who started treatment at the Republican TB Centre in Tashkent, Uzbekistan: the first cohort included all those who started and completed the intensive phase of treatment on an inpatient basis between January and December 2010; and the second cohort included all those who started and completed the intensive phase of treatment on an ambulatory and outpatient basis between January and December 2011. During the study period, there were two pilot projects in Uzbekistan for MDR-TB treatment. The first was in Tashkent, based in the Republican TB Centre, which was providing treatment to all patients with MDR-TB countrywide, except those in the autonomous Republic of Karakalpakstan, since the second pilot project for MDR-TB treatment, led by Médecins Sans Frontières, was conducted there.

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**BOX 1. TREATMENT REGIMEN FOR MULTIDRUG-RESISTANT TUBERCULOSIS AND DEFINITIONS OF FINAL TREATMENT OUTCOMES AS USED IN TASHKENT, UZBEKISTAN: 2010–2011**

**Treatment regimen for MDR-TB**

- **Intensive phase (6 months):** kanamycin/capreomycin, ofloxacin, prothionamide and, depending on the type of resistance detected through drug-resistance testing, the use of ethambutol, pyrazinamide, cycloserine and para-aminosalicylic acid (PAS).
- **Continuation phase (18 months):** ofloxacin, ethionamide and, depending on the type of resistance detected through drug-resistance testing, the use of ethambutol, pyrazinamide, cycloserine and PAS.

**Final TB treatment outcomes**

- **Cured:** treatment completed as recommended by the national policy and five consecutive cultures taken at least 30 days apart that are negative during the last 12 months of treatment.
- **Treatment completed:** treatment completed as recommended by the national policy but no record that five consecutive cultures taken at least 30 days apart are negative during the last 12 months of treatment.
- **Death:** a patient who dies for any reason during the course of treatment.
- **Failure:** a patient who has had not less than two of the five consecutive cultures taken in the final 12 months and whose cultures are positive, or for whom if any one of the final three cultures are positive.
- **Lost to follow-up:** a patient whose treatment was interrupted for 2 consecutive months or more.
- **Favourable treatment:** the sum of “cured” and “treatment completed” outcomes.
DATA VARIABLES, SOURCES OF DATA AND DATA COLLECTION

Data variables for the two cohort populations included baseline data comprising the TB registration number, type of treatment in the intensive phase (ambulatory or hospitalized), date of starting treatment, residence status, age, sex, education, employment status, marital status, HIV status, history of diabetes mellitus, smoking history and alcohol use; adverse drug reactions, including the type of reaction and month of treatment when the reaction occurred; and final treatment outcomes (as defined in Box 1). The sources of data for the study were the Tashkent City TB Dispensary register of MDR-TB patients, the MDR-TB patient cards and the medical history of the patients in their inpatient files while on hospital-based treatment. The data were collected into an EpiData questionnaire file.

DATA ANALYSIS

The data were single entered into EpiData 3.1 (EpiData Association, Odense, Denmark) and also into Stata (Version 12; Stata Corporation, College Station, Texas, United States of America). Data were summarized using descriptive statistics. Treatment outcomes and the type and severity of drug reactions of patients treated on an inpatient basis were compared with those of patients treated on an ambulatory outpatient basis, using the uncorrected chi-square test with Fisher's exact test for cells in which the number of patients was five or fewer. The significance level was set at 5% using two-tailed P values.

ETHICS

Permission to conduct this study was obtained from the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan. Ethical approval was additionally sought from the Ethics Advisory Group of the International Union against Tuberculosis and Lung Disease in Paris, France.

RESULTS

There were 211 patients in the study, 129 (61%) who started and completed the intensive phase of treatment in hospital and 82 (39%) who started and completed the intensive phase as ambulatory outpatients. Baseline characteristics are shown in Table 1. There were no significant differences between the two groups with respect to sociodemographic characteristics, clinical features or comorbidities.

### TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS WHO, DURING THE INTENSIVE PHASE OF TREATMENT, WERE EITHER AMBULATORY OR RECEIVED TREATMENT IN HOSPITAL, TASHKENT, UZBEKISTAN, 2010–2011

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ambulatory treatment, n (%)</th>
<th>Hospitalized treatment, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>82</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>50 [61]</td>
<td>89 [69]</td>
<td>0.231</td>
</tr>
<tr>
<td>Female</td>
<td>32 [39]</td>
<td>40 [31]</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD), years</td>
<td>45.1 ± 1.3</td>
<td>42.0 ± 1.1</td>
<td>0.07</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary/secondary</td>
<td>52 [64]</td>
<td>108 [83]</td>
<td>0.156</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>16 [20]</td>
<td>36 [28]</td>
<td>0.098</td>
</tr>
<tr>
<td>Married</td>
<td>46 [56]</td>
<td>78 [60]</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>13 [16]</td>
<td>11 [9]</td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>48 [58]</td>
<td>89 [70]</td>
<td></td>
</tr>
<tr>
<td>Disabled</td>
<td>18 [22]</td>
<td>24 [18]</td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>0</td>
<td>2 [2]</td>
<td></td>
</tr>
<tr>
<td>HIV status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>8 [10]</td>
<td>7 [5]</td>
<td>0.223</td>
</tr>
<tr>
<td>Negative</td>
<td>73 [89]</td>
<td>122 [94]</td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td>1 [1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6 [7]</td>
<td>11 [8]</td>
<td>0.779</td>
</tr>
<tr>
<td>No</td>
<td>74 [91]</td>
<td>117 [91]</td>
<td></td>
</tr>
<tr>
<td>Alcohol misuse*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>61 [75]</td>
<td>112 [87]</td>
<td></td>
</tr>
<tr>
<td>No data</td>
<td>7 [8]</td>
<td>3 [2]</td>
<td></td>
</tr>
<tr>
<td>Smoking*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 [51]</td>
<td>68 [53]</td>
<td>0.415</td>
</tr>
<tr>
<td>No</td>
<td>28 [34]</td>
<td>58 [45]</td>
<td></td>
</tr>
<tr>
<td>Type of MDR-TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>17 [21]</td>
<td>24 [19]</td>
<td>0.703</td>
</tr>
<tr>
<td>Previously treated</td>
<td>65 [79]</td>
<td>105 [81]</td>
<td></td>
</tr>
<tr>
<td>Adverse reactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>45 [55]</td>
<td>111 [86]</td>
<td>0.01</td>
</tr>
<tr>
<td>No</td>
<td>37 [45]</td>
<td>18 [14]</td>
<td></td>
</tr>
</tbody>
</table>

MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis.

*Includes patients known to be HIV positive and those who were detected during the treatment.

* Includes patients previously diagnosed with diabetes mellitus and those who were detected during the treatment through measurement of fasting blood glucose.

* Information collected from the patients during interview.
Treatment outcomes between the two groups of patients are shown in Table 2. There were no significant differences except for a higher proportion of patients completing treatment with no bacteriology in the hospitalized group compared with the ambulatory group ($P < 0.01$). Among those with unfavourable outcomes, treatment failure was high, accounting for about 25% of all outcomes in each of the groups.

### TABLE 2. TREATMENT OUTCOMES FOR MDR-TB PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS WHO, DURING THE INTENSIVE PHASE OF TREATMENT, WERE EITHER AMBULATORY OR RECEIVED TREATMENT IN HOSPITAL, TASHKENT, UZBEKISTAN, 2010–2011

<table>
<thead>
<tr>
<th>Treatment outcomes</th>
<th>Ambulatory treatment, $n$ (%)</th>
<th>Hospitalized treatment, $n$ (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total evaluated</td>
<td>82</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Favourable outcomes</td>
<td>52 (63)</td>
<td>68 (53)</td>
<td>0.126</td>
</tr>
<tr>
<td>Cured</td>
<td>38 (46)</td>
<td>63 (49)</td>
<td>0.72</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>14 (17)</td>
<td>5 (4)</td>
<td>&lt; 0.01*</td>
</tr>
<tr>
<td>Unfavourable outcomes</td>
<td>30 (37)</td>
<td>61 (47)</td>
<td>0.126</td>
</tr>
<tr>
<td>Death</td>
<td>5 (8)</td>
<td>17 (16)</td>
<td>0.11</td>
</tr>
<tr>
<td>Failure</td>
<td>16 (25)</td>
<td>27 (26)</td>
<td>0.80</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (9)</td>
<td>14 (13)</td>
<td>0.39</td>
</tr>
<tr>
<td>Transferred out</td>
<td>3 (5)</td>
<td>3 (3)</td>
<td>0.57</td>
</tr>
</tbody>
</table>

MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis.

* Fisher’s exact test, as the number of patients in one cell is five.

Adverse drug reactions were recorded in 45 (55%) patients on ambulatory therapy compared with 111 (86%) on hospitalized therapy ($P < 0.001$). The frequencies of different types of adverse drug reactions are shown in Table 3. Some patients had two or more different types of drug reaction. For all drug reactions, except for “other”, there was a higher frequency in patients receiving hospitalized therapy compared with those receiving ambulatory care. The timing of when adverse drug reactions were recorded is shown in Table 4.

### DISCUSSION

This is the first study in Uzbekistan to assess and compare the treatment outcomes and frequency of drug reactions between patients with MDR-TB receiving ambulatory therapy and those receiving hospitalized therapy during the intensive period of treatment. These different models of care happened opportunistically because of the reconstruction of the main MDR-TB treatment centre in Tashkent, which meant that for one year patients had no alternative but to receive treatment on an ambulatory basis. Patients in each group were similarly matched at baseline by sociodemographic and clinical characteristics and were treated with identical regimens and in line with the national protocol for MDR-TB. The patients included all those treated for MDR-TB in the country during the study period from 2010 to 2011. Treatment outcomes were similar between the two groups, with a tendency to more favourable outcomes in those receiving ambulatory therapy. A higher proportion of patients on hospitalized therapy reported adverse outcomes, with each type of outcome being more frequently reported.

### TABLE 3. ADVERSE DRUG REACTIONS IN PATIENTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS WHO, DURING THE INTENSIVE PHASE OF TREATMENT, WERE EITHER AMBULATORY OR RECEIVED TREATMENT IN HOSPITAL, TASHKENT, UZBEKISTAN, 2010–2011

<table>
<thead>
<tr>
<th>Adverse drug reactions</th>
<th>Ambulatory treatment, $n$ (%)</th>
<th>Hospitalized treatment, $n$ (%)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total evaluated</td>
<td>82</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal$^a$</td>
<td>30 (37)</td>
<td>105 (81)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hepatotoxic$^c$</td>
<td>10 (12)</td>
<td>32 (25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nephrotoxic$^c$</td>
<td>1 (1)</td>
<td>18 (14)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Central nervous system$^d$</td>
<td>15 (18)</td>
<td>77 (60)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Joint disorders$^e$</td>
<td>3 (4)</td>
<td>23 (18)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Cardiovascular disorders$^f$</td>
<td>4 (5)</td>
<td>23 (18)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Skin allergic reactions$^g$</td>
<td>3 (4)</td>
<td>28 (22)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Other$^h$</td>
<td>0</td>
<td>6 (5)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis.

$^a$ Abdominal pain, diarrhoea, vomiting, nausea, gastritis.

$^b$ Abnormalities of liver enzymes, jaundice, hepatitis.

$^c$ Elevation of serum creatinine, urine proteinuria.

$^d$ Dizziness, peripheral neuropathy, depression, sleep disorders, seizures, psychosis.

$^e$ Arthralgia and arthritis.

$^f$ Cardiac arrhythmia, chest pain thought to be ischaemic.

$^g$ Ototoxicity, a combination of different adverse reactions.

$^h$ Fisher’s exact test, as the number of patients in one or both cells is five or fewer.
A good social support network to facilitate adherence and recognize and manage adverse drug reactions, control procedures, adequate numbers of trained which include hospital bed capacity, good infection control procedures, adequate numbers of trained health-care workers who can administer treatment and recognize and manage adverse drug reactions, a good social support network to facilitate adherence and ambulatory or received treatment in hospital, Tashkent, Uzbekistan, 2010–2011

The strengths of this study were the full national sample of MDR-TB patients registered and treated during the 2-year period, the identical regimens and protocols used for all patients, and the well-defined and rigorous follow-up of final treatment outcomes. The researchers also followed STROBE (STrengthening the Reporting of Observational studies in Epidemiology) guidelines and sound ethical principles for conducting and reporting on this observational study (11, 12). There were some limitations in that these were secondary data from registers and patient cards, and for the reporting of adverse outcomes this might have been incomplete for those on ambulatory therapy. In addition, one important limitation of the study was that no follow-up was conducted after the treatment finished.

The study findings open the debate about hospitalized patients compared with ambulatory patients. The most common time for drug reactions to be reported was in the first month for ambulatory patients and in the third, fourth or fifth month for those receiving hospitalized therapy.

The high proportion of patients in both ambulatory and hospitalized care whose treatment for MDR-TB failed is a cause for concern. As these were secondary data, there is no further information about these patients for this study. However, it raises concerns about whether patients had pre-XDR or XDR (extensively drug-resistant TB – defined as MDR-TB plus resistance to a fluoroquinolone and one of three second-line injectable drugs), which is more difficult to treat and associated with worse treatment outcomes than those seen in patients with just MDR-TB (19, 20).

Loss to follow-up with all MDR-TB treatment regimens and with different models of care is a concern, and a shorter and less toxic MDR-TB treatment regimen would facilitate ambulatory care, compliance with treatment and adherence to medication. A 9-month regimen was first implemented with excellent results among MDR-TB patients in Bangladesh (21, 22), and this has since been modified and implemented as a 12-month regimen in Cameroon (23). These shorter and more patient-acceptable regimens pave the way for more effective and better tolerated treatment for this group of patients. A randomized clinical trial sponsored by the International Union Against Tuberculosis and Lung Disease is currently in progress to evaluate the “9-month Bangladesh regimen” and assess whether second-line injectable agents, which cause problems with hearing impairment, can be replaced by new oral anti-tuberculosis drugs such as bedaquiline or delamanid.

The large number of adverse drug reactions reported by the patients in this study on both ambulatory and

### Table 4. Timing of Adverse Drug Reactions in Patients with Multidrug-Resistant Tuberculosis Who, During the Intensive Phase of Treatment, Were Either Ambulatory or Received Treatment in Hospital, Tashkent, Uzbekistan, 2010–2011

<table>
<thead>
<tr>
<th>Timing of adverse drug reactions in relation to start of MDR-TB treatment</th>
<th>Ambulatory treatment, n (%)</th>
<th>Hospitalized treatment, n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>82 (46)</td>
<td>129</td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>38 (46)</td>
<td>18 (14)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Month 2</td>
<td>11 (13)</td>
<td>10 (8)</td>
<td>0.19</td>
</tr>
<tr>
<td>Month 3</td>
<td>11 (13)</td>
<td>26 (20)</td>
<td>0.21</td>
</tr>
<tr>
<td>Month 4</td>
<td>14 (17)</td>
<td>50 (39)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Month 5</td>
<td>2 (2)</td>
<td>21 (16)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Month 6</td>
<td>0 (0)</td>
<td>2 (2)</td>
<td>0.75</td>
</tr>
<tr>
<td>Month 7 and after</td>
<td>1 (1)</td>
<td>2 (2)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

MDR-TB: multidrug-resistant tuberculosis; SD: standard deviation; TB: tuberculosis.

* Fisher’s exact test, as the number of patients in one or both cells is five or fewer.
hospitalized treatment is in line with the findings of previous studies (24, 25). These reactions are a source of global public health concern, since they substantially contribute to morbidity, mortality, loss to follow-up and increased health-care costs. In a recent study in Nigeria, most patients on MDR-TB treatment experienced adverse drug reactions (mainly gastrointestinal, neurological, ototoxic and psychiatric) in the first 1–2 months of treatment, with many of these reactions resolving in later months. (25) It is not clear why, in the present study, there were different frequencies of drug reactions or different time periods for reporting between ambulatory and hospitalized care. However, it is well recognized that differences in reporting may be observed between different treatment centres and this may relate to the way these reactions are perceived by patients and health-care workers alike (25).

There is one important policy implication from this study that is whether the National TB Programme in Uzbekistan is prepared to make the change to ambulatory therapy for the intensive phase of treatment for patients with MDR-TB. This could be piloted again within the routine setting, with careful monitoring and evaluation, especially with regard to reporting and managing adverse drug reactions. This would be more patient-friendly, consume fewer resources, result in less exposure of health-care staff within the TB centre to nosocomial transmission of MDR-TB and XDR-TB, and reduce the risk of re-infection with different strains of *Mycobacterium tuberculosis* for TB patients (26, 27). However, there could be a risk of transmission of MDR-TB among households and in the community during treatment in an ambulatory regimen, which requires further in-depth research and analysis.

With the growing and severe burden of MDR-TB in Uzbekistan, and an estimated 23% of new and 62% of previously treated patients having this infectious disease (28), a decision about the model of care is an important health priority for the country.

In conclusion, this study shows that patients in Uzbekistan treated for MDR-TB with ambulatory care during the intensive phase of treatment had similar outcomes to those treated with hospitalized care. The national TB programme needs to use the data from this study to decide whether to continue and scale-up an ambulatory model of care for its patients.

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