Adverse Events Associated with Treatment of Multidrug-Resistant Tuberculosis in China: An Ambispective Cohort Study

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Background: Adverse events are under-appreciated negative consequences that are significant clinical problems for patients undergoing anti-MDR-TB treatment due to longer duration of treatment and more need for concurrent use of multiple second-line drugs.

The aim of this study was to determine the incidence of adverse events and their impact on MDR-TB therapy and treatment outcome, and to identify possible drug-event pairs in China.

Material/Methods: An ambispective cohort study was conducted based on hospital medical records, which included a retrospective study that enrolled 751 MDR-TB patients receiving standardized regimen between May 2009 and July 2013, and a follow-up investigation of treatment outcome conducted in December 2016 in China. Adverse events were determined according to laboratory results or clinical criteria. Cox’s proportional hazards regression models were used for evaluating associations.

Results: There were 681 (90.7%) patients experienced at least 1 type of adverse event and 55.2% of them required a changed MDR-TB treatment; 51 (6.8%) patients required permanent discontinuation of the offending drug due to adverse events. The occurrence of adverse events was associated with poor treatment outcome (adjusted hazard ratio, 1.54; 95% CI 1.21, 1.87). A total of 10 different drug-event pairs were identified.

Conclusions: Adverse events occurred commonly during MDR-TB treatment in China, and often resulted in MDR-TB treatment change. The occurrence of adverse events affected MDR-TB poor outcome after treatment.

MeSH Keywords: China • Drug-Related Side Effects and Adverse Reactions • Tuberculosis, Avian

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Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis (TB) caused by organisms that are resistant to isoniazid and rifampicin, the 2 most powerful anti-TB drugs [1]. According to reports of the World Health Organization (WHO), an estimated 480 000 people worldwide developed MDR-TB in 2015, and an additional 100 000 people with rifampicin-resistant (RR) TB were newly eligible for MDT-TB treatment [2]. As the second highest MDR-TB incident country in the world, China accounted for 45% of the 580 000 cases together with the Indian and the Russian Federation, with 6.6% of new TB cases and 30% of previously treated cases having MDR/RR-TB [3].

Medications for MDR-TB consisting of multiple first-line and second-line drugs for 24 months are less potent, more toxic, and much more expensive than those for drug-susceptible TB [1,4–6]. Due to longer duration of treatment and more requirement for concurrent use of multiple second-line drugs, adverse events are considered as major concerns among patients undergoing MDR-TB treatment [7–11]. Patients may experience adverse events ranging from trivial side-effects to life-threatening complications, which may result in temporary interruption or persistent discontinuation of chemotherapy [12]. This non-adherence may diminish the effectiveness of chemotherapy, cause a poor outcome following treatment, and, in particular, increase risk of extensively drug-resistant TB (XDR-TB) [8,13].

There is no global consensus on the overall incidence of adverse events related to MDR-TB treatment, because that the incidence ranges from 18% to 100% [7–11,14–17]. Our previous review [14] found that most studies had a relatively small sample size, and different definitions of adverse events were used in different works. Moreover, little information on the incidence of adverse events in Chinese MDR-TB patients is available in published work, and whether the occurrence of adverse events affects the treatment outcome, especially in China, largely remains unknown.

In this study, we aimed to evaluate the incidence of adverse events associated with MDR-TB therapy so as to identify related drugs and to investigate their impact on MDR-TB treatment outcome via a large hospital-based ambispective cohort in China.

**Material and Methods**

**Ethics statement**

The ambispective cohort study was approved by the Ethics Committee of the Center for Tuberculosis Control and Prevention of China. Written informed consent was obtained from participants or their surrogates before enrollment.

**Patient’s enrollment**

An ambispective cohort study was conducted based on hospital medical records from 8 hospitals in 5 provinces (Henan, Shandong, Jiangsu, and Guangdong). It included a retrospective study that enrolled 751 MDR-TB patients receiving standardized regimen according to "Regulations on the Prevention and Control of MDR-TB in China” [18] between May 2009 and July 2013, and a follow-up investigation of treatment outcome conducted in Dec 2016 in China. Patients were enrolled in this cohort if they: (1) had been diagnosed as MDR-TB based on a drug susceptibility test; (2) agreed to receive an MDR-TB treatment; (3) had continuously received 6 or more months of MDR-TB therapy.

**Treatment**

All patients received standardized MDR-TB regimen, consisting of pyrazinamide (Z), a parenteral agent, including amikacin (Am), kanamycin (Km), or capreomycin (Cm); a fluoroquinolone agent, including Levofloxacin (Lfx) or Moxifloxacin (Mfx); prothionamide (Pto) and para-aminosalicylic acid(PAS)/ethambutol (E); and cycloserine(Cs) if could be obtained. The selection of parenteral agent, fluoroquinolone agent, and PAS/E was based on the results of drug susceptibility tests. Initially, all medications were administrated simultaneously. All medications lasted for 24 months except parenteral agent, which lasted for at least 6 months according to “Regulations on the Prevention and Control of MDR-TB in China” [18]. All patients were asked to refill drugs from the outpatient clinic every month in the first 6 months and every 2 months in the following 18 months. All the patients were adherent to the treatment and education was given to patients about the treatment possible adverse events and duration. The drugs and their dosages are shown in Table 1.

**Data collection**

Data were collected through chart review of medical records, including baseline characteristics of adverse events induced by anti-TB treatment, drugs administered in the regimen, and information on adverse events. Adverse events were monitored based on clinical symptoms and signs, as well as laboratory test results.

**Symptoms signs and Laboratory tests**

Audiometric and visual examination was performed prior to initiation of MDR-TB therapy. Once MDR-TB therapy started, patients were followed up daily by trained specialists to administer directly observed therapy. During each clinical visit, patients were questioned about the occurrence of any symptom
or sign related to adverse events, and their responses were documented in the medical records.

Before initiation of MDR-TB therapy, all patients had completed baseline laboratory tests, including blood routine test, urine routine test, liver function test, renal function test, blood electrolyte test, and thyroid function test. All laboratory tests except thyroid function test were performed monthly in the first 6 months and every 2 months thereafter until the MDR-TB treatment was completed.

Follow-up

To obtain the outcomes of patients who received treatment during July 2013, a follow-up investigation was conducted in Dec 2016. This investigation collected the treatment outcome and occurrence time by examining the records of patient registries in the China Program for the Global Fund to Fight TB, based on registry number.

### Table 1. Medications and dosages prescribed to MDR-TB patient.

| Drug | Specification | Daily dosage |
|------|---------------|--------------|
| Z    | Domestic 250 mg | 1500 mg (<50 kg); 1750 mg (≥50 kg); Maximum dose: 2000 mg |
|      | Imported 500 mg | 30–40 mg/kg (<33 kg); 1000–1750 mg (33–50 kg); 1750–2000 mg (51–70 kg); 2000–2500 mg (≥70 kg) |
| Am   | Domestic 200 mg | 400 mg (<50 kg); 400–600 mg (≥50 kg); Maximum dose: 800 mg |
|      | Imported 1000 mg | 15–20 mg/kg (<33 kg); 500–750 mg (33–50 kg); 1000 mg (≥50 kg) |
| Km   | Domestic 500 mg | 500 mg (<50 kg); 750 mg (≥50 kg); Maximum dose: 1000 mg |
|      | Imported 1000 mg | 15–20 mg/kg (<33 kg); 500–750 mg (33–50 kg); 1000 mg (≥50 kg) |
| Cm   | Domestic 750 mg | 750 mg |
|      | Imported 1000 mg | 15–20 mg/kg (<33 kg); 500–750 mg (33–50 kg); 1000 mg (≥50 kg) |
| Lfx  | Domestic 100 mg | 400 mg (<50 kg); 500 mg (≥50 kg); Maximum dose: 600 mg |
|      | Imported 200–400 mg | 15–20 mg/kg (<33 kg); 750 mg (33–70 kg); 750–1000 mg (≥70 kg) |
| Mfx  | Domestic 400 mg | 400 mg |
|      | Imported 400 mg | 7.5–10 mg/kg (<33 kg); 400 mg (≥33 kg) |
| Pto  | Domestic 100 mg | 600 mg (<50 kg); 600–800 mg (≥50 kg); Maximum dose: 800 mg |
|      | Imported 250 mg | 15–20 mg/kg (<33 kg); 500 mg (33–50 kg); 750 mg (51–70 kg); 750–1000 mg (≥70 kg) |
| PAS  | Domestic 500 mg/2000 mg | 8000 mg (<50 kg); 100000 mg (≥50 kg); Maximum dose: 12000 mg |
|      | Imported 4g | 150 mg/kg (<33 kg); 8g (≥33 kg) |
| E    | Domestic 250 mg | 750 mg (<50 kg); 1000 mg (≥50 kg); Maximum dose: 1500 mg |
|      | Imported 100–400 mg | 25 mg/kg (<33 kg); 800–1200 mg (33–50 kg); 1200–1600 mg (51–70 kg); 1600–2000 mg (≥70 kg) |
| Cs   | Imported 250 mg | 15–20 mg/kg (<33 kg); 500 (33–50 kg); 750 (51–70 kg); 750–1000 mg (≥70 kg) |

### Definitions

Adverse events are defined in Table 2. For adverse events that confirmed by laboratory tests, an adverse event was considered to occur if at least 1 laboratory value was abnormal. For adverse events not defined by laboratory tests, an event was considered to occur if physicians documented the event in the patient chart according to clinical criteria and the patient-reported signs or symptoms.

Treatment outcome of MDR-TB was defined according to WHO guidelines [19] and was classified into 2 groups: successful outcome (cured, treatment completed), and poor outcome (treatment failed, died).

### Statistical analysis

The baseline characteristics of participants were described as median (interquartile range, IQR) for continuous variables, and percentages for categorical variables. Frequency and outcome...
of each type of adverse event was calculated. Impact on MDR-TB therapy of adverse events were reported using descriptive analysis. Cox’s proportional hazards regression models were used to detect the association. Besides crude HR calculation, adjusted multi-variable models were used, including age, sex, history of TB treatment, history of hepatitis, and history of adverse events induced by TB treatment. Statistical analyses were performed using SPSS 22.0. Tests were conducted with a two-sided significance level at 0.05.

### Results

#### Baseline characteristics

A total of 751 patients were included in the cohort. All patients had received at least 6 months of therapy at the time of analysis, when most adverse events have occurred. The median length of MDR-TB therapy was 17.27 (IQR, 8.50–24.37) months, and the median age of patients was 44.00 (IQR, 30.00–56.00) years. Of all patients, 550 (73.2%) were male. The median weight at the start of therapy for these patients was 55.25 (50.00–62.00) kg. There were 695 (92.5) patients with only pulmonary TB, and 56 (7.5%) patients had extra-pulmonary TB. Twenty-two (2.9) patients had history of hepatitis, and 276 (36.8%) had 1 or more comorbidity at baseline. There were 651(86.7%) patients who had been treated with TB previously, and of these patients, 133 had previously experienced adverse events induced by anti-TB treatments. The baseline characteristics of the 751 patients who completed treatment are shown in Table 3.

#### Frequency and outcome of adverse events

At least 1 type of adverse events was experienced by 681(90.7%) of 751 MDR-TB patients. Table 4 demonstrates the frequency and outcome of each type of adverse event in this cohort. Most adverse events occurred during the first 6 months of MDR-TB treatment. Some adverse events were cured or improved after treatment change, and a few of them were unimproved. Of all types of adverse events, the 2 most common types were arthralgia (67.5%) and gastrointestinal disorders (65.4%). Hypothyroidism, dermatologic disorders, hematologic disorders, hepatotoxicity, and ototoxicity were experienced by 148 (19.7%), 131 (17.4%), 115 (15.3%), 86 (11.5%), and 44 (5.9%) patients, respectively. Ninety-seven (12.9%) patients

### Table 2. Definitions of adverse events.

| Adverse events            | Definition                                                                                                                                 |
|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Hepatotoxicity            | (1) Elevation of serum transaminases greater than 3 times of the normal upper limit with symptoms; (2) elevation of serum bilirubin greater than 2 times of the normal upper limit with symptoms; (3) elevation of serum transaminases or serum bilirubin greater than 5 times of the normal upper limit with or without symptoms |
| Nephrotoxicity            | Elevation of at least one serum creatinine value greater than 133μmol/l                                                                |
| Ototoxicity               | Tinnitus, hearing loss confirmed by physical examination or audiometry, presence of disequilibrium                                      |
| Peripheral neuropathy     | Numbness, weakness, tingling, burning/pain in the extremities, diagnosed by physician or electromyography                                  |
| Central nervous system disorders | Headache, dizziness and seizure activity as reported by patient or witness                                                        |
| Psychiatric disorders     | Presence of depression, anxiety, psychosis, suicide, nightmares and convulsion                                                        |
| Dermatologic disorders    | Skin change including rash, itch, bronzing, black pigmentation and photosensitivity reaction                                          |
| Arthralgia                | Elevated uric acid, or with pain, swelling or stiffness in the joints reported by patients                                            |
| Gastrointestinal disorders| Presence of nausea, vomiting, anorexia, abdominal pain, diarrhea, epigastric discomfort, hematemesis, melena, positive endoscopic findings |
| Hypokalemia               | At least one serum potassium value < 3.5 mmol/l                                                                                    |
| Hypothyroidism            | At least one measure of serum thyroid stimulating hormone greater than the normal upper limit                                             |
| Visual impairment         | Presence of visual changes, including vision loss, pain on moving the eye                                                             |
| Hematologic disorders     | Decrease of hemoglobin, leukocyte or platelet count to less than the normal lower limit                                               |
experienced central nervous system disorders after a median of 119 days of treatment. Peripheral neuropathy and psychiatric disorders occurred in 8 (1.1%) and 3 (0.4%) patients, respectively, after a median of 6 months.

Table 3. Baseline characteristics of MDR-TB patients (N=751).

| Characteristics | Median (IQR) |
|-----------------|--------------|
| Age             | 44.00 (30.00–56.00) years |
| Length of MDR-TB treatment | 17.27 (8.50–24.37) months |
| Weight at start of therapy | 55.25 (50.00–62.00) kg |

| Characteristics | N (%) |
|-----------------|-------|
| Gender          |       |
| Male            | 550 (73.2) |
| Female          | 201 (26.8) |
| Race            |       |
| Chinese Han population | 743 (98.9) |
| Others          | 8 (1.1) |
| MDR-TB category |       |
| Pulmonary TB    | 695 (92.5) |
| With extra pulmonary TB | 56 (7.5) |
| Previous TB treated history |       |
| Yes             | 651 (86.7) |
| No              | 100 (13.3) |
| History of adverse events induced by TB treatment |       |
| Yes             | 133 (21.4) |
| No              | 518 (79.6) |
| History of hepatitis |       |
| Yes             | 22 (2.9) |
| No              | 729 (97.1) |
| Baseline comorbidity |       |
| Yes             | 276 (36.8) |
| Diabetes        | 84 (30.3) |
| Chronic obstructive pulmonary disease | 54 (19.7) |
| Pulmonary heart disease | 42 (15.2) |
| Others          | 96 (34.8) |
| No              | 475 (63.2) |

Impact on treatment of MDR-TB and Treatment Outcome

Regarding the impact of adverse events on treatment of MDR-TB, most patients had symptomatic treatment and examination, and few of them were treated in the hospital; 376 (50.1%) of 751 patients required a change of MDR-TB chemotherapy due to adverse events. Most of the patients experienced dose decrease, medication administration change, or temporary interruption of the offending drugs or treatment, and 51 (6.8%) of 751 patients required permanent discontinuation of the offending drug due to adverse events. Table 5 shows the influence of treatment due to each kind of adverse event and implicated drugs in this retrospective study.

Until Dec 2016, of a total of 751 patients, 282 (37.5%) were cured, 109 (14.5%) completed treatment, 148 (19.7%) had treatment failure, 71 (9.4%) died during treatment, 103 (13.7%) discontinued treatment for more than 2 months (e.g., due to pregnancy or economic reasons) or were lost to follow-up, and 38 (5.1%) patients were not evaluated. Of a total of 610 patients with treatment outcome at this time, the analysis indicated that the adverse events were associated with poor treatment outcome, with an unadjusted HR of 1.43 (95%CI, 1.25, 1.72) and adjusted HR of 1.54 (95% CI 1.21, 1.87).

Association between Drug Use and Adverse Events

The adjusted model determined 10 possible drug-event pairs: Z-artralgia, Pto-artralgia, Z-gastrointestinal disorders, Lfx-gastrointestinal disorders, PTO-gastrointestinal disorders, PAS-gastrointestinal disorders, Z-hematologic disorders, Pto-hematologic disorders, Cm-hypokalemia, and Pto-central nervous system disorders. Table 6 presents the corresponding drug-event pairs.

Discussion

This study was based on chart review of medical records, had a large sample size, and reflected the incidence of adverse events following MDR-TB therapy in a real-world population in geographically diverse areas in China. Initially, we found that 90.7% of patients developed at least 1 type of adverse events after MDR-TB chemotherapy due to adverse events. Peripheral neuropathy and psychiatric disorders occurred in 8 (1.1%) and 3 (0.4%) patients, respectively, after a median of 6 months.
monitoring with proper management may be important in treating MDR-TB patients, thereby preventing poor outcomes and extensive drug resistance.

The frequency of adverse events in our study was consistent with that in previous studies [7–12,21–25], but with higher rates. Several factors may have contributed to this result. First, participants in our study were monitored more frequently than those in previous studies, thus increasing the chance of detecting adverse events [25]. Secondly, the sample size of most previous studies [14] was small (median sample size: 80; interquartile range: 45–177), making the incidence of adverse events consistent with results of Shin et al. [21]. In addition, the incidence of psychiatric disorders in our study was generally lower than in other studies [7,10,11,21]. This may be because few patients can obtain cycloserine in this cohort in the whole treatment period before 2013, as cycloserine was the leading drug associated with psychiatric disorders [18]. As shown in the experiment, we observed that 57 and 89 patients were on cycloserine and ethambutol, respectively, and out of these, more than half of patients had gastrointestinal disorders [28]. Consistent with previous studies [7,10,11,14,20,21], our results show that approximately half of patients required a change in MDR-TB therapy, whereas only 7.5% (51/681) required a permanent discontinuation of the offending drug, which was consistent with previous studies [7–12,20,21]. This is the largest study to date of MDR-TB patients undergoing treatment in China, and it thus provides valuable information on adverse events in the Chinese population and enhances our understanding of the situation.

Arthralgia and gastrointestinal disorders were the 2 most common types of adverse events. Gastrointestinal disorders often result in a change of MDR-TB treatment, while arthralgia seldom does. Hypothyroidism developed in 19.7% of patients in our study, while Furin et al. [11] reported a 10% hypothyroidism in their cohort and Törün et al. [10] detected only 1.1% in their series. Possible reasons for this disparity might be that thyroid function was monitored more frequently in our study regardless of whether patients developed relevant symptoms, whereas other studies [10,11] only measured thyroid stimulating hormone in symptomatic patients. Hepatotoxicity was also common, and only 10 (11.6%) patients required permanent discontinuation of the offending drug, which was consistent with results of Shin et al. [21]. In addition, the incidence of psychiatric disorders in our study was generally lower than in other studies [7,10,11,21]. This may be because few patients can obtain cycloserine in this cohort in the whole treatment period before 2013, as cycloserine was the leading drug associated with psychiatric disorders [18]. As shown in the experiment, we observed that 57 and 89 patients were on cycloserine and ethambutol, respectively, and out of these, more than half of the patients had developed adverse effects, which is consistent with previous studies. For example, Bloss et al. reported that about 58.4% of patients had gastrointestinal disorders [28].

### Table 4. Frequency and outcome of adverse events in retrospective study in China (N=751).

| Adverse events   | Frequency of adverse events N (%) | Median interval of adverse events occurrence in days (IQR) | Outcome of adverse events N (%) |
|------------------|----------------------------------|----------------------------------------------------------|---------------------------------|
| Arthralgia       | 507 (67.5)                       | 41.0 (28.0–93.0)                                         | Cured 253 (49.9)                |
|                  |                                  |                                                          | Improved 151 (29.8)             |
|                  |                                  |                                                          | Unimproved 103 (20.3)           |
| Gastrointestinal disorders | 491 (65.4) | 35.0 (28.0–91.0)                                         | Cured 104 (21.2)                |
|                  |                                  |                                                          | Improved 317 (64.6)             |
|                  |                                  |                                                          | Unimproved 70 (14.3)            |
| Hypothyroidism   | 148 (19.7)                       | 202.5 (151.3–363.5)                                      | Cured 40 (27.0)                 |
|                  |                                  |                                                          | Improved 84 (56.8)              |
|                  |                                  |                                                          | Unimproved 24 (16.2)            |
| Dermatological disorders | 131 (17.4) | 86.0 (31.0–147.0)                                         | Cured 55 (42.0)                 |
|                  |                                  |                                                          | Improved 73 (55.7)              |
|                  |                                  |                                                          | Unimproved 3 (2.3)              |
| Hematologic disorders | 115 (15.3) | 118.0 (41.0–295.0)                                         | Cured 74 (64.3)                 |
|                  |                                  |                                                          | Improved 32 (27.8)              |
|                  |                                  |                                                          | Unimproved 9 (7.8)              |
| CNS disorders    | 97 (12.9)                        | 119.0 (39.0–289.0)                                        | Cured 13 (13.4)                 |
|                  |                                  |                                                          | Improved 71 (73.2)              |
|                  |                                  |                                                          | Unimproved 13 (13.4)            |
| Hepatotoxicity   | 86 (11.5)                        | 59.0 (30.0–116.0)                                         | Cured 43 (50.0)                 |
|                  |                                  |                                                          | Improved 33 (38.4)              |
|                  |                                  |                                                          | Unimproved 10 (11.6)            |
| Hypokalemia      | 52 (6.9)                         | 65.5 (30.5–120.0)                                         | Cured 44 (84.6)                 |
|                  |                                  |                                                          | Improved 6 (11.5)               |
|                  |                                  |                                                          | Unimproved 2 (3.8)              |
| Ototoxicity      | 44 (5.9)                         | 56.5 (31.5–124.8)                                         | Cured 10 (22.7)                 |
|                  |                                  |                                                          | Improved 31 (70.5)              |
|                  |                                  |                                                          | Unimproved 3 (6.8)              |
| Visual impairment | 19 (2.5)                      | 186.0 (84.0–428.0)                                        | Cured 3 (15.8)                  |
|                  |                                  |                                                          | Improved 15 (78.9)              |
|                  |                                  |                                                          | Unimproved 1 (5.3)              |
| Nephrotoxicity   | 14 (1.9)                         | 92.0 (62.0,188.5)                                         | Cured 13 (92.9)                 |
|                  |                                  |                                                          | Improved 1 (7.1)                |
|                  |                                  |                                                          | Unimproved 0 (0)                |
| Peripheral neuropathy | 8 (1.1)                      | 170.5 (157.0–348.3)                                       | Cured 2 (25.0)                  |
|                  |                                  |                                                          | Improved 6 (75.0)               |
|                  |                                  |                                                          | Unimproved 0 (0)                |
| Psychiatric disorders | 3 (0.4)                       | 187.0 (49.0–325.0)                                        | Cured 1 (33.3)                  |
|                  |                                  |                                                          | Improved 1 (33.3)               |
|                  |                                  |                                                          | Unimproved 1 (33.3)             |

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permanent discontinuation. This indicates that most adverse events could be managed through close monitoring and proper correction of contributing factors, thus increasing adherence to MDR-TB therapy. Discontinuation of the offending drug was only performed when necessary.

The higher mortality compared to other research is likely due to the high average age and serious complication of the population in our study. The frequency of death due to other reasons, such as cardiovascular disease, was 36.6% (26/71). Regarding the association between adverse events and poor treatment outcome, Shin et al.[21] drew the opposite conclusion, that patients who experienced adverse reactions and were adherent to MDR-TB therapy may be monitored and followed up more closely by physicians, and thus are more likely to achieve favorable treatment outcomes. This situation was likely caused by the different definition of adverse event and adverse reaction.

Some likely drug events were not observed in this research, probably due to the frequent change of drugs used during the treatment. It generally took a certain amount of time for the adverse events caused by drugs to develop; thus, it is possible that the adverse events occurred after the patient stopped treatment.

### Table 5. Influence of treatment due to adverse events in retrospective study in China.

| Adverse events       | Symptomatic treatment N (%) | Examination N (%) | Hospitalization N (%) | Dosing decrease N (%) | Medication administration change N (%) | Drug substitution N (%) | Drug or treatment discontinuation N (%) | Drugs implicated | Treatment permanent discontinuation N (%) |
|----------------------|-----------------------------|------------------|-----------------------|-----------------------|----------------------------------------|-------------------------|----------------------------------------|-----------------|------------------------------------------|
| Arthralgia (N=507)   | 52 (10.3)                   | 492 (97.0)       | 0                     | 4 (0.8)               | 2 (0.4)                                | 8 (1.6)                 | 2 (0.4)                                | Z, Lfx          | 0                                        |
| Gastrointestinal disorders (N=491) | 271 (55.2)           | 4 (0.8)          | 21 (4.8)              | 18 (3.7)              | 158 (32.2)                            | 99 (20.2)               | 57 (11.6)                             | All             | 39 (7.9)                                 |
| Hypothyroidism (N=148) | 91 (61.5)                | 139 (93.9)      | 2 (4.8)               | 0                     | 0                                      | 5 (3.4)                 | 9 (6.1)                               | Pto, PAS        | 0                                        |
| Dermatological disorders (N=131) | 32 (24.4)                | 44 (33.6)       | 2 (1.4)               | 0                     | 21 (16.0)                             | 19 (14.5)               | 21 (16.0)                             | All             | 0                                        |
| Hematologic disorders (N=115) | 17 (14.8)                | 108 (93.9)      | 2 (1.5)               | 0                     | 0                                      | 0                       | 0                                      | NE              | 0                                        |
| CNS disorders (N=97) | 29 (29.9)                 | 1 (1.0)          | 0                     | 11 (11.3)             | 5 (5.2)                               | 13 (13.4)               | 7 (7.2)                               | All             | 6 (6.2)                                  |
| Hepatotoxicity (N=86) | 83 (96.5)                | 86 (100.0)      | 10 (11.6)             | 9 (10.5)              | 2 (2.3)                               | 7 (8.1)                 | 44 (39.5)                             | All             | 10 (11.6)                                |
| Hypokalemia (N=52)  | 33 (63.5)                  | 47 (90.4)       | 1 (1.9)               | 0                     | 0                                      | 0                       | 0                                      | NE              | 0                                        |
| Ototoxicity (N=44)   | 1 (2.3)                    | 8 (18.2)        | 0                     | 4 (9.1)               | 3 (6.8)                               | 15 (34.1)               | 5 (11.4)                               | Km, Crm         | 2 (4.5)                                  |
| Visual impairment (N=19) | 8 (42.1)                  | 5 (26.3)        | 1 (7.1)               | 1 (5.3)               | 5 (26.3)                              | 3 (15.8)                | 0                                      | E, Pto          | 0                                        |
| Nephrotoxicity (N=14) | 0                        | 3 (21.4)        | 0                     | 0                     | 0                                      | 0                       | 1                                      | Pto, PAS        | 0                                        |
| Peripheral neuropathy (N=8) | 0                         | 1 (12.5)        | 0                     | 0                     | 0                                      | 0                       | 2                                      | Pto, Cs         | 0                                        |
| Psychiatric disorders (N=3) | 1 (33.3)                  | 0 (0.0)         | 0                     | 0                     | 3 (100%)                              | 0                       | Cs                                     | 1 (33.3)        |                                          |
using drugs, which could produce a biased result and show as the null hypothesis in the correlation study. Moreover, the treatments to the subjects in this study were more or less similar, causing an imbalanced sample size of the exposure group versus the non-exposure group and an insufficient total sample size. Therefore, future studies should address these issues by including MDR-TB patients from different hospitals and various projects to diversify regimens and minimize the sample size difference between the exposure group and the non-exposure group.

Some limitations are of our study need to be mentioned. Firstly, reporting bias might exist, as data were obtained retrospectively through chart review, especially for adverse events not defined by laboratory tests, such as gastrointestinal disorders, which might overestimate or underestimate the incidence of adverse events [25]. Secondly, the classification of adverse events in this study was mainly based on the affected systems suggested by experts, not precisely on the Common Terminology Criteria for Adverse Events. Thus, it can be questioned when comparing the incidence of adverse events among similar studies. Third, little information on HIV status was obtained and reported in this cohort, which is an important baseline characteristic [26]. For the establishment of a common data model of MDR-TB, a larger sample size is required because rates for other types of adverse events were relatively lower except for gastrointestinal damage and joint damage. This in turn leads to fewer other adverse events, and the intensity of the association of certain drug events was not calculated or the results were unstable, which might have a negative effect on performing sub-analysis with each regimen. In addition, some important confounding factors might not have been collected in this study. Electronic medical records are designed for daily use in hospital clinical diagnosis and treatment, not for analysis of adverse reactions/events of drugs used, so the records might lack information needed to detect adverse events, and these were likely to result in bias of the study. Although we did not perform relevant sub-analysis based on each drug, our results still suggest the utility of the implemented prospective hospital-based cohort study to construct an MDR-TB common data model with good validity and reliability, to include possible confounding factors in the study of MDR-TB patients, in order to further calculate the correlation strength of drug and adverse events for evaluation of the model. Importantly, because the MDR-TB patients received combination drug treatment (multiple drugs were administered at the same time), which might affect the sub-analysis based on each drug, taking into account the interactions between drugs, follow-up studies can try to calculate the association between different drug combinations and single adverse events. However, the prevalence of HIV in China is relative low, so this research may reflect the real association between adverse events and the treatment of MDR-TB in China.

Adverse events occur commonly during MDR-TB treatment in China, and often result in MDR-TB treatment change. The occurrence of adverse events leads to MDR-TB poor outcome after treatment. Close monitoring with proper management

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### Table 6. Association between drug use and adverse events in retrospective study in China (N=751).

| Adverse events          | Drug | Use, n (%) | Unadjusted HR (95%CI) | P-value | Adjusted HR (95%CI) | P-value |
|-------------------------|------|------------|-----------------------|---------|---------------------|---------|
| Arthralgia              | Z    | 488 (56.8) | 21 (34.4)             | 2.03 (1.31, 3.14) | 0.002 | 2.10 (1.36, 3.26) | 0.001 |
| Arthralgia              | Pto  | 462 (56.4) | 47 (46.5)             | 1.34 (1.00, 1.81) | 0.054 | 1.38 (1.02, 1.87) | 0.038 |
| Gastrointestinal disorders | Z    | 468 (54.4) | 25 (41.0)             | 1.58 (1.05, 2.36) | 0.027 | 1.58 (1.06, 2.37) | 0.025 |
| Gastrointestinal disorders | Lfx  | 467 (54.8) | 26 (38.2)             | 1.52 (1.02, 2.25) | 0.039 | 1.53 (1.02, 2.29) | 0.042 |
| Gastrointestinal disorders | Pto  | 462 (56.4) | 31 (30.7)             | 2.32 (1.61, 3.34) | <0.001 | 2.32 (1.61, 3.34) | <0.001 |
| Gastrointestinal disorders | PAS  | 454 (60.0) | 39 (23.9)             | 3.39 (2.43, 4.72) | <0.001 | 3.34 (2.39, 4.65) | <0.001 |
| Hematologic disorders  | Z    | 129 (15.0) | 2 (3.3)               | 5.19 (1.28, 20.98) | 0.021 | 5.37 (1.33, 21.73) | 0.018 |
| Hematologic disorders  | Pto  | 124 (15.1) | 7 (6.9)               | 2.35 (1.10, 5.04) | 0.028 | 2.38 (1.11, 5.10) | 0.029 |
| Hypokalemia             | Cm   | 20 (10.4)  | 32 (4.4)              | 2.91 (1.83, 4.65) | <0.001 | 2.89 (1.81, 4.61) | 0.001 |
| Central Nervous system disorders | Pto | 92 (10.7) | 5 (5.0)               | 2.44 (0.99, 6.99) | 0.052 | 2.48 (1.01, 6.10) | 0.048 |
should be given to MDR-TB patients to adverse effects after anti-MDR-TB treatment.

Conclusions

Adverse events occur commonly during MDR-TB treatment in China, and often result in MDR-TB treatment change. The occurrence of adverse events leads to MDR-TB poor outcome after treatment. Much importantly, on the basis of the understanding of the significance of adverse effects in MDR-TB treatment, further investigation should be performed emphasizing the occurrence of adverse events in different phases of MDR-TB treatment, and corresponding relationships with comorbidities, advanced age, and HIV infection, all of which should be further studied.

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