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Title: High rates of treatment success in pulmonary multidrug-resistant tuberculosis by individually tailored treatment regimens

Running title: Optimal multidrug-resistant tuberculosis treatment outcomes

Authors: Ioana D. Olaru[1-2], Christoph Lange [1-5], Alexander Indra[6], Liliya Meidlinger[6], Steliana Huhulescu[6], Rudolf Rumetshofer[7]

Affiliations: [1]Division of Clinical Infectious Diseases, Research Center Borstel and [2]German Center for Infection Research, Clinical Tuberculosis Center, Borstel, Germany; [3]International Health / Infectious Diseases, University of Lübeck, Lübeck, Germany; [4]Department of Medicine, Karolinska Institute, Stockholm, Sweden; [5]Department of Internal Medicine, University of Namibia School of Medicine, Windhoek, Namibia; [6] Austrian Agency for Health and Food Safety (AGES), Vienna, Austria; Department of Respiratory and Critical Care Medicine, Otto Wagner Hospital, Vienna, Austria

Address for correspondence: Professor Christoph Lange, Clinical Infectious Diseases, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany; clange@fz-borstel.de; T +49 45371883321, F+49 45371883130

Secondary correspondence: Ioana D. Olaru, Clinical Infectious Diseases, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany; iolaru@fz-borstel.de T: +49 4537 188 0

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AI contributed to the collection and analysis of data, revising the manuscript and approved the final version of the draft for publication.

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## Abstract

Rationale

We evaluated whether treatment outcomes for patients with multidrug-resistant and extensively drug-resistant tuberculosis can be substantially improved, when sufficient resources for personalizing medical care are available.

Objectives

To describe the characteristics and outcomes of patients with pulmonary multidrug-resistant tuberculosis from the Otto Wagner Hospital in Vienna, Austria.

Methods

Retrospective single-centre study at the Otto-Wagner-Hospital, Vienna, Austria. The records of patients with multidrug-resistant tuberculosis were reviewed for epidemiological, clinical, laboratory, treatment and outcome data.

Results

Ninety patients with pulmonary multidrug-resistant tuberculosis were identified. Median age was 30 years (interquartile range 26-37). All patients were of non-Austrian origin and 70 (78%) came from the former Soviet Union States. Thirty-nine (43%) patients had multidrug-resistant tuberculosis, 28 (31%) had additional bacillary resistance to at least one second-line injectable drug, 9 (10%) to a fluoroquinolone, 14 (16%) patients had extensively drug-resistant tuberculosis. In 97.8% (n=88) of patients different drug combinations were used for treatment. Sixty-five (72.2%) patients had a successful treatment outcome, 8 (8.9%) defaulted, 3 (3.3%) died, 8 (8.9%) continued treatment in another country and their outcome was unknown, and 6 (6.7%) were still on therapy. None of the patients experienced treatment failure. Treatment outcome for extensively drug-resistant tuberculosis was similar to that of multidrug-resistant tuberculosis.

Conclusions

High rates of treatment success can be achieved in patients with multidrug-resistant and extensively drug-resistant tuberculosis when individualized tailored treatment regimen can be provided.

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Key words: drug resistance, MDR-TB, outcome, treatment, tuberculosis

## Introduction

Despite Global efforts, tuberculosis (TB) remains a leading cause of morbidity and mortality representing the tenth most common cause of death worldwide (1). Although the incidence of TB has registered a descending trend in recent years, the emergence and increase in multidrug- resistant (MDR) TB incidence is a cause of great concern. According to the World Health Organization (WHO), an estimated 480,000 cases of MDR-TB have occurred in 2013 resulting in 210,000 deaths (2). MDR-TB is defined as bacillary resistance to isoniazid and rifampicin, while extensively drug-resistant (XDR)-TB is defined by additional resistance to at least one second-line injectable drug (amikacin, kanamycin, capreomycin) and at least one fluoroquinolone (3). The WHO recommends that patients with MDR-TB receive prolonged antimicrobial treatment of at least 20 months (4), including a minimum of 4 second-line drugs that are likely to be effective in the therapy plus pyrazinamide. MDR-TB treatment is frequently associated with adverse drug events (5), with high costs (6), and high rates of loss to follow-up and failure (7-11). Additionally, owing to limited possibilities to test for drug-resistance and to optimise regimens in many settings where the global burden of MDR-TB is highest, treatment for MDR-TB is often standardized irrespective of the severity of disease and the resistance pattern of the associated strain.

Poor treatment outcomes were reported in a meta-analysis of over 6700 patients, where MDR-TB treatment success ranged from 64% in patients with MDR-TB and no additional resistance to injectable drugs or fluoroquinolones to 40% in patients with XDR-TB (8). Additionally, according to data from the European Centre for Disease Prevention and Control (ECDC) analysing treatment outcomes, treatment success was registered in only 46% of MDR-TB and only 23.2% of XDR-TB cases

(10). Furthermore, access to MDR-TB treatment is often difficult with only a third of the estimated cases being enrolled on treatment in 2013 (2).

While the European Region of the WHO has the highest proportion of all patients with MDR-TB identified world-wide, the vast majority of these patients live in eastern part of the European Region, especially in countries from the former Soviet Union. Compared to the European Union/ European Economic Area countries, where a total of only 1255 patients with laboratory-confirmed MDR-TB were identified in 2013, there were 33,679 patients with MDR-TB identified in Eastern Europe during the same time period (10). Furthermore, an estimated 100,000 MDR-TB cases occurred in India in China (2).

Poor treatment outcomes that have been reported for MDR-TB may not be applicable when resources for diagnosis and treatment are readily available and MDR-TB management can be optimized. Austria has a low incidence of TB, where only 16 patients with M/XDR-TB were registered in 2013 (12), more than half (57%) of the patients diagnosed with MDR-TB from Austria are treated at the Otto-Wagner Hospital in Vienna. This hospital has a dedicated unit for the treatment of patients with M/XDR-TB, where highly specialized care can be provided under optimal circumstances. In addition to continuous and unrestricted drug-availability as well as rigorous monitoring during the course of therapy (clinical, laboratory, microbiological and radiological), the management of all patients includes regular physiotherapy and psychological counselling sessions supporting treatment adherence and coping with the adverse events of therapy. Considering the large number of patients originating from outside Austria, interpreters are present when required, to assist patients with communication issues. Furthermore social workers form the department of public health as well as an on-site fully-dedicated social worker, provide assistance with the

administrative and insurance-related issues and organize further care after discharge from hospital.

We evaluated treatment outcomes for patients with M/XDR-TB under personalized medical care.

Some of the results of this study have been previously reported in the form of an abstract (13).

## Methods

*Patient population*

Patients with microbiologically-confirmed pulmonary MDR-TB and positive cultures for *M. tuberculosis* from respiratory samples, admitted at the Otto Wagner Hospital, Vienna for treatment between January 2003 and December 2012 were included in the study. Otto Wagner Hospital is a referral center with extensive expertise in the treatment of patients with TB from Austria.

*Data collection*

Patients were identified using the department patient register which included all patients with M/XDR-TB hospitalized at the site. Entries were cross-referenced with the microbiological registries to identify *M. tuberculosis* strains with rifampicin and isoniazid resistance. Patient records were reviewed for epidemiological, clinical, laboratory, treatment and outcome data and information was recorded in an anonymized database which was further analysed.

*Drug susceptibility testing*

Drug susceptibility testing was performed in a specialized laboratory at the Institute for Medical Microbiology and Hygiene, Austrian Agency of Health and Food Safety and confirmed at the National Reference Center for Mycobacteriology, Borstel, Germany, one of the WHO supranational reference laboratory for tuberculosis. All patients included in the study had a positive *Mycobacterium tuberculosis* culture available for drug susceptibility testing.

Susceptibility testing was performed for the following drugs: isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, streptomycin, amikacin, capreomycin, fluoroquinolones, prothionamide, cycloserine, *para*-aminosalicylic acid (PAS), and linezolid.

*Treatment and outcome*

Patients were considered to receive an appropriate MDR-TB treatment-regimen once they received at least 4 drugs in combination therapy that were thought to be effective according to the results of drug susceptibility testing, including a second-line injectable drug for the intensive phase of treatment (14). TB treatment was directly observed during the whole course of therapy. To ascertain the microbiological response to treatment, sputum cultures were collected on a monthly basis during hospitalization and every 1-2 months onwards until the end of therapy. Outcome was ascertained using the revised WHO definitions (3). Patients were considered to have a favourable outcome if they were either cured or had completed the treatment or an unfavourable outcome in the case of default, treatment failure or death.

*Statistical analysis*

Data processing and analysis were performed using SPSS v17.0 (SPSS Inc., Chicago, IL, USA). Mann-Whitney U test was used to test for differences between continuous variables and chi-square test or Fisher's exact test were used for categorical variables. The level of significance was set at $\alpha=0.05$. Multivariate analysis using backward stepwise logistic regression was then used to predict treatment outcome when the p-value from the univariate analysis was <0.20.

*Ethics*

The study was approved by the ethics committee of the city of Vienna (Ethikkommission der Stadt Wien: EK 14-240-VK).

## Results

*Patient characteristics*

A total of 94 patients with M/XDR-TB who were admitted during the study period were identified. Four patients had extrapulmonary M/XDR-TB, and were excluded from the analysis. Median patient age at diagnosis was 30 years (interquartile range (IQR) 26-37). Male to female ratio was 1.5:1. All patients were of non-Austrian origin and came from the Russian Federation (n=55, 61.1%), Georgia (n=11, 12.2%), Romania (n=11, 12.2%) or other countries (13, 14.4%). Fifty of the patients from the Russian Federation were from Chechnya. Seventeen patients were intravenous drug users, and 52 (58%) were active smokers. All patients were tested for HIV infection, but none were HIV-seropositive. The characteristics of the patients included in the study are presented in Table 1.

*Drug susceptibility testing*

Thirty-nine (43%) patients had MDR-TB only, 28 (31%) had additional resistance to at least one second-line injectable drug, 9 (10%) to a fluoroquinolone, while 14 (16%) of patients had XDR-TB. The patients with XDR-TB were originally from Chechnya (n=9), Romania (n=3), Georgia (n=1) and China (n=1). Resistance to at all first-line drugs was recorded in 40 (44%) of patients. The results of the drug susceptibility testing are shown in Figure 1. Of note is that 8 (8.9%) *M. tuberculosis* strains were susceptible to rifabutin.

*Management and treatment outcome*

Median time from hospital admission to the start of an appropriate M/XDR-TB treatment was 23.5 days (IQR 0.8-45).

Eighty-eight different drug combinations were used for the treatment of the 90 patients (97.8%) treatment. The drug regimens according to their composition are represented in Figure 2. The intensive phase contained a median of 5 drugs (IQR 5-6), while in the continuation phase, a median of 3 drugs (IQR 3-4) were used.

Smear conversion occurred after a median 61 days (IQR 22-135) following the initiation of adequate treatment while culture conversion occurred after a median of 62 days (34-112.8 days). Only 3 (3.3%) patients did not experience a culture conversion. Figure 3 shows smear and culture conversion during anti-TB treatment. Culture conversion occurred in 40 (46%) patients within the first 2 months of effective M/XDR-TB therapy, and in 72 (82.8%) patients within 6 months.

The median duration of the intensive phase was 123 days (IQR 82-228) and continuation phase was 494 days (IQR 388-599 days). The overall median duration of therapy was 21 months (IQR 18-24 months); in patients with a favourable

outcome, the median duration of therapy was 23 months (IQR 19-24 months) while in patients who experienced an unfavourable outcome it was 4 months (IQR 3-18 months, p <0.001). One patient defaulted before therapy could be initiated.

The median duration of inpatient stay was 141 days (IQR 96.5-230.3 days) while the median duration of treatment in the out-patient setting was of 15 months (IQR 12-23 months).. Patients with smear positive tuberculosis had a significantly longer hospital stay with a median duration of 191 days (IQR 108.5-243) compared to smear negative patients - median duration 102.5 days (IQR 67.5-134.8, p <0.001). Additionally, the median length of hospital stay was longer in patients with XDR-TB in comparison to patients with non-XDR-TB (335 vs. 128 days, p <0.001).

Surgery was performed in 10 (11.1%) of patients. Of the nine patients with a known outcome, 6/9 (66.7%) had a favourable outcome. For facilitating the administration of parenteral therapy, 48 (53.3%) of patients received a totally implantable central venous access system (port-a-cath).

As shown in Table 2, 65 (72.2%) patients had a favourable treatment outcome (56 fulfilled the criteria for cure and 9 completed treatment), 8 (8.9%) defaulted, 3 (3.3%) died, 8 (8.9%) continued the treatment in their home-country after hospital discharge and their outcome was therefore unknown, and 6 (6.7%) were still on therapy. One of the patients who died had concomitant central nervous system TB. If only the cases with a known outcome are considered, then 85.5% of patients had a successful outcome. Out of 14 patients with XDR-TB, nine (64%) were cured, one (7%) died and four (29%) were still on treatment. None of the patients included in the study experienced treatment failure. Of the seven patients who were treated with bedaquiline, five were still on treatment when the data were analysed, one was transferred to another treatment facility and one died. All patients treated with

bedaquiline, who had a prolonged culture positivity, achieved culture conversion. Of the 14 patients who had received fusidic acid, 13 had a favourable outcome, while one died (p=0.68). In the univariate analysis the duration of therapy (p <0.01), treatment with cycloserine (p <0.01), not receiving treatment with pyrazinamide (p=0.04) and a negative culture status at six months (p=0.04) were associated with a favourable treatment outcome. In the multivariate analysis the duration of therapy (OR 0.66, 95%CI 0.51-0.86; p=0.002) and culture status at 6 months (OR 0.04, 95%CI 0.02-0.70; p=0.03) were associated with a favourable outcome.

*Adverse events*

Gastrointestinal adverse events occurred in 74 (82.2%) patients, polyneuropathy in 48 (53.3%), ototoxicity in 31 (34.4%), psychiatric adverse effects in 44 (48.9%), and liver enzymes were elevated during therapy in 44 (48.9%) of patients. Treatment with linezolid was more frequently associated with polyneuropathy (62.3% versus 34.5%, p=0.023), while ototoxicity was associated with amikacin therapy (52.2% versus 28.4%, p=0.046). Ototoxicity was present in 25% of patients who had received capreomycin versus 42% of patients without capreomycin treatment, p=0.92.

## Discussion

While treatment outcome for patients with M/XDR-TB in Europe are frequently reported to be poor (15), we are able to show that treatment outcomes for pulmonary M/XDR-TB can be substantially improved in a setting where patient management is individualized. By using tailored drug regimen, treatment success rates close to the target proposed by the WHO (13) can be achieved. In this study from a single

referral centre in Austria treatment success rates were over 72%, (and over 85% in patients with a definite outcome) which contrasts with the ECDC data which reports a successful treatment outcome in only 46% of patients from Europe (10). One explanation for this large difference might be the incomplete reporting of treatment outcomes to the ECDC and a larger proportion of lost to follow-up due to migration, as well as an offsetting contribution by countries with a large number of MDR-TB patients and low treatment success rates such as Romania and Lithuania (10). Furthermore, individualized therapy is also likely to have played an important contribution to achieving high rates of treatment success, considering that in this study 88 different drug-combinations were used.

With the advent of two new drugs for the treatment of MDR-TB and XDR-TB, treatment outcomes may improve substantially. As 6 of the 7 patients receiving a bedaquiline based treatment regimen experienced sustained culture conversion it is hoped that treatment outcomes may improve in general in the European region, when these drugs will become universally available. Recently it has been reported, that 28 of 29 (97%) patients with culture-positive pulmonary M/XDR-TB who were treated with a bedaquiline containing regimen, experienced culture conversion at 6 months of treatment (16). Furthermore, the 6 months culture status is a very good approximation for achieving a successful treatment outcome in patients treated for MDR-TB (17).

While analyses of large patient cohorts describe unfavourable outcomes in more than half of patients with MDR-TB, studies from individual countries or specialized centres report significantly higher rates of treatment success. For example, studies on selected patient cohorts from other European countries, describe treatment success rates of 59% in Germany (18), 68% in Belgium (19), 71% in the United

Kingdom (20), 76% in Switzerland (21), and 79% in the Netherlands (22). Interestingly, the overall and MDR-TB treatment success rates in Austria were lower than the ones from this study, of 66% and 65%, respectively, emphasizing the importance of highly- specialized management (10).

All patients with M/XDR-TB in this study are not of Austrian origin. The ECDC TB report also suggests that over half of patients with TB in a lot of the countries of Western Europe are of foreign origin (10). This underscores the importance of migration in the epidemiology of MDR-TB. While in the countries of Western Europe most patients with MDR-TB have access to appropriate treatment, in other countries such as Russia less than half of the estimated 44,000 patients with MDR-TB were enrolled on treatment in 2011 (23), while in Ukraine, a country with a high-burden of MDR-TB due to conflict and population displacement many patients have difficulties in accessing treatment (24). More than half of the patients with M/XDR-TB in this study were from Chechnya. This might be because Austria has the second largest Chechen diaspora in Europe with a large proportion of refugees (25) and in Chechnya about a half of TB cases are MDR (26).

Another factor that contributes to treatment accessibility and success is the cost of MDR-TB therapy. While a full course of MDR-TB treatment costs 70 times more than for pan-susceptible TB, costs for XDR-TB might be as 280-fold higher making it a considerable burden on countries where M/XDR-TB are prevalent (6).

Interestingly, almost a tenth of the *M. tuberculosis* strains isolated were still susceptible to rifabutin. This underscores the importance of drug susceptibility testing for rifabutin, and if susceptible, including it in the therapy regimen which, due to its effectiveness, could potentially lead to a shorter duration of therapy and improved treatment outcomes.

A number of drugs of unclear efficacy against *M. tuberculosis* were used for the treatment of MDR-TB. Fusidic acid, an antibiotic which works via protein synthesis inhibition and active on gram-positive bacteria, was used as part of the drug regimen in almost a fifth of patients in the study. There was a trend showing a higher rate of favourable outcome in patients receiving fusidic acid, but the difference was not significant. *In vitro* studies have shown that fusidic acid has an inhibitory effect on *M. tuberculosis* growth (27, 28). As this drug has not been evaluated in early bactericidal activity studies or in clinical trials fusidic acid should be explored as a repurposed drug for the treatment of MDR-TB.

Over two thirds of patients in this study were treated with linezolid, which has been shown to be effective in patients with M/XDR-TB (18, 29). A recently published meta-analysis on linezolid-containing regimens reported favourable outcomes in 83% of patients treated with linezolid (30), however most of the studies were retrospective and had no control arm. Unfortunately, linezolid therapy is associated with frequent and sometimes severe adverse events requiring treatment discontinuation (30, 31). In the present study, linezolid therapy was also significantly associated with polyneuropathy in over 60% of patients.

The multivariate analysis showed that a longer total duration of therapy, and the status of sputum culture at 6 months were associated with a favourable outcome.

The *M. tuberculosis* strains from the patients included in the study had high rates of additional resistance to anti-tuberculosis drugs other than rifampicin and isoniazid.. Over 44% of strains had resistance to all first-line drugs, 49% had resistance to prothionamide, 46% had resistance to at least one second-line injectable drug and over a quarter had resistance to fluoroquinolones. These findings are in line with other recent observations on the level of bacillary drug resistance of MDR- *M.*

*tuberculosis* in the region (32, 33).This represents higher rates of resistance than that reported in studies using standardized treatment regimens for MDR-TB (34) and suggests that a standardized treatment approach should not be followed in the European Region as patients may be treated with second line antituberculosis drugs that are not effective. Standardized treatment could lead to further acceleration of drug-resistance development. It is important to notice that with an individualize treatment approach high treatment success rates could be achieved despite the "MDR-TB plus" scenario in patients treated for M/XDR-TB in Vienna.

MDR-TB requires a prolonged duration of therapy and is associated with an increased length of hospital stay, frequent and sometimes irreversible adverse events and extremely high costs. Due to the physical and psychological difficulties experienced by patients during the course of treatment, specialized support is of great value. It is very likely that the regular psychological counselling and social support given to the patients from this study, played an important contribution to improve treatment adherence and attain high rates of treatment success in this setting.

Although this study is retrospective and lacks a direct comparison to other management strategies, it provides unique information on a large number of patients with pulmonary M/XDR-TB from a single-centre from a Western European country of a low tuberculosis-incidence.

In conclusion this study shows that high rates of successful treatment outcome can be achieved in patients with M/XDR-TB in Europe when the drug regime is individualized to the results of 2$^{nd}$ line drug susceptibility testing and 2$^{nd}$ line drugs are available for the treatment without restrictions. Additionally, the adequate funding to provide medications, appropriate testing and supportive care, treatment

adherence due to prolonged hospitalization and effective management of adverse events also played an important role in the high rates of treatment success. The results also underscore the importance of a multidisciplinary treatment approach comprising individualized patient care, as well as psychological and social support to improve adherence to therapy and for the early detection and management of treatment-related adverse events (35). With these combined efforts, treatment outcomes for patients with M/XDR-TB can be substantially improved.

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## Tables and figures

**Figure 1**. Spectrum of first- and second line anti-tuberculosis drug-resistance in 90 strains of *M. tuberculosis* from patients with M/XDR-TB at Otto-Wagner Hospital, Vienna (Austria) admitted between 2003 and 2012.

**Figure 2.** Drugs regimens for the treatment of M/XDR-TB.
Regimens are represented according to their composition. In the central square it is shown how many patients received fluoroquinolones, aminoglycosides, both or none. Drugs are added along the lines. The number in the circle represents the number of the patients who go through that particular node. The black point (•) represents the number of patients ending the regimen in that node. AMC amoxicillin clavulanic acid; BDQ bedaquiline; CFZ clofazimine; CLA clarithromycin; CS cycloserine; DDS dapsone; EMB ethambutol; FQ fluoroquinolones; FUS fusidc acid; IMP imipenem; INJ second-line injectable drugs; LZD linezolid; PAS para aminosalicylic acid; PTO prothionamide; PZA pyrazinamide; RFB rifabutin; SXT trimethoprim-sulfamethoxazole.

**Figure 3.** Smear (A) and culture (B) conversion during anti-tuberculosis treatment.
Smear conversion is shown only for patients with a positive smear at treatment initiation.

588 **Table 1**. Characteristics of 90 patients with M/XDR-TB admitted between 2003 and

589 2012 at the Otto-Wagner Hospital, Vienna (Austria)

| Variable | MDR-TB<br>N = 76 | XDR-TB<br>N = 14 | p-value |
|---|---|---|---|
| Male gender, n (%) | 45/76 (59.2) | 9/14 (64.3) | 0.722 |
| Age (years), median (IQR) | 30 (25.3-35.3) | 33.5 (28.8-42.3) | 0.101 |
| Country of birth, n (%)<br>Former Soviet Union<br>Other | <br>60/76 (78.9)<br>16/76 (21.1) | <br>10/14 (71.4)<br>4/14 (28.6) | <br>0.503 |
| Previous TB treatment, n (%) | 38/69 (55.1) | 10/13 (76.9) | 0.142 |
| Cavitary disease, n (%) | 50/76 (65.8) | 12/14 (85.7) | 0.211 |
| Smear positive at diagnosis, n (%) | 50/75 (66.7) | 11/14 (78.6) | 0.535 |
| Resistance to all first-line drugs, n (%) | 31/76 (40.8) | 9/14 (64.3) | 0.104 |
| Resistance to fluoroquinolones, n (%) | 9/75 (12) | 14/14 (100) | NA |
| Resistance to second-line injectable drugs, n (%) | 28/76 (36.8) | 14/14 (100) | NA |
| Number of drugs in the intensive phase, median (IQR) | 5 (5-6) | 6 (6-6.3) | 0.021 |

| | | | |
|---|---|---|---|
| Number of drugs in the continuation phase, median (IQR) | 3 (3-4) | 4 (3-4) | 0.051 |
| Linezolid treatment, n (%) | 49/76 (64.5) | 12/14 (85.7) | 0.177 |
| Bedaquiline treatment, n (%) | 3/76 (3.9) | 4/14 (28.6) | 0.010 |
| Days in hospital, median (IQR) | 128 (89.8-212.5) | 335 (190.5-436.5) | <0.001 |
| Duration of treatment (months), median (IQR) | 19.5 (17.8-24) | 24 (22.3-24.8) | 0.012 |
| Culture conversion, n (%) | 71/65 (95.9) | 14/14 (100) | 1.00 |
| Time to smear conversion (days), median (IQR) | 56.5 (21-119.5) | 128 (56-269.5) | 0.024 |
| Time to culture conversion (days), n (%) | 61 (30.8-96) | 110 (54.8-288.8) | 0.010 |

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592 **Table 2.** Treatment outcomes in patients with M/XDR-TB

| | MDR-TB<br>N = 76 | XDR-TB<br>N = 14 |
|---|---|---|
| Favourable outcome (cured + completed) | 56 (73.7) | 9 (64.3) |
| Cured | 47 (61.8) | 9 (64.3) |
| Completed | 9 (11.8) | 0 (0) |
| Unfavourable outcome (died + failure) | 2 (2.6) | 1 (7.1) |
| Died | 2 (2.6) | 1 (7.1) |
| Failure | 0 (0) | 0 (0) |
| Unknown outcome (default + transferred out) | 16 (21) | 0(0) |
| Default | 8 (10.5) | 0 (0) |
| Transferred out | 8 (10.5) | 0 (0) |
| Still on treatment | 2 (2.6) | 4 (28.6) |

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