Treatment outcomes of MDR-TB patients in Nepal on a levofloxacin containing standardized regimen: retrospective single center study

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ABSTRACT

Background
Multi-drug resistant tuberculosis is a growing threat and poses a major challenge in
global TB control and elimination efforts. Information on demographic and clinical
characteristics along with treatment outcomes data could be useful in evaluating
the performance of available regimens. The aims of this study were to estimate the
treatment success in patients on a levofloxacin containing standard MDR-TB regimen
and to explore the association between various risk factors and treatment outcomes.

Methods
We performed a retrospective chart review of MDR-TB patients receiving a standard
regimen at the German Nepal Tuberculosis Project Clinic (GENETUP), Nepal
between 2014–2016. Data were extracted from the patients’ medical records. De-
scriptive statistics were used to summarize the available clinical, demographic and
diagnostic information. Univariate/multi-variate analyses were performed to study
the association of risk factors with outcome variable.

Results
Out of 113 available patients’ medical records, 87 were included. The median age of
included patients was 29 years (22–40 IQR) and median body weight at the time of
admission was 48 kg (44–58 IQR). The median time to both sputum smear (n=66)
and culture conversion (n=74) was 30 days (30–60 IQR). At day 90 of treatment 58
(87.9 %) patients had negative sputum smear microscopy and 71 (98.6 %) patients were
sputum culture negative. The side effects did not seem to interfere with the treatment
outcomes. We found a high treatment success rate of 95 % for the fully evaluable cohort
(n=83) and 78.21 % for the initial cohort (n=101) including lost to follow-up and
transferred out patients. There was no difference in time to sputum culture conversion
within 100 days of treatment between patients with pre-disposing risk factors and
without, which could be due to the low statistical power and unavailability of patient
information in patients who were lost to follow up and transferred out.

Conclusion
This study showed good treatment outcome after programmatic treatment in combi-
nation with-drug susceptibility testing results (phenotypic and genotypic) of
Nepalese MDR-TB patients on ambulatory care. Incompleteness of follow-up data
makes it difficult to translate results to the total population.
INTRODUCTION

Tuberculosis (TB) is the leading infectious disease caused by Mycobacterium tuberculosis that kills more people than HIV/AIDS every year. In 2017, an estimated 10 million (range 9.0–11.1 million) people developed TB and 1.3 million (range 1.2–1.4 million) died from it. Multi-drug resistant TB (MDR-TB), a form where the infecting strain is resistant to two important first line drugs (isoniazid and rifampicin) have created havoc in TB control and has greatly hampered the TB elimination process. The incidence of MDR-TB is around 3.5 % in new TB cases and 18 % in previously treated TB cases (1).

Later generation fluoroquinolones (levofloxacin and moxifloxacin) are the founding pillars in both standardized (20–24 months duration) and short course 9-month regimens in use for treating MDR-TB (2,3). Moxifloxacin exhibits a two-stage resistance mechanism; compared to levofloxacin (4), it has demonstrated better results in pre-clinical studies; minimal inhibitory concentrations (MIC) are lower, kill rate of M. tuberculosis strains is high, and there is a higher proportion of relapse free cure in animal models. The results of clinical trials in MDR-TB patients however do not mirror the pre-clinical studies. Surprisingly, new results on patients treated with the shorter 9-month regimen suggested that when gatifloxacin was replaced by high dose levofloxacin or moxifloxacin in an optimized background regimen, levofloxacin was able to better prevent the selection of resistant mutants over moxifloxacin (A. van Deun, 49th Union World Conference, 26 October 2018). Moreover, a recent hollow fiber infection model study found that levofloxacin performed better than moxifloxacin in terms of speed of Mtb kill and time to acquired drug resistance (5). In other clinical studies, both levofloxacin and moxifloxacin were found to be equally efficacious based on sputum culture conversion (88.3 % vs 90.5 %) and treatment outcomes (84.4 % vs 79.7 %, P=0.53) (6,7). However, patients in the levofloxacin group had more musculoskeletal adverse events than in the moxifloxacin group (79.2 % vs 63.5 %, P=0.03) (6,7). Levofloxacin- and moxifloxacin containing regimens had similar treatment outcomes in all four published clinical studies (6–9). Moxifloxacin use is associated with QT prolongation. With the recently endorsed oral 20-month MDR-TB regimen that comprises novel drugs
like bedaquiline which is not only highly effective but also cardiotoxic (2,10), QT prolongation by bedaquiline, delamanid and moxifloxacin has become a major concern (11). Therefore, levofloxacin is receiving increasing attention due to its good efficacy and cardiac safety profile in newer combination regimens that are currently being evaluated.

In the light of available evidence, this study aims to explore the link between various risk factors and treatment outcomes in patients under a standardized regimen for MDR-TB treatment, including levofloxacin as a fluoroquinolone. The risk factors we explore include co-morbidities such as diabetes mellitus and HIV; renal and hepatic function; advanced age; low body weight; and adverse events. Therefore, the primary objective of this study was to assess the impact of co-variates (demographic and clinical) in sputum smear/culture conversion and in treatment outcomes of MDR-TB patients. Furthermore, this study aims to explore the eligibility of patients with baseline resistance to more than one first line drug for the shorter 9-month regimen.

**METHODS**

**Study population and study design**
A retrospective chart review was performed for all MDR-TB patients receiving Lfx as part of their standard MDR-TB regimen enrolled for treatment at the German Nepal Tuberculosis Project (GENETUP), National Anti-Tuberculosis Association, Kathmandu, Nepal between April 2014 — December 2016. The study was approved by the Ethical Review Board of Nepal Health Research Council, Kathmandu, Nepal (Reg. No. 283/2018). Being a retrospective study, the need for written informed consent from participants was waived. To protect patients’ privacy, each patient was assigned a unique identification code, which was decoded in a separate document, only accessible to two researchers and the principal investigator.

At that time, the standardized treatment regimen endorsed by the National Tuberculosis Program (NTP), Nepal lasted for 18–24 months and included levofloxacin, kanamycin, ethionamide, cycloserine and pyrazinamide along with additional vitamin B6 supplement (pyridoxine) and gastric acid suppressive drugs (ranitidine or pantoprazole).
All patients with no age and bodyweight restrictions, diagnosed and registered as MDR-TB at GENETUP clinic were eligible if they received levofloxacin, along with other second line drugs in the treatment regimen. Patients with missing records/incomplete information were excluded, those who were shifted to pre-XDR category, patients transferred to other treatment centers, patients lost to follow up were also excluded. In GENETUP clinic, all patients were tested for HIV as a standard procedure.

Demographic and clinical information including age, sex, bodyweight, ethnicity, co-morbidities, previous TB history and treatment with first- or second-line drugs, alcohol consumption, renal function and liver enzyme markers; diagnostic information including baseline sputum smear and sputum culture grading, chest radiography, site of TB infection, susceptibility pattern (DST) to first- and second-line drugs; and primary and secondary treatment outcomes (sputum smear and culture conversion at day 90 with final treatment outcomes at 20–24 months) were extracted from patients’ medical records.

**Culture, DST and clinical variables**

Sputum samples were collected from patients before initiation of treatment and every month until 8 months followed by 10, 12, 16, 18, 20, 22, and 24 months of treatment for smear microscopy and culture on Löwenstein-Jensen (LJ) media. Phenotypic first-line DST was carried out at critical concentrations; isoniazid (0.2 µg/ml), rifampicin (4.0 µg/ml), ethionamide (2 µg/ml), streptomycin (4 µg/ml), levofloxacin (2 µg/ml), kanamycin (30.0 µg/ml) and capreomycin (40.0 µg/ml) from positive cultures in LJ media by indirect proportion method. Growth inhibition on para-nitro benzoic acid (500 µg/ml) and nitrate reduction test were used to differentiate *Mycobacterium tuberculosis* complex from non-tubercular mycobacterium (NTM). The genotypic DST for isoniazid (*katG* and *inhA* gene), rifampicin (*rpoB* gene) were performed from direct sputum samples. For second line drugs, molecular line probe assay (Hain Life Science, GenoType MTBDRsl) was used to identify *Mycobacterium tuberculosis* complex and its resistance pattern to fluoroquinolones (ofloxacin, ciprofloxacin and moxifloxacin: *gyrA* gene), aminoglycosides (kanamycin, capreomycin, amikacin, viomycin: *rrs* gene and eis promoter genes) and ethambutol (*embB* gene).
from positive cultures. To evaluate the safety of the multi-drug regimen, all recorded adverse events and lab test results at three different time periods were retrieved from the medical record.

**Statistical analysis and outcomes**

The association of variables under study to sputum culture conversion within the first 100 days of treatment (yes/no) was performed using univariate analysis. These factors included age, body weight at admission, body weight after 8 months of treatment, body weight below 35 kg, gender, HIV status, co-morbidities, prior anti TB therapy, and presence of cavitary lesions. A p-value <0.05 was considered significant. All statistical analysis were performed in SPSS (version 23.0 for Windows). Categorical data were expressed in frequencies and percentages whereas continuous variables were presented as median and interquartile range or mean and standard deviation or both. Depending on the distribution of continuous variables, non-parametric tests were used for calculation of p-value, where applicable. Chi square or Fisher’s exact test were used for categorical variables, whereas independent sample t-test, Mann-Whitney or Wilcoxon signed rank test were used for continuous variables.

The MDR-TB treatment outcomes are defined based on WHO guidelines adopted by the NTP, Nepal (12). This study utilized Laserson’s recommendations to note the treatment outcomes where deaths included all deaths irrespective of the cause during the course of MDR-TB treatment (13). Successful treatment outcome relates to cure and treatment completion whereas adverse treatment outcome is characterized by failure, death, relapse or loss to follow up. The primary outcome variable was sputum culture conversion within 100 days of treatment.

**RESULTS**

A total of 87 MDR-patients were included in this retrospective chart review (see Figure 1. for the flow chart). Baseline characteristics of these 87 patients are summarized in Table 1. The median age was 29 years (22–40 IQR) and body weight at the time of admission was 48 kg (44–58 IQR). The median bodyweight after eight months of treatment

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increased significantly (p=0.000) to 55 (47–60 IQR). Of the 87 patients, 48 (55.2%) were male. Overall, 6 (6.9%) patients had diabetes mellitus and 3 (3.45%) were HIV positive. Other common co-morbidity was seizure disorder in 4 (4.6%) patients.

Pulmonary TB was the most common diagnosis in 82 (94.3%) patients; 5 (5.8%) had extra-pulmonary TB. The majority of the patients — 77 (88.5%) — had prior anti-TB therapy. Among these retreated patients, 31 (36.0%) had failed on a six-month treatment regimen with first-line drugs and 18 (20.9%) had failed on the eight-month retreatment regimen with first-line drugs including streptomycin. Of the remaining patients, 15 (20.8%) were previously cured, 11 (14.3%) completed the previous TB treatment and in 2 (2.6%) patients, prior treatment outcomes were unknown. Of 87 patients, 66 (75.9%) were positive for sputum microscopy and 21 (24.1%) were negative at the time of admission. Likewise, at baseline, 74 (85.1%) patients were culture positive, 11 (12.6%) were culture negative; in the remaining 2 MDR-TB (2.3%) patients baseline culture data was missing. In the final statistical analysis, only baseline culture positive patients were included. Since 2 of 74 culture positive patients did not have information on 100 days sputum culture conversion, they were further excluded from the analysis.
Patients were treated for a median period of 20 months (20 to 24; min, max) and received 750–1000 mg levofloxacin once daily corresponding to a dose of median 15.63 (13.16–17.00 IQR) mg/kg.

Similarly, other drugs in the regimen included kanamycin at a median dose of 16.67 mg/kg (15.27–17.49 IQR), cycloserine at 11.11 mg/kg (10.42–12.50 IQR) and ethionamide at 11.11 mg/kg (10.42–12.50 IQR).
equivalent to once daily dose of 500–750 mg, and pyrazinamide at 26.67 mg/kg (24.43–27.99 IQR) corresponding 1200–1600 mg once daily dosing.

Side effects of medical treatment in all 87 patients were as follows; 55 (64.8 %) patients had arthralgia; 50 (58.8 %) experienced gastrointestinal symptoms, 20 (23.5 %) reported dizziness/vertigo, 7 (8.2 %) experienced hypothyroidism, and 7 (8.2 %) experienced hearing loss. Central nervous system side effects were reported by 12 (14.1 %) — these consisted of sleep disturbances or minor mood changes, 4 (4.7 %) had depression, 3 (3.5 %) had psychosis and 1 (1.2 %) had suicidal thoughts. Alopecia was reported by 1 (1.2 %) patient.

Primary and secondary treatment outcomes
The median time to both sputum smear (n=66) and culture conversion (n=74) was 30 days (30–60 IQR). At 90 days of treatment (n=66), 58 (87.9 %) patients had negative sputum smear microscopy and 71 (98.6 %) patients (n=72) were sputum culture negative. Regarding treatment outcomes (n=87), 69 (79.3 %) patients were cured, 10 (11.5 %) completed the treatment, 4 (4.6 %) were still on treatment, 1 (1.2 %) was lost-to follow up, and 3 (3.5 %) died. Among three deaths, one died because of TB, one committed suicide, and one died at an intensive care unit due to other complications. After exclusion of four patients who were still on treatment, the successful outcome rate for fully evaluable cohort (n=83) was 95 % in our study. Moreover, based on standards proposed by Laserson et al., the successful outcome rate for the initial MDR-TB cohort (n=101) including those that moved out or were lost to follow up was 78 %.

The lab test results at three different time-periods in MDR-TB patients are summarized in Table 2. The majority of patients had hyperuricemia (male: 30/38 at baseline, 35/41 at 3 months and 33/42 at 5–8 months; female: 18/33 at baseline, 24/32 at 3 months and 27/32 at 5–8 months). One patient had baseline hypokalaemia; hyponatremia was found in 1 other patient at baseline, 5 patients at 3 months and 1 patient at 5–8 months. None of the patients had hyperkalaemia. All patients had normal creatinine level at baseline, however, 1 patient had increased creatinine levels beyond normal at 3 and 5–8 months of treatment. Based on ALT, AST, and bilirubin levels none of the patients had to
## Table 2: Hepatic enzymes and renal function tests in MDR-TB patients

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Normal Reference level</th>
<th>At baseline</th>
<th>3 months</th>
<th>5–8 months</th>
<th>p-value (baseline and 3 months)</th>
<th>p-value (baseline and 5 to 8 months)</th>
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<tbody>
<tr>
<td><strong>HEPATIC ENZYMES</strong></td>
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<tr>
<td>Alanine amino transferase</td>
<td>5.0–40.0</td>
<td>17.0 (12.0–23.5) (n=84)</td>
<td>12.0 (9.0–18.5) (n=77)</td>
<td>15.0 (10.0–22.3) (n=50)</td>
<td>0.004*</td>
<td>0.302*</td>
</tr>
<tr>
<td>(ALT), IU/L</td>
<td></td>
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<tr>
<td>Aspartate transaminase</td>
<td>5.0–37.0</td>
<td>26.0 (18.0–38.0) (n=84)</td>
<td>27.0 (20.0–36.0) (n=77)</td>
<td>30.0 (21.0–42.0) (n=50)</td>
<td>0.516*</td>
<td>0.445*</td>
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<tr>
<td>(AST), IU/L</td>
<td></td>
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<tr>
<td>Alkaline phosphatase,</td>
<td>65.0–305.0</td>
<td>180.0 (143.0–215.0) (n=83)</td>
<td>171.0 (136.0–212.0) (n=77)</td>
<td>179.5 (150.0–242.0) (n=47)</td>
<td>0.211*</td>
<td>0.488*</td>
</tr>
<tr>
<td>IU/L</td>
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<tr>
<td>Bilirubin total, µmol/L</td>
<td>6.8–17.1</td>
<td>10.3 (8.6–11.9) (n=84)</td>
<td>10.3 (8.6–11.9) (n=77)</td>
<td>10.3 (8.6–11.9) (n=49)</td>
<td>0.694*</td>
<td>0.735*</td>
</tr>
<tr>
<td>Bilirubin conjugated, µmol/L</td>
<td>0.2–6.8</td>
<td>5.1 (3.4–5.1) (n=80)</td>
<td>5.1 (3.4–5.1) (n=74)</td>
<td>5.1 (3.4–5.1) (n=46)</td>
<td>0.868*</td>
<td>0.364*</td>
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<tr>
<td><strong>RENAI MARKERS</strong></td>
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<tr>
<td>Creatinine, µmol/L</td>
<td>Males n&lt;124</td>
<td>53.0–123.8</td>
<td>70.7 (61.8–79.5) (n=86)</td>
<td>70.7 (61.8–79.5) (n=85)</td>
<td>79.6 (61.8–88.4) (n=82)</td>
<td>0.011#</td>
</tr>
<tr>
<td></td>
<td>Females n&lt;107</td>
<td>44.2–106.8</td>
<td>4.1 (3.8–4.4) (n=86)</td>
<td>4.0 (3.8–4.4) (n=84)</td>
<td>4.2 (3.9–4.5) (n=85)</td>
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<tr>
<td>Potassium, mmol/L</td>
<td>3.5–5</td>
<td>4.1 (3.8–4.4) (n=86)</td>
<td>4.0 (3.8–4.4) (n=84)</td>
<td>4.2 (3.9–4.5) (n=85)</td>
<td>0.760#</td>
<td>0.324#</td>
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<tr>
<td>RENAL MARKERS</td>
<td>Normal Reference level</td>
<td>At baseline</td>
<td>3 months</td>
<td>5–8 months</td>
<td>p-value (baseline and 3 months)</td>
<td>p-value (baseline and 5 to 8 months)</td>
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<tr>
<td><strong>Sodium, mmol/L</strong></td>
<td>135–146</td>
<td>143.0 (140.0–144.5) (n=85)</td>
<td>144.0 (141.0–145.0) (n=84)</td>
<td>144.0 (141.0–145.0) (n=85)</td>
<td>0.006*</td>
<td>0.130*</td>
</tr>
<tr>
<td><strong>Urea, mmol/L</strong></td>
<td>3.6–16.0</td>
<td>6.24 (5.4–8.2) (n=83)</td>
<td>7.49 (5.7–10.4) (n=85)</td>
<td>6.78 (5.7–9.3) (n=82)</td>
<td>0.005*</td>
<td>0.125*</td>
</tr>
<tr>
<td><strong>Uric acid, mmol/L</strong></td>
<td>M: n&lt;0.42</td>
<td>0.41 (0.33–0.53) (n=78)</td>
<td>0.48 (0.41–0.59) (n=78)</td>
<td>0.51 (0.39–0.59) (n=80)</td>
<td>0.006#</td>
<td>0.011#</td>
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<tr>
<td>F: n&lt;0.35</td>
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#= paired t-test; *= wilcoxon signed-rank test. Data are presented as median (IQR) for all continuous variables. Renal function was defined based on creatinine level. Creatinine level = 132–194 µmol/L was considered impaired and >203 µmol/L was considered severely impaired; Hyponatremia = serum sodium below 135 mmol/L, severe hyponatremia was less than 115 mmol/L; Hypokalemia = potassium less than 3.5 mmol/L; hyperkalemia = potassium levels higher than 6 mmol/L. Hyperuricemia = levels above the upper limit of normal for both males and females.
temporarily or permanently interrupt the treatment due to hepatotoxicity. The levels of ALT did not escalate more than 3–5 times the upper limit of normal (14). The use of levofloxacin is associated with disabling and permanent side effects involving muscles, joints, tendons, peripheral nerves and central nervous system and retains warnings from FDA and EMA (15,16). In this cohort, 55 (65 %) patients reported complaints recorded as arthralgia. This particular side effect could be associated with levofloxacin use. The central nervous system and psychiatric adverse reactions could be attributed to both levofloxacin and cycloserine. Overall, patients tolerated the regimen well and reported side effects did not interfere with the treatment outcome results.

Furthermore, we evaluated the proportion of patients with available DST results on first- and second-line drugs for their potential eligibility in a shorter 9-month MDR-TB regimen. The results from both phenotypic and genotypic testing revealed that 52 % of the MDR-TB patients (n=74) had resistance to ethambutol and all were resistant to isoniazid (n=24 and n=9).

In a univariate analysis, none of the variables (age, body weight at admission, body weight after 8 months of treatment, body weight below 35 kg, gender, HIV status, co-morbidities, prior anti TB therapy and presence of cavitary lesions) significantly influenced time to sputum culture conversion within 100 days of treatment.

**DISCUSSION**

This study evaluated the performance of a levofloxacin containing standardized MDR-TB regimen in the referral clinic of Nepal. In a previous study by Malla and colleagues, 70 % of the MDR-TB out-patients were reported to be cured on a regimen containing ofloxacin. The other study by Kakchapati et al. evaluated factors associated with MDR-TB treatment outcomes (17). However, no such studies have been performed after replacement of ofloxacin by levofloxacin in Nepal.

We found a high treatment success rate of 95 % for the fully evaluable cohort (n=83), and 78.21 % for the initial cohort (n=101) including lost to follow-up and transferred out patients. This result should be interpreted with caution. First, in our database we excluded patients
who were classified as pre-XDR, based on results from genotypic susceptibility testing early on, were also excluded because they were put on a different regimen containing moxifloxacin and not levofloxacin. Second, our study is a single center study. Only patients managed in the GENETUP clinic in Katmandu were studied. This center in the capital of Nepal is well equipped with molecular and phenotypic DST. In this center, the treatment success rates for MDR-TB cases were 69.2% in 2016 and 79.7% in 2017. In relation to drug exposure, 30% of the patients at GENETUP clinic who were enrolled for a prospective pharmacokinetic study between 2016–2017, did not meet the established levofloxacin target for efficacy on once daily 750–1000 mg dosing (18). A study in Brazil found a treatment success rate of 60% in a large MDR-TB cohort. The use of levofloxacin was associated with 1.7-fold higher chance of successful outcome compared to ofloxacin (19).

Treatment success rate is a potentially biased outcome parameter; our primary efficacy end point to estimate the usefulness of LFX was time to sputum culture conversion within 100 days of treatment, even though treatment outcome data were available for all patients until 20–24 months after start of treatment. There was a trend for improved weight gain among patients who were sputum culture converted within 100 days of treatment compared to those who were not converted. Similarly, age was lower in the culture conversion group. Advanced age (>65 years) is known to be negatively associated with culture conversion. Since only 1 patient in our cohort was 71 years, we could not investigate this effect. Furthermore, we could not estimate the risk posed by co-morbidities on the outcome variable for two reasons. First, for both diabetes mellitus and HIV, sample size was less than 10 for this sub-group analysis. Second, sputum culture conversion within 100 days of treatment was as high as 95.8%. With this high conversion rate, the potential negative effect of pre-disposing variables could not be detected.

Regarding eligibility of patients for the shorter 9-month MDR-TB regimen, based on WHO guidelines released on May 2016 (20), it is unclear if patients with resistant strains to ethambutol would qualify (21). Van Deun and colleagues have argued that the standardized 9-month regimen was designed for low-resource settings where gatifloxacin and kanamycin were crucial in achieving sputum conversion,
and clofazimine, gatifloxacin and pyrazinamide contributed to shortening of the treatment duration. Ethambutol and isoniazid in combination with prothionamide played only supportive roles, therefore, full susceptibility to these drugs was not of paramount importance while qualifying patients for a shorter regimen (22). Furthermore, the routine drug resistance survey in Nepal showed a higher proportion of resistance to second line drugs, with resistance to fluoroquinolones alone at 39.3% among MDR-TB patients (12). This implies that 40% of the MDR-TB patients might require pre-XDR TB treatment. Since January 2018, the NTP of Nepal has endorsed the 9-month shorter regimen for the treatment of MDR-TB replacing gatifloxacin with weight band moxifloxacin dosing (600 mg or 800 mg) in all TB treatment centers, with the support of the Damien Foundation. The treatment outcome results from the shorter 9-month regimen in a high-incidence, high-fluoroquinolones resistant setting like Nepal will be communicated to the TB community when available.

This study has several limitations. First, being a retrospective study with a small sample size, the generalizability is limited. Second, the data presented in this study does not represent the nationwide sampling but only that of GENETUP referral clinic of Nepal. Furthermore, lack of difference in treatment outcomes between pre-disposing risk-factors and non-risk factors groups could be due to the lower statistical power and high proportion of cure and completion rates compared to lost-to-follow up, death and relapse, due to unavailability of patient information in the latter group. Pooling individual patient data from several treatment outcome studies as has been done by the Canadian team led by Menzies, would likely improve the statistical power for future studies to detect a difference in the response (23). It is also imperative to have a standardized data collection strategy for wider generalization of results.

Nevertheless, our study has two major strengths. First, availability of complete treatment outcome data along with all significant clinical variables and drug susceptibility testing results (phenotypic and genotypic) makes it relevant and provides a data-rich description of MDR-TB patients treated in an out-patient setting.

In conclusion, there was no difference in time to sputum culture conversion within 100 days of treatment and cure rates between patients with pre-disposing risk factors and those without. For future studies,
it is important to ensure the availability of comparable data for both treatment success and failure category. In addition, our findings cannot be generalized. Studies including data from all patients in the NTP enrolled in all MDR-TB treatment centers is crucial.

REFERENCES


(11) Guglielmetti L, Tiberi S, Burman M, Kunst H, Wejse C, Togonidze T, et al. QT prolongation and cardiac toxicity of new tuberculosis drugs in Europe:


