Time to initiation of multidrug-resistant tuberculosis treatment and its relation with outcome in a high incidence district in Lima, Peru

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Abstract

OBJECTIVE To determine the time from diagnosis to start of multidrug resistant tuberculosis (MDR TB) treatment in Lima, Peru.

METHODS We studied new smear-positive TB adults that were started on MDR TB treatment or that were switched to it between June 2008 and December 2011.

RESULTS Time from the first positive smear to MDR-TB treatment was >30 days in 35% (13/37) of patients. Among the 27% (24/88) of patients that switched to MDR-TB treatment, time from the last dose of a drug-susceptible regimen was >30 days.

CONCLUSION Start of and switching to MDR TB treatment is still delayed.

Keywords tuberculosis, multidrug resistant, time to treatment, Peru

Introduction

Prompt start of treatment for multidrug-resistant tuberculosis (MDR-TB) is essential to achieve cure and to reduce transmission. The diagnostic delay attributable to the long turnaround time of conventional culture and drug susceptibility testing (DST) can now be overcome with molecular tests that diagnose MDR-TB in 90 min (WHO 2013). However, to entail clinical and public health impact, diagnosis must be followed by rapid initiation of the appropriate treatment, adherence to it and completion (Davis et al. 2012; Pai et al. 2012).

Multidrug-resistant tuberculosis treatment is complex because of its length and rate of adverse events. Cure rates are lower than those of drug-sensitive TB (Orenstein et al. 2009). MDR-TB treatment can be individualised to a patient’s DST or standardised to DST patterns based on national surveys. In Peru, the progressive strengthening of MDR-TB management by the National TB programme (NTP) and Reference Laboratory (NRL) included the scaling up of faster DST and the decentralisation of MDR-TB care (Yagui et al. 2006; Shin et al. 2008). We determined the time span between TB diagnosis and initiation of MDR-TB treatment in Lima, Peru, to identify possible delays.

Methods

Study setting

The study district’s annual incidence for all TB forms is 95 per 100,000 inhabitants, and 8% of new patients have MDR-TB (Ministerio de Salud 2010). The Ministry of Health provides free TB care in 34 facilities under directly observed therapy. The NTP establishes predetermined criteria to identify MDR-TB suspects: previous TB treatment, immunosuppression, exposure to prisons or health facilities, contact with an MDR-TB case or of a TB case that failed treatment or died, and persistent positive smears during treatment. In addition, the health facility staff may consider that a patient is at risk of MDR-TB in the absence of one of the NTP pre-established criteria.

At the study district, apart from the Löwenstein-Jensen proportion method, a rapid nitrate-reductase colorimetric assay is performed since 2007. It is a low-cost DST method that uses conventional materials and when carried out on a smear-positive sputum sample, results are available in 21–28 days.

In parallel, the chest physician performs a clinical evaluation and requests complementary laboratory tests. An
expert committee that meets periodically evaluates the patient’s files to design the individualised regimen. If neither the patient nor a close contact has a DST, a standardised regimen is started. This standardised regimen is constructed on the basis of national drug susceptibility surveys.

Study design
We retrospectively studied new smear-positive pulmonary TB adults diagnosed in the district between June 2008 and December 2011 that received a MDR-TB treatment: those who were started on it were defined as ‘starters’ and those who were switched to it after starting a standard regimen for drug susceptible were defined as ‘switchers’. We reviewed clinical files and patient’s records for the treatment start and end dates as well as the regimens used.

Statistical analysis
For ‘starters’, we calculated the time from the first smear-positive result to the first MDR-TB treatment dose. For ‘switchers’, we calculated the time from the first smear-positive result to the first dose of the drug-susceptible regimen and the time elapsed between the last dose of it and the first dose of MDR-TB treatment. Times to start on and switch to MDR-TB treatment were tested against treatment outcomes which we classified as favourable (cure or treatment completion) and adverse (death, default, failure or transfer out).

Ethical considerations
The Institutional Review Board at Universidad Peruana Cayetano Heredia and at Antwerp University approved this study.

Results
During the study period, 127 patients were treated for MDR-TB: 37 (29%) ‘starters’ and 90 (71%) ‘switchers’. At least one NTP pre-established criterion to request a DST was registered in 30 (81%) ‘starters’, but also in 31 (34%) ‘switchers’. The date when the treatment was changed was not available for two ‘switchers’, and they were excluded from the analysis. Median times to initiation and switching of treatment are shown in Table 1. MDR treatment was initiated after more than 30 days in 35% (13/37) of ‘starters’. Among ‘switchers’, the time between treatment regimes was 1 day in 18% (16/88) of patients, 1–7 days in 26% (23/88) of patients, 1–4 weeks in 30% (26/88) and over 1 month in 26% (23/88) of patients. No treatment outcome was available for 5.5% (7/127): four were still on treatment and three had missing information. Among the remaining 120 patients, a favourable outcome was present in 26 (77%) ‘starters’ and in 55 (64%) ‘switchers’; eight (24%) of the ‘starters’ and 31 (36%) of the ‘switchers’ had an adverse outcome (RR 1.2 (95% CI 0.9–1.5). Overall, 23 (19%) patients defaulted. Median time to MDR-TB treatment initiation among ‘starters’ was similar in those with an adverse outcome, 25 [interquartile range (IQR), 18–30] days and, in those with a favourable outcome, 26 (IQR, 18–41) days ($P = 0.6$). Among ‘switchers’, the time to switch was 11.5 (IQR, 2–35) days in those with a favourable outcome and 22 (IQR, 2–48) days in those with an adverse outcome ($P = 0.1$).

Discussion
In our study, initiation of MDR-TB treatment took more than one month in 35% of the ‘starters’. Likewise, among ‘switchers’, the period in between regimens was generally long. We did not have sufficient power to

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<tr>
<th>Table 1</th>
<th>Time to initiation and switch of treatment regimens</th>
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<tr>
<td></td>
<td>Time in days</td>
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<td>N</td>
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<tr>
<td>Patients starting on MDR-TB treatment</td>
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<tr>
<td>Between first positive smear and MDR-TB treatment</td>
<td>37</td>
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<tr>
<td>Patients starting on DS-TB treatment</td>
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<tr>
<td>Between first positive smear and DS-TB treatment</td>
<td>90</td>
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<td>On DS-TB treatment</td>
<td>88</td>
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<td>Between last dose of DS-TB and first dose of MDR-TB treatment</td>
<td>88</td>
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MDR-TB, multidrug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis.
demonstrate an impact of time to treatment initiation on outcomes.

The reduction in diagnostic delay achieved by tools, such as the nitrate-reductase colorimetric assay and even more so with molecular assays, has apparently not been echoed by a sufficient reduction in treatment delay. For instance, in two recent South African studies conducted under routine conditions, genotype MTBDRplus reduced the laboratory processing time but not the time to notification of the results; median time between sputum collection and MDR-TB treatment was 55 and 62 days (Hanrahan et al. 2012; Jacobson et al. 2013). Also in South Africa, 85% of patients from a paediatric cohort had a median time of 100 days between MDR-TB diagnosis with GeneXpert MTB/RIF and treatment initiation (Theron et al. 2014). Compared to the studies above that used molecular methods, we found a much shorter but still considerable time to MDR-TB treatment initiation. The reduction in the delay may be a result of the NTP and NRL efforts in recent years to improve MDR-TB management such as decentralising laboratory infrastructure and decreasing bureaucracy between first line health services and expert committees that design individualised treatment regimens. Despite these efforts, treatment delay has been reduced but not to a negligible length. The 30-day delay in 35% of ‘starters’ is partly due to the time required for the periodically meeting expert committees to decide on the regimen for the treatment becoming available at the health facility. Also, patients have to undergo baseline laboratory tests and medical consultations before MDR-TB treatment is started. The NTP has made these evaluations free of cost for patients, but scheduling of appointments can still take a few days.

Reductions of the delay of MDR-TB diagnostic obtained with rapid DST will translate into swift treatment initiation if the steps that follow MDR status ascertainment are concurrently addressed. The evaluation of the patient before MDR-TB treatment initiation, the decision on and prescription of the regimen, the availability of the drugs, to name but a few, depend on multiple persons and components of a health system. Setting up efficient organisational flows managed by trained staff equipped with the resources required could enhance the impact of the introduction of new diagnostic tools and improved MDR-TB treatment regimens (Clouse et al. 2012; Pai et al. 2012).

In recent studies, implementation of molecular tests did not reduce TB morbidity and mortality (Hanrahan et al. 2012; Theron et al. 2014). A delayed start or switch to MDR-TB treatment could be playing a role in individual treatment outcomes. In addition, provider delay weakens the messages to patients on the importance of adherence to achieve bacteriological clearance and to avoid acquisition or amplification of resistance.

When this study was concluded, the NTP had issued new guidelines recommending universal DST with rapid, including molecular, tests. This constitutes an opportunity to further reduce delays in all patients and should reinforce MDR-TB management. We found that in an urban district, where faster diagnostic tests for MDR-TB were already implemented, start of and switching to MDR-TB treatment were still delayed. This study emphasises that implementation of improved technologies needs simultaneous implementation of strategies to speed up treatment initiation.

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**References**


L. Otero et al.  **MDR TB treatment initiation**


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