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Time to initiation of multidrug resistant tuberculosis treatment in a high incidence district in Lima, Peru

L Otero[1,3], **A De Orbegoso**[1], **AF Navarro**[1], **J Ríos**[2], **T Párraga**[1], **E Gotuzzo**[1], **C Seas**[1], and **P Van der Stuyft**[3,4]

[1]Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru

[2]Dirección de Salud Lima Sur, Ministerio de Salud, Lima, Peru

[3]Unit of General Epidemiology and Disease Control, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium

[4]Department of Public Health, Ghent University, Belgium

Abstract

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

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 minutes (WHO, 2013). However, to entail clinical and public health impact it is necessary that diagnosis is followed by a rapid initiation of the appropriate treatment, adherence to it and completion (Pai *et al.* 2012; Davis *et al.* 2012).

MDR-TB treatment is complex. It takes 18 months or more, has a higher rate of adverse events and is less effective than treatment for drug susceptible TB. The average proportion that gets cured is 62% and 12% default treatment (Orenstein *et al.* 2009). In many settings, an expert committee designs and prescribe individual MDR-TB regimen. Regimens can be individualized to a patient's DST or standardized to DST patterns based on national surveys. The complexities of the former could reduce its higher individual effectiveness.

Correspondence: Larissa Otero, Universidad Peruana Cayetano Heredia, Av. Honorio Delgado 430, San Martín de Porres, Lima 31, Larissa.otero@upch.pe.

The progressive strengthening of MDR-TB management by the National TB program (NTP) and Reference Laboratory (NRL) included the scaling up of faster DST and the decentralization of MDR-TB care (Shin *et al.* 2008; Yagui *et al.* 2006). We studied the time elapsed from TB diagnosis to the initiation of MDR-TB treatment in Lima, Peru to determine 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. Following NTP guidelines, MDR-TB is suspected among those previously treated for TB, immunosuppressed, exposed to prisons or health facilities, contacts of an MDR-TB case or of a TB case that failed treatment or died, and among patients with persistent positive smears during treatment. Apart from the Löwenstein-Jensen proportion method, a rapid nitrate-reductase colorimetric assay is performed since 2007. In parallel, a chest physician performs a clinical evaluation and requests complementary laboratory tests. The patient's files are then evaluated by a committee that meets periodically to design the individualized regimen. If neither the patient nor a close contact has a DST, a standardized regimen is started. This standardized regimen is constructed on the basis of national drug susceptibility surveys.

Study design

We studied new smear-positive pulmonary TB adults diagnosed in the district between June 2008 and December 2011 and 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 favorable (cure or treatment completion) and adverse (death, default, failure or transfer out).

Ethical considerations

The Ethics Committee 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 criterion to request a DST was present in 30 (81%)

"starters", but also in 31 (34%) "switchers". The date when the treatment was changed was not available in two "switchers" and they were excluded from the analysis. Median times to initiation and switching of treatment are shown in the table. MDR treatment was initiated more than 30 days in 35% (13/37) of "starters". Among "switchers", the time in-between treatments was one day in 18% (16/88) of patients, one to seven days in 26% (23/88) of patients, one to four weeks in 30% (26/88) and over one month in 26% (23/88) of patients. No treatment outcome was available for 5.5% (7/127) patients: four were still on treatment and three had missing information. Among the remaining 120 patients, a favorable 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), 18.5–30) days and, in those with a favorable 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 favorable 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 demonstrate an impact of time to treatment initiation on outcomes.

The consistent reduction in diagnostic delay achieved by rapid tools, in particular 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 MTBDR*plus* reduced the laboratory processing time but not the time between notification of the results; median time between sputum collection and MDR-TB treatment was 55 and 62 days (Jacobson, *et al.* 2013; Hanrahan *et al.* 2012). 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.* 2013). Compared to the studies above, we found a much shorter but still considerable time to MDR-TB treatment initiation, probably as a result of the NTP and NRL efforts in recent years to improve MDR-TB management.

Reductions of the delay of MDR-TB diagnostic obtained with rapid DST will not lead to sufficiently short times to treatment initiation if the steps that follow MDR status ascertainment are not 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 organizational flows managed by trained staff 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.* 2013). A delayed starting or switching to

MDR-TB treatment could be playing a role on 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.

Since this study was concluded, the NTP has 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. However, 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 was still delayed. This study emphasizes that implementation of improved technologies needs simultaneous implementation of strategies to speed up treatment initiation.

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Table

Time to initiation and switching of treatment regimens

	Time in days				
	N	**Median**	**25th–75th percentile**	**Min**	**Max**
Patients starting on MDR-TB treatment					
Between first positive smear and MDR-TB treatment	37	25	16–41	3	81
Patients starting on DS-TB treatment					
Between first positive smear and DS-TB treatment	90	4	2–7	−5	28
On DS-TB treatment	88	105	60–157	14	238
Between last dose of DS-TB and first dose of MDR-TB treatment	88	11.5	2.5–35.5	1	124

Abbreviations: MDR-TB: multidrug resistant tuberculosis, DS-TB: drug susceptible tuberculosis.

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