Retreatment management strategies when first-line tuberculosis therapy fails

J. C. Saravia,* S. C. Appleton,† M. L. Rich,‡ M. Sarria,* J. Bayona,†‡§ M. C. Becerra†‡§

* National Tuberculosis Control Program, Dirección de Salud III Lima Norte, Lima, † Socios En Salud Sucursal Peru/Partners in Health, Lima, Peru; ‡ Department of Social Medicine, Harvard Medical School, Boston, § Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital, Boston, Massachusetts, USA

SUMMARY

SETTING: Public ambulatory centers in northern Lima, Peru.

OBJECTIVE: To compare two retreatment strategies in Category I failures.

DESIGN: Retrospective cohort study of Category I failures enrolled between February 1997 and October 2001. Strategy A was a nationwide approach, applying a Category II regimen; if that regimen failed, a standardized regimen including second-line drugs was used. Strategy B was a pilot protocol designed to diagnose and treat multidrug-resistant tuberculosis (MDR-TB); this strategy included drug susceptibility testing (DST) and eliminated the Category II regimen.

RESULTS: Of 125 patients that Category I failed to cure, 73 entered Strategy A and 52 entered Strategy B. Almost 90% of those with DST results had MDR-TB. Strategy B was three times more likely than Strategy A to cure patients (79% vs. 38%, RR = 2.9, 95%CI 1.7–5.1) and five times more likely to cure patients than the Category II regimen alone (79% vs. 15%, RR 5.2, 95%CI 3.0–9.2). Strategy B also significantly reduced delays to MDR-TB diagnosis and to the initiation of MDR-TB therapy.

CONCLUSIONS: Under program conditions, a retreatment strategy based on DST and eliminating the Category II regimen can improve clinical outcomes among Category I treatment failures found to have active, infectious MDR-TB.

KEY WORDS: treatment failure; Category I regimen; multidrug-resistant tuberculosis; Category II; DOTS-Plus

EACH YEAR, 9 million people are diagnosed with tuberculosis (TB) disease, 95% of whom live in developing countries.1 In Peru, more than half of all TB cases are detected in Lima, the capital, as are over 80% of all multidrug-resistant tuberculosis (MDR-TB) cases—patients with Mycobacterium tuberculosis strains resistant to at least isoniazid (H, INH) and rifampin (R, RMP). Since 1990, Peru has implemented a model program that follows the DOTS strategy.2 A first-line (Category I) regimen used nationally cures over 90% of new patients presenting with smear-positive TB, and fails to cure fewer than 2%.3 This highly successful regimen is strictly supervised, and consists of 2 months of INH, RMP, ethambutol (E, EMB), and pyrazinamide (Z, PZA) administered daily, followed by 4 months of INH and RMP administered twice weekly (2HREZ/4H2R2).

Until 2001, previously treated patients in whom the Category I regimen failed were assigned a standardized short-course retreatment regimen (Category II) (Table 1).4 The effectiveness of Category II for Category I failures has been questioned.5 The 2003 World Health Organization (WHO) treatment guidelines indicate that alternatives to Category II are needed for Category I failures.6 Category II regimens are particularly problematic in the setting of a good DOTS program like those in Peru and Vietnam, where most Category I failures have MDR-TB.7–9 In such settings, no reports exist of effective, alternative retreatment strategies for Category I treatment failures.

Most countries do not currently have the resources required to conduct drug susceptibility testing (DST) on all newly enrolled patients. For many countries the first priority is to invest in building and sustaining a strong DOTS program. In areas where good DOTS programs have been established but MDR-TB mutants are already prevalent, however, what will be needed is an approach that efficiently identifies patients highly likely to have MDR-TB and appropriately triages them into effective MDR-TB therapy. Such an approach should aim to reduce the interval of infectiousness and improve cure rates in MDR-TB patients.

We sought to compare the effectiveness of a pilot
protocol with the routine retreatment strategy applied to Category I failures. Both of these strategies were applied under program conditions, and all regimens were strictly supervised.

MATERIALS AND METHODS

Study setting
The Ministry of Health (MOH) jurisdiction, the Servicios Básicos de Salud de Comas (SBS Comas), comprises 42 ambulatory public health centers in three contiguous districts of northern Lima (Carabayllo, Comas and Independencia). This region has a population of approximately 820,000. In 2000, the notification rate of pulmonary TB cases based on passive case finding was over 200 per 100,000 population.

Patient population
We reviewed the clinical records of all patients enrolled in the Category I regimen (2HREZ/4H3R3) between February 1997 and October 2001. These patients had never been treated for tuberculosis disease. According to program guidelines, treatment failure with Category I was defined as persistent smear positivity in a patient after the fourth month of directly supervised therapy, or two consecutive persistent positive smears, confirmed by culture, after two consecutive negative smears. We abstracted data from the charts of all those patients classified as treatment failures with Category I. Only patients who initiated retreatment before 30 April 2002 were included.

Two retreatment strategies
The two strategies were applied to patients in whom Category I failed in approximately the same period and in the same region of northern Lima. Category I failures were treated according to one of the two paths depicted in the Figure: according to the national guidelines (Strategy A) or according to the pilot protocol (Strategy B). Table 1 lists all the regimens used along these two paths. A ‘standardized’ regimen includes the same drugs and weight-based doses without consideration of DST results; an ‘empiric’ regimen is one applied while awaiting DST results; and an ‘individualized’ treatment regimen (ITR) is the final regimen based on DST results.

Existing approach (Strategy A)
Strategy A was the approach used at national level, in which Category I failures received the 8-month Category II regimen (Table 1). This regimen differs from that used in other countries, as it extends the use of streptomycin (SM) to at least 3 months rather than the more common 2-month duration. The Category II regimen was designed and introduced under the direction of WHO advisors in 1995; between 1995 and 2001, national program guidelines recommended the use of this regimen for Category I failures regardless of DST results.

Patients in whom Category II failed were subsequently treated with an 18-month standardized treatment regimen (STR) that included second-line drugs (Table 1), again without using DST data. This stan-

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Table 1 Composition and duration of regimens used in two study strategies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Definition and dosing (dosing based on mg/kg for adults and children)</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I regimen (2HREZ/4H3R3)</td>
<td>Directly observed 6-month regimen consisting of 2 months of INH (5 mg/kg/d), RMP (10 mg/kg/d), EMB (20 mg/kg/d), and PZA (25 mg/kg/d), administered daily, followed by 4 months of INH (15 mg/kg) and RMP (10 mg/kg) administered twice weekly.</td>
<td>A and B</td>
</tr>
<tr>
<td>Category II regimen (3SHREZ/5H3R3E3)</td>
<td>Directly observed 8-month retreatment regimen consisting of 3 months of SM (15 mg/kg/d), INH (5 mg/kg/d), RMP (10 mg/kg/d), EMB (20 mg/kg/d), and PZA (25 mg/kg/d) administered daily, followed by 5 months of INH (15 mg/kg), RMP (10 mg/kg), and EMB (40 mg/kg) administered twice weekly.</td>
<td>A</td>
</tr>
<tr>
<td>STR for MDR-TB (3 KM CPX ETH EMB PZA/15 CPX ETH EMB PZA)</td>
<td>Directly observed standardized 18-month retreatment regimen consisting of 3 months of KM (15 mg/kg/d, not &gt;1 g/kg/d), CPX (20 mg/kg/d, not &gt;1.2 g/kg/d), ETH (15 mg/kg/d, not &gt;750 mg/kg/d), EMB (20 mg/kg/d, not &gt;1.2 g/kg/d), and PZA (25 mg/kg/d) administered daily, followed by 15 months of CPX (20 mg/kg/d, not &gt;1 g/kg/d), ETH (15 mg/kg/d, not &gt;750 mg/kg/d), EMB (20 mg/kg/d, not &gt;1.2 g/kg/d), and PZA (25 mg/kg/d, not &gt;1.5 g/kg/d) also given daily.</td>
<td>A</td>
</tr>
<tr>
<td>ETR—empiric treatment regimen for MDR-TB</td>
<td>The same as STR, except that it is changed once DST is known.</td>
<td>B</td>
</tr>
<tr>
<td>ITR—individualized treatment regimen for MDR-TB</td>
<td>A directly observed regimen of 18–24 months designed according to the DST profile of the patient’s infecting organism. The number of drugs used in the regimen consisted of five or more drugs demonstrating susceptibility to the infecting strain. The drugs used were chosen from a hierarchical method using sensitive agents from the following drug groups: first-line drugs (EMB and/or PZA), an injectable agent (SM, KM, or CM), a fluoroquinolone (CPX or OFX), and oral bactericidal agents (ETH, CS, PAS). In cases of very high resistance when the organism could not be considered to be susceptible to five of the above listed drugs, CFZ and/or amoxicillin-clavulanate was added to the ITR. High-end dosing of all agents was the norm.</td>
<td>B</td>
</tr>
</tbody>
</table>

H, INH = isoniazid; R, RMP = rifampin; E, EMB = ethambutol; Z, PZA = pyrazamide; S, SM = streptomycin; STR = standardized treatment regimen; MDR-TB = multidrug-resistant tuberculosis, defined as resistance to at least H and R; KM = kanamycin; CPX = ciprofloxacin; ETH = ethionamide; DST = drug susceptibility testing; CM = capreomycin; CS = cycloserine; PAS = para-aminosalicylic acid; OFX = ofloxacin; CFZ = clofazimine.
Retreatment when first-line TB therapy fails

A standardized regimen for MDR-TB is the first to be used by a national tuberculosis program (NTP) on a countrywide basis.12 Strategy A thus refers to the application, among Category I failures, of a Category II regimen followed by STR if Category II also fails.

**Pilot protocol (Strategy B)**

Beginning in October 1997, a pilot approach to managing Category I failures was introduced in one health jurisdiction in northern Lima. For Category I patients who were persistently smear-positive at month 4 or later, a TB physician could submit the patient’s sputum for culture and DST, and patients were started on an empiric treatment regimen (ETR) for MDR-TB (Table 1). At the discretion of the TB physician, a decision could be made based on clinical criteria to submit a sputum specimen earlier than month 4.

If DST results showed resistance to only INH and RMP, the ETR was continued unchanged. If, however, DST results also showed resistance to other drugs, the patient received an ITR tailored to the susceptibility profile of the infecting strain. The ITR consisted of five or more drugs to which the infecting strain demonstrated in vitro susceptibility (Table 1).13,14

Three additional steps were applied to reduce delays to MDR-TB diagnosis and therapy. First, we worked with NTP workers in local health centers so they knew that if a Category I patient remained smear-positive or had poor clinical or radiologic evolution, a culture could be requested as early as month 2 of Category I. Second, a designated worker was assigned to visit the regional laboratory every week to collect culture results and transport them to the regional office responsible for monitoring TB treatment outcomes (SBS Comas). A weekly review of any positive culture results was implemented, and patients with a positive culture result were promptly referred for consultation with an MOH TB physician, without waiting for the local health centers to receive the culture result and request a consultation with an MOH TB physician. Finally, in a patient in whom Category I failed, DST was requested as soon as a positive culture result was obtained.

**Bacteriologic and drug susceptibility testing**

In all regimens all patients had a sputum specimen tested every month. Smear microscopy and culture were conducted in local and regional public health laboratories. Smear microscopy results were classified as ‘1’, ‘11’, and ‘111’ to indicate the presence of 1–10 acid-fast bacilli (AFB)/field/100 fields, 1–10 AFB/field/50 fields, and >10 AFB/field/20 fields, respectively.10

Susceptibility to PZA was determined using the Wayne method in Dubos media.15–17

For Strategy B patients only, specimens with confirmed growth of *M. tuberculosis* were also submitted.
to the Massachusetts State Laboratory Institute, Jamaica Plain, MA, for testing against 10 drugs by the proportion method: INH 0.2 μg/ml, 1.0 μg/ml, and 5.0 μg/ml; RMP 1.0 μg/ml; EMB 5.0 μg/ml; SM 2.0 and 10.0 μg/ml; kanamycin (KM) 5.0 μg/ml; capreomycin 10.0 μg/ml; cycloserine (CS) 30.0 μg/ml; ethionamide 5.0 μg/ml; ciprofloxin 2.0 μg/ml. The BACTEC technique was used for PZA at 100.0 μg/ml.

Outcome definitions
Treatment outcomes in the study were determined using all available bacteriologic results collected by 30 April 2003; the time elapsed in therapy was calculated using 30 May 2003 as an endpoint.

Outcome definitions followed national guidelines.10 As noted, failure was defined as a positive culture at or after the fourth month of Category I therapy. Cure was defined as the absence of a positive smear or culture indicative of failure. Default was defined as discontinuation of therapy for any reason for at least 30 days, and death due to any cause was registered. For Category II, the same definitions were used for default and death; completion was defined as the absence of a positive smear or culture at the end of therapy, and failure required a positive culture at the end of therapy.11 Patients receiving STR or who remained on ETR were classified as cured if they had a negative culture in the last 3 months of therapy or at month 18.10

A patient who received an ITR was classified as cured if at least 12 months of consecutive negative cultures were recorded during therapy; treatment failure was defined by the presence of any positive culture in the last 12 months of treatment.13 Outcomes for patients still receiving an MDR-TB regimen at the time of this analysis were classified as follows: likely cure, a patient who received at least 12 months of therapy where the six most recent culture results were negative; likely failure, a patient who received at least 12 months of therapy, with one or more positive cultures among the six most recent culture results. Such interim definitions have been used elsewhere as surrogates for MDR-TB treatment outcomes.18

**Time to diagnosis and therapy**
For the two strategies we compared the time in months between initiating Category I and initiating an MDR treatment regimen: the STR regimen in Strategy A and the ETR regimen in Strategy B.

**Data collection**
We reviewed clinical charts for each patient included in the study to confirm the absence of TB therapy prior to Category I and to obtain the bacteriologic results confirming the failure of Category I. Data were entered into a database created with MS Access 2000 (Microsoft Corp, Seattle, WA). Analyses were done using MS Excel 2000 (Microsoft Corp) and SAS Version 8.1 (SAS Institute, Inc, Cary, NC).

**Analysis**
We used the χ² test to compare categorical variables, and compared differences in means with Student’s t-test. Tests were two-sided, and a P value of 0.05 was considered statistically significant. We also calculated the relative risks (RR) of cure to compare among treatment strategies.

**RESULTS**
From February 1997 to October 2001 in the SBS Comas region of northern Lima, Category I failed to cure 123 never-treated patients. These patients were then retreated either with the national strategy (Strategy A) or with a pilot strategy (Strategy B); assignment was not random, but depended on the ability and willingness of each health center to implement the pilot protocol as well as on other constraints on these centers.

August 2000 was the last month in which Strategy A was used for any Category I failure in this region. By then only 20% of Strategy B patients had been enrolled; the remaining 80% were enrolled between August 2000 and October 2001. Table 2 summarizes the characteristics of patients treated with the two strategies. No significant differences were evident between

| Table 2: Characteristics of Category I failures recorded at the time of initiation of Category I regimen |
|---------------------------------|---------|---------|---------|--------|
| Characteristics          | Strategy A (n = 73) | Strategy B (n = 52) | P       |
| Age (median, range)      | 26.6    | Range (11–55) | 27.4    | Range (14–75) | 0.51 |
| Women                   | 24      | 32.9     | 22      | 42.3    | 0.23 |
| With known MDR-TB contact | 16     | 22.0     | 18      | 34.6    | 0.09 |
| With contact who died with TB | 14     | 19.2     | 14      | 26.9    | 0.35 |
| With diabetes mellitus | 8       | 11.0     | 1       | 1.9     | 0.05 |
| Who had ever been a health worker (n = 85)* | 5       | 9.8 (of 51) | 2       | 5.9 (of 34) | 0.52 |
| With initial bacillary load of 3+ (n = 107)* | 24      | 41.1 (of 57) | 16      | 32.0 (of 50) | 0.28 |

(*) Data not available for all patients.

MDR-TB = multidrug-resistant tuberculosis, defined as resistance to at least isoniazid and rifampin.
the groups (P > 0.05). The majority of patients in both groups were male, and the median age was 27 years. Routine testing for human immunodeficiency virus (HIV) infection was not available; four patients (two in each strategy) had a prior HIV-positive diagnosis when they initiated the Category I regimen.

Clinical outcomes

Table 3 summarizes the clinical outcomes of the two strategies. Strategy A was applied in 73 patients, all of whom were treated with Category II: 11 (15.1%) were cured, 54 (74.0%) failed, 5 (7%) died, and 3 (4%) defaulted. Of the 54 patients who failed, 39 continued therapy with the 18-month STR (Figure). Of these, 17 (44%) were cured, 13 (33%) failed, 4 (10%) died, and 5 (13%) defaulted. The probability of cure in patients in Strategy A was 38.4%, 28 patients of the original 73. Of the 54 patients in whom Category II failed, only 39 took STR and 15 were lost to follow-up.

Strategy B was used in 52 patients who received ETR, ETR followed by ITR, or ITR from the start. For patients whose isolates demonstrated resistance only to INH, RMP and SM, ETR was used as the definitive regimen unless subsequent DST reports during therapy indicated further resistance or if the patient was not progressing clinically. Only four patients remained on ETR once DST was known; two of these died after receiving ETR for 1 month or less, and the remaining two were cured.

In Strategy B, 34 of the 52 patients were still in therapy at the time of this analysis; all had received at least 12 months of therapy and could be classified according to the interim outcome definitions. Overall, 41 (78.8%) of the 52 patients were cured or classified as likely to be cured, 4 (7.7%) had defaulted, 5 (9.6%) had died, and 2 patients (3.9%) still in therapy were determined as likely failures.

In summary, Strategy B patients were significantly more likely to be cured than Strategy A patients (79% vs. 38%, RR 2.9, 95% confidence interval [CI] 1.7–5.1). Strategy B patients were also five times more likely to be cured than those who received only Category II (79% vs. 15%, RR 5.2, 95%CI 3.0–9.2).

Time to MDR-TB diagnosis and MDR-TB therapy

The two strategies also produced different delays to three time points: 1) classification of Category I failure, 2) MDR-TB diagnosis, and 3) initiation of MDR-TB therapy (Table 4). In Strategy A, these intervals are reported only for those patients who received STR (n = 39), as the Category II regimen alone is not considered to be MDR-TB therapy.

DST results were not used to adjust the regimens in Strategy A, although isolates were routinely tested to confirm the diagnosis of MDR-TB. Strategy A patients had a greater interval from the start of Category I therapy to the time of collection of the first specimen DST, waiting a median of 5.2 months before...
a specimen was submitted for DST, compared to 3.8 months for Strategy B patients ($P < 0.001$), and a median time of 8.8 months from the definition of Category I failure to the initiation of an MDR-TB regimen, compared to 1.8 months for Strategy B patients ($P < 0.001$).

**Amplification of resistance during ineffective regimens**

At Category I failure and prior to receiving any retreatment regimen, 91 (72.8%) of the 125 patients had a DST result available. Of these, 80 (88.0%) had isolates demonstrating resistance to both INH and RMP, while only 12.1% (11/91) had isolates resistant to only INH and RMP; 37 of the 80 patients (46.3%) had isolates resistant to both INH and RMP as well as to PZA, 47 (58.8%) to EMB, 27 (33.8%) to both PZA and EMB, and 55 (66.3%) to SM.

Thirty-one (42.5%) of the 73 patients treated with the Category II regimen had a DST result before and after exposure to the regimen. All 31 had resistant organisms prior to Category II, three of whom initiated with isolates resistant to all five drugs in that regimen. Eighteen (64%, 95% CI 47–82) of the remaining 28 patients at risk for accruing additional resistance acquired additional resistance to at least one drug (Table 5).

**DISCUSSION**

To date, no prospective or retrospective studies have compared two strategies for the treatment of MDR-TB in Category I failures. The present study shows that dramatically different outcomes are possible in the management of such patients, even in a resource-poor region. We compared two approaches: Strategy A, two consecutive standardized regimens independent of DST data, and Strategy B, an empiric regimen subsequently modified based on DST results.

A limitation to the study is that it is not a clinical trial but rather describes the gradual introduction of a pilot protocol under program conditions. All Category I failures in the area were eligible to be assigned to either strategy, but assignment was not random: patients were managed by Strategy B if health center staff were able to submit sputum samples promptly for DST and obtain an evaluation by a TB physician to initiate ETR or ITR. Multiple factors therefore likely affected which patients were managed by Strategy B, and may have been associated with better patient follow-up. Nevertheless, the differential outcomes are striking and suggest the need to further examine Strategy B.

The cure achieved with the Category II regimen of Strategy A was especially poor (15%). These findings coincide with a growing body of evidence that Category II regimens result in poor outcomes when used in Category I failures.5,9,19–24 The evidence from Vietnam, where the DOTS strategy is functioning well and MDR strains are prevalent, is especially compelling.9,24 Elsewhere, however, it is not certain whether Category II will produce such high failure rates.25 Nonetheless, these data taken together indicate that the standard Category II retreatment regimen can no

### Table 5 Resistance profiles in isolates of 31 patients before and after Category II regimen failure

<table>
<thead>
<tr>
<th>Patients (n)</th>
<th>DST before Category II</th>
<th>DST after Category II failure</th>
<th>Change in DST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with second isolate resistant to additional drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>INH-RMP-EMB-SM</td>
<td>INH-RMP-PZA-EMB-SM</td>
<td>+PZA</td>
</tr>
<tr>
<td>2</td>
<td>INH-RMP</td>
<td>INH-RMP-SM</td>
<td>+SM</td>
</tr>
<tr>
<td>2</td>
<td>INH-RMP-EMB</td>
<td>INH-RMP-EMB-SM</td>
<td>+SM</td>
</tr>
<tr>
<td>2</td>
<td>INH-RMP-PZA-EMB</td>
<td>INH-RMP-PZA-EMB-SM</td>
<td>+EMB</td>
</tr>
<tr>
<td>2</td>
<td>INH-RMP-PZA-SM</td>
<td>INH-RMP-PZA-SM</td>
<td>+INH +PZA +SM</td>
</tr>
<tr>
<td>1</td>
<td>INH-RMP</td>
<td>INH-RMP-PZA</td>
<td>+PZA</td>
</tr>
<tr>
<td>1</td>
<td>INH-EMB</td>
<td>INH-RMP-PZA-EMB</td>
<td>+RMP +SM</td>
</tr>
<tr>
<td>1</td>
<td>INH-PZA</td>
<td>INH-RMP-PZA-SM</td>
<td>+EMB</td>
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<tr>
<td>1</td>
<td>INH-RMP-EMB</td>
<td>INH-RMP-PZA-EMB</td>
<td>+EMB</td>
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<tr>
<td>1</td>
<td>INH-RMP-SM</td>
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<td>+EMB</td>
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<tr>
<td>1</td>
<td>INH-RMP-SM</td>
<td>INH-RMP-EMB</td>
<td>+EMB</td>
</tr>
<tr>
<td>Patients with second isolate resistant to fewer drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>INH-RMP-PZA-SM</td>
<td>INH-RMP-PZA</td>
<td>−SM</td>
</tr>
<tr>
<td>1</td>
<td>INH-RMP-PZA-EMB-SM</td>
<td>INH-RMP-PZA</td>
<td>−EMB −SM</td>
</tr>
</tbody>
</table>

| Patients with no change | | | |
| 3 | INH-RMP-PZA-EMB-SM | INH-RMP-PZA-EMB-SM | No change |
| 2 | INH-RMP-EMB-SM | INH-RMP-EMB-SM | No change |
| 2 | INH-RMP-PZA | INH-RMP-PZA | No change |
| 1 | INH-RMP-PZA-SM | INH-RMP-PZA-SM | No change |
| 1 | INH-EMB | INH-EMB | No change |
| 1 | SM | SM | No change |
| 1 | INH | INH | No change |

DST = drug susceptibility testing; INH = isoniazid; RMP = rifampin; EMB = ethambutol; SM = streptomycin; PZA = pyrazinamide.
longer be considered a sound medical option for Category I failures and that effective, rational strategies that include second-line drugs are required.

Careful scrutiny of our findings is important in the context of a shifting paradigm in tuberculosis control, especially for a number of countries beginning to implement DOTS-Plus programs. The findings are particularly important for those countries that ensure strict supervision of therapy and use RMP in the continuation phase of Category I. In Lima, the low cure rate for the Category II regimen used in Strategy A is not surprising given the resistance profiles found among Category I failures. An additional striking finding was that more than half of Category I failures with MDR-TB had strains also resistant to SM, a drug they had never received. This suggests that these patients were infected with strains already resistant to SM. Primary SM resistance could be due to the cycling of failing patients with drug-resistant disease through the ineffective Category II regimen, where they acquired further resistance to SM and infected others with these highly-resistant strains. Finally, of those patients who began Category II with drug-resistant strains, after exposure to this failed regimen two thirds had strains that had acquired resistance to other drugs. This risk estimate coincides with the 64% risk observed in Vietnam, and provides further evidence that ineffective short-course regimens can worsen existing resistance.

The outcomes of the second regimen (STR) used in Strategy A have been reported in a national cohort in Peru; this regimen cured fewer than half of the patients enrolled. STR may not have performed well for a number of reasons. Perhaps most importantly, the regimen included only three new drugs along with two drugs (EMB and PZA) to which the patients had already been exposed; 75% were already resistant to EMB and/or PZA. In addition, KM was used for only 3 months, while in the United States the recommended use is 6 months after culture conversion. Furthermore, Strategy A did not have the strong social or adverse event management support of Strategy B, which may have resulted in more patients abandoning Strategy A than Strategy B, despite the latter receiving regimens that are more toxic and difficult to take (most ITR included PAS and CS); default in Strategy A may also have been due to patients’ discouragement at remaining persistently smear-positive.

The results observed in northern Lima indicate that the poor outcomes of Strategy A are not inevitable, as Strategy B cured almost 80% of the Category I failures enrolled. Despite the encouraging results of Strategy B, it is possible that the outcomes could have been even better. With a stronger empiric regimen, for example, one including PAS or CS, a higher cure rate might have been achieved, and the time to initiation of ETR could be further reduced from a median of 2 months to 1–2 weeks.

Whether a stronger STR used immediately to treat Category I failures could have resulted in better outcomes is not known. A reasonable approach for using an STR in Category I failures is to monitor the DST profiles in this group to determine if the proposed regimen will be adequate. It is also vital to monitor outcomes while the STR is being implemented and make program-level adjustments if poor outcomes are documented. The most recent WHO treatment guidelines indicate the importance of alternatives to Category II when Category I failures are highly likely to have MDR-TB. The results of the present study provide further evidence that recommending Category II for these patients would be both ineffective and dangerous, because the approach delays time to effective treatment and exacerbates existing resistance profiles.

Our findings indicate that the Category II regimen should no longer be recommended for patients in whom supervised first-line therapy fails, particularly in patients with proven MDR-TB. The present study shows that under program field conditions, an alternative retreatment strategy that eliminates Category II and uses an empiric regimen, followed by an individualized regimen based on drug susceptibility testing, can significantly improve outcomes in the treatment of Category I failures.

Acknowledgements
The authors are grateful for the support of Thomas J White and the Bill & Melinda Gates Foundation.

References
CONTEXTE: Centres publics ambulatoires au nord de Lima, Pérou.

OBJECTIF: Comparer deux stratégies de retraitement dans les échecs de Catégorie I.

SCHEMA: Etude rétrospective de cohorte sur les échecs de Catégorie I enrôlés entre février 1997 et octobre 2001. La stratégie A a consisté dans l’approche nationale appliquée aux régimes de Catégorie II ; en cas d’échec de ce régime, un régime standardisé incluant des médicaments de seconde ligne est utilisé. La stratégie B a consisté en un protocole-pilote élaboré pour diagnostic et traiter la tuberculose à germes multirésistants (TB-MR) ; cette stratégie a comporté des tests de sensibilité aux médicaments (DST) et a écarté le régime de Catégorie II.

RÉSUMÉ: Sur 125 patients non guéris par le régime de Catégorie I, 73 ont été traités par la stratégie A et 52 par la stratégie B. Près de 90% des sujets où les DST étaient disponibles avaient une TB-MR. La stratégie B a comporté trois fois plus de chances de guérir des patients que la stratégie A (79% vs. 38% ; RR = 2,9 ; IC95% 1,7–5,1) ; elle a été cinq fois plus susceptible de guérir les patients que le seul régime de Catégorie II (79% vs. 15% ; RR = 5,2 ; IC95% 3,0–9,2). La stratégie B a également réduit de manière significative les délais de diagnostic de la TB-MR et la mise en route du traitement de la TB-MR.

CONCLUSIONS: Dans les conditions du programme, une stratégie de retraitement basée sur DST et éliminant le régime de Catégorie II peut améliorer les résultats cliniques dans les échecs du traitement de Catégorie I chez qui on a décelé une TB-MR active et contagieuse.
RESUMEN

LUGAR: Establecimientos de salud en el norte de Lima, Perú.

OBJETIVO: Comparar dos estrategias de retratamiento en pacientes que fracasan al Esquema I.

DISEÑO: Estudio retrospectivo de cohorte de fracasos al Esquema I que iniciaron este esquema entre febrero de 1997 y octubre de 2001. La Estrategia A fue el método utilizado al nivel nacional que aplicó un Esquema II; si este esquema también fracasó, se administró un esquema estandarizado que incluyó drogas de segunda línea. La Estrategia B fue un protocolo piloto con el propósito de facilitar el diagnóstico y el tratamiento de la tuberculosis multidrogo-resistente (TB-MDR); esta estrategia incluyó prueba de sensibilidad y eliminó el uso del Esquema II.

RESULTADOS: De los 125 pacientes que fracasaron al Esquema I, 73 ingresaron a la Estrategia A y 52 a la Estrategia B. Casi el 90% de aquellos con resultados de prueba de sensibilidad tenían TB-MDR. La Estrategia B tuvo tres veces más probabilidad de curar a pacientes en comparación a la Estrategia A (79% vs. 38%; RR 2.9; 95%CI 1.7–5.1) y cinco veces más probabilidad de curarlos en comparación al uso del Esquema II solo (79% vs. 15%; RR 5.2; 95%CI 3.0–9.2). La Estrategia B también redujo significativamente la demora al diagnóstico de la TB-MDR y al inicio de tratamiento para TB-MDR.

CONCLUSIÓN: Bajo condiciones de programa, una estrategia de retratamiento que utiliza eficientemente pruebas de sensibilidad y elimina el Esquema II puede mejorar los resultados clínicos en pacientes que fracasan el Esquema I y que tienen TB-MDR activa.