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Representative drug susceptibility patterns for guiding design of retreatment regimens for MDR-TB

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SUMMARY

BACKGROUND: There is no gold standard on how national tuberculosis programs should design retreatment regimens. Often drug susceptibility testing (DST) is not available for all patients, and representative DST patterns in patient populations are used to guide therapy.

OBJECTIVES: To examine DST patterns in different patient populations based on previous treatment and to estimate the number of effective anti-tuberculosis agents in several retreatment regimens.

METHODS: We reviewed DST results from patients treated with individualized regimens in Peru between January 1998 and July 2004. We stratified patients into four groups based on previous treatment exposure from Group 1 who had failed only one regimen to Group 4 who had failed three regimens. We compared resistance frequencies across the four groups. In Groups 1 and 3, the number of likely effective agents under six possible retreatment regimen scenarios was estimated.

RESULTS: Resistance to second-line drugs was significantly higher in groups with more previous courses of treatment. A few retreatment regimens could be identified that would allow at least 80% of patients to receive at least four likely effective drugs.

CONCLUSION: Because it is associated with resistance frequencies, previous treatment exposure can serve to guide the design of non-individualized MDR-TB regimens.

KEY WORDS: retreatment; drug resistance; tuberculosis; standardized; individualized; MDR-TB

THE WORLD HEALTH ORGANIZATION (WHO) estimates that every year almost 300 000 new cases of multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid [H, INH] and rifampicin [R, RMP]) develop.[1] Projections indicate that there are three times as many prevalent cases as new cases in a year.[2] Recently, the WHO recommended the use of regimens with second-line drugs in patients who are known or suspected to have MDR-TB.[3]

Individualized treatment regimens (ITRs) based on drug susceptibility testing (DST) results are most commonly used for MDR-TB patients in high-income countries. More than 14 published reports exist of MDR-TB patient cohorts treated with ITRs.[4,5] In poorer regions, DST is not routinely available. Several TB programs have employed a standardized treatment regimen (STR) for MDR-TB. Four studies have reported experience with STRs that include second-line drugs: Peru,[6] Bangladesh,[7] Korea,[8] and South Africa.[9] To date, the clinical success of STRs has not equaled that of many ITR-based programs, with no reported cure rates greater than 70%.

Empiric treatment regimens (ETRs) are generally customized to an individual's treatment and contact history but used in the absence of, or while awaiting, DST results. Some programs use a combination of ETR with STR or ITR (Figure). Some may conduct susceptibility testing to a few drugs and then adjust the regimen systematically. For example, South Africa uses an STR that includes ethambutol (E, EMB), which is replaced by cycloserine (CS) if EMB resistance is found.[9]

The most extensive experience using a STR with second-line drugs comes from Peru. Beginning in the mid 1990s, the National TB Program (NTP) built a model DOTS program and used exclusively the WHO-recommended Category II as the STR for retreatment cases.* In 1997, the Peruvian program began treating

* The WHO-recommended standardized regimen for new cases of tuberculosis is referred to as Category I and consists of 2 months of H, R, pyrazinamide (Z), and E, followed by 4 months of HR. Category II is used in previously treated cases and consists of 2 months of HREZ and streptomycin (S), followed by 1 month of HREZ, followed by 5 months of HRE.

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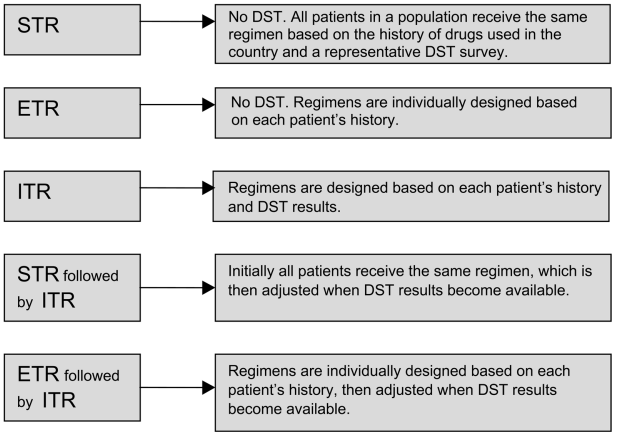

Figure Treatment strategies used in the treatment of MDR-TB. STR = standardized treatment regimen; DST = drug susceptibility testing; ETR = empiric treatment regimens; ITR = individualized treatment regimen; MDR-TB = multidrug-resistant tuberculosis.

Category II failures with an STR that included second-line drugs. This STR regimen (henceforth 'STR-Peru') consisted of EMB, pyrazinamide (PZA), ciprofloxacin (CFX), and ethionamide (ETH) for 18 months, and kanamycin (KM) for the first 3–4 months. In 2001, Category II was discontinued for use in Category I failures; instead, these patients received STR-Peru. Unfortunately, both Category II and STR-Peru have demonstrated high failure rates,[6,10] as neither approach was tailored to a resistance profile that reflected the infecting isolates for the patient group to be treated. In 1996, Partners In Health, a non-governmental organization, started treating failures of Category II and failures of the STR-Peru with individualized regimens.[11]

We sought to examine the differences in distribution of resistance frequency in relation to categories of previous treatment exposure. We further aimed to estimate the expected success of each of several retreatment regimens in light of the resistance profiles of the patients to be treated.

METHODS

We reviewed DST performed at Massachusetts State Laboratory Institute (MSLI) for 979 patients who received an ITR in Peru between January 1998 and July 2004. We included data from patients whose prior treatment history matched one of four groups (see below). If the treatment history did not match one of the four groups the patient was not included in the study. DST results were included from specimens collected after the last previous regimen and before ITR. These restrictions were incorporated to have the DST patterns accurately represent treatment history.

Approval for the study was obtained from the Institutional Review Board of Brigham and Women's Hospital, Boston, MA.

All patients had failed at least one previous regimen. Patients were stratified into four groups based on previous treatment exposure prior to ITR enrollment (Table 1). Group 1 included patients who remained smear-positive (treatment failures) after receiving only Category I (HREZ). Patients in Group 2 remained smear-positive after receiving Category I and Category II (HREZS) regimens; Group 3 remained smear-positive after receiving Category I and STR-Peru; and Group 4 patients remained smear-positive after having received Category I, Category II, and STR-Peru. Although patients in Group 1 were from one health jurisdiction in northern Lima (SBS Comas), Groups 2, 3, and 4 were from all parts of Peru. Group 1 was chosen from only one area of Lima because this was the only area where routine DST to first- and second-line drugs was done at the time of Category I failure.

All DST was performed at the MSLI in Boston, MA.[11] Data were abstracted from a web-based electronic medical record backed by an Oracle database.[12] We employed the term 'likely effective' to refer to a drug to which in vitro susceptibility was documented—or to which resistance had not been documented—prior to initiation of treatment with that agent.

Analyses of the resistance frequencies by exposure group were performed using MS Excel 2000 (Microsoft Corp, Redmond, WA) and SAS Version 9.1 (SAS Institute, Inc, Cary, NC). Pair-wise comparisons were performed using Fisher's exact test with Group 1 as the baseline. Tests were two-sided and a P value of 0.01 was considered statistically significant. This level of significance was chosen because multiple comparisons were performed.

Table 1 Previous treatment exposure groups

Group	*n*	Sex		Average age, years	Previous TB regimens *n*	Treatment history	Unique drugs used in all previous regimens *n*
		Male *n* (%)	Female *n* (%)				
1	86	52 (60.5)	32 (39.5)	29	1	Failure of WHO Category I treatment	4
2	54	30 (55.6)	24 (44.4)	27.2	2	Previously treated with WHO Category I and failure of WHO Category II regimen	5
3	59	39 (66.1)	20 (33.9)	30.6	2	Failure of WHO Category I and STR-Peru	7
4	173	104 (60.1)	69 (39.9)	31.1	3	Previously treated with WHO Category I and failure of WHO Category II and STR-Peru treatments	8

WHO =World Health Organization; STR = standardized treatment regimen.

Table 2 Resistance frequencies by treatment exposure group

	Resistance frequency			
Drug	Group 1 (n = 86) %	Group 2 (n = 54) %	Group 3 (n = 59) %	Group 4 (n = 173) %
Rifampicin	82.6	96.3	91.5	93.6
Isoniazid	88.4	98.2	94.9	100.0
Ethambutol	56.5	75.0	77.1	81.5
Pyrazinamide	38.1	51.0	70.9	71.8
Streptomycin	68.6	79.6	79.3	83.2
Kanamycin	11.6	18.4	54.7	30.5
Capreomycin	8.1	9.09	37.0	24.7
Ciprofloxacin	3.5	4.65	8.9	13.0
Ethionamide	18.6	29.2	50.9	49.1
Cycloserine	1.2	0.0	2.2	1.3
PAS	2.4	0.0	4.1	10.1

PAS = para-aminosalicylic acid.

We considered six alternative retreatment regimen scenarios. Three of these were those used in Peru (Category II, STR-Peru, and ITR) and we considered three other alternatives: 1) KM+PZA+CFX+ETH+CS, 2) KM+PZA+CFX+ETH+CS+para-aminosalicylic acid (PAS), and 3) capreomycin (CPM)+CFX+CS+PAS. The three alternative regimens were chosen based on the principles of MDR-TB regimen design described in other sources.[4,13,14] For Groups 1 and 3, we estimated the number of effective or 'likely effective' drugs patients would have received had they been treated with each of the six retreatment alternatives.

RESULTS

Comparison of drug resistance patterns in four treatment exposure groups

The resistance frequencies for each group are reported in Table 2. As expected, resistance was associated with exposure to a greater number of regimens and drugs. Table 3 is a pair-wise comparison of resistance that compares Group 1 with Groups 2, 3, and 4. Although resistance to all drugs—except CS and PAS—occurred more frequently in Group 2 than in Group 1, these differences were not significant. The Table shows significantly more resistance in Group 3 to PZA, KM, CPM, and ETH. The difference in EMB resistance (56.4% in Group 1 and 77.1% in Group 3) was of borderline significance (P = 0.013). Statistically significant differences were observed between Groups 1 and 4 in resistance to INH, RMP, EMB, PZA, KM, ETH, and CPM. Streptomycin (SM) resistance was 15% higher in Group 4 (P = 0.01) than in Group 1. No statistically significant difference in resistance frequency was observed for CFX, CS, or PAS in any of the comparisons.

Estimating the number of drugs likely to be effective in an STR or ETR

We considered six retreatment regimen alternatives: three that had been applied in Peru (Category II, STR-Peru, and ITR) and three hypothetical STRs (regimens 4, 5 and 6 in Table 4).

Table 4 shows the estimates of the expected number of effective or likely effective drugs in each scenario. If Group 1 patients (Category I failures) were treated with the Category II regimen, 76.7% would receive only two or fewer likely effective drugs. The STR-Peru would result in 16.3% of patients receiving two or fewer likely effective drugs. An ITR based on DST results would not place any Group 1 patients on two or fewer likely effective drugs. For Group 3, none of the regimens considered could avoid placing a small percentage of patients on two or fewer likely effective drugs.

DISCUSSION

This type of exercise will be important for the dozens of countries seeking approval from the WHO Green Light Committee (GLC) for access to second-line drugs and who plan to use an STR strategy. The exercise to estimate the number of likely effective drugs in a standardized or empiric regimen is relatively simple, yet informative. Charts similar to Tables 2 and 4 can be created by any program to aid in regimen design. Different retreatment regimens may be needed for dif-

Table 3 Comparison of resistance frequencies

	Group 1 (n = 86)	Group 2 (n = 54)		Group 3 (n = 59)		Group 4 (n = 173)	
Drug	%	%	P value	%	P value	%	P value
Rifampicin	82.6	96.3	0.017	91.5	0.147	93.6	<0.01
Isoniazid	88.4	98.2	0.051	94.9	0.241	100.0	<0.01
Ethambutol	56.5	75.0	0.044	77.1	0.013	81.5	<0.001
Pyrazinamide	38.1	51.0	0.156	70.9	<0.001	71.8	<0.001
Streptomycin	68.6	79.6	0.175	79.3	0.183	83.2	0.01
Kanamycin	11.6	18.4	0.310	54.7	<0.001	30.5	<0.001
Capreomycin	8.1	9.09	1	37.0	<0.001	24.7	<0.01
Ciprofloxacin	3.5	4.65	1	8.9	0.232	13.0	0.021
Ethionamide	18.6	29.2	0.196	50.9	<0.001	49.1	<0.001
Cycloserine	1.2	0.0	1	2.2	1	1.3	1
PAS	2.4	0.0	1	4.1	0.625	10.1	0.047

PAS = para-aminosalicylic acid.

Table 4 Predicted susceptibility to six retreatment regimens

Regimen number	Retreatment regimen	Group 1 Patients with strains susceptible to ⩾4 drugs %	Group 1 3 drugs %	Group 1 ⩽2 drugs %	Group 3 Patients with strains susceptible to ⩾4 drugs %	Group 3 3 drugs %	Group 3 ⩽2 drugs %
1	HREZS (STR-Category II)	14.0	9.3	76.7	3.4	1.7	94.9
2	E+Z+KM+CFX+ETH (STR-Peru)	55.8	27.9	16.3	33.9	13.6	52.5
3	ITR	93.0	7.0	0.0	67.8	28.8	3.4
4	KM+Z+CFX+ETH+CS	81.4	16.3	2.3	45.8	27.1	30.5
5	KM+CFX+ETH+CS+PAS	93.0	7.0	0.0	64.4	27.1	8.5
6	CPM+CFX+CS+PAS	84.9	15.1	0.0	64.4	30.5	5.1

See text for further descriptions of STR-Category II and STR-Peru.
H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin; STR = standardized treatment regimen; KM = kanamycin; CFX = ciprofloxacin; ETH = ethionamide; ITR = individualized treatment regimen; CS = cycloserine; CPM = capreomycin; PAS = para-aminosalicylic acid.

ferent patient groups depending on treatment history and the DST survey results in the group.

The present exercise does not prove that standardized regimens with a low predicted number of likely effective drugs would lead to poor outcomes. To demonstrate such an effect, a sufficient number of patients with similar treatment history would have to be randomized to a set of retreatment alternatives and followed prospectively. This would be unethical, as some patients would be treated with drugs to which their *Mycobacterium tuberculosis* strains were known to be resistant. All patients whose DST data were included in this exercise were treated with an ITR, and outcomes will be reported elsewhere.

We do know the outcomes of the retreatment strategies used in Peru, in patients whose exposure experience was similar to Groups 1 and 2. Among Category I failures in northern Lima who were treated with a Category II regimen between 1997 and 2001, only 15% were cured.[15] Among patients with the same treatment history as Group 2, the STR-Peru cured only 48%.[6]

We considered two or fewer effective drugs as an inadequate regimen.[16] A literature review of MDR-TB treatment programs revealed that between four and six drugs were used in all reported cohorts.[4] We suggest, therefore, that STRs and ETRs should be designed to place as many patients as possible on at least four drugs considered likely to be effective. The choice of the four drugs should be based on representative DST data or on individual treatment histories. This often means that standardized and empiric regimens contain five or six drugs, so that all or most patients are expected to receive at least four likely effective drugs. Not all second-line drugs are equally effective, nor are DST results uniformly reproducible or predictive of clinical utility. This is further reason to err on the side of caution and begin a retreatment STR or ETR for MDR-TB with five or six drugs. Nonetheless, four-drug regimens such as regimen number 6 in Table 4 could be very effective when all the drugs in the regimen have a high probability of being effective against the strain.

If the STR-Peru had been designed to cover a higher percentage of patients with four effective drugs using survey DST and drug history data, outcomes might have been better. There are, however, other possible reasons for that regimen's poor results. These include: use of the injectable for only 3 or 4 months (many experts recommend longer use);[17] a relatively low dose (1000 mg/day) of the fluoroquinolone (CFX); ancillary medicines to treat adverse events were not provided free of charge; and the use of social support was limited.[15] Identifying MDR-TB earlier in the course of the disease may also contribute to improved outcomes.

As DST patterns in populations are likely to change over time in response to drug exposure, the exercise of obtaining local representative DST patterns in each population must be repeated periodically. Different STRs and strategies may therefore be required for different sub-populations, and may require revision over time.

A high prevalence of MDR-TB in Category I failures is not unique to Peru, and has been documented in India,[18] Vietnam,[19] Rwanda,[20] Thailand,[21] and Ecuador.[22] However, not all Category I failures have such high MDR-TB prevalence.[23,24] Relapses and returns after default often have low or moderate prevalence of MDR-TB.[19,21,25] When a specific population has low or moderate MDR-TB prevalence, it may be more difficult to find a single retreatment regimen that optimizes outcomes. Ideally, patients should receive INH and RMP if their strains are susceptible to these drugs, and should not be exposed to toxic second-line drugs if they are not needed. In low to moderate risk groups, most programs using STR will still need DST for at least INH and RMP, so they can identify patients with resistant disease who need a retreatment regimen different from the WHO Category II regimen.

Although exposure history is important, in all groups considered in this analysis resistance was documented to agents the patients had not received. This may be due to primary resistance. It is striking to note that 69% of Group 1 patients had strains resistant to SM, a drug they had never received but which has been

used extensively in the country. This suggests that many Peruvian patients who failed Category I were initially infected with a drug-resistant strain.

Another factor in the apparently greater frequency of resistance in Groups 3 and 4 may be the phenomenon of cross resistance. Resistance may be acquired to certain agents that share mechanisms of action or structure with agents that patients have previously received. In Groups 3 and 4, none of the patients received CPM, yet resistance to the agent was relatively common (37.0% and 24.7%, respectively). Primary CPM resistance is uncommon in Peru and therefore an unlikely explanation. Groups 3 and 4 did have exposure to KM. Some cross resistance between KM and CPM has been reported.[14,26–28]

The study has two principal limitations. First, the critical concentrations of susceptibility testing for second-line drugs for DST and how these correlate to clinical effectiveness are still under investigation. If in vitro results do not correlate well with in vivo response, the significance of estimating likely effective drugs may be less meaningful.

Second, the study only included 372 patients of 918 who were eligible for ITR under Partners In Health and had DST at MSLI during the study period. (Failures of Category I, Category II and STR-Peru were eligible for ITR.) Patients were excluded because treatment history did not exactly match one of the groups or because DST was conducted early in treatment and results may not reflect the resistance pattern of the strain at the time of treatment failure. We are confident that patients in each group had their past treatment history accurately indicated, but excluding the other patients makes results less applicable to situations where treatment history is not as clear. In addition, including other groups, for example, patients who had DST at month 2 of Category II treatment would not accurately represent DST patterns at the time of failure (month 5).

It is essential that STRs with second-line drugs cure the majority of patients treated. When STRs fail, further acquired resistance is likely.[29] These patients will likely also have progressive disease that may be very difficult or even impossible to cure; these highly resistant mutants can continue to be transmitted to others. Because of the poor outcomes of the STR-Peru regimen, Peru has abandoned this regimen for treating Category I and II failures and instead begun to use an ETR strategy followed by ITR.[30] The ETR will be designed using aggregate DST results of targeted patient populations.

In summary, we have described the different resistance frequencies in patient groups with different treatment exposure histories and argued that this variability may be an important factor in outcomes of standardized and empiric regimens. Evaluating the drug susceptibility patterns in patient groups with different treatment history would allow NTPs to estimate the number of likely effective agents in alternate retreatment regimens under consideration. More investigation is required to determine the optimal protocols for designing standardized and empiric retreatment regimens and evaluating how these compare with individualized alternatives.

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RÉSUMÉ

CONTEXTE : Il n'existe pas de standard de qualité sur la manière dont les programmes nationaux de tuberculose devraient élaborer leurs régimes de retraitement. Souvent, les tests de sensibilité aux médicaments (DST) ne sont pas disponibles pour l'ensemble des patients, et ce sont les types de sensibilité représentatifs dans les populations de patients qui sont utilisés comme guides pour le traitement.

OBJECTIFS : Examiner les types de sensibilité médicamenteuse dans différentes populations de patients en fonction des traitements antérieurs et estimer le nombre d'agents antituberculeux efficients dans certains régimes de retraitement.

MÉTHODES : Nous avons réexaminé les résultats des tests de sensibilité chez les patients traités avec des régimes individuels au Pérou entre janvier 1998 et juillet 2004. Les patients ont été stratifiés en quatre groupes en se basant sur le nombre de traitements qu'ils avaient subis antérieurement : depuis le Groupe 1 où un régime seulement avait échoué jusqu'au Groupe 4 où trois régimes avaient échoué. Nous avons comparé les fréquences de résistance dans ces quatre groupes. Dans les Groupes 1 et 3, on a estimé le nombre d'agents potentiellement efficients parmi six scénarios possibles de régimes de retraitement.

RÉSULTATS : La résistance aux médicaments de seconde ligne est significativement plus élevée dans les groupes qui ont reçu un plus grand nombre de traitements antérieurs. On a pu identifier un petit nombre de régimes de retraitement qui devraient permettre à 80% au moins des patients de bénéficier d'au moins quatre médicaments potentiellement efficients.

CONCLUSION : Le fait d'avoir subi des traitements antérieurs peut servir de guide pour élaborer des régimes non individualisés de MDR-TB, puisqu'il est associé avec la fréquence des résistances.

RESUMEN

ANTECEDENTES : No existen normas internacionales para guiar a programas nacionales de tuberculosis en el diseño de esquemas de retratamiento. A menudo, no se dispone de pruebas de sensibilidad (PS) a drogas para todos los pacientes, y para guiar el diseño del esquema de retratamiento se consideran patrones de PS obtenidas en representativas poblaciones de pacientes.

OBJETIVOS : Examinar los patrones de sensibilidad a drogas en diversas poblaciones de pacientes que se clasifican de acuerdo al previo tratamiento y estimar el número de drogas antituberculosas probablemente efectivas si se hubiese utilizado cada uno de varios esquemas de retratamiento.

MÉTODOS : Revisamos los resultados de PS de pacientes que recibieron esquemas individualizados en el Perú entre enero de 1998 y julio de 2004. Dividimos a los pa-

cientes en cuatro grupos de acuerdo a la historia de previo tratamiento : desde el Grupo 1 quienes habían fracasado solo un esquema hasta el Grupo 4 quienes habían fracasado tres esquemas. Comparamos las frecuencias de resistencia en los cuatro grupos. En los Grupos 1 y 3, se estimó el número de drogas probablemente efectivas bajo seis posibles escenarios de esquema de retratamiento.

RESULTADOS : La resistencia a las drogas de segunda línea fue significativamente mas frecuente en los grupos con mayor número de previos tratamientos. Se pudo identificar unos pocos esquemas de retratamiento que hubiesen permitido que por lo menos 80% de pacientes reciban por lo menos cuatro drogas probablemente efectivas.

CONCLUSIÓN : Por ser asociada a la frecuencia de resistencia, la historia del previo tratamiento puede guiar el diseño de esquemas no-individualizados para el tratamiento de la tuberculosis multidrogo-resistente.