

## Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis

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### SUMMARY

**SETTING:** A community-based treatment program for multidrug-resistant tuberculosis (MDR-TB) in an urban shantytown of Lima, Peru.

**OBJECTIVES:** To ascertain the occurrence of serious adverse effects associated with therapy for MDR-TB in northern Lima, Peru, where therapy was individualized according to drug-susceptibility testing of patients' infecting strains and delivered through a community-based program.

**DESIGN:** A retrospective record review of 60 patients who had received individualized therapy for MDR-TB between September 1996 and October 1998.

**RESULTS:** Although adverse effects were common, they occurred less frequently than previously reported in the literature and were rarely life-threatening. Effects occurring most frequently in this population included: mild gastritis (100%), dermatological effects (43.3%), periph-

eral neuropathy (16.7%), depression (18.3%), and anxiety (11.7%). These effects never resulted in the discontinuation of anti-tuberculosis therapy, and only occasionally resulted in the suspension of an agent (11.7%).

**CONCLUSION:** In young patients with little comorbid disease, multidrug, long-course regimens rarely caused life-threatening adverse effects. Common side effects may be managed successfully on an out-patient basis through a community-based treatment program in conjunction with MDR-TB experts, even in resource-poor settings. The very low rate of default in this cohort offers hope that strategies to manage the adverse effects may reduce the incidence of abandonment of therapy and increase rates of cure.

**KEY WORDS:** tuberculosis; antimicrobial resistance; adverse effects

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) is a growing problem throughout the world.<sup>1-6</sup> The importance of recognizing and responding to this crisis has been noted.<sup>7</sup> Although strategies that prevent the creation of MDR-TB, such as DOTS, remain critical, there are settings in which short-course chemotherapy alone will fail to cure a growing fraction of patients.<sup>4,8</sup> Recently an article by Espinal and colleagues concluded that ". . . any good TB control strategy should allow for the use of second-line drugs provided all possible measures are taken to . . . prevent the development of further drug resistance."<sup>9</sup>

The mechanisms by which strains of *Mycobacterium tuberculosis* acquire clinically significant resistance have been reviewed elsewhere.<sup>10-16</sup> Selection for resistant organisms has been attributed to the use, in TB therapy, of too few medications, at too low doses, for too short a period of time.<sup>17</sup> Long regimens with

multiple medications are thus the rule in the effective chemotherapy of MDR-TB.<sup>18-21</sup> In fact, in settings of MDR-TB outbreaks in the United States, some have advocated the use of initial empiric regimens containing as many as seven drugs.<sup>22</sup> Once the regimen is adjusted to reflect the drug resistance profile of the infecting strain, MDR-TB therapy often lasts 24 months.<sup>23</sup>

Long-term use of multidrug regimens has raised concern over the possibility of excessive adverse effects among patients being treated. There exists a large literature on adverse effects of anti-tuberculosis medications, which range from minor (e.g., changes in color of skin or bodily fluids, headache) to life-threatening (e.g., hepatitis, renal failure).<sup>24-51</sup> These effects, although not standardized in any way across studies, are summarized in Table 1. Some effects, as defined in this table, are nearly ubiquitous in patients

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**Table 1** Definitions of adverse effects evaluated in the Lima cohort

Adverse effect	Symptoms associated in the literature with these effects
Mild gastritis	Irritation of the stomach manifested by nausea, vomiting, abdominal pain, and/or reflux
Severe gastritis	Inflammation of the upper GI tract serious enough to cause GI bleeding as evidenced by hematemesis, the presence of melena, positive occult blood on stool analysis or by endoscopic findings
Central nervous system	Severe headache not relieved by non-prescription analgesics; seizure activity of any type as reported by the patient or witnessed by another individual
Peripheral nervous system	Peripheral neuropathy: numbness, tingling or burning in the trunk or extremities; diminished or absent reflexes; nerve-conduction studies consistent with peripheral neuropathy; vestibular side effects; presence of at least one month of persistent, myasthenia-like syndrome, nystagmus, dizziness and/or loss of balance
Hepatitis	Elevation of serum transaminases or serum bilirubins to more than twice normal values*
Psychiatric	Presence of one or more of the following: depression, anxiety, and/or psychotic symptoms as defined by DSM IV criteria and/or as evaluated by a psychiatrist using DSM IV criteria
Dermatologic	Any skin change including rash, bronzing, and/or photosensitivity reaction
Musculoskeletal	Presence of joint pain, joint swelling, or persistent muscle aches lasting more than one month
Renal	A rise of 0.5 or more in serum creatinine from patient's baseline
Otologic	Hearing loss confirmed by physical examination or audiometry
Ocular	Presence of visual changes suggestive of optic neuritis, including vision loss, pain on moving the eye, or loss of color vision; or the presence of optic neuritis as confirmed by an ophthalmologist. Red/green color testing was used as a screening measure in patients with symptoms
Hypothyroidism	Serum thyroid stimulating hormone (TSH) greater than 10.0 IU/mL†

\* We used a very sensitive measure for hepatitis to ensure all cases would be found; in spite of this quite sensitive measure, there was still only one patient with hepatitis.

† Not all patients had screening TSH levels performed. Those with depression, those with symptoms of hypothyroidism (e.g., constipation, dry skin, fatigue), and those with palpable goiters had TSH levels checked. GI = gastrointestinal; DSM = Diagnostic and Statistical Manual of Mental Disorders.

receiving multidrug anti-tuberculosis treatment (e.g., mild gastritis) and rarely require the discontinuation of therapy. Other, more severe effects (e.g., hepatitis, renal failure, severe gastritis) have been reported infrequently but may require more dramatic interventions.<sup>26</sup>

We sought to ascertain the occurrence of serious adverse effects associated with therapy for MDR-TB in northern Lima, Peru, where therapy was individualized according to patients' infecting strains and delivered through a community-based treatment program in a resource-poor setting. We further sought to determine whether existing clinical strategies would permit, under local TB program conditions, the man-

agement of adverse effects without requiring the discontinuation of MDR-TB therapy.

## STUDY POPULATION AND METHODS

The patients included in this study lived in three districts of northern Lima, Peru, and were diagnosed with MDR-TB between September 1996 and October 1998, after failing directly observed short-course chemotherapy. Patients were included in this particular analysis if they had received 6 or more months of MDR-TB therapy in the period between August 1996 and March 1999. Because many of the adverse effects that are reported here may occur later in the course of therapy, 6 months was chosen as the minimum duration. A total of 60 patients met this inclusion criteria and were enrolled in the study.

All MDR-TB diagnoses were confirmed by standard laboratory methods; we have described this referral and diagnostic system elsewhere.<sup>6</sup> All patients subsequently received individualized therapy through a community-based, DOTS-Plus program that we have also described elsewhere.<sup>8,52-55</sup> In summary, this program consisted of a daily, directly observed regimen tailored to each patient according to the results of drug-susceptibility testing. Patients were followed closely by a small team of nurses and physicians who saw them on a weekly basis, both in patients' homes and in office visits, but most daily care was delivered by community-health workers trained to administer directly observed therapy and to assess and triage common problems. During each clinical visit, patients were questioned regarding adverse effects, and their responses were documented in the clinical record.

A complete clinical evaluation was performed for each patient prior to enrollment. Baseline laboratory analyses included a complete blood count; blood urea nitrogen (BUN); serum creatinine; tests of hepatic function (serum transaminases, serum bilirubin, alkaline phosphatase); ELISA for human immunodeficiency virus (HIV); and VDRL (venereal disease research laboratory testing) serology. Additionally, psychiatric and audiometric evaluations were performed prior to initiation of MDR-TB therapy. Routine testing of BUN, serum creatinine, serum transaminases and serum bilirubins was then conducted at 6-monthly intervals during therapy. All other laboratory analyses were performed when indicated by patient symptoms.

Charts were reviewed by a clinician trained in the management of MDR-TB (JJF); the presence of symptoms suggestive of adverse effects as well as the severity of these adverse effects were noted. Any ambiguous cases were reviewed by a team of three clinicians trained in the management of MDR-TB. Laboratory evidence was used whenever available. In cases where the clinical histories were suggestive of adverse effects and laboratory data were not available, however, the

patient was classified as having the adverse effect in question. DSM IV criteria were used for diagnosing depression.

### Analysis

All data were entered in Microsoft Excel (97); means, standard deviations, and frequencies were calculated using Epi-Info 6.0 (CDC, Atlanta, GA).

## RESULTS

A total of 60 patients had received at least 6 months of therapy at the time of this analysis. The median age of these patients was 26 (range 12–60) years and the median duration of therapy at the time of evaluation was 20.0 (range, 6–25) months. Of these patients, 29 (48.3%) were female. The median initial weight for these patients was 52 kg (see Table 2).

One-half (50.0%) had one or more comorbid conditions at the time of enrollment in individualized MDR-TB therapy; depression (defined using DSM IV criteria) was the most frequent baseline finding, occurring (alone or with other conditions) in 38.3% of the patient population. Other comorbid conditions at MDR-TB diagnosis included HIV (1.7%); alcoholism (3.3%); type 2 diabetes (1.7%); epilepsy (1.7%); aortic stenosis (1.7%); prostatic hypertrophy (1.7%); and cerebrovascular disease (1.7%).

Table 3 lists the medications and the dosages commonly used to treat MDR-TB patients in this program. The percentage of patients recorded is the percentage receiving each drug for at least one month.

MDR-TB patients in this treatment cohort received a median of 8.0 (5–12) anti-tuberculosis drugs. All patients received a minimum of 6 months of daily therapy with at least one parenteral agent (streptomycin, kanamycin, amikacin or capreomycin). The median duration of DOTS-Plus therapy with a parenteral medication was 20 (3–46) months, representing a median cumulative dose of 338 g. For patients who were infected with strains of *M. tuberculosis* resistant to seven or more drugs, concurrent use of two parenteral agents was considered, depending on the degree of parenchymal damage and clinical response to therapy;

**Table 2** Patient characteristics (*n* = 60)

Patient characteristic	Percentage or median (range)
Median age	26 (12–60) years
Sex	51.7% male 48.3% female
Median weight at start of therapy	52 (36–81) kg
Median length of time on MDR-TB treatment	20.0 (6–25) months
Median number of anti-tuberculosis drugs received in DOTS-Plus regimen	8.0 (5–12)
Percentage with one or more baseline comorbid conditions	50.0%
Percentage with depression as only baseline comorbidity	26.7%

**Table 3** Medications and dosages delivered to DOTS-Plus patients

Medication	Maximum dosage	Number of patients receiving each agent (%)
Isoniazid (INH)	900 mg twice weekly	25 (41.7)
Rifampicin (RMP)	600 mg/day	3 (5.0)
Pyrazinamide (PZA)	30 mg/kg/day	23 (38.3)
Ethambutol (EMB)	25 mg/kg/day	17 (28.3)
Streptomycin (SM)	1 g/day	23 (38.3)
Kanamycin (KM)	1 g/day	22 (36.7)
Capreomycin (CM)	1 g/day	42 (70.0)
Amikacin (AMK)	1 g/day	8 (13.3)
Ciprofloxacin (CPX)	1500 mg/day	53 (88.3)
Ofloxacin (OFX)	800 mg/day	7 (11.7)
Sparfloxacin (SPX)	400 mg/day	9 (15.0)
Ethionamide (THA)	1000 mg/day	49 (81.7)
Cycloserine (CS)	1000 mg/day	60 (100)
Para-aminosalicylic acid (PAS)	12 g/day	57 (95.0)
Clofazimine (CFZ)	300 mg/day	27 (45)
Amoxicillin-clavulanic Acid (AMX-CLV)	1500 mg/day	38 (63.3)
Clarithromycin (CLR)	1000 mg/day	3 (5.0)
Rifabutin (RFB)	300 mg/day	1 (1.7)
Thiacetazone (THZ)	150 mg/day	1 (1.7)

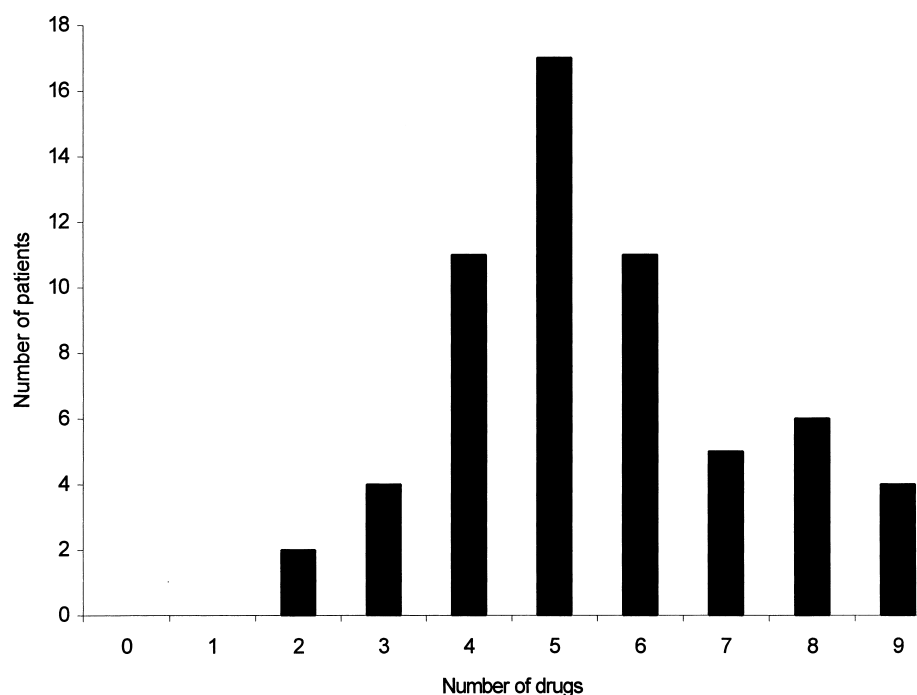
5% (three) of the patients received more than one parenteral medication concurrently and all three had resistance to nine or more anti-tuberculosis medications. One of these patients died of what appeared to be bacterial sepsis, and did have an elevated creatinine in this setting; the other two did not experience additional toxicity from the two parenteral medications.

The resistance patterns of the 60 patients are reported in the Figure. The infecting isolates of these patients were found to be resistant to a median of 6 (2–12) drugs. All were sick with strains resistant to at least isoniazid and rifampicin, and most were sick with strains resistant to all of the first-line drugs used in the initial treatment and retreatment regimens of Peru's National TB Program.

Life-threatening adverse effects were rare in this cohort (Table 4). Only two patients (3.3%) experienced renal toxicity, which was diagnosed after a median of 14.5 months of therapy; one (1.7%) was diagnosed with hepatitis after 3 months of therapy.

A few side effects were more common. Nearly half of the patients (43.3%) experienced dermatological effects: bronzing occurred in 25 and photosensitivity in two (not shown). Peripheral nervous system effects occurred in 12 patients (20%) after a median of 7.5 months of therapy. Depression was also relatively common; it was newly diagnosed in 11 (18.3%) patients after a median of 8.5 months. Although 7 of 60 patients experienced adverse effects serious enough to require the suspension of one or more of the anti-tuberculosis medications they were receiving, none of the patients had reactions requiring the complete discontinuation of treatment.

Patients responded well to these multidrug regi-



**Figure** Frequency of resistance at treatment initiation in cohort ( $n = 60$ ).

mens; preliminary treatment results in this cohort have been reported elsewhere.<sup>55</sup> Fifty of the 60 (83.3%) were culture-negative at the time of this analysis; two (3.3%) had abandoned therapy; seven (11.7%) had died (four while culture-positive and three while culture-negative); only one patient (1.7%) remained smear-positive after 6 months of multidrug therapy.

## DISCUSSION

Most adverse effects occurred surprisingly infrequently in this cohort of Peruvian MDR-TB patients

receiving individualized MDR-TB therapy. We had expected these effects to occur as frequently as or more frequently than reported in the literature in light of the long anti-tuberculosis treatment history and the extensive use of toxic second-line drugs that distinguish these patients from those in most other cohorts. Patients in this cohort had received a median of 3 (1–8) anti-tuberculosis regimens before beginning individualized therapy for MDR-TB.

A review of the literature shows the frequency of side effects in the northern Lima cohort relative to the frequency in other cohorts (see Table 5). These studies represent the collective experiences of thousands of patients receiving a broad range of treatment regimens for both drug-susceptible and drug-resistant disease. In one 1993 landmark study on the treatment of MDR-TB, Goble and colleagues report that 30% of patients had adverse effects requiring discontinuation of one or more anti-tuberculosis medications.<sup>56</sup> Although the northern Lima cohort received comparable regimens at comparable doses for comparable periods of time, discontinuation was not as common; in less than 20% of patients were one or more drugs suspended.

Not only was discontinuation less common, but certain adverse effects were reported less frequently in the northern Lima cohort than might have been expected based on prior experience. Of note, hepatitis occurred in only 1.7% of this cohort, while in previous studies this condition has been reported to occur in as many as 30% of patients. Although mild gastritis was frequent in this cohort, severe gastrointestinal effects—characterized by gastric bleeding—were rare, occurring in only one patient (1.7%). Renal failure,

**Table 4** Incident adverse effects in treatment cohort ( $n=60$ )

Adverse effect	Patients experiencing each effect $n$ (%)	Mean interval from initiation of therapy to occurrence of adverse effect in months (SD)
Mild gastritis	60 (100)	Not available
Dermatological effects	26 (43.3)	Not available
Peripheral nervous system	12 (20.0)	9.0 (4.6)
Depression	11 (18.3)	9.1 (4.9)
Anxiety	7 (11.7)	8.5 (4.7)
Hypothyroidism	6 (10.0)	10.8 (2.3)
Psychotic symptoms	6 (10.0)	3 (4.4)
Central nervous system (seizure or intractable headache)	5 (8.3)	6.4 (2.4)
Arthralgias/arthritis	4 (6.7)	7.8 (7.5)
Hearing loss	4 (6.7)	13.8 (7.7)
Renal toxicity	2 (3.3)	14.5 (2.1)
Hepatitis	1 (1.7)	3 (0.0)
Severe gastritis	1 (1.7)	1 (0.0)
Optic neuritis	0 (0.0)	0.0

**Table 5** Frequency of reported side effects in patients receiving anti-tuberculosis therapy

Adverse effect	Frequency reported in Lima cohort (%)	Frequency reported in the literature (%)
Psychiatric effects (including one or more of the following: depression, anxiety, psychosis)	36.7	3–13 <sup>57–61</sup>
Peripheral neuropathy	16.7	<1 <sup>26,33,57,62–65</sup>
Hypothyroidism	10.0	≥23 <sup>66–70</sup>
Central nervous system effects	8.3	1.5–30 <sup>33–35,42,44,45,57,59,71,72</sup>
Hearing loss	6.7	4–25 <sup>26,32,34,47,73,74</sup>
Musculoskeletal (arthralgia/arthritis)	6.6	up to 70 <sup>33,75,76</sup>
Renal failure	3.3	9–13 <sup>26,33,47,48,77</sup>
Hepatitis	1.7	0.5–30 <sup>25,27,30,57,78–80</sup>
Severe gastrointestinal effects	1.7	1.5–35 <sup>26,32,33,41,42,49</sup>
Mild gastritis	100	6–60 <sup>26,33,34,81,82</sup>
Ocular effects	0.0	

optic neuritis, and hypothyroidism all also occurred much less frequently in the northern Lima cohort than in other study populations, although it should be noted that due to a lack of resources only patients with symptoms of hypothyroidism (e.g., constipation, dry skin, fatigue, myxedema), a palpable thyroid or those with depression were screened by checking serum TSH (thyroid stimulating hormone) levels. This may have resulted in a falsely low prevalence of hypothyroidism in this cohort.

The lower than expected frequency of certain adverse effects and of discontinuation of therapy may be attributable to a number of factors. First, the Lima cohort had frequent contact with providers—usually three times daily. This permitted close monitoring of potential adverse effects and prompt implementation of management strategies designed to minimize these effects. Second, the patients in the Lima cohort were acutely aware of the seriousness of their disease and the absence of options for cure if they chose to discontinue therapy. All had chronic MDR-TB, and most had failed previous regimens of empiric short-course chemotherapy and had been declared untreatable by local providers (and international policy for resource-poor countries).

Some effects were, however, more common in the northern Lima cohort than in other published studies. These include depression, which was newly diagnosed in 18.3% of patients. Although 100% of the cohort received cycloserine—making comparison within the group impossible—it is remarkable that depression was by far the most common comorbid condition diagnosed *prior to* the initiation of MDR-TB therapy. Most of these patients were living in extremely difficult socio-economic circumstances and had a hopeless medical prognosis on diagnosis with MDR-TB. Notably, many patients diagnosed as depressed at the outset of therapy had a decrease in dysphoria with therapy: 39% of patients with depression diagnosed at the outset of therapy were no longer depressed after 6 months of therapy.

Peripheral neuropathy was also encountered more

frequently than expected in this population: 16.7% of the population had significant peripheral neuropathy, as compared to less than 1% of patients receiving a range of anti-tuberculosis therapies reported in the literature. It should be noted, however, that all 10 patients experiencing peripheral neuropathy had received previous regimens containing at least one neurotoxic drug prior to beginning treatment for MDR-TB; 90% received more than one of these agents (streptomycin, isoniazid, ethionamide). Furthermore, patients in this cohort had, in addition to previous exposure to aminoglycosides, high-grade resistance and significant lung parenchymal damage. Many patients with long histories of previous failed therapies elected to continue therapy with drugs felt to be likely culprits; all received high-dose pyridoxine (which may have paradoxically contributed to a worsening of neuropathy), and many received other agents (such as tricyclics, gaba-pentin) in order to attenuate neurotoxicity. As noted, cumulative doses of aminoglycosides and capreomycin were high in this cohort.

## CONCLUSIONS

There are several limitations to the data reported above. First, the study was done retrospectively and is thus limited. Prospective studies on a second cohort of patients are currently underway. Second, due to lack of resources, screening could not be performed on all patients for all the conditions mentioned above. This may have led to an underestimate of the prevalence of some of the adverse effects in this cohort. In spite of these limitations we believe that these data yield important information regarding the adverse effects observed using second-line anti-tuberculosis agents to treat MDR-TB in resource-poor settings.

The theoretical risk of adverse effects often prevents physicians and public-health officials from taking proper action to treat MDR-TB. In a cohort of young, chronic patients without severe comorbid disease, however, it appears that even high-dose, multi-

drug regimens—even when received for as long as 24 months—rarely cause life-threatening adverse effects. Most adverse effects were either tolerated by patients or relieved with palliative measures delivered in the home. Although regimens were adjusted, discontinuation of therapy due to the occurrence of an adverse effect was never indicated. This success also underscores the importance of community-health worker participation in this treatment-delivery strategy, which allowed early identification of adverse effects and timely intervention. In this cohort, most adverse effects were managed on an out-patient basis with the help of simple clinical algorithms and input from a team of international MDR-TB experts. These results are encouraging, and offer another compelling reason to provide adequate and timely therapy for persons with MDR-TB. We conclude that individualized MDR-TB therapy is possible, even under difficult field conditions with the supervision of international experts in the field of MDR-TB. The very low rate of default in this cohort offers hope that strategies to manage adverse effects may reduce the incidence of abandonment of therapy and increase rates of cure.

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## R É S U M É

**CADRE :** Un programme de traitement basé sur la collectivité et s'adressant à la tuberculose à germes multi-résistants (TB-MR) dans un bidonville urbain de Lima au Pérou.

**OBJECTIFS :** Mettre en évidence l'apparition d'effets collatéraux sérieux associés au traitement pour la TB-MR dans le Nord de Lima au Pérou où le traitement est individualisé en fonction des tests de sensibilité des souches infectantes des patients et administré grâce à un programme basé sur la collectivité.

**SCHÉMA :** Revue rétrospective des dossiers de 60 patients qui avaient reçu un traitement individualisé pour une TB-MR entre septembre 1996 et octobre 1998.

**RÉSULTATS :** Bien que les effets collatéraux aient été fréquents, ils sont survenus moins souvent qu'on ne l'a signalé antérieurement dans la littérature et n'ont constitué que rarement une menace pour la vie. Les effets collatéraux les plus fréquents dans cette population ont comporté : une gastrite légère (100%), des symptômes

dermatologiques (43,3%), une neuropathie périphérique (16,7%), une dépression (18,3%), et de l'anxiété (11,7%). Ces effets n'ont jamais entraîné l'interruption du traitement antituberculeux et n'ont provoqué qu'occasionnellement la suspension de l'administration d'un médicament (11,7%).

**CONCLUSION :** Chez de jeunes patients où la co-morbidité est faible, des régimes au long cours faisant appel à de multiples médicaments ne causent qu'exceptionnellement des effets collatéraux menaçant la vie. Les effets collatéraux habituels peuvent être pris en charge avec succès sur une base ambulatoire, même dans des contextes à faibles ressources, grâce à un programme de traitement basé sur la collectivité, en collaboration avec des experts de la TB-MR. Le taux très bas d'abandons dans cette cohorte permet d'espérer que les stratégies pour la prise en charge des effets collatéraux pourront diminuer l'incidence des abandons de traitement et augmenter les taux de guérison.

## R E S U M E N

**MARCO DE REFERENCIA :** Un programa de tratamiento basado en la comunidad para tuberculosis multirresistente (TB-MR) en un barrio urbano de Lima, Perú.

**OBJETIVOS :** Determinar la existencia de reacciones adversas graves asociadas con el tratamiento de TB-MR en el norte de Lima, Perú, donde se individualizó la terapia de acuerdo con las pruebas de sensibilidad de las cepas y se la suministró a través de un programa basado en la comunidad

**MÉTODO :** Informe retrospectivo de 60 pacientes que recibieron un tratamiento individualizado por TB-MR entre el mes de setiembre de 1996 y octubre de 1998.

**RESULTADOS :** Aunque las reacciones adversas fueron frecuentes, no lo fueron tanto como lo refiere la bibliografía y raramente ponían en peligro la vida. Las reacciones más frecuentes en esta población fueron : gas-

tritis moderada (100%), reacciones cutáneas (43,3%), neuropatías periféricas (18,3%), depresión (16,7%) y ansiedad (11,7%). Estas reacciones nunca produjeron la interrupción del tratamiento antituberculoso y sólo ocasionalmente llevaron a la suspensión de una droga (11,7%).

**CONCLUSIÓN :** En pacientes jóvenes con poca co-morbididad, los esquemas múltiples y prolongados producen raramente reacciones que ponen en riesgo la vida. Las reacciones adversas comunes pueden ser manejadas con éxito en un régimen ambulatorio en programas basados en la comunidad junto con expertos en TB-MR, aún en ambientes con escasos recursos. La baja tasa de abandonos en esta cohorte sugiere que las estrategias para manejar las reacciones adversas pueden reducir la incidencia de abandonos y aumentar las tasas de curación.