

Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative

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SUMMARY

Adverse events associated with second-line drugs have been mentioned as obstacles in the management of multidrug-resistant tuberculosis (MDR-TB). Data on adverse events were collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast). The results show that among 818 patients enrolled on MDR-TB treatment only 2% of patients stopped treatment, but

30% required removal of the suspected drug(s) from the regimen due to adverse events. The study shows that adverse events are manageable in the treatment of MDR-TB in resource-limited settings provided that standard management strategies are applied.

KEY WORDS: MDR-TB; DOTS-Plus; adverse events; second-line drugs

MULTIDRUG-RESISTANT tuberculosis (MDR-TB), defined as TB resistant to at least isoniazid and rifampicin, is a threat to DOTS, the World Health Organization (WHO) recommended strategy for TB control. In 1999, WHO and its partners launched the DOTS-Plus for MDR-TB initiative to develop global policy on the management of MDR-TB and to enable access to second-line drugs under rational use. As part of this process, and under the continuous monitoring of the Green Light Committee (GLC), several DOTS-Plus pilot projects have been established to evaluate the feasibility and cost-effectiveness of using second-line drugs for managing MDR-TB.¹ Adherence to treatment is a critical factor in the management of MDR-TB, and adverse events associated with second-line drugs could have a severe impact on adherence.² Limited evidence of adverse events is available from resource-limited settings.³⁻⁶ This report presents data on adverse events from five DOTS-Plus pilot projects in resource-limited settings.

STUDY POPULATION AND METHODS

Data were collected using a standard data collection form from DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Rus-

sian Federation (Tomsk Oblast). The sites were asked to select from a list of 25 adverse events, but were also given the opportunity to list additional adverse events. Patients enrolled at each site who completed at least one month of treatment between October 1998 and December 2002 were considered for analysis.

Adverse events were assessed for second-line drugs included in the WHO Model List of Essential Drugs: amikacin (AMK), capreomycin (CM), ciprofloxacin (CFX), cycloserine (CS), ethionamide (ETH), kanamycin (KM), ofloxacin (OFX), para-aminosalicylic acid (PAS), and prothionamide (PTH). Drugs belonging to the same pharmaceutical class were grouped as follows: AMK and KM as aminoglycosides, ETH and PTH as thioamides, and CFX and OFX as fluoroquinolones. Drugs were administered at the following daily dosages: AMK (1000 mg or 15 mg/kg), CM (1000 mg), CS (500-1000 mg), CFX (750-1500 mg), ETH (500-1000 mg), KM (1000 mg or 15 mg/kg), OFX (600-800 mg), PAS (8-12 g), and PTH (500-1000 mg). Aminoglycosides and CM were administered for between 6 and 18 months, and the other drugs for 18-24 months. Treatment regimens varied across projects, as the treatment is tailored according to drug susceptibility patterns.

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Table 1 Treatment continuity in patients enrolled on MDR-TB treatment and included in this analysis (Estonia, Latvia, Peru [Lima], the Philippines [Manila] and the Russian Federation [Tomsk Oblast])

	Estonia <i>n</i> (%)	Latvia <i>n</i> (%)	Peru (Lima) <i>n</i> (%)	Philippines (Manila) <i>n</i> (%)	Russia (Tomsk Oblast) <i>n</i> (%)	Total <i>n</i> (%)
Patients enrolled in MDR-TB treatment	136 (16.6)	367 (44.9)	73 (8.9)	85 (10.4)	157 (19.2)	818 (100)
Patients who stopped treatment due to adverse reactions	4 (2.9)	6 (1.6)	0 (0)	7 (8.2)	0 (0)	17 (2.1)
Patients who required drug removal from the regimen due to adverse reactions	58 (42.6)	89 (24.2)	25 (34.2)	42 (49.4)	31 (19.7)	245 (30.0)
	0.34–0.51*	0.20–0.29*	0.23–0.45*	0.39–0.60*	0.14–0.26*	0.27–0.33*

* 95% confidence limit.

MDR-TB = multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampicin).

RESULTS

In total, 818 patients enrolled on MDR-TB treatment in Estonia (136 patients), Latvia (367 patients), Peru (Lima) (73 patients), the Philippines (Manila) (85 patients) and the Russian Federation (Tomsk Oblast) (157 patients) were included in the study. Only 2.1% (17/818) of the patients stopped treatment, but 30% (245/818) required removal of the suspected drug(s) from the regimen due to adverse events (Table 1). In Table 2, results are reported for adverse events occurring in at least two projects and in more than 1% of the sample population (22 of 70 total adverse events). To ensure consistency in reporting suspect drugs, only

Table 2 Frequency of adverse events and suspected agents among 818 patients receiving MDR-TB treatment in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast)

Adverse event*	Suspected agent(s) [†]	Affected <i>n</i> (%)
Nausea/vomiting	PAS, TM, FQ	268 (32.8)
Diarrhoea	PAS, TM	173 (21.1)
Arthralgia	FQ, TM, CS, AG	134 (16.4)
Dizziness/vertigo	CS, CM, AG, FQ	117 (14.3)
Hearing disturbances	CM, TM, AG	98 (12.0)
Headache	CS, FQ	96 (11.7)
Sleep disturbances	CS, FQ	95 (11.6)
Electrolyte disturbances	CM, TM	94 (11.5)
Abdominal pain	PAS, TM	88 (10.8)
Anorexia	PAS, TM	75 (9.2)
Gastritis	TM, PAS	70 (8.6)
Peripheral neuropathy	TM, AG, CS	65 (7.9)
Depression	CS	51 (6.2)
Tinnitus	CM, CS, AG	42 (5.1)
Allergic reaction	FQ	42 (5.1)
Rash	FQ, PAS	38 (4.6)
Visual disturbances	CS, TM	36 (4.4)
Seizures	CS	33 (4.0)
Hypothyroidism	TM, PAS	29 (3.5)
Psychosis	CS	28 (3.4)
Hepatitis	TM	18 (2.2)
Renal failure/nephrotoxicity	AG, CM	9 (1.2)

* Adverse events occurring in at least two projects and in more than 1% of the sample population are listed.

[†] To ensure consistency, only drugs suspected in at least two projects for a particular adverse event are presented.

MDR-TB = multidrug-resistant tuberculosis (resistance to at least isoniazid and rifampicin); PAS = para-aminosalicylic acid; TM = thioamides; FQ = fluoroquinolones; CS = cycloserine; AG = aminoglycosides; CM = capreomycin

those drugs suspected by at least two projects for a particular adverse event are presented. The five most common adverse events were nausea/vomiting (32.8%), diarrhoea (21.1%), arthralgia (16.4%), dizziness/vertigo (14.3%) and hearing disturbances (12%) (Table 2).

DISCUSSION

These data are the first available evidence of the prevalence of adverse events associated with the use of second-line drugs within the context of GLC-approved DOTS-Plus pilot projects in resource-limited settings and within the aegis of the national tuberculosis control programme. Although the management of MDR-TB is a complex health intervention requiring multidrug therapy for 18–24 months, this study demonstrates that adverse reactions do not appear to be a major obstacle to the implementation of DOTS-Plus projects. Studies undertaken in non-resource-limited settings (the United States and Hong Kong) show that respectively 30% and 19% of MDR-TB patients had to discontinue the suspected drug(s) as a result of adverse events.^{7,8} These findings are similar to the results found in this cohort of MDR-TB patients and indicate that adverse events can also be appropriately managed in resource-limited settings. There are several possible explanations for the differences in the number of patients requiring drugs to be removed from the regimen due to adverse events in Latvia and the Russian Federation compared to in Estonia and the Philippines (Table 1). These include differences in training, variation in health care workers' ability to detect adverse events and the use of different treatment regimens and combinations of drugs. Only 2.1% of patients stopped treatment due to adverse events. This is likely due to the aggressive management strategies adopted by DOTS-Plus projects. These include altering dosages when appropriate, administration of ancillary drugs to treat adverse events, and discontinuation of some drugs. In addition, all projects have conducted special training on adverse events to second-line drugs and have developed standard protocols for

their registration. Adverse events can be detected by community health workers or nurses, but in all five sites the diagnoses are confirmed by a physician.

CONCLUSIONS

Some limitations exist in this analysis. First, the projects did not use standardised definitions of adverse events, their diagnosis or their degree of severity. Consequently, the frequency and severity of events reported may have been variable across programmes. Next, most programmes use additional drugs to treat patients with MDR-TB. These include first-line drugs and other second-line drugs that are also associated with adverse events. As a result, although we present drugs 'suspected' of causing adverse events, other drugs may have contributed to these events. In addition, this group of patients used second-line drugs (i.e., those on the WHO Model List of Essential Drugs) provided by the same procurement agency to ensure drug quality. The quality of the first-line drugs and other second-line drugs is not regulated in the same way and may be a factor associated with adverse events. Lastly, conditions present at baseline may have been reported as adverse events in some groups, leading to an overestimation of events in the population.

In spite of these limitations, in 98% of patients with MDR-TB treated with second-line drugs in five sites it was possible to avoid the complete cessation of therapy. Nevertheless, to promote effective and rational use of second-line drugs in DOTS-Plus settings, standard protocols for the management of adverse

events should be developed based on the validation of existing protocols.

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References

- 1 Gupta R, Cegielski J P, Espinal M A, et al. Increasing transparency in partnerships for health: introducing the Green Light Committee. *Trop Med Int Health* 2002; 7: 970-976.
- 2 World Health Organization. Guidelines for establishing DOTS-plus pilot projects for the management of MDR-TB. In: Gupta R, Arnadottir T, eds. WHO/CDS/TB/2000.279. Geneva, Switzerland: WHO, 2000.
- 3 Tahaoglu K, Torun T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001; 345: 170-174.
- 4 Suarez P G, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of a standardised second-line drugs treatment for chronic tuberculosis patients: national cohort study in Peru. *Lancet* 2002; 359: 1980-1989.
- 5 Furin J J, Mitnick C D, Shin S S, et al. Occurrence of serious adverse events in patients receiving community based therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2001; 5: 648-655.
- 6 Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348: 119-128.
- 7 Goble M, Iseman M D, Madsen L A, Waite D, Ackerson L, Horsburgh C R Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328: 527-532.
- 8 Yew W W, Chan C K, Chau C H, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000; 117: 744-751.

RÉSUMÉ

Des effets défavorables associés aux médicaments de deuxième ligne ont été signalés comme obstacles à la prise en charge des tuberculoses à germes multirésistants (TB-MR). Les données concernant les effets défavorables ont été recueillies dans cinq sites DOTS-Plus en Estonie, en Lituanie, au Pérou (Lima), aux Philippines (Manille) et dans la Fédération Russe (Oblast de Tomsk). Les résultats montrent que parmi 818 patients enrôlés

dans un traitement TB-MR, 2% seulement ont dû arrêter le traitement, mais que chez 30%, l'existence d'effets défavorables a exigé de retirer du régime les médicaments suspectés. L'étude montre qu'il est possible de prendre en charge les effets défavorables dans le traitement de la TB-MR dans des contextes à ressources limitées, pourvu que l'on applique les stratégies standard de prise en charge.

RESUMEN

Los efectos adversos asociados a las drogas anti-tuberculosas de segunda línea han sido mencionados como un obstáculo para el manejo de la tuberculosis multiresistente a drogas. Cinco proyectos DOTS-Plus en Estonia, Letonia, Perú (Lima), Filipinas (Manila) y Rusia (Tomsk) recolectaron datos sobre efectos adversos a estas drogas.

Los resultados muestran que entre 818 pacientes en tratamiento solo 2% suspendieron tratamiento, y 30% requirieron cambio de droga debido a reacciones adversas. Este estudio muestra que los efectos adversos en el tratamiento de tuberculosis multiresistente son manejables con estrategias estandarizadas en sitios con recursos limitados.