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High levels of resistance to second-line anti-tuberculosis drugs among prisoners with pulmonary tuberculosis in Georgia

L. Jugheli,*† L. Rigouts,* I. C. Shamputa,*‡ W. Bram de Rijk,* F. Portaels*

*** Mycobacteriology Unit, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium; † International Committee of the Red Cross, Tbilisi, Georgia; ‡ Microbiology Unit, Tropical Diseases Research Centre, Ndola, Zambia**

SUMMARY

SETTING: Penitentiary system of Georgia.

OBJECTIVE: To determine the prevalence of resistance to second-line drugs among prisoners with pulmonary tuberculosis (PTB).

DESIGN: Retrospective evaluation of resistance to second-line drugs in tuberculosis (TB) patients treated from 2001 to 2003.

RESULTS: The overall observed prevalence of multidrug-resistant TB (MDR-TB) was 14.4% (39/270). The lowest resistance was found for ofloxacin (OFX), which was 2.2% (6/270) overall and 5.1% (2/39) among MDR patients. Isolates from four non-MDR patients who had never received anti-tuberculosis treatment were found to be resistant to OFX. Resistance to kanamycin and capreomycin occurred simultaneously only among MDR patients and was observed in 17/39 cases (43.6%). High rates of resistance to ⩾2 second-line drugs (18/39, 46.2%) and ⩾3 second-line drugs (10/39, 25.6%) were observed among all MDR-TB patients, reaching respectively 59.3% and 29.6% among previously treated MDR-TB cases. Only one patient was found to be resistant to four second-line drugs. No extensively drug-resistant TB (XDR-TB) according to the latest definition was detected.

CONCLUSION: Our findings reveal a serious threat to the TB control efforts in the study population.

KEY WORDS: MDR-TB; XDR-TB; TB in prisons

TUBERCULOSIS (TB) remains a public health threat, particularly in the developing world. Although the first-line anti-tuberculosis drugs rifampicin (RMP), isoniazid (INH), ethambutol (EMB, E), pyrazinamide (PZA) and streptomycin (SM, S) were discovered several decades ago, they are still used today in standard short-course regimens for the treatment of TB. These regimens are, however, ineffective for treating patients infected with multidrug-resistant TB (MDR-TB, defined as resistance to at least the two most powerful anti-tuberculosis drugs, RMP and INH), leading to the use of less effective and more toxic second-line drugs (SLD), such as aminoglycosides, fluoroquinolones, para-aminosalicylic acid (PAS), ethionamide (ETH) and capreomycin (CM) for treatment of MDR-TB.[1]

The collapse of public health infrastructures and the worsening of economic conditions after the collapse of the Soviet Union led to a rapid increase in the occurrence of TB in the former Soviet republic of Georgia. Prisoners were particularly affected by this political and economic turmoil. A study carried out in 1997 showed that the prevalence of TB in the penitentiary system was 5995 cases per 100 000,[2] nearly 200 times more than the World Health Organization (WHO) reported prevalence for smear-positive TB in the general population of Georgia. Of all patients included in this study, 77.9% were resistant to at least one first-line drug and 13.0% had MDR-TB.[2]

The International Committee of the Red Cross (ICRC) has been supporting the Ministry of Justice of Georgia in running the DOTS-based TB control programme in the penitentiary system since 1998. After the successful implementation of the programme, a proposal was submitted to the Green Light Committee (GLC) to start treatment of incarcerated MDR-TB patients, and permission was granted. (The GLC is a WHO initiative that helps countries gain access to high-quality SLDs for treatment of people with MDR-TB in line with WHO guidelines.)

This retrospective study was undertaken 1) to determine the prevalence of resistance to SLDs among prisoners with pulmonary TB (PTB) in Georgia, and 2) to assess the future strategy for applying SLD-based regimens according to the drug resistance patterns found.

MATERIALS AND METHODS

The present study was conducted from 2001 to 2003, in all prisons of Georgia except for pre-trial detention

Correspondence to: Françoise Portaels, Mycobacteriology Unit, Institute of Tropical Medicine, B-2000 Antwerp, Belgium. Tel: (+32) 3 247 6317. Fax: (+32) 3 247 6333. e-mail: portaels@itg.be

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centres, with the approval of the country's Ministry of Justice. The samples tested were drawn from a larger study on the prevalence of mixed *Mycobacterium tuberculosis* infection.[3] At least one specimen was collected from each consecutive newly registered sputum smear-positive patient and cultured for drug susceptibility testing (DST) against first- and second-line drugs. No patient was sampled twice. Considerable effort was made to identify patients as new or retreatment cases. New cases were defined as patients who, on direct inquiry, denied any previous anti-tuberculosis treatment or had been treated for <1 month. Retreatment cases were defined as those who acknowledged previous anti-tuberculosis treatment for >1 month. This definition also included patients who relapsed after previous successful TB treatment, those whose treatment had failed and those who had defaulted and had returned to the health provider.

The samples, preserved in 0.5% cetylpyridinium chloride medium at room temperature, were decontaminated using a modified Petroff method[4] and inoculated onto Löwenstein-Jensen (LJ) medium at the Georgian National Reference Laboratory (NRL). The *M. tuberculosis* isolates obtained were sent to the Institute of Tropical Medicine (Antwerp, Belgium) for DST. After initial DST and DNA fingerprinting analyses,[3] isolates were stored at −70°C and recovered on LJ medium for the present study.

DST was performed according to the standard proportion method[5] against a single critical concentration of five SLDs: kanamycin (KM), ofloxacin (OFX), CM, ETH and PAS. The concentrations used were respectively 6.0, 4.0, 10.0, 10.0 and 0.5 μg/ml. All pure active substances were obtained from Sigma-Aldrich (Bornem, Belgium) or Acros Organon (Geel, Belgium). Middlebrook 7H11 agar (BD Diagnostic Systems, Sparks, MD, USA) was used for all drugs except for PAS, which was tested on LJ medium.

All tubes were incubated at 37°C with 5% CO_2 supply (except for PAS). The results were read after 28 days of incubation, and resistance was reported when colonies in the drug-containing tubes appeared ⩾1% compared to the drug-free control. DNA fingerprinting was carried out for all OFX- and CM/KM-resistant isolates by insertion sequence IS*6110*-restriction fragment length polymorphism (RFLP),[6] and profiles were compared using the BioNumerics software (version 3.0, Applied Maths, Sint-Martens-Latem, Belgium).

Collection of patient data was done from and restricted to the study file of the initial study.[3] This anonymised file was stored at the NRL in Tbilisi, Georgia. Statistical analysis was carried out using Stata 8.0 (Stata Corporation, College Station, TX, USA).

Ethical approval was not required for this retrospective study.

RESULTS

A total of 458 *M. tuberculosis* isolates were obtained from all newly registered sputum smear-positive male patients admitted to the prison TB hospital during the study period. As all isolates were sent abroad, DST for the first- and second-line drugs was performed for only 270 strains, due to transportation delays and loss of viability. The median age of the tested group was 30 years (range 20–63), which is comparable to the group of patients excluded (29.5 years, range 20–73). Rank sum test showed that the age distribution of both groups was not significantly different ($P = 0.54$).

A total of 183 (68%) *M. tuberculosis* isolates were obtained from new cases and 87 from retreatment cases (Table 1). An analysis of the treatment history of included and excluded patients showed that the test group mainly comprised new cases (68%), while the majority of the excluded patients were retreatment cases ($P < 0.001$). Thirty-nine (14.4%) strains were found to be MDR, of which 12 were from new cases and 27 from previously treated patients (Table 1). Among the isolates from 231 non-MDR patients, 56 showed resistance to INH and 175 were pan-susceptible or resistant to SM and/or EMB (Table 2).

Table 1 compares the number of strains resistant to each SLD separately for all 270 patients in comparison to the 39 MDR patients. While the highest percentage of resistance to a single SLD among all non-MDR patients was 6.7% (ETH), among MDR patients it was more than 6-fold higher (43.6%) for KM and CM. Resistance to these two drugs was not found among

Table 1 Resistance of *M. tuberculosis* isolates to each second-line drug individually

		All patients			MDR patients		
Second-line drugs	Concentration, mg/l	New cases (n = 183) n (%)	Previously treated cases (n = 87) n (%)	Total (N = 270) n (%)	New cases (n = 12) n (%)	Previously treated cases (n = 27) n (%)	Total (N = 39) n (%)
KM	6.0	2 (1.1)	15 (17.2)	17 (6.3)	2 (16.7)	15 (55.6)	17 (43.6)
CM	10.0	2 (1.1)	15 (17.2)	17 (6.3)	2 (16.7)	15 (55.6)	17 (43.6)
OFX	4.0	5 (2.7)	1 (1.1)	6 (2.2)	1 (8.3)	1 (3.7)	2 (5.1)
ETH	10.0	7 (3.8)	11 (12.6)	18 (6.7)	2 (16.7)	9 (33.3)	11 (28.2)
PAS	0.5	4 (2.2)	4 (4.6)	8 (3.0)	2 (16.7)	4 (14.8)	6 (15.4)

MDR = multidrug-resistant; KM = kanamycin; CM = capreomycin; OFX = ofloxacin; ETH = ethionamide; PAS = para-aminosalicylic acid.

Table 2 Complete second-line drug resistance profiles in relation to first-line resistance patterns

Resistance profiles	All patients (N = 270) n (%)	Pan-susceptible + S/E/SE resistant			H/HS/HE/HSE resistant			MDR patients		
		New cases (n = 132) n (%)	Previously treated cases (n = 43) n (%)	Total (n = 175) n (%)	New cases (n = 39) n (%)	Previously treated cases (n = 17) n (%)	Total (n = 56) n (%)	New cases (n = 12) n (%)	Previously treated cases (n = 27) n (%)	Total (n = 39) n (%)
Susceptibility to all SLDs	233 (86.3)	128 (97.0)	41 (95.3)	169 (96.6)	33 (84.6)	16 (94.1)	49 (87.5)	7 (58.3)	8 (29.6)	15 (38.5)
OFX	6 (2.2)	4 (3.0)	0	4 (2.3)	0	0	0	1 (8.3)	1 (3.7)	2 (5.1)
ETH	8 (3.0)	0	2 (4.7)	2 (1.1)	4 (10.3)	1 (5.9)	5 (8.9)	0	1 (3.7)	1 (2.6)
PAS	4 (1.5)	0	0	0	1 (2.6)	0	1 (1.8)	2 (16.7)	1 (3.7)	3 (7.7)
PAS-ETH	2 (0.7)	0	0	0	1 (2.6)	0	1 (1.8)	0	1 (3.7)	1 (2.6)
KM-CM	7 (2.6)	0	0	0	0	0	0	0	7 (25.9)	7 (17.9)
KM-CM-ETH	8 (3.0)	0	0	0	0	0	0	2 (16.7)	6 (22.2)	8 (20.5)
KM-CM-PAS	1 (0.4)	0	0	0	0	0	0	0	1 (3.7)	1 (2.6)
KM-CM-PAS-ETH	1 (0.4)	0	0	0	0	0	0	0	1 (3.7)	1 (2.6)

S = streptomycin; E = ethambutol; H = isoniazid; MDR = multidrug-resistant; SLD = second-line drug; OFX = ofloxacin; ETH = ethionamide; PAS = para-aminosalicylic acid; KM = kanamycin; CM = capreomycin.

non-MDR patients. The lowest resistance was detected for OFX.

Table 2 shows the complete SLD resistance profiles for patients broken down by the results of first-line DST. Of the 270 patients included in the study, 233 (86%) were susceptible to all SLDs tested and 18 (7%) were resistant to only one drug. As expected, the percentage of strains susceptible to SLD dropped from 96.6% among pan-susceptible and S/E/SE-resistant isolates to 38.5% among patients with MDR-TB, while the number of patients resistant to several drugs increased accordingly.

Alarmingly high rates of strains resistant to ⩾2 SLDs (16/27, 59.3%) and ⩾3 SLDs (8/27, 29.6%) were observed among previously treated MDR-TB patients. In contrast, 17% (2/12) were found to be resistant to >2 SLDs among new MDR-TB cases. Only one patient was found to be resistant to four SLDs. As shown in Table 2, resistance to OFX appeared only as monoresistance and was found among both MDR (n = 2) and non-MDR (n = 4) patients. Fingerprinting of these six isolates did not show any similarity in IS*6110*-RFLP patterns, suggesting independent acquisition of resistance. In contrast, none of the isolates were monoresistant to KM or CM; resistance to these two drugs was always seen in combination, and only among MDR-TB patients. Moreover, KM-CM resistance was seen mostly among previously treated patients. IS*6110*-RFLP fingerprinting of these isolates revealed a cluster comprising five isolates and another group of four isolates that were very similar, differing by only one or two IS*6110* bands, suggesting recent transmission.

According to the 'original' definition of extensively drug-resistant TB (XDR-TB), i.e., an MDR-TB case resistant to at least three of the six main classes of SLDs,[7] 25.6% of the patients harboured XDR-TB, while using the most recent definition, i.e., MDR-TB + resistance to any fluoroquinolone and to at least one of the three injectable drugs, none of the patients had XDR-TB.

DISCUSSION

This report is to our knowledge the first attempt to assess the prevalence of resistance to SLDs among prisoners in Georgia. Although patient intake was done systematically (inclusion of all smear-positive PTB cases) and is therefore representative, the final study population may not be completely representative.

Random selection occurred as a result of culturing, subsequent shipment, sub-culturing and DST of *M. tuberculosis* isolates. Complete DST results for all four first-line drugs and five SLDs were therefore available for only 270 of the 458 initially included isolates. As seen from the statistical analysis, the final study population differed significantly from the total population in the case distribution, as the number of new cases was higher in the study population. Given the fact that MDR-TB was observed mainly among retreatment cases and that resistance to SLDs was more prevalent among retreated MDR-TB cases, we conclude that this bias can only lead to underreporting of resistance to SLDs.

No data are yet available on resistance to either first- or second-line drugs among the civilian population of Georgia, and this prison-specific data should not be extrapolated to the general population. Nevertheless, our data from the prison situation can be of importance for the general population as well, as transmission of MDR-TB between these two settings is possible.[8]

In our study, we observed high levels of resistance to SLDs among MDR-TB patients, and our findings support data presented by Shah et al. from March 2006,[7] showing an even higher rate of XDR-TB (26%) than reported for the geographic region that includes Georgia (12–17%). The definition of XDR-TB was

redefined in October 2006, in the light of which none of the patients from our study group were XDR-TB. Nevertheless, the problem of high resistance rates in the study population remains a topical issue. According to the latest WHO publication,[1] two baseline principles are recommended when treating MDR-TB: 1) the regimens should consist of at least four drugs with certain, or almost certain, effectiveness against the infecting organism, and 2) anti-tuberculosis drugs should be placed into five groups in order of potency, evidence of efficacy and experience of use and drug class, and administered based on these groups. Patients classified as XDR-TB according to the 'old' definition are eligible for neither Group 1 (first-line) nor Group 2 (injectable) drugs, as all of them show resistance to these drugs. The latter are considered as one of the core elements for treating MDR-TB. Moreover, it is impossible to comply with the first WHO principle, as these patients are resistant to $\geqslant$3 anti-tuberculosis drugs. To design a treatment regimen for these prisoners, Group 5 drugs (clofazimine [CFZ], amoxicillin, clarithromycin and linezolid) should be utilised. These, however, are not recommended by the WHO for routine use in MDR-TB treatment, as these types of regimens are associated with worse outcomes for treatment of MDR-TB. The addition of INH in combination with CFZ to the regimens may be considered to contribute to the efficacy of the treatment, as demonstrated by Van Deun et al. in Bangladesh.[9]

It is unlikely that the observed rates of resistance to SLDs among prisoners occurred due to the acquisition of resistance following the official use of these drugs. In the Georgian penitentiary system, every prisoner has had access to high quality first-line treatment since 1998, but so far there has been no possibility of receiving professionally designed MDR-TB treatment when needed. Factors that may have contributed to this high level of resistance include uncontrolled circulation and use of SLDs within and outside the prison system, and reports of doctors prescribing one or two SLDs for several months at a time, against National Tuberculosis Programme recommendations. The most 'popular' SLDs available on the Georgian market, in order of importance, are KM/amikacin, OFX and prothionamide.

While the highest resistance was found for KM, which was expected because of its widespread use, quite unexpectedly all patients who were resistant to this drug were also resistant to CM. This latter drug is not widely available, is expensive and is therefore not utilised in Georgia. The observed resistance cannot therefore be fully explained by its misuse. A number of publications report cross-resistance between CM and KM.[10–13] These studies describe isolates resistant to CM and KM caused by mutations in the *rrs* gene. Tsukamura described isolates recovered from patients treated with KM as being resistant to KM and CM, and the resistance of these strains to CM varied with the level of KM resistance.[12] The isolates with a high level of KM resistance were generally CM-resistant,[12] which is consistent with our finding. Conversely, it is a well-known fact that common prison conditions such as overcrowding, poor ventilation and poor nutrition are the best grounds for the circulation of a limited number of strains. This may partially explain the spread of isolates with identical patterns of resistance to KM and CM, which is corroborated by DNA fingerprinting results, showing similarity of the strains in 52.9% (9/17) of the cases.

Another noteworthy finding was OFX resistance among patients who had never received anti-tuberculosis treatment and were susceptible to first-line drugs or resistant only to SM and/or EMB. This observation may be attributed to the wide use of fluoroquinolones due to its broad spectrum of activity against gram-negative and gram-positive organisms. Several reports suggest that resistance to quinolones may develop quite rapidly.[14–16] In a setting with a high incidence of TB, it is possible that patients who are in the early stage of TB without being diagnosed are treated for concomitant disease with quinolones, which then acts as monotherapy for TB. Monoresistance to fluoroquinolones has also been detected among non-MDR-TB patients in Benin (F Portaels, personal communication), Rwanda,[17] Taiwan[18] and Thailand.[19] In general, OFX resistance among MDR-TB prisoners in Georgia (5.1%) was comparable to ciprofloxacin resistance among MDR-TB patients from the Samara region in Russia (4.2%),[20] but was much lower than the 15.2% OFX resistance observed among MDR-TB patients in Taiwan.[18]

CONCLUSION

Despite its limitations, this study provides the first report on levels of resistance to SLDs among prisoners in Georgia. It also documents the existence of a group of patients who, without being XDR-TB, still constitute a serious threat to TB control efforts in prisons. The data presented underscore the serious problems stemming from misuse of anti-mycobacterial drugs. Great care should be taken to ensure full adherence to second-line treatment to prevent the generation of pan-resistant strains with the potential for transmission community-wide and virtually no possibility of cure for the patient.

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RÉSUMÉ

CONTEXTE : Le système pénitentiaire de Géorgie.
OBJECTIF : Déterminer la prévalence de la résistance aux médicaments de deuxième ligne chez les prisonniers atteints de tuberculose (TB) pulmonaire.
SCHÉMA : Evaluation rétrospective de la résistance aux médicaments antituberculeux de deuxième ligne chez les patients traités entre 2001 et 2003.
RÉSULTATS : La prévalence globale observée de la multirésistance (TB-MDR) a été de 14,4% (39/270). La résistance la moins fréquente a concerné l'ofloxacine (OFX), qui atteignait respectivement 2,2% (6/270) et 5,1% (2/39) parmi l'ensemble des patients et les patients MDR. Les isolats provenant de quatre patients non-MDR qui n'avaient jamais reçu aucun traitement antituberculeux se sont avérés résistants à l'OFX. La résistance à l'égard de la kanamycine et de la capréomycine s'est développée simultanément, uniquement chez les patients MDR, et a été observée dans 17 des 339 cas (43,6%). Des taux élevés de résistance à l'égard de ⩾2 médicaments de deuxième ligne (46,2% ; 18/39) et à l'égard de ⩾3 médicaments de deuxième ligne (25,6% ; 10/39) ont été observés chez tous les patients TB-MDR et ont même atteint respectivement 59,3% et 29,6% parmi les patients TB-MDR traités antérieurement. On n'a trouvé qu'un seul patient résistant à l'égard de quatre médicaments de deuxième ligne. On n'a détecté aucun cas de résistance étendue aux médicaments TB (TB-XDR) selon la dernière définition de cette résistance.
CONCLUSION : Nos observations indiquent une menace sérieuse pour les efforts de lutte antituberculeuse dans la population étudiée.

RESUMEN

MARCO DE REFERENCIA : Sistema penitenciario de Georgia.
OBJETIVO : Determinar la prevalencia de resistencia a los medicamentos antituberculosos de segunda línea en los detenidos con tuberculosis (TB) pulmonar.
MÉTODO : Evaluación retrospectiva de la resistencia a

los medicamentos antituberculosos de segunda línea en pacientes tratados entre 2001 y 2003.

RESULTADOS : La prevalencia global de TB multidrogorresistente (MDR) fue 14,4% (39/270). La prevalencia más baja fue la resistencia a ofloxacino (OFX) : 2,2% global (6/270) y 5,1% (2/39) en los pacientes con TB-MDR. Aislados clínicos provenientes de cuatro pacientes sin TB-MDR ni antecedente de tratamiento antituberculoso exhibieron resistencia a OFX. La resistencia a kanamicina y capreomicina apareció en forma simultánea solo en pacientes con TB-MDR, en 17 de los 39 casos (43,6%). Se observaron altos índices de resistencia a dos o más medicamentos de segunda línea (46,2% ; 18/39) y a tres o más medicamentos (25,6% ; 10/39) en todos los pacientes con TB-MDR, llegando hasta 59,3% y 29,6% respectivamente en los pacientes en tratamiento o previamente tratados. Solo se encontró un paciente con resistencia a cuatro medicamentos de segunda línea. No se observó ningún caso de TB extremadamente resistente (TB-XDR), según su definición más reciente.

CONCLUSIÓN : Estos resultados ponen de manifiesto la existencia de una grave amenaza a los esfuerzos de control de la TB en la población estudiada.