

Barriers to reaching the targets for tuberculosis control: multidrug-resistant tuberculosis

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Abstract The development and expansion of WHO's DOTS strategy was successful, with 83% of the world's population living in countries or parts of countries covered by this strategy by the end of 2004.

Treatment success in the 2003 DOTS cohort of 1.7 million patients was 82% on average, close to the 85% target. Treatment success was below average in the African Region (72%), which can be partly attributed to occurrence of HIV co-infection, and in the European Region (75%), partly due to drug resistance. Drug resistance, specifically multidrug resistance and extensive drug resistance, is a serious threat to public health in all countries, especially in the Russian Federation, where the highest rates of multidrug resistance are presently accompanied by a rapid increase in HIV infection.

Based on the experience of the first projects approved by the Green Light Committee, the treatment success of patients with multidrug-resistant tuberculosis (MDR-TB) is lower than that of drug-susceptible cases, but nevertheless reaches 70%.

The collaborative effort of different organizations, professionals and communities is needed to address the development and spread of multidrug resistance and extensive drug resistance, which combined with the epidemic of HIV infection is one of the barriers to dealing effectively with TB. This effort should be directed towards facilitating the diagnosis and treatment of TB patients, in particular by improving access to drug susceptibility testing and strengthening treatment delivery by rigorous adherence to DOTS as outlined by the Stop TB Partnership.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

"The existence, in the lungs, of those peculiar productions to which the name of Tubercles has been restricted by modern anatomists, is the cause, and constitutes the true anatomical character, of Consumption" (Bishop, 1918).¹

In 2004 it was estimated that 4.3% of all new and previously treated tuberculosis (TB) cases worldwide were multidrug-resistant (MDR-TB).²

The United States Centers for Disease Control and Prevention (CDC) and WHO published, in 2006, the results of a worldwide survey³ examining resistance to second-line anti-TB drugs, showing that 2% of *Mycobacterium tuberculosis* isolates were extensively resistant (XDR-TB), that is strains resistant to at least rifampicin and isoniazid, a fluoroquinolone and one or more of the following injectable drugs: kanamycin, amikacin, capreomycin. In the Republic of Korea and Latvia, the proportion of XDR-TB cases among MDR-TB cases was as high as 15% and 19%, respectively, over the period 2000–2004. Patients with

XDR-TB were 64% more likely to die or have treatment failure than patients with MDR-TB.³ In the United States of America, the cure rate of XDR-TB patients was 31%, which is only slightly greater than the estimated proportion of spontaneously healed tuberculosis.⁴ Highly drug-resistant TB in a setting in rural South Africa with a high prevalence of HIV infection was reported in 2006, with 98% mortality within 30 days of seeking care.^{5,6}

From a short-term perspective it is difficult to estimate the global trend in drug resistance, but in the period since 1943 there is hardly any doubt that resistance has increased. For patients with drug-resistant TB this means that they might be in a similar situation as in the pre-chemotherapy era, when individuals with TB were "consumed" by the disease.

Background

The first anti-TB drug, streptomycin, was isolated in 1943 and its therapeutic introduction saved many lives. However, early trials in United Kingdom

and the USA showed that resistance to streptomycin developed during monotherapy and that patients' symptoms deteriorated.^{7,8} The concept of combined chemotherapy was based on this observation. By 1950, the success of combined drug chemotherapy for TB was established.⁹ In the following decades more drugs were introduced for the TB treatment, and unfortunately further resistance developed.¹⁰

In 1960, the British Medical Research Council developed fully-supervised chemotherapy to ensure patient adherence to the prescribed treatment regimen, which was proved to prevent development of multidrug resistance.¹¹ It was not, however, until the 1980s that the International Union Against Tuberculosis and Lung Disease (IUATLD) gradually implemented this fully-supervised chemotherapy under programmatic conditions in the United Republic of Tanzania and other African countries.¹²

In the 1990s, WHO developed the DOTS strategy as a package of five elements aimed at achieving at least 70%

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detection and 85% cure rate. This strategy, which is now a fundamental pillar of the new Stop TB strategy announced in 2006,¹³ has been widely accepted. Out of a total of 211 countries and territories, 200 report annually to WHO on their progress achieved in TB control. By the end of 2004, 83% of the world's population lived in countries or parts of countries covered by DOTS.

Treatment success in 2003 by a cohort of 1.7 million patients was 82% on average, very close to the global target of 85% set for 2005. However, treatment success was below average in the African Region (72%), which can be partly attributed to HIV co-infection, and in the European Region (75%), partly due to drug resistance.¹⁴

Almost 40 years after introduction of directly observed combination chemotherapy for TB, and with the accumulated knowledge of the mechanisms leading to development of drug resistance, the latter still remains one of the main barriers to TB control. The management of patients with drug-resistant TB is more complicated because of the longer treatment time, lesser effectiveness of second-line anti-TB drugs and more side-effects. Furthermore, the high price of second-line drugs means that management of MDR-TB is a significant financial burden on programmes.^{15,16}

What do we know about the prevalence of drug resistance?

Since 1994, data on anti-TB drug resistance have been collected globally by various WHO/IUATLD Global Projects on Anti-Tuberculosis Resistance Surveillance and published in 1997, 2001 and 2004; the last report includes data from

77 countries or settings. Already in 1994, anti-TB drug resistance was reported in virtually every country surveyed.

In 2004, resistance data were available on 55 779 never previously treated cases, representing 20% of the reported global new smear-positive TB cases.^{17,18} Of the ten countries or areas with the highest prevalence of MDR-TB (Fig. 1), all of which had a prevalence of > 6.5% of drug resistance among never-previously-treated cases, six were in Eastern Europe^{17,18} with prevalences of MDR-TB as follows: 14.2% (Kazakhstan); 13.7% (Tomsk oblast, Russian Federation); 13.2% (Karakalpakstan, Uzbekistan); 12.2% (Estonia); 9.4% (Lithuania); and (9.3%) Latvia. Drug-resistance data were available for the city of Dashoguz in Turkmenistan (3.8%) and Orel oblast in the Russian Federation (2.6%).^{17,18}

Although the probability of drug resistance is 3 to 4 times higher in re-treated than in never previously treated patients, data on resistance in the former group is scarce. Only 8405 previously treated cases, representing 2.3% (the denominator does not include relapses) of reported previously treated cases, were surveyed. The reported highest values of MDR-TB among previously treated cases were in Oman (58.3%) and Kazakhstan (56.4%),^{17,18} followed by Lithuania (53.3%), Estonia (45.3%), Tomsk oblast in the Russian Federation (43.6%), Orel oblast in the Russian Federation (42.4%), Karakalpakstan in Uzbekistan (40.2%), Egypt (38.2%) and Henan in China (36.6%).^{17,18}

WHO estimates that 62% of the global total of 424 000 cases of MDR-TB are in China, India and the Russian

Federation. XDR-TB has been identified in over 40 countries on six continents.³ Additional surveys, which complement the existing data, are under way in China, India and the countries of the former Soviet Union.²

Global response to the MDR-TB challenge

In 1999, WHO established the Working Group on DOTS-Plus for MDR-TB to explore the feasibility, effectiveness and cost-effectiveness of treating MDR-TB under programmatic conditions in low- and middle-income countries. In 2001 it was integrated into the Stop TB Partnership in 2001 and is now named the Stop TB Working Group on MDR-TB (see: <http://www.stoptb.org/>).

The Green Light Committee (GLC), housed and managed by WHO, was launched as a subgroup of the Working Group in 2000. The aim of the GLC is to increase access to low-price, quality-assured second-line drugs worldwide, while ensuring their proper use to prevent increased drug resistance.¹⁵

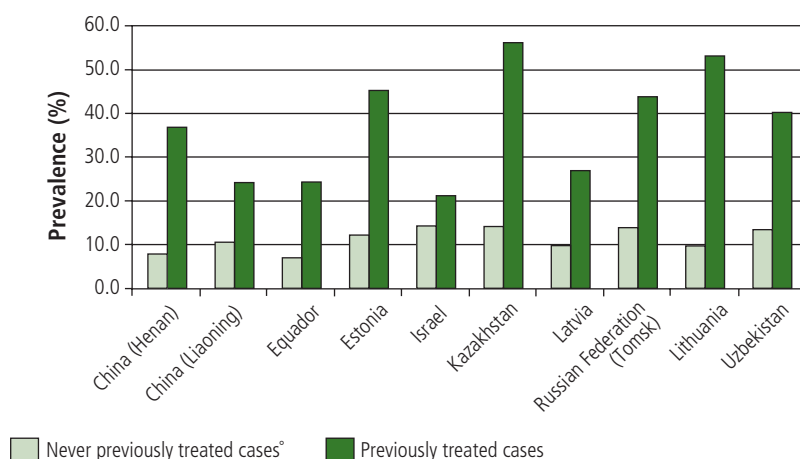
Through negotiations with pharmaceutical companies, the GLC was able to reduce the cost of second-line drugs, making them affordable for middle- and low-income countries. The prices have been reduced by up to 99% compared with prices in the open market.¹⁶ The first countries to benefit from the GLC mechanism were Estonia, Latvia, Peru, the Philippines, and the Russian Federation (Tomsk oblast). By December 2006 there were 53 GLC-approved projects in 42 countries worldwide.

The GLC has assisted WHO in developing a policy and technical guidelines for management of drug-resistant TB¹⁹ and is assisting countries in developing technically and scientifically consistent proposals for projects on management of MDR-TB to access quality-assured second-line drugs. Many countries are receiving external financial assistance for their projects, especially through the Global Fund to Fight AIDS, Tuberculosis and Malaria.¹⁴

Culture and drug susceptibility tests for all cases of TB are considered the gold standard for diagnosis, treatment and surveillance of drug resistance. However, such tests are not feasible routinely in most settings, where WHO instead recommends periodic surveys to monitor trends.¹⁸

The Global Plan to Stop TB 2006–2012 includes the provision of culture

Fig. 1. Prevalence of multidrug-resistant tuberculosis (MDR-TB) in the ten countries or areas where it is most prevalent



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and drug susceptibility testing by 2015 to all re-treatment cases in at-risk populations, such as category I failures and contacts of patients with MDR-TB.^{14,18}

The treatment success for drug-resistant TB, in particular MDR-TB and XDR-TB, is lower than that of drug-sensitive TB.³ The encouraging treatment success rates for MDR-TB patients from GLC-approved projects in Estonia, Latvia, the Philippines (Manila) and the Russian Federation (Tomsk oblast) have been as high as 70%; higher among never previously treated patients (77%) and lower (69%) among previously treated patients.²⁰

Conclusion

More than 40 years after the introduction of supervised combination che-

motherapy for treatment of TB, many countries, particularly developing countries, have not adopted the principles of international standards of care with DOTS,²¹ thus contributing to the development and spread of drug-resistant TB. These standards should be adopted by following the 2005 Stop TB strategy.

Drug resistance, particularly MDR-TB and XDR-TB, is a serious challenge that is jeopardizing TB control worldwide. Careful data collection and analyses from the GLC-approved project sites has provided more information about successes and challenges in managing drug-resistant cases. The most worrisome situation is in the former Soviet Union, where the highest rates of MDR-TB and XDR-TB are combined with the fastest-growing

epidemic of HIV infection in the world.

The joint efforts of different organizations, professionals and communities is needed to address the development and spread of MDR-TB and XDR-TB, which combined with HIV epidemic is one of the barriers in dealing effectively with TB. This effort should be directed at facilitating diagnosis and treatment of TB patients, in particular by improving access to drug susceptibility testing and strengthening treatment delivery by rigorous adherence to DOTS as outlined by the Stop TB Partnership. ■

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Résumé

Obstacles à la réalisation des objectifs de la lutte antituberculeuse : tuberculoses multirésistantes

Le développement et l'élargissement de la stratégie DOTS de l'OMS se sont opérés avec succès, le taux de couverture des divers pays du monde ou des parties de pays couverts par cette stratégie atteignant 83 % à la fin de l'année 2004.

En 2003, on a relevé, parmi une cohorte de 1,7 millions de malades, un taux de succès du traitement de 82 % en moyenne, proche de l'objectif de 85 %. Ce taux était inférieur à la moyenne dans la Région africaine de l'OMS (72 %), résultat partiellement attribuable à la fréquence de la co-infection TB/VIH, et dans la Région européenne de l'OMS (75 %), du fait notamment de la pharmacorésistance aux antituberculeux. Cette pharmacorésistance, et plus particulièrement la multirésistance et la pharmacorésistance étendue, représentent une menace grave pour la santé publique dans tous les pays, notamment la Fédération de Russie, où des taux élevés de multirésistance s'observent en même de temps qu'une rapide propagation de l'infection à VIH.

D'après l'expérience acquise avec les premiers projets approuvés par le Comité Feu vert, le taux de succès du traitement est moindre chez les personnes atteintes de tuberculose multirésistante (TB-MR) que chez les cas sensibles aux antituberculeux, mais atteint néanmoins 70 %.

Un effort de collaboration entre les diverses organisations, professions et communautés s'impose pour faire face au développement et à la propagation de la multirésistance et de la pharmacorésistance étendue qui, en association avec l'épidémie d'infection à VIH, font partie des obstacles à une prise en charge efficace de la TB. Cet effort doit avoir pour objectif de faciliter le diagnostic et le traitement des malades tuberculeux, à travers notamment un élargissement de l'accès aux tests de pharmacosensibilité et une amélioration de la délivrance du traitement, reposant sur une observance plus stricte du DOTS, comme le préconise le Partenariat Halte à la tuberculose.

Resumen

La tuberculosis multirresistente, un obstáculo para alcanzar las metas de la lucha antituberculosa

El desarrollo y expansión de la estrategia DOTS de la OMS fue un gran éxito, pues al final de 2004 la cobertura de la misma era del 83% de la población de los países o zonas considerados.

El éxito terapéutico en la cohorte de 1,7 millones de pacientes tratados con DOTS en 2003 fue del 82% por término medio, cerca de la meta del 85%. El éxito terapéutico se situó por debajo de la media en la Región de África (72%), lo que puede atribuirse parcialmente a la aparición de la coinfección por VIH, así como en la Región de Europa (75%), en parte debido a la farmacorresistencia. Este problema, específicamente la multirresistencia y la farmacorresistencia extensa, es una grave amenaza para la salud pública en todos los países, sobre todo en la Federación de Rusia, donde a las tasas más elevadas de multirresistencia se une un rápido aumento de la infección por VIH.

A juzgar por la experiencia de los primeros proyectos

aprobados por el Comité Luz Verde, el éxito terapéutico entre los pacientes con tuberculosis multirresistente (TB-MR) es inferior al de los casos sensibles a los medicamentos, pero no obstante alcanza el 70%.

Es preciso un esfuerzo de colaboración entre diferentes organizaciones, profesionales y comunidades para abordar el desarrollo y propagación de la multirresistencia y la farmacorresistencia extensa, que sumadas a la epidemia de infección por VIH constituyen uno de los obstáculos al tratamiento eficaz de la tuberculosis. Este esfuerzo debe orientarse a facilitar el diagnóstico y el tratamiento de los pacientes con tuberculosis, en particular mejorando el acceso a las pruebas de farmacosensibilidad y fortaleciendo el suministro de tratamiento mediante un cumplimiento riguroso del DOTS conforme a lo indicado por la Alianza Alto a la Tuberculosis.

ملخص

العوائق أمام بلوغ أهداف مكافحة السل: السل المقاوم لأدوية متعدّدة

وبناءً على الخبرات المكتسبة من المشاريع الأولى التي حازت على موافقة لجنة الضوء الأخضر، فإن معدلات نجاح المعالجة لدى مرضى السل المقاوم لأدوية متعدّدة كانت أخفض مما لدى الحالات المستجيبة للأدوية، ولكنها مع ذلك وصلت إلى 70%. وتمس الحاجة إلى الجهود التعاونية التي تضم منظمات وأطباء ومجتمعات لمجابهة نشوء وانتشار المقاومة لأدوية متعدّدة والمقاومة الشديدة للأدوية، وهما يتحالفان مع العدوى بجائحة الإيدز ليشكّلوا معاً أحد العوائق أمام المعالجة الفعّالة للسل. وينبغي توجيه الجهود لتسهيل التشخيص والمعالجة لمرضى السل، ولاسيما لتحسين الحصول على اختبارات الاستجابة للمعالجة وتعزيز المعالجة بزيادة الالتزام باستراتيجية المعالجة القصيرة الأمد للسل تحت الإشراف المباشر، كما تنص عليه الشراكة من أجل دحر السل.

حقّق تطوير وتوسيع استراتيجية منظمة الصحة العالمية للمعالجة القصيرة الأمد تحت الإشراف المباشر نجاحاً ملحوظاً تمثل بتغطية 83% من سكان العالم الذين يعيشون في البلدان أو في أجزاء من البلدان المغطّاة بهذه الاستراتيجية عام 2004.

وقد حقّقت هذه المعالجة عام 2003 نجاحاً لدى 1.7 مليون مريض بلغ في معدله الوسطي 82%، وهو ما يقرب من 85% من الهدف المتوخّى تحقيقه. إلا أن نجاح المعالجة كان أقل من المعدل الوسطي في الإقليم الأفريقي (72%) ويعود ذلك جزئياً إلى العدوى المصاحبة بالإيدز، وإلى المقاومة للمعالجة ولاسيما المقاومة لأدوية متعدّدة، والمقاومة الشديدة للأدوية. وهذه المقاومة من التحدّيات الخطيرة التي تواجهها الصحة العمومية في جميع البلدان، ولاسيما في الاتحاد الروسي، حيث تترافق أعلى معدلات المقاومة لأدوية متعدّدة في الوقت الحاضر مع ازدياد سريع في العدوى بالإيدز.

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Round Table Discussion

Case study: South Africa

Karin Weyer^a

For the past decade, a concerted effort to reform TB control in South Africa has resulted in changes in case-finding and treatment policies, standardization of recording and reporting systems, and monitoring of the performance of control programmes using pre-defined indicators; these changes were all made in line with the internationally recommended DOTS strategy. The essential elements of the revised strategy,¹ implemented in 1996 after TB was declared a national emergency, include bacteriological confirmation of disease, standardized first-line treatment regimens that are exclusively based on fixed-dose combination formulations and an electronic recording and reporting system. Expansion of the DOTS strategy followed rapidly: in 2003 there was complete coverage in all nine provinces, covering 183 health districts. Comprehensive programmatic management of patients with MDR-TB became national policy in 2000 and was implemented through a network of dedicated provincial MDR-TB referral centres.

Despite these efforts, however, TB incidence and case-fatality rates have increased threefold in South Africa over the ensuing decade.² More than 400 000 cases of TB require treatment annually, but cure rates barely reach 50%,² reflecting the classic mistake made in TB control of identifying cases but not treating them adequately. TB mortality is at an all-time high. There are some 10 000 incident cases of MDR-TB per year,³ representing the largest MDR-TB burden in Africa and further pointing towards a failure of TB control. Although a favourable outcome (cure and treatment completed) is achieved in more than 80% of MDR-TB patients who complete the full course of standardized treatment, deaths (up to 20% of patients who started treatment), defaulting from treatment (up to 25% of patients) and failure of treatment (around 10%) reduce the overall effectiveness of the programme to less than 50% (South African Medical Research Council, unpublished data, 2002–2004). Worryingly, patients with XDR-TB have been identified in each of the nine provinces over the past 18 months.

Determinants of the worsening TB epidemic in South Africa are diverse and multifactorial. Historically, there has been a legacy of neglect, poor management of patients and fragmented health services.⁴ Contemporary barriers to effective TB control in South Africa are similar to those elsewhere in Africa, and include an exploding HIV epidemic, deteriorating socioeconomic conditions among already vulnerable populations and constraints on human resources in the health-service sector. Although TB control has been fully integrated into primary health-care services and decentralized to district level, delivery is hampered by competing health priorities, slow district reform and deficient management capacity, especially at the level of implementation. Unemployment rates of up to 40%, as well as the resultant migration and massive growth in

informal urban settlements, lead to failures in supervision of treatment and follow-up. Reasons for defaulting from TB and MDR-TB treatment include patients' perceptions of negative attitudes among health-care workers, substance abuse and employment concerns.^{5,6}

However, it is the lost opportunity for early, effective HIV intervention in South Africa that has brought the weaknesses in TB control into sharp focus. At least 60% of TB patients are estimated to be coinfecting with HIV;² this is most strikingly reflected in the excess and rising mortality. Up to half of patients categorized as treatment defaulters in the aforementioned research studies were subsequently found to have died, and the reason for death was often reported as being HIV-related.^{5,6} HIV-associated transmission of XDR-TB and the exceptionally high risk of mortality in HIV-positive people coinfecting with XDR-TB⁷ amplify public health concerns over the threat of a virtually untreatable TB epidemic occurring within the context of HIV coinfection.

The view expressed in the base paper that drug-resistant TB poses a major threat to achieving global targets for TB control also holds true for South Africa. In addition, however, the 2005–2006 XDR-TB outbreak in KwaZulu-Natal⁷ serves as a serious warning that gains made in HIV care and treatment might be lost if drug-resistant TB is not effectively and rapidly addressed. Several epidemiological and genetic studies have confirmed both nosocomial and community transmission of drug-resistant TB in South Africa. Increased access to HIV treatment and care will inadvertently bring together highly vulnerable individuals with infectious cases of MDR-TB and XDR-TB, often in settings where large numbers of people congregate. The lack of adequate and appropriate infection-control measures in most public health settings, juxtaposed with an extremely high prevalence of HIV (both in patients and health-care workers), represent a public health emergency requiring much earlier detection of drug resistance, segregation of infectious patients, urgent improvements in infection control measures and a rapid, appropriate response to outbreaks.

Dire predictions of the impact of HIV on TB and MDR-TB in South Africa were made in 1999.⁴ Sadly, what had been mere assumptions at the time now seem to have come true. Substandard care, fertile conditions for transmission and the rapidly progressing HIV epidemic all impede the ability of South Africa to reach the required targets for TB control; they also contribute to establishing the endemicity and spread of drug-resistant TB. A dynamic and exceptionally strong collaboration between HIV and TB control programmes will be required to avert large-scale HIV-associated epidemics of drug-resistant TB. Failure to engage in such collaborations is bound to have devastating consequences. ■

Competing interests: None declared.

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The Philippines case study

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Most TB patients in the Philippines are treated by private practitioners who do not conform to the international standard of TB care.¹ We established a private-public mix DOTS (PPMD) centre to engage private physicians in the DOTS strategy.² The cure rate in new cases was 83.9% and failure was 0.01%, with corresponding rates in previously treated cases of 58.6% and 39.7%, respectively. All isolates from the treatment failures were MDR-TB, indicating failure of previous TB treatment outside DOTS.

As a DOTS-Plus pilot project, the Green Light Committee (GLC) of the working group on multidrug-resistant TB provided this PPMD access to second-line anti-TB drugs (SLDs) and technical assistance. Our experience illustrates the challenges in MDR-TB management.

More effective anti-TB drugs needed

SLDs used in the management of MDR-TB are less effective, requiring prolonged regimens, and are also associated with significant side-effects.³ Although MDR-TB management was found to be highly cost-effective in our setting, drugs alone cost US\$ 3500 per patient.⁴ Additionally, drug supplies are limited in the face of increased demand with resources provided by the Global Fund to Fight AIDS, TB and Malaria; this is another challenge to drug availability.

With the widespread use of SLDs, XDR-TB (MDR-TB with simultaneous resistance to a fluoroquinolone and one of the injectable SLDs) that is virtually incurable with the available drugs has emerged.⁵ Although there is substantial fluoroquinolone resistance among the MDR-TB isolates,⁶ XDR-TB was noted in only 4.6% of MDR-TB patients treated. Although there was no known HIV co-infection in these patients, the risk for failure or death from XDR-TB nevertheless was twice as high as that for other MDR-TB patients.⁷

Mobilization of more resources and engagement of the scientific community and the pharmaceutical industry to accelerate the development of affordable, novel anti-TB agents is essential for an effective response to the threat of MDR-TB, particularly XDR-TB.

Rapid methods for diagnosis needed

The diagnosis of MDR-TB relies on conventional culture and drug sensitivity testing (DST). The lag time to MDR-TB diagnosis in 2003 to 2005 declined from 8.5 ± 3.8 months to 5.0 ± 2.3 months and delay of treatment was 10.6 ± 5.6 months to 6.7 ± 3.3 months from consultation (personal communication, unpublished data). In our experience, 12%–20% of confirmed MDR-TB patients died during the long process of diagnosis, 7% while awaiting treatment, 4% to 7% refused treatment, and 22% to 26% were lost before treatment. The public health consequences of continuing transmission, further amplification of resistance, clinical deterioration and death before management underscore the need for rapid methods of MDR-TB diagnosis for more timely treatment.

Enhancing treatment adherence

Cure rates in our cohorts increased from 50% to 74% from 1999 to 2004, with corresponding declines in death and failure rates.⁷ However, the default rate during the prolonged treatment regimen, owing largely to adverse drug events, remained substantial. When patients were referred back from the treatment centre to the DOTS facilities, including PPMDs, within the communities where they live during the continuation phase of treatment, the default rate substantially declined compared to patients who continued to report daily to the treatment centre.⁸

Management of adverse drug events, group therapy sessions on psychosocial issues, and engaging patient volunteers as treatment partners were also implemented to improve treatment adherence.

Mainstreaming MDR-TB management into DOTS

To attain the goal of a TB-free world, addressing MDR-TB and other major challenges is one of the key strategies. As DOTS implementation prevents generation of MDR-TB, programmatic MDR-TB management prevents generation of XDR-TB and halts the transmission of MDR-TB. The major challenge of mainstreaming MDR-TB management into the national tuberculosis programme is the development of human resources to provide appropriate services for MDR-TB management. ■

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Treatment and management of MDR-TB in Latvia

Vaira Leimane^a

Background

Latvia has consistently ranked among the countries with the highest rates of MDR-TB in the world. In the first Global Tuberculosis Drug Resistance Survey (1996), 14.4%, or 1 out of 7, of all newly diagnosed sputum smear-positive tuberculosis cases in Latvia were diagnosed as MDR-TB.¹

Data also show that the proportion of cases with additional resistance to second-line anti-tuberculosis drugs is high. In the meantime, HIV seroprevalence is increasing among TB patients.

Latvia, with an estimated population of 2.35 million, joined the European Union on 1 May 2004. The Latvian economy had been severely affected by the collapse of the Soviet Union, with gross domestic product (GDP) per capita falling by nearly 35% in real terms in 1992. The GDP per capita in 1999 was US\$ 4200, increasing to US\$ 11 500 in 2004. Latvia concurrently experienced dramatic increases in TB morbidity and mortality peaking in 1998, together with the appearance of drug-resistant and MDR-TB.^{2,3}

Latvia adopted WHO's recommended DOTS strategy for TB control in 1996 and subsequently introduced MDR-TB management⁴ in 1997. This relies on MDR-TB treatment with individualized regimens under the *consilium* or expert consultation process. The treatment is provided at four inpatient treatment centres (including a prison TB ward) followed by outpatient directly observed therapy. All funding for TB and MDR-TB control comes from the government. In 2000 Latvia's National Tuberculosis Program (NTP) sought MDR-TB management support from the Green Light Committee (GLC) and got approval to treat 350 more MDR-TB patients.

The GLC enabled Latvia to treat all patients diagnosed with MDR-TB.

Epidemiology

In 1991, the incidence of TB was 29 cases per 100 000 population,⁵ increasing to 74/100 000 in 1998 and then declining to 53.5/100 000 in 2005. Case finding shows 49% case detection by smear microscopy.

Drug-resistant TB case detection strategy in Latvia is based on drug sensitivity tests (DST) on solid media. For high-risk MDR-TB cases, the BACTEC/MIGT system is used, as well as the INNO LiPA test to detect rifampicin resistance in 2–4 days.

Extensive resistance to first- and second-line drugs among MDR-TB patients is well known in Latvia. One of the reasons is the country's long and extensive use of second-line drugs before implementing the DOTS strategy. Extensive resistance affects the MDR-TB treatment regimen and outcomes. For cohorts registered from 2000 to 2005, resistance to kanamycin was 49%; capreomycin, 39%; ofloxacin, 9%; protheonamide, 30%; para-aminosalicylic acid, 31%; and thiacethasone, 23%.

In the first worldwide survey, published in May 2006, estimates for years 2000–2004 showed that 19% of MDR-TB patients have resistance to first-line drugs defined as MDR-TB plus resistance to three drugs of six classes of second-line drugs.⁶

Using the new revised extensive drug resistance (XDR-TB) definition of resistance to at least rifampicin and isoniazid, additional resistance to any fluoroquinolone and to any of three second-line injectable drugs (capreomycin, kanamycin or amikacin), such extensively resistant TB was found in 39 cases, or 5.2% of all MDR-TB cases registered during the past six years.

Two-thirds, or 67%, of MDR-TB patients out of 820 treated in the years 2000–2003 were cured; 6% were dead; 14% defaulted; and treatment failed in 13% of cases.^{7,8} The treatment success rate for XDR-TB patients is low: out of all 48 patients treated from 2000 to 2005 (including MDR-TB retreatment cases with XDR-TB), only 18 (38%) were cured, while treatment failed for 22 (46%).

Among all MDR-TB cases in the cohorts, 3% were co-infected with HIV; this proportion increased to 12% among XDR-TB cases. Treatment success for TB/HIV co-infected new patients, at 74%, is similar to overall treatment success for new TB patients, but the HIV-associated MDR-TB success rate is 56%.

Overall, Latvia's success with the DOTS program is encouraging: 84% of all registered cases, including outcomes of MDR-TB after 2 years, were cured in cohort 2002, which is close to the level of performance (85%) recommended by WHO (Table 1).⁹ Newly registered MDR-TB cases were reduced by 46%, with 332 cases in 1997 falling to 153 registered in 2005.

Conclusion

MDR-TB management is effectively implemented under routine program conditions in Latvia. Using an individual

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Table 1. All registered MDR-TB cases in Latvia, 1995–2005

| | Primary | Acquired | Total | XDR-TB (MDR-TB + resistance to any second-line injectable + fluoroquinolone) |
|------|---------|----------|-------|--|
| 1995 | 19 | 28 | 47 | |
| 1996 | 82 | 175 | 257 | |
| 1997 | 117 | 215 | 332 | |
| 1998 | 96 | 231 | 327 | |
| 1999 | 101 | 175 | 276 | |
| 2000 | 90 | 153 | 243 | 4 |
| 2001 | 100 | 132 | 232 | 1 |
| 2002 | 88 | 124 | 212 | 7 |
| 2003 | 83 | 80 | 163 | 5 |
| 2004 | 111 | 76 | 187 | 15 |
| 2005 | 99 | 54 | 153 | 7 |

approach to the management of MDR-TB can cure more than two-thirds of patients in settings with high MDR-TB prevalence and extensive resistance to first- and second-line drugs.¹⁰

Challenges for TB care in Latvia

An area of concern is treatment default, especially among MDR-TB cases (14%), among those with TB/HIV and MDR-TB/HIV¹¹ co-infection, and among patients with extensive drug resistance.

Rapid drug-resistant case detection, appropriate treatment, extended contact investigation, infection control

measures and case management strengthening to decrease treatment interruptions and default are the main challenges Latvia faces in achieving the TB-related Millennium Development Goals. ■

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