Eliminating the category II retreatment regimen from national tuberculosis programme guidelines: the Georgian experience

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Problem The category II retreatment regimen for management of tuberculosis in previously treated patients was first introduced in the early 1990s. It consists of 8 months of total therapy with the addition of streptomycin to standard first-line medications. A review of 6500 patients on category II therapy in Georgia showed poor outcomes and high rates of streptomycin resistance.

Approach The National Tuberculosis Program used an evidence-based analysis of national data to convince policy-makers that category II therapy should be eliminated from national guidelines in Georgia.

Local setting The World Health Organization tuberculosis case-notification rate in Georgia is 102 per 100 000 population. All patients receive culture and drug susceptibility testing as a standard part of tuberculosis diagnosis. In 2009, routine surveillance found multidrug-resistant tuberculosis in 10.6% of newly diagnosed patients and 32.5% of previously treated cases.

Relevant changes Category II retreatment regimen is no longer used in Georgia. Treatment is guided by results of drug susceptibility testing – using rapid, molecular tests where possible – for all previously treated tuberculosis patients.

Lessons learnt There was little resistance to policy change because the review was initiated and led by the National Tuberculosis Program. This experience can serve as a successful model for other countries to make informed decisions about the use of category II therapy.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Management of patients who have been previously treated for tuberculosis (TB) has been a cause of much debate.[1] In 1991, the World Health Organization (WHO) recommended the use of the "category II retreatment regimen" for all patients with a prior history of TB treatment.[2,3] The category II regimen added streptomycin to the first-line agents and extended treatment to 8 months. Multiple observational studies have examined outcomes among individuals receiving category II treatment and shown mixed results. Overall success rates are in the 60–80% range,[4,5] with notably worse outcomes seen among patients who failed or relapsed after their initial treatment episode.[6,7]

WHO TB treatment guidelines published in 2010 recommend treatment guided by drug susceptibility testing – using rapid, molecular tests where possible – for all previously treated patients.[3] The category II regimen, however, is still recommended for certain patients who return after default or relapse in settings with low risk of multidrug-resistant TB (MDR-TB). There is little documentation concerning implementation of these guidelines and category II remains the standard of care for patients requiring retreatment in most settings in the world. This paper presents the experience of Georgia – a country with a substantial population of previously treated patients and high rates of MDR-TB – in eliminating category II therapy from its National TB Program (NTP) guidelines.

Local setting

Georgia is a country of 4.4 million people located in the South Caucasus region. The WHO TB case notification rate is 102 per 100 000 population.[8] All Georgian TB patients receive culture and drug susceptibility testing as a standard part of diagnosis. In 2009, routine surveillance found MDR-TB in 10.6% of newly diagnosed patients and 32.5% of previously treated cases.[9] Programmatic management of drug-resistance TB in Georgia was started in 2006 and in 2009 the country achieved universal access to MDR-TB treatment.

Approach

An operational assessment of the utility of category II in Georgia was done in July and August 2010, led by members of the Georgian NTP with a WHO-recruited consultant. The steps taken were: (i) programme review, (ii) consensus building, and (iii) implementation planning (Table 1).

Programme review

Outcomes of patients treated with category II were assessed in addition to the local epidemiology and programme resources in Georgia. More than 6500 patients received category II therapy between 2007 and 2009 and their outcomes are shown in Table 2.

Georgia has a high burden of TB, particularly drug-resistant TB. Prevalence of HIV in the country is low (< 1%). Culture of

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Table 1. **Key steps in review of category II retreatment regimen in Georgia**

Step	Data	Conclusion/recommendation
Programme review	Outcomes poor	Category II is inadequate therapy for the management of retreatment TB patients in Georgia
	Drug susceptibility testing done on all patients, MDR-TB programme exists	Georgia has sufficient resources to implement other strategies for patients
Consensus building	Project led by National TB Program and thus consensus built rapidly	Category II not relevant for any persons in Georgia; recommendation endorsed by providers
	Evidence-based review with frank discussion	
Implementation planning	Improved diagnostics, ongoing treatment and monitoring	Ongoing operational research

MDR-TB, multidrug-resistant tuberculosis; TB, tuberculosis.

Table 2. **Treatment outcomes among patients on category II retreatment regimen in Georgia, 2007–2009**

Outcome	2007		2008		2009	
	No.	%	No.	%	No.	%
Success[a]	1311	59	1178	52	1369	64
Failed	231	10	531	23	275	13
Defaulted	307	14	147	7	237	11
Died	164	7	118	5	84	4
Transferred out	103	5	102	5	58	3
Unknown	109	5	178	8	131	6
Total	**2225**		**2254**		**2154**	

[a] Combined cure and completion.

Box 1. **Summary of main lessons learnt**

- The National Tuberculosis Program initiated and led the policy decision and worked closely with health-care providers to build consensus.
- Evidence-based analysis was used to support the decision.
- Time and resources were committed to expand access to rapid, molecular-based drug susceptibility testing and management of drug-resistance.

the *Mycobacterium tuberculosis* and drug susceptibility testing is done for all patients diagnosed with TB and Georgia has the resources (human and financial) to continue to do this. It also has a national programme for managing drug-resistant TB. Patients with documented resistance are given treatment regimens based on drug susceptibility test results.

Consensus building

Following this review, the NTP decided to no longer recommend category II treatment in Georgia because of: (i) poor outcomes among patients on category II therapy; (ii) high rates of streptomycin resistance among previously treated patients; (iii) lack of evidence to support category II; and (iv) widespread access to both drug susceptibility testing and treatment for drug-resistant TB. The NTP concluded that patients with documented resistance, including those with mono-resistance, would receive a regimen based on drug susceptibility test results. Those with a history of previous treatment who had pan-susceptible disease would receive HREZ (first-line drugs).

Consensus building was initiated and led by the Georgian NTP; as such, there was strong political will. It held a series of meetings with TB care providers to review and discuss the decision openly. Most of the NTP staff in Georgia are actively involved in TB patient care, and ongoing provider relationships allowed for rapid consensus building. The NTP also used an evidence-based analysis to support its decision. There were some concerns that previously treated patients with pan-susceptible disease still needed a "stronger" regimen but, upon further review, there was little evidence to support this claim. There was little resistance to this policy change so, once internal consensus was reached, the NTP applied for regulatory changes and category II was removed from recommendations for TB treatment.

Implementation

Following the elimination of category II treatment, the programme has committed time and resources to expanding access to rapid, molecular-based drug susceptibility testing. Georgia will also continue its commitment to universal management of all forms of drug-resistant TB and monitor resistance and patient outcomes. Operational research on the discontinuation of category II treatment – including cost implications and provider and patient experiences – will be carried out as funding permits.

Lessons learnt

The experience from Georgia is an important example of how category II treatment can be successfully removed from NTP guidelines in settings where it is of limited utility. Georgia used an operational assessment of its national data to reach consensus on the use of category II within its specific context. There was little resistance to policy change in the country because the review was initiated and led by the NTP. Although it may not be possible to generalize this experience to all settings, the review was done retrospectively and outcome data are pending, the Georgian experience may serve as a roadmap for other countries.

The operational assessment concluded that there were no patients in Georgia for whom category II treatment was appropriate. Patients with a history of previous treatment who have pan-susceptible disease are now treated with first-line drugs. Patients with mono- or poly-resistance are treated with appropriate regimens. Patients with MDR-TB are treated with second-line therapy.

Georgia is a unique setting but other countries with different profiles may be able to use this model to determine

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whether they should use category II. Each country will need to do its own programme review of category II outcomes. They can then use these data to prioritize whether they will continue to use category II or invest in improved diagnostics and drug-resistant TB treatment or both. This paper presents an important example of putting WHO recommendations into action. It is hoped the experience from Georgia can inspire other TB programmes to assess the utility of category II regimens – and other programmatic TB recommendations – in their settings (Box 1). ■

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ملخص

زالة نظام تكرار علاج الفئة الثانية من توجيهات البرنامج الوطني لمكافحة السل: التجربة الجورجية

المشكلة تم طرح نظام تكرار علاج الفئة الثانية لإدارة مرض السل لدى المرضى الذين سبق علاجهم، لأول مرة في أوائل التسعينيات. ويتكون النظام من 8 أشهر من العلاج الشامل بإضافة ستربتومايسين إلى أدوية الخط الأول المعتادة. وكشفت مراجعة لحالات 6500 مريض من الخاضعين لعلاج الفئة الثانية في جورجيا عن نتائج ضعيفة ومعدلات مرتفعة لمقاومة ستربتومايسين.

الأسلوب استخدم البرنامج الوطني لمكافحة السل تحليلاً معتمدًا على الأدلة للبيانات الوطنية لإقناع صناع السياسة بضرورة إزالة علاج الفئة الثانية من التوجيهات الوطنية في جورجيا.

المواقع المحلية يبلغ معدل الإبلاغ عن حالات السل في جورجيا وفق منظمة الصحة العالمية 102 حالة لكل 100000 نسمة. ويتم إجراء مزرعة واختبار حساسية للعقار على جميع المرضى كجزء معياري من تشخيص السل. وفي 2009، كشفت المراقبة الدورية عن سل مقاوم لأدوية متعددة لدى 10.6٪ من المرضى الذين تم تشخيصهم حديثًا و32.5٪ من الحالات التي سبق علاجها.

التغيُّرات ذات الصلة لم يعد نظام تكرار علاج الفئة الثانية مستخدمًا في جورجيا. ويسترشد العلاج بنتائج اختبار الحساسية للعقار – باستخدام اختبارات جزيئية سريعة حيثما يُمكن – لجميع مرضى السل الذين سبق علاجهم.

الدروس المستفادة كانت هناك بعض المقاومة لتغيير السياسة نظرًا لبدء المراجعة وإدارتها بواسطة البرنامج الوطني لمكافحة السل. ويمكن استخدام هذه التجربة كنموذج ناجح للبلدان الأخرى لاتخاذ قرارات مستنيرة بشأن استخدام علاج الفئة الثانية.

摘要

取消美国国家结核病防治项目指南的 II 类再治疗方案：乔治亚州的经验

问题 二十世纪九十年代初，复诊患者的结核病控制首次引入了 II 类再治疗方案。此方案全部疗程为期八个月，除了使用标准一线药物之外，还添加了链霉素。对乔治亚州接受 II 类治疗的 6500 名患者展开的审查显示该方案预后不良且链霉素耐药率高。

方法 美国国家结核病防治项目使用全国数据的循证分析说服决策者应在乔治亚州取消国家结核病防治项目指南的 II 类治疗。

当地状况 乔治亚州的世界卫生组织结核病病例发现率为每 10 万人 102 例。作为结核病诊断的标准组成部分，所有患者均接受了培养物和药物敏感性测试。2009 年，常规监测发现 10.6% 的初诊患者和 32.5% 的复诊病例患者患有耐多药结核病。

相关变化 乔治亚州不再使用 II 类再治疗方案。所有复诊的结核病患者接受在药物敏感性测试结果指导下的治疗—如有可能，使用快速的分子测试。

经验教训 由于此次审查由美国国家结核病防治计划发起并领导，政策改变并没有遇到多少阻力。此次经验可作为其他国家制定关于使用 II 类治疗的知情决策的成功模式。

Résumé

Suppression du schéma de retraitement de catégorie II des directives thérapeutiques nationales du programme de lutte contre la tuberculose : l'expérience géorgienne

Problème Le schéma de retraitement de catégorie II dans le cadre de la prise en charge de la tuberculose chez des patients ayant déjà suivi un traitement a été initié au début des années 1990. Il consiste en 8 mois de traitement complet, avec l'ajout de streptomycine aux médicaments de première intention standard. Une étude portant sur 6 500 patients sous traitement de catégorie II en Géorgie a révélé de mauvais résultats, ainsi que des taux élevés de résistance à la streptomycine.

Approche Le programme national de lutte contre la tuberculose a recouru à une analyse factuelle des données nationales pour convaincre les responsables politiques qu'il convenait de supprimer le traitement de catégorie II des directives thérapeutiques nationales géorgiennes.

Configuration locale Le taux de notification des cas de tuberculose à l'Organisation mondiale de la Santé en Géorgie est de 102 pour 100 000 habitants. Tous les patients se soumettent à des prélèvements d'expectoration et à des tests de sensibilité aux antituberculeux, conformément aux diagnostics standard de la tuberculose. En 2009, un contrôle de routine constatait une tuberculose multi-résistante dans 10,6% des nouveaux cas diagnostiqués et dans 32,5% des cas traités antérieurement.

Changements significatifs Le schéma de retraitement de catégorie II n'est plus utilisé en Géorgie. Le traitement est désormais orienté en fonction des tests de sensibilité aux antituberculeux avec, si possible, l'utilisation de tests moléculaires rapides, chez tous les patients précédemment traités contre la tuberculose.

Leçons tirées Le changement de politique a rencontré peu de résistance, car l'étude a été engagée et menée par le programme national de lutte contre la tuberculose. Cette expérience peut servir de modèle réussi pour permettre à d'autres pays de prendre des décisions éclairées sur le recours au traitement de catégorie II.

Резюме

Устранение режима лечения больных с диагностической категорией II из методических рекомендаций Национальной программы по борьбе с туберкулезом: грузинский опыт

Проблема Режим лечения больных с диагностической категорией II предназначен для лечения туберкулеза у пациентов, уже проходивших лечение. Этот режим, который начали применять в начале 90-х гг., включает в себя 8 месяцев общей терапии с добавлением стрептомицина к стандартным лекарственным препаратам первой линии. Анализ данных 6500 пациентов, проходящих в Грузии лечение для больных с диагностической категорией II, выявил низкую эффективность лечения и высокий уровень невосприимчивости к стрептомицину.

Подход В рамках Национальной программы по борьбе с туберкулезом был применен научно-основанный анализ данных, полученных в национальном масштабе. Полученные результаты были предоставлены директивным органам в качестве обоснования для устранения режима лечения больных с диагностической категорией II из национальных методических рекомендаций Грузии.

Местные условия Показатель Всемирной Организации Здравоохранения по регистрации случаев заболевания туберкулезом в Грузии составляет 102 случая на 100 000 человек. В рамках стандартной процедуры диагностики туберкулеза всем пациентам проводится тестирование на восприимчивость к лекарственным средствам и осуществляется посев. В процессе проведения планового наблюдения в 2009 г., у 10,6% впервые диагностированных пациентов и у 32,5% пациентов, проходивших лечение ранее, выявлен туберкулез с широкой лекарственной устойчивостью.

Осуществленные перемены Режим лечения больных с диагностической категорией II в Грузии более не используется. Лечение всех пациентов, уже проходивших лечение от туберкулеза, проводится по результатам тестирования на восприимчивость к лекарственным средствам, которое, по возможности, проводится с использованием молекулярных экспресс-тестов.

Выводы Данное изменение в проводимой политике не встретило значительного сопротивления, поскольку исследование было инициировано и проводилось под руководством Национальной программы по борьбе с туберкулезом. Полученный опыт может служить в качестве успешной модели для других стран для того, чтобы принимать обоснованные решения в отношении применения режима лечения больных с диагностической категорией II.

Resumen

Eliminación de las pautas de repetición del tratamiento de categoría II de las directrices del Programa Nacional contra la Tuberculosis: el caso de Georgia

Situación A principios de la década de los 90 se introdujeron las pautas de repetición del tratamiento de categoría II para la gestión de la tuberculosis en pacientes previamente tratados. Consiste en un tratamiento total de 8 meses de duración en el que se añade estreptomicina a los fármacos de primera línea. Un examen de 6500 pacientes en tratamiento de categoría II en Georgia ofreció unos resultados deficientes y unas tasas elevadas de resistencia a la estreptomicina.

Enfoque El Programa Nacional contra la Tuberculosis empleó un análisis de los datos nacionales basado en la evidencia para convencer a los responsables de que la categoría II del tratamiento debería ser eliminada de las directrices nacionales en Georgia.

Marco regional La tasa de notificación de casos de tuberculosis de la Organización Mundial de la Salud en Georgia es de 102 por cada 100 000 personas. A todos los pacientes se les realiza un análisis de cultivo y una prueba de sensibilidad a los medicamentos como parte del procedimiento habitual de diagnóstico de la tuberculosis. En 2009, una vigilancia rutinaria detectó tuberculosis multirresistente en un 10,6% de los pacientes diagnosticados recientemente y en un 32,5% de los casos tratados previamente.

Cambios importantes Las pautas de repetición del tratamiento de categoría II han dejado de emplearse en Georgia. El tratamiento se guía por los resultados de la prueba de sensibilidad a los medicamentos (siempre que es posible se emplean pruebas moleculares, muy rápidas) para todos los pacientes tratados previamente contra la tuberculosis.

Lecciones aprendidas Se observó poca resistencia al cambio de estrategia porque fue el Programa Nacional contra la Tuberculosis quien inició y dirigió el examen. La presente experiencia puede servir como modelo de éxito para otros países a la hora de tomar decisiones bien informadas acerca del uso del tratamiento de categoría II.

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