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Introducing new and repurposed TB drugs: the endTB experience

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SUMMARY

In 2015, the initiative Expand New Drug Markets for TB (endTB) began, with the objective of reducing barriers to access to the new and repurposed TB drugs. Here we describe the major implementation challenges encountered in 17 endTB countries. We provide insights on how national TB programmes and other stakeholders can scale-up the programmatic use of new and repurposed TB drugs, while building scientific evidence about their safety and efficacy. For any new drug or diagnostic, multiple market barriers can slow the pace of scale-up. During 2015–2019, endTB was successful in increasing the number of patients receiving new and repurposed TB drugs in 17 countries. The endTB experience has many lessons, which are relevant to country level introduction of new TB drugs, as well as non-TB drugs and diagnostics. For example: the importation of TB drugs is possible even in the absence of registration; emphasis on good clinical monitoring is more important than pharmacovigilance reporting; national guidelines and expert committees can both facilitate and hinder innovative practice; clinicians use new and repurposed TB drugs when they are available; data collection to generate scientific evidence requires financial and human resources; pilot projects can drive national scale-up.

KEY WORDS: bedaquiline; delamanid; clofazimine; linezolid; MDR-TB; XDR-TB

IN 2015, THE INITIATIVE Expand New Drug Markets for TB (endTB) began with the objective of reducing barriers to access to the new and repurposed TB drugs. In this article, "new TB drugs" refers to bedaquiline (BDQ) and delamanid (DLM), which were developed specifically for the treatment of TB. "Repurposed TB drugs" include linezolid (LZD) and clofazimine (CFZ), which were originally developed for the treatment of other diseases. Prior to launching endTB in 2015, the availability of these drugs for multidrug-resistant TB (MDR-TB) was limited. BDQ was approved by the US Food and Drug Administration in 2012, but available only through compassionate use until late 2014. DLM was approved by the European Medicines Agency in 2013 and available only through compassionate use or company donation until early 2016. LZD was approved for treatment of other bacterial infections in the early 2000s, but evidence for its use in TB was limited,[1] and its high commercial price was a major barrier. CFZ had been used for decades to treat leprosy. Its use in MDR-TB treatment was mostly limited to the WHO-approved shorter regimen and individualised extensively drug-resistant TB (XDR-TB) regimens in some countries.[2,3]

endTB includes three major scientific studies: the endTB Observational Study (NCT02754765), which includes more than 2700 patients started on BDQ and DLM containing regimens in 17 countries;[4] the endTB Clinical Trial (NCT02754765), a multi-country, open-label, randomised comparison of five novel nine

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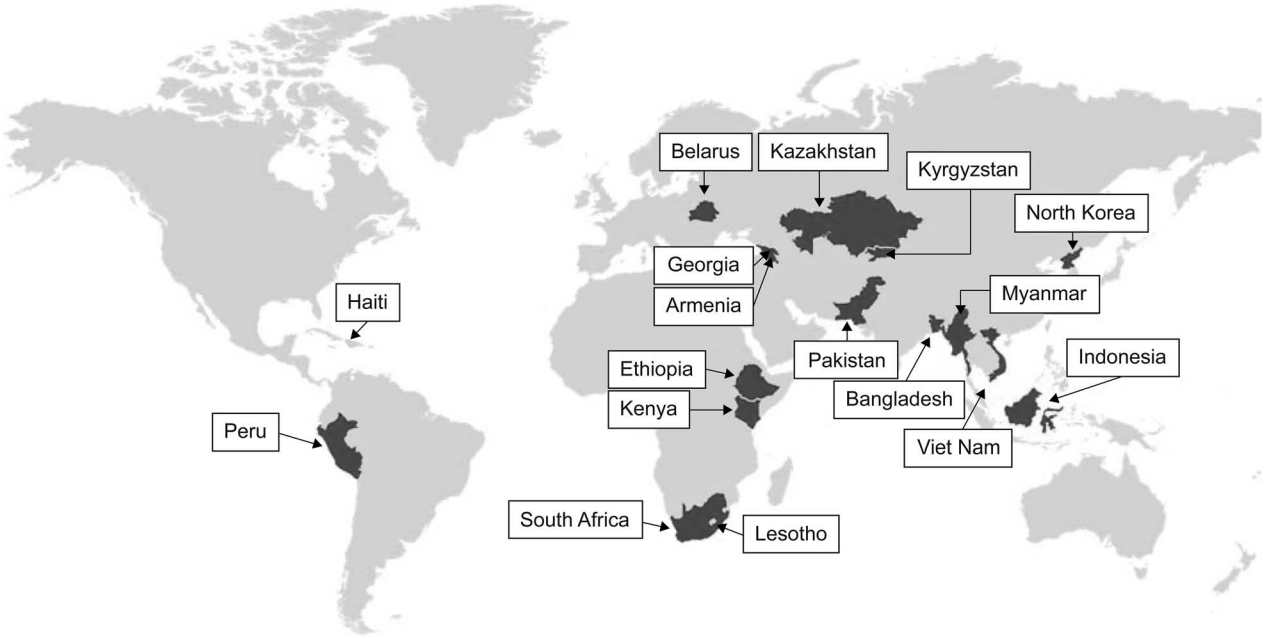

Figure 1 The 17 countries in the endTB Observational Study.

month regimens against a 20 month control regimen in MDR-TB; and the endTB-Q Clinical Trial (NCT03896685), a multicountry, open-label, randomised comparison of a shorter regimen against a long control regimen for quinolone-resistant MDR-TB.

For any new drug or diagnostic, multiple market barriers can slow the pace of scale-up, even if the new drug or diagnostic appears to be superior to old ones. New drugs are often very expensive and the Ministry of Health (MOH) may be unable to afford them for patients. Also, new drugs may not be available to buy at any price, because they cannot be imported due to registration and other restrictions. National guidelines may not recommend new TB drugs, or recommend them only in special cases because of a lack of scientific evidence. Physicians may be reluctant to prescribe new drugs if they are unfamiliar and they are not emphasised in national guidelines. Unfortunately, this failure to prescribe new TB drugs leads to few patients receiving them, few physicians experience using them, and there is a continued lack of scientific evidence to support their use.[5]

In the case of drug-resistant TB, these market barriers are particularly frustrating for clinicians, because the older, second-line TB drugs and regimens are widely recognised as inadequate. Bringing new and better TB drugs and regimens into the hands of physicians so they can be prescribed for MDR-TB patients who have greatest need, is not just ethical—it is the fastest way to build capacity, experience and the scientific evidence base.

During 2015–19, endTB was successful in 17 countries in increasing the number of patients receiving new and repurposed TB drugs (Figure 1). For example, even at the end of the enrollment period, it was estimated that more than half of all patients prescribed DLM globally were receiving it within the framework of endTB. The endTB experience has many lessons relevant to country level introduction of new TB drugs, as well as non-TB drugs and diagnostics.

Lesson 1: Importation of TB drugs is possible even in the absence of registration (delivery)

When launching endTB, it was thought that the absence of registration of the new TB drugs, BDQ and DLM, would be a major challenge to their importation. Armenia, South Africa and Peru were the only countries in which BDQ was registered before the start of endTB, while DLM was registered in none. The registration of a new drug is largely the responsibility of the manufacturer, and many developing countries are too small to be considered profitable markets. Pushing manufacturers to register their medicines in endTB countries was one of the advocacy tasks originally envisioned in endTB. At the current time, a registration dossier for BDQ has been submitted in most of the countries in which endTB is active. In some however, the dossier is still under assessment and in others, local market authorisations cannot be granted locally due to lack of phase III data mandatory under national regulations (Table 1). DLM is not registered in most countries, but is expected to be registered by early 2021 using the WHO Collaborative Procedure for Accelerated Registration.[6] LZD and CFZ are also still not registered in many countries for an MDR-TB indication, as are many of the older second-line TB drugs. CFZ was registered with an MDR-TB indication for the first time worldwide in South Africa in 2019.

Table 1 Status of BDQ registration in the 17 endTB countries, 2020

BDQ is registered	Registration dossier is under assessment	Local market authorisations cannot be granted due to lack of Phase III data	Registration dossier not submitted
• Peru • Indonesia • Armenia • South Africa • Belarus • Ethiopia	• Kenya (since 2016) • Bangladesh (since 2015) • Viet Nam (since 2013) • Myanmar (since 2018)	• Kazakhstan • Kyrgyzstan • Georgia	• North Korea • Haiti • Lesotho • Pakistan

BDQ = bedaquiline; endTB = Expand New Drug Markets for TB.

Despite this, most countries had drug regulatory systems that allowed importation of unregistered drugs through a waiver from the MOH. This was the method used in almost all endTB countries. It is difficult to say if registration would have made it easier to import drugs. In the case of BDQ in Peru, although it was registered, importation was permitted only for specific cohorts of patients by the national drug regulatory agency. In several of the endTB countries (such as Armenia), Médecins Sans Frontières had extensive experience importing drugs for compassionate use programs before the start of endTB. While this proved to be an important conduit that allowed both physicians and their patients to benefit from the new TB drugs, the compassionate use channel, which benefits a small number of individual patients, is not a programmatic solution where drugs are required for larger numbers of patients. Finally, while importation of unregistered drugs was possible through waivers, other bureaucratic delays, including custom clearance, were still relevant and significant.

Lesson 2: Emphasis on good clinical monitoring is more important than pharmacovigilance reporting (delivery)

Pharmacovigilance (PV) was considered to be very important at the beginning of endTB. BDQ and DLM had not been used much outside of small Phase II clinical trials. There was a black box warning for BDQ, and there was a possibility that rare toxicities would be found as these drugs were used more widely. Certainly post-marketing surveillance and sentinel site surveillance are recognised as increasingly important for the introduction of a new drug.[7,8] However, PV reporting is difficult to implement in resource-poor settings. Almost every endTB country had PV systems that had been established well before the introduction of new TB drugs, but TB physicians and nurses rarely reported serious adverse events that occurred in the treatment of patients with older second-line TB drugs, which are notoriously toxic.

In endTB, the analysis of PV data was centralised to relieve as much as possible the work placed on the national TB programs.[9] endTB emphasised the importance of early detection and clinical monitoring for side effects to improve patient care.[10] To this end, sites were provided with equipment and training to screen for the most common adverse events, not just for the new TB drugs, but also repurposed and older TB drugs. Table 2 shows the high frequency of screening that resulted from this approach. The focus on clinical monitoring had a secondary effect on increasing PV reporting as well. The PV support provided by endTB often improved or revitalised a national PV for TB drugs. This data were shared with the WHO's active drug safety monitoring and management (aDSM) Global Database.[11]

Another important aspect of the endTB focus of improving clinical monitoring was that adverse events appear to have been diagnosed at lower grades and often resolved with appropriate management. For example, while hearing loss in patients receiving an injectable was common, two-thirds of the cases of injectable-induced hearing loss were reported to have a grade of 1–2 (mild or moderate).[9] It is likely that the injectables rarely caused complete hearing loss because physicians and nurses were regularly screening for hearing loss with audiometry. Strong clinical monitoring also benefited patients with co-morbidities such as HIV, diabetes and viral hepatitis, by identifying adverse events that are more common in these complex patients.

Lesson 3: National guidelines and expert committees can both facilitate and hinder innovative practice (acceptability/adaptability)

At the beginning of endTB, WHO recommendations regarding new TB drugs had been issued the year prior, but national guidelines had not been revised in some countries. endTB conducted a number of regional trainings (e.g., Armenia, Viet Nam, India, Lesotho, Papua New Guinea) to train site clinicians on the latest WHO recommendations. The endTB Clinical Guide also included significant information on the repurposed TB drugs and was adopted by some countries into their national TB treatment guidelines.[12] WHO recommendations about the new TB drugs contained limited information about drugs such as LZD and CFZ, which are needed because the new TB drugs BDQ and DLM could not be prescribed in isolation.

Table 2 Key monitoring tests in the first 6 months of starting bedaquiline or delamanid

Measure	Measured at treatment initiation *n* (%)	Measured during follow-up *n* (%)	Number of follow-up measures among all Median [IQR]	Number of follow-up measures among patients with ≥1 measure Median [IQR]	Monitoring interval days Median [IQR]	Incidence per 6 patient-months
Clinical visit ($n = 2315$)	2315 (100)	2153 (93.0)	7 [5–7]	7 [6–7]	29 [26–32]	6.0
ECG ($n = 2315$)	2145 (92.7)	2235 (96.5)	5 [4–6]	5 [4–6]	33 [29–48]	4.7
Brief peripheral neuropathy screen ($n = 1859$*)	1605 (86.3)	1689 (89.2)	5 [4–6]	5 [4–6]	31 [29–42]	4.6
Haemoglobin ($n = 1859$*)	1813 (97.5)	1821 (98.0)	5 [4–6]	5 [4–6]	32 [29–45]	5.0
Audiometry ($n = 953$†)	727 (76.9)	682 (71.6)	3 [0–5]	4 [3–5]	31 [29–38]	3.0

* Patients receiving linezolid.
† Patients receiving an injectable.
IQR = interquartile range; ECG = electrocardiogram.

During the initial introduction of new TB drugs, many physicians lacked confidence and needed clinical advice. This was particularly true for special cases, such as pregnant women or when using new drugs beyond what was recommended by WHO (such as prescription of BDQ or DLM for more than 24 weeks or concomitantly). Committees of clinical experts (national or international) played an important role in overcoming this lack of experience.[13] In some countries, however, expert committees decided on a case-by-case basis which patients could receive the new TB drugs. As patient numbers increased, these committees sometimes acted as an administrative bottleneck for patients to access new TB drugs. Physicians who practiced in countries without national committees were often more flexible and innovative in selecting patients who could benefit from the new or repurposed drugs. Internationally, endTB created a Medical Committee that allowed allows physicians in any endTB country to directly ask questions about clinical management (Table 3).

Lesson 4: Clinicians use new and repurposed TB drugs when they are available (delivery)

Some MOH placed restrictions on the use of these drugs (age was the most common), but in general individual physicians were free to use the drugs when they thought the patient could benefit from them. At the beginning of endTB, patients were mostly infected with highly resistant strains such as XDR or pre-XDR-TB. But this shifted over time, with an increasing number of patients enrolled due to inability to tolerate older second-line TB drugs.

Also, both WHO and national guidelines tended to be conservative about which patients should receive the new TB drugs. For example, the WHO does not recommend that BDQ and DLM be routinely prescribed for more than six months, and that BDQ and DLM be used at the same time, classifying this use as "off label". As national guidelines generally follow WHO recommendations closely, this has had the effect globally of significantly reducing the scientific evidence related to these two important practices. At endTB sites, however, both of these practices increased with time, increasing with patient need and clinician experience. By the end of the project, 1625 patients received BDQ and 1052 patients received DLM, for more than 180 days. At least 416 patients received both BDQ and DLM at the same time. Data from these patients have already informed national guidelines in endTB countries, and areas expected to inform subsequent WHO recommendations.

The endTB Observational Study also included many important groups of patients that often are not well represented in clinical trials because of their complexity. In endTB sites that were simultaneously enrolling patients into the endTB Clinical Trial, the endTB Observational Study was an important option for patients who were too complex or sick for the trial. An important proportion of patients were infected with fluoroquinolone-resistant (51%) and XDR-TB (28%) strains. The endTB Observational Study also enrolled a large number of children ($n = 91$) and pregnant women ($n = 37$), which will help to inform safety recommendations in these crucial patient populations.

Table 3 The endTB Medical Committee

A virtual committee of experienced, international MDR-TB clinicians was created to answer questions by email from clinicians in the field. Some committee members were affiliated with endTB Consortium partners, but others were completely independent. The terms of reference were reviewed by an ethical review committee. A secretariat was responsible for receiving inquiries from the field, removing all identifiers, circulating to the committee members and compiling opinions into a formal letter that was sent back to the field. Cases reviewed included requests for compassionate use, "off label" use (in children, pregnant women), use of new drugs longer than 24 weeks and in combination and advice on challenging cases (e.g., non-response to treatment, adverse events, multiple comorbidities). During the period April 2015–December 2019, over 500 cases were reviewed.

endTB = Expand New Drug Markets for TB; MDR-TB = multidrug-resistant tuberculosis.

Lesson 5: Data collection to generate scientific evidence requires financial and human resources (acceptability/adaptability)

The endTB Observational Study was a unique opportunity to gather scientific data in a systematic manner on some of the first patients to use new and repurposed TB drugs in routine care. Close follow-up was of the greatest importance, but particularly difficult in patients who often had long history of unsuccessful treatment, highly resistant TB, multiple comorbidities and social and economic barriers to adequate health care. Each endTB site had years (and sometimes decades) of experience providing care to MDR-TB patients. Each site had extensive experience with their own methods to improve patient retention and adherence, such as patient education and counselling, financial incentives and enablers or community health workers to provide education and support.

At the field level, both financial and human resources were required to collect high quality data. For example, in almost all countries, the regular national TB laboratory network performed all drug susceptibility testing and monitoring cultures. But endTB staff were required to track down laboratory results and ensure they were entered into the endTB Observational Study database. At the central level, the endTB Consortium created a number of tools to facilitate data abstraction from clinical records, including a standardised set of variables and a data dictionary that clearly defined every variable. The endTB Electronic Medical Record was used in all countries for patient or program management. Data from each country EMR were exported and combined into a central database at regular intervals. The central endTB team also coordinated data cleaning by identifying incomplete or incorrect data and regularly sending data queries to the country endTB teams.

Lesson 6: Pilot projects can drive national scale-up (delivery)

There have been a number of factors driving scale-up of the new and repurposed TB drugs including: new WHO recommendations that expanded indications for the use of these drugs; the availability of these drugs through the Global Drug Facility; and the decreased cost of several repurposed drugs such as LZD and CFZ driven by the market entrance of additional quality-assured generic version. endTB has played a major role in multiple countries to support expanded indications and promote access of these drugs to all patients who need them.

endTB has supported MOHs and national TB programmes to analyse data from their own patients enrolled in the Observational Study, which has informed revisions of several country national guidelines. Most importantly, physicians have had direct experience in prescribing these drugs and have seen both effective treatment and side effects. These are the same physicians who write national guidelines and advise other physicians, so these experiences are invaluable. One of the most important challenges facing countries was transitioning funding for the purchase of new and repurposed drugs to domestic or international funding (such as the Global Fund). Funding began to transition only after countries gained experience and national guidelines changed. A good example of how the early adoption of these drugs has helped incorporate these drugs into domestic budgets and national strategic plans has been Kazakhstan (Table 4).

Table 4 endTB provides a blueprint for national scale-up in Kazakhstan

When endTB started, experience with bedaquiline and delamanid was limited to 10 patients treated through compassionate use programmes. Importation of endTB drugs using the single waiver importation mechanism took some time, but the first endTB patients were enrolled in February 2016 in five regions of Kazakhstan, in close partnership with the NTP and regional TB services.
The initial experience with the new and repurposed drugs was good, and the MOH requested endTB to scale-up to additional five regions of Kazakhstan, including those with the highest burden of DR-TB in the country. During February 2016–September 2018, 675 patients were enrolled, the largest endTB country cohort.
In addition to drugs, endTB provided extensive clinical and programmatic accompaniment, setting up programmatic elements targeting adherence to therapy, such as video-observed therapy and patient-centred, home-based accompaniment models of care. Using new TB drugs allowed Kazakhstan to transition towards using fully oral, injection-free regimens and ambulatory care service delivery for MDR-TB.
As a result of the successful introduction of new TB drugs and regimens as a part of endTB, the NTP institutionalised their use in an updated version of the national decree on TB control, guidelines and protocols. The remaining seven regions began implementing new TB drugs and regimens. In 2019, the MOH started procurement of bedaquiline, linezolid, clofazimine and delamanid for more than 2000 patients from the Global Drug Facility.

endTB = Expand New Drug Markets for TB; NTP = National Tuberculosis Programme; TB = tuberculosis; MOH = Ministry of Health; DR-TB = drug-resistant TB; MDR-TB = multidrug-resistant TB.

CONCLUSION

In the course of introducing new and repurposed TB drugs to multiple countries, endTB has encountered and overcome many barriers. Our experience is likely to be relevant to the uptake of future drugs developed for TB and other diseases. Every country was unique in the pace of progress, but there were several important practices that were key to overcoming the barriers to transitioning the new drugs into routine programmatic use. Waivers played an important role for new and repurposed TB drugs and can facilitate the importation of drugs that have yet to be locally registered. Improving clinical monitoring of patients identifies adverse events early and improves patient

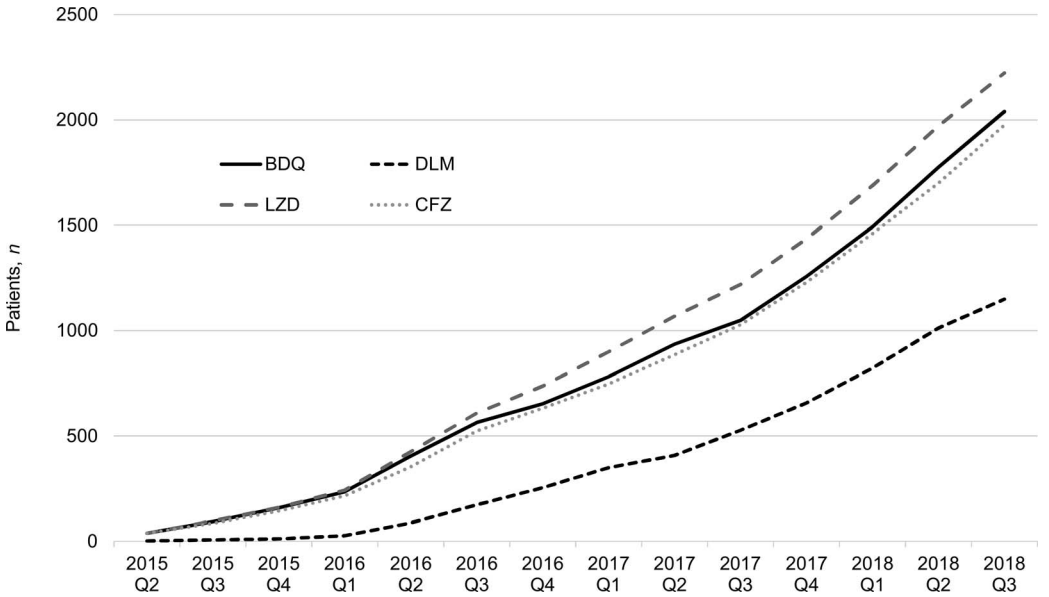

Figure 2 Number of endTB patients prescribed new and repurposed TB drugs. BDQ = bedaquiline; DLM = delamanid; LZD = linezolid; CFZ = clofazimine.

outcomes. It also has a secondary effect of increasing PV reporting, which is an important part of the process of introducing new drugs. Physicians need support and advice during the initial phases of roll out of new drugs, and committees of clinical experts can be a helpful way to provide this support (provided they remain in an advisory role and do not become an administrative bottleneck). When supplies of new drugs are restricted, clinicians will save them for the sickest patients. When supplies are readily available, clinicians will use them more widely for patients who can benefit. Post-marketing PV and observational cohort studies are important, but good quality data require additional financial and human resources. Data generated in countries have a strong effect on national policy change. Combined with WHO guideline changes, rapid scale-up is possible.

Conflicts of interest: none declared.

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RÉSUMÉ

Le projet *endTB* (*Expand New Drug Markets for TB*) a débuté en 2015 avec l'objectif de réduire les obstacles à l'accès aux nouveaux médicaments de la TB ainsi qu'aux médicaments recyclés. Cet article décrit les défis majeurs de la mise en œuvre rencontrés dans 17 pays endTB et offre un aperçu de la manière dont les programmes nationaux de lutte contre la TB et autres parties prenantes peuvent accélérer l'utilisation par les programmes de médicaments de la TB nouveaux et recyclés tout en apportant des preuves scientifiques de leur sécurité et de leur efficacité. Pour un quelconque médicament nouveau ou un nouvel outil de diagnostic, de nombreux obstacles liés au marché peuvent ralentir le rythme de l'expansion. Entre 2015 et 2019, endTB a été une réussite dans 17 pays en augmentant le nombre de patients recevant des médicaments TB nouveaux et recyclés. L'expérience de endTB offre de nombreuses leçons relatives à l'introduction dans les pays de nouveaux médicaments TB, ainsi que de médicaments non-TB et d'outils de diagnostic : l'importation de médicaments TB est possible même en l'absence d'enregistrement; mettre l'accent sur un bon suivi clinique est plus important que les rapports de pharmacovigilance ; les directives nationales et les comités d'experts peuvent à la fois faciliter et entraver les pratiques innovantes ; les cliniciens utilisent les médicaments TB nouveaux et recyclés quand ils sont disponibles ; le recueil de données visant à apporter des preuves scientifiques requiert des ressources financières et humaines; les projets pilotes peuvent être le moteur de l'expansion nationale.

RESUMEN

El Proyecto *endTB* (*Expand New Drug Markets for TB*) se inició en el 2015 con el objetivo de disminuir los obstáculos del acceso a los fármacos contra la TB nuevos y los destinados a un nuevo uso. En el presente artículo se describen las principales dificultades de ejecución encontradas en 17 países de *endTB* y se contribuye a la comprensión de la forma como los Programas Nacionales de Tuberculosis y otros interesados directos pueden ampliar el uso programático de los fármacos nuevos y los destinados a un nuevo uso, al tiempo que se genera evidencia científica sobre su seguridad y eficacia. Todo nuevo fármaco o medio diagnóstico multiplica las barreras de mercado y lentifica el ritmo de la ampliación de escala. Del 2015 al 2019, *endTB* fue exitoso en 17 países al aumentar el número de pacientes que recibían fármacos contra la TB, nuevos o destinados a un nuevo uso. La experiencia de *endTB* aporta muchas enseñanzas relacionadas con la introducción a nivel nacional, tanto de nuevos fármacos contra la TB como de otros fármacos y medios diagnósticos: es posible importar fármacos contra la TB, incluso sin autorización de comercialización; la prioridad atribuida a un buen seguimiento clínico es más importante que la notificación en materia de farmacovigilancia; las directrices y los comités de expertos nacionales facilitan pero también pueden obstaculizar las prácticas innovadoras; los médicos utilizan los fármacos nuevos o destinados a un nuevo uso cuando están disponibles; la recogida de datos con el fin de generar evidencia científica exige recursos económicos y humanos; los proyectos piloto pueden impulsar la ampliación a escala nacional.