

Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis

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SUMMARY

Several new classes of anti-tuberculosis agents are likely to become available in the coming decade. Ensuring prompt access to these drugs for patients without other treatment options is an important medical and public health issue. This article reviews the current state of 'compassionate use' and 'expanded access' programs for these new drugs, and identifies several shortcomings that will limit patient access to the drugs. A series of five steps is outlined that will need to be taken by national health

bodies, international agencies and non-governmental organizations to prevent undue delays in access to new tuberculosis drugs for patients who could benefit from them. Following these steps can ensure that patients will be able to benefit from access to these drugs, while minimizing the risk of emergence of resistance to the drug.

KEY WORDS: pre-approval access; expanded access program; pre-marketing access; import waiver; open enrollment trial

MULTIDRUG-RESISTANT (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) are rapidly growing threats to global health. A 2010 report by the World Health Organization (WHO) estimated that over 440 000 new cases of MDR-TB occurred in 127 countries in 2008, causing 150 000 deaths; this represents a 55% increase in the number of cases since 2000.¹ It is further estimated that up to 10% of these >440 000 annual MDR-TB incident cases also have XDR-TB, which has been identified in 84 countries worldwide.² Current treatment regimens for MDR-TB have only a 58–67% success rate,³ and mortality may be as high as 20%.^{4–7} Regimens for MDR-TB treatment are given for 18–24 months and are expensive and poorly tolerated. In patients who fail to respond but do not die, *Mycobacterium tuberculosis* may develop additional resistance, resulting in XDR-TB.⁸ Successful treatment of XDR-TB is even less common.^{9–11} It is estimated that only about 19% of MDR or XDR-TB cases have access to diagnosis and some kind of treatment.² There is therefore a pressing need for improved diagnosis and treatment of MDR-TB.

Several reports have identified new anti-tuberculosis drug development as a critical global public health need.^{12,13} Six new anti-tuberculosis agents are currently in Phase I, II or III clinical trials: OPC-67683

(delamanid), TMC-207 (bedaquiline), PA-824, SQ-109, PNU-100480 and AZD-5847.¹⁴ These agents include four drug classes not previously used for the treatment of TB: diarylquinolines, nitroimidazole derivatives, ethylene diamines and oxazolidinones. The anticipated availability of effective new classes of anti-tuberculosis agents offers hope that new and more effective regimens for treatment of MDR- and XDR-TB can be developed. Such new regimens could greatly improve the treatment of patients with drug-resistant TB. However, translation of clinical trial results to effective treatment of patients with MDR-TB in program settings will require new challenges to be addressed.¹⁵

This article describes the potential scenarios likely to occur in the compassionate use of new TB drugs when they have shown evidence of efficacy and safety in Phase IIb/III trials, identifies potential problems that could delay access to investigational drugs by patients in need, and outlines steps that could be taken to reduce these delays.

PROVISION OF INVESTIGATIONAL NEW DRUGS TO PATIENTS IN NEED

The advent of new anti-tuberculosis agents is especially critical for patients who are facing broad-spectrum

or progressively drug-resistant TB disease and whose treatment options have been exhausted. For such persons, it is essential that access to new agents be provided in a timely manner. Many countries have established processes that allow distribution of an investigational new drug (IND) to patients in need prior to regulatory approval, commonly termed ‘compassionate use’ or ‘expanded access’ programs. These programs have been developed to provide patients with controlled access to medications that have demonstrated efficacy but are not yet available to the general public as the regulatory process is not complete. Such programs have long been used for patients with cancer or human immunodeficiency virus infection (HIV),^{16,17} but not for TB. From 1983 to 1988, the Division of TB Elimination of the Centers for Disease Control and Prevention (CDC) oversaw domestic distribution of rifabutin for non-tuberculous mycobacteria,¹⁸ but the scale of that program was much more modest than is anticipated for a new TB drug, where the global burden of disease is far larger.

An annex of the ‘Guidelines for the programmatic management of drug-resistant tuberculosis’, published by the WHO in 2008, outlines the various mechanisms for use of experimental TB drugs outside of clinical trials. The objective of this document was to encourage national health authorities of countries with a high TB burden to develop or update the necessary framework (regulation, pharmacovigilance and patient protection mechanisms) to facilitate access to the potential benefit of compassionate use programs for patients in need, and to ensure that adequate precautions exist to protect them from undue risks.¹⁹

STAGES OF INTRODUCTION OF NEW DRUGS TO CLINICAL USE

The introduction of a new therapeutic agent is a continuous process that passes through three stages, as shown in the Figure. These stages may occur at different times in different countries, but always follow the same progression. Once a pivotal trial is completed that demonstrates effectiveness of the agent, an application can be made for initial regulatory approval. The period between this application and the time that the initial reference approval is granted is termed the ‘pre-approval’ period. Following this, there is a period of variable duration when specific country approval is applied for, which we will term the ‘interim’ period. After country-specific approval is granted, the drug can be marketed; this is termed the ‘post-approval’ period.

‘COMPASSIONATE USE’ AND ‘EXPANDED ACCESS’ PROGRAMS

There is no universally accepted definition for the terms ‘compassionate use’ or ‘expanded access’. We

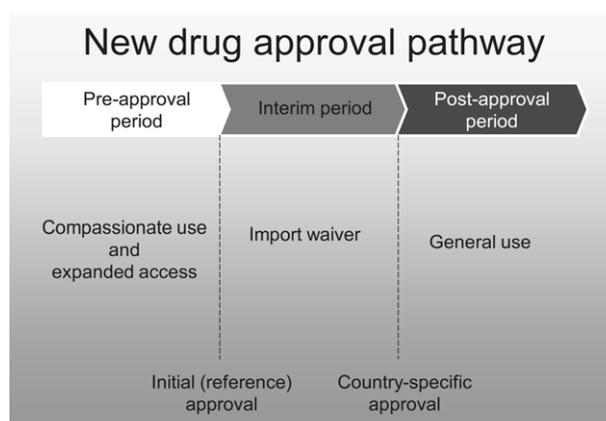


Figure Types of programs allowing access to new drugs and their relationship to the new drug approval pathway.

propose the following terminology to differentiate between the two types of programs (both during the ‘pre-approval’ period).

Compassionate use (CU) is used to refer to programs for which a physician requests a drug for a specific individual patient. The physician usually applies directly to the manufacturer. The manufacturer provides the drug to the physician for use for that specific patient, and the patient’s condition must meet criteria established by the manufacturer, usually based on the absence of any other treatment with any likelihood of success. The manufacturer provides guidelines on the use of the drug, but does not monitor its use or outcomes. In general, the country of residence is required to have regulations in place permitting such ‘compassionate use’ of an unapproved drug. The physician is responsible for following local regulations, such as importation or the need for Institutional Review Board (IRB) approval.

Expanded Access Programs (EAP) refers to programs that focus on enrolling groups of patients; in this way they are a type of clinical trial. In an EAP, the manufacturer sets up a trial into which patients can be enrolled if they meet specific criteria. Rather than evaluating individual patients case by case on the basis of need, a target population for enrollment is defined and only those patients who meet the enrollment criteria can participate. There is more emphasis on patient follow-up than in the CU mechanism, and data collection on safety and follow-up/treatment outcome is requisite. The drug is used on an open-label basis, and its use is required to follow program guidelines. In this situation, the program is established in specific countries, where it is registered as a clinical trial. Access is thus limited to the countries where the trial is taking place.

As an example, EAPs for new HIV drugs have, in some cases, facilitated rapid accrual of additional efficacy and safety data,^{20–22} often as a condition of accelerated approval. However, an additional incentive for EAP of new HIV drugs has been to serve as an

'early launch' for the new product.²³ EAPs for new HIV drugs are more common than for TB, and serve as an example of what could also be achieved for TB. Unfortunately, the limited potential for profit from new TB drugs in many countries with a large burden of disease may limit early launch as a stimulus to EAPs for new TB drugs.

Unfortunately, such clear definitions of CU and EAP are not routinely applied, either in the literature or in regulatory guidelines. Each country decides its own regulations and applies its own definitions, leading to a wide variety of global programs using similar terminology. For example, in the United States, the Food and Drug Administration (FDA) does not differentiate between CU and EAP, instead referring to all programs as 'expanded access' and defining them as 'a means by which manufacturers make IND available, under certain circumstances, to treat a patient with a life-threatening condition who cannot participate in a controlled clinical trial . . . the primary intent of expanded access is to provide treatment for a patient's disease or condition, rather than to collect data about the study drug' (<http://www.nlm.nih.gov/services/ctexpaccess.html>).

In the European Union (EU), the primary mechanism is termed CU, and is used to describe access to an unlicensed drug for patients who have an unmet therapeutic need. CU programs are only available to patients with life-threatening, long-lasting and seriously disabling illnesses. According to the European Medicines Authority (EMA), 'CU programs are coordinated and implemented by the EU Member States, which decide independently how and when to open such programs according to national rules and legislation.'²⁴ Most, but not all, EU countries allow CU.

In Canada, CU and EAPs are distinct. If a new treatment has been shown to have sufficient efficacy for a given indication, if no alternative effective safe remedy is available and if its safety profile can be characterized well enough that a subject can understand the risks, a patient can apply to receive access to the new treatment through the 'Special Access Program' (SAP) of Health Canada.²⁵ This program, often referred to as CU, provides a supply of INDs to an individual patient. In addition, Health Canada may decide that a company wishing to make a new treatment available to patients must do so through an Expanded Access Protocol, with a more rigorous data collection mechanism.

Not only are the regulations country-specific, but some countries also require an import certificate. Conversely, in other countries, an import certificate will suffice without other regulatory reviews.²⁶ Regulations about payment, liability, adverse event reporting and the need for prior licensure in another jurisdiction are also highly variable. Moreover, some hospitals within a jurisdiction may require IRB clearance for use among patients in their institution, while others will not.

PRINCIPLES OF PRE-APPROVAL TUBERCULOSIS DRUG DISTRIBUTION PROGRAMS

To formulate a proposal about how to facilitate patient access to new anti-tuberculosis agents while minimizing the emergence of resistance to these drugs, Research Excellence to Stop TB Resistance (RESIST-TB, <http://www.resisttb.org/>) convened a working group in April 2010. This group included participants from industry, TB programs, the TB patient community, civil society, the WHO, the Stop TB Partnership and the CDC. We discussed these issues on conference calls and in a face-to-face meeting. The Critical Path to TB Drug Regimens' (CPTR) Access and Appropriate Use Workgroup subsequently provided substantial input to further develop these concepts. The principles of pre-approval TB drug distribution programs were identified as follows.

The objective of pre-approval access to a TB drug is to provide access to those most in need. Patients who are failing or very likely to fail treatment of highly resistant forms of TB are in the greatest need of new drugs. For many patients with XDR-TB, there are almost no additional drugs available for treatment, and currently available regimens have poor outcomes, particularly in patients with HIV infection.^{27,28} As new drugs become available, mechanisms need to be developed to provide early access to patients with XDR-TB and 'pre-XDR' (resistance to isoniazid and rifampin plus a quinolone or a second-line injectable agent, but not both) prior to regulatory approval, and within the context of the country's regulatory system. These mechanisms must take into account the following overarching principles (Table):

Protect patients

The patient must be well informed about the drug, its intended actions and potential side effects, and its possible impact on other conditions or treatments. It is critical that the patient is informed of the risks, potential benefits, and alternatives, and understands that there is no guaranteed benefit from the experimental drug. Informed consent is thus an integral part of this process. In this respect, some countries (the United States and some EU countries) require approval from an oversight body (IRB or human subjects committee) to authorise pre-approval drug distribution programs. In addition, patients should be provided with culturally appropriate information explaining the risks and benefits of their treatment regimens so that they can make informed decisions.

Table Goals of a compassionate use/early access program for new tuberculosis drugs

Protect patients
Minimize the risk of treatment failure and emergence of resistance
Exercise fairness
Comply with regulatory guidance

Minimize the risk of treatment failure and emergence of resistance

It is essential that the addition of an investigational agent to a treatment regimen of a person with MDR- or XDR-TB be in conjunction with the most effective companion regimen possible, so as to treat the patient in the most effective way while simultaneously minimizing the likelihood of emergence of resistance to the new drug. Pre-approval drug distribution programs can only be considered if conditions for the adequate management of drug-resistant TB patients are in place: optimal treatment regimens using quality-assured companion drugs; close clinical, biological and bacteriological monitoring; and careful treatment follow-up linked to proper patient education, and full adherence and psychosocial support.

Exercise fairness

Depending on the ability of the manufacturer to supply drugs to the pre-approval distribution program, the amount of drugs available may not be enough to meet the demand, even after limiting access to those in greatest need. Careful attention may also need to be paid to the process for gaining access to the new drugs, to prevent favoritism.

Comply with regulatory guidelines

All CU/EAP programs must comply with regulatory guidelines in the country where the drug is to be used. As noted, regulatory guidelines for providing access to investigational agents vary widely from country to country. In many high MDR-TB burden countries there is no regulatory or legal framework that would allow the compassionate use of a new drug.²⁹

CHALLENGES TO SUCCESSFUL PRE-APPROVAL TUBERCULOSIS DRUG DISTRIBUTION PROGRAMS

Diversity of regulatory requirements

As noted, the presence of an effective regulatory framework permitting CU varies widely from country to country. Among the high MDR-TB burden countries,² only Georgia and Latvia specifically authorize CU. In other high-burden countries, such as India, regulations are in place that allow importation of unregistered medicines that can be used for CU, although there is no specific legal or regulatory provision allowing for a CU program. CU is specifically prohibited in Russia and China. In some other countries, individual patient access to new drugs in the absence of a formal framework can be organized by arrangement with the Ministry of Health.

When CU is not an option, establishment of an EAP may be the only way to provide access to a new drug for patients in need. This will require the manufacturer to design and implement a treatment protocol. As such protocols are essentially clinical trials,

most countries have the regulatory framework to allow such protocols. The implementation of these protocols requires dedicated trained staff and a clinical trials infrastructure, and is limited to specific trial sites. Planning ahead for such programs will be important so that access to a new drug by patients in such countries is not substantially delayed.

Minimizing the emergence of resistance to the new drug

Distributing a drug will provide little benefit to patients if the drug is not used in an effective manner. It is therefore imperative that appropriate use be assured. The treatment regimen that accompanies a new drug must be the most effective companion regimen possible, thus minimizing the risk of emergence of resistance to the new drug. This implies that access to quality-assured in vitro drug susceptibility testing (DST) of patient isolates is assured so that these results can be used to guide the selection of the best companion drugs and ensure proper monitoring. Guidance on the use of the new drug would be provided best by experts in the treatment of drug-resistant disease, particularly those familiar with current global standards for the management of drug-resistant disease. Without simultaneous access to a variety of quality-assured second-line anti-tuberculosis agents, the benefit the patient receives by accessing the new drug will be short-lived. Lack of DST, lack of regular supplies of quality-assured companion agents and lack of clinical expertise currently limit the geographic regions where pre-approval access to new TB drugs can be made available.³⁰

There is an inherent tension in that those patients at greatest need, such as those with XDR-TB, are also those least likely to have effective companion drugs available for use with the new drug. Without access to effective companion drugs, resistance to the new drugs will rapidly emerge, limiting the benefit to the patient and, over time, to the community as a whole. Expanded availability of second- and third-line agents that meet international standards of quality (WHO prequalified or approved by a stringent regulatory authority) will therefore need to accompany CU or EAP. Such availability is hampered by the lack of local registration of such agents and a sufficiently competitive global market for second-line drugs. A clearly defined regulatory pathway for second-line TB drugs would therefore facilitate effective implementation of new TB drugs.

Ensuring adherence to the new drug and companion drugs will be essential. The WHO acknowledges that 'programs have an ethical obligation to follow up with patients who are having problems with adherence.'³¹ This obligation is even more compelling when patients, such as those with XDR-TB, have nearly exhausted all their TB treatment options.³² For these reasons, pre-approval use of a new drug can only be considered when the following optimal conditions

of MDR-TB management are in place: a guaranteed supply of quality-assured effective companion drugs; clinical, biological and bacteriological monitoring; and adherence support and follow-up. DST results by a validated laboratory are also critical to decision making and need to be assured. In addition to the basic components of regular MDR-TB case management, specific safety monitoring is required for the use of a new drug, and a reporting system should be in place to promptly report any adverse events.

To ensure good practice and equity, requests for such access should be sent to a specifically established medical committee accredited by the national regulatory agency. This committee should review each request for pre-approval access and make decisions, taking into consideration the nature of the medical condition and the available information regarding the safety and efficacy of the drug. The committee should also make sure that all requirements for proper treatment are met by the requesting facility and that equitable access is given to all eligible patients. The input of civil society and patient organizations is critical in facilitating an open and equitable process. The work of the committee should be monitored to ensure it is facilitating access to quality care without causing unnecessary delays.

BALANCING THE RISKS AND BENEFITS OF PRE-APPROVAL ACCESS TO NEW TUBERCULOSIS DRUGS

It is therefore clear that a balance must be achieved between the risks and benefits of such a program. There are clear benefits for patients whose disease is controlled and whose lifespan is extended due to access to the new medications. The risks include failure of the new drug due to the development of resistance or intolerance and specific toxicities of the new drug. This balance can be positively altered by a high standard of care at the clinical sites managing the administration of the new drugs and careful monitoring of patient responses. The risk-benefit trade-off may thus vary from country to country and from site to site within a given country. The identification or establishment of clinical centers that possess the required expertise, monitoring and laboratory capability will certainly favorably alter the balance.

Donor agencies, international organizations, technical agencies and global health initiatives should provide support to countries in developing clinical centers that can ensure a high standard of care for treatment of patients with MDR-TB. Such centers would ensure that patients with MDR-TB have access to *in vitro* DST against second-line drugs and individualized treatment regimens with quality-assured second-line drugs. This could both facilitate access to the new antimycobacterial agents and optimize companion drug regimens, thus ensuring maximum benefit for patients.

FACILITATING ACCESS TO NEW TUBERCULOSIS DRUGS IN THE 'INTERIM PERIOD'

Registration of a new drug in a developing country usually occurs following approval by the FDA in the USA or the EMA in Europe, although direct approval can also occur.³³ Approval by the FDA or EMA can be time-consuming unless specific 'accelerated' approval is sought. For many drugs that are not expected to be widely used in the USA and Europe, gaining regulatory approval from the FDA or EMA can be challenging, but in the case of new TB drugs this has not been a major impediment. Moreover, at the EMA there is a specific regulatory pathway for approval of drugs that are not seeking an indication for use in Europe (Article 58, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000157.jsp&mid=WC0b01ac05800240d1).

Once such a 'reference' approval is granted, some countries allow importation of drugs for serious or life-threatening conditions that have been approved in another jurisdiction for individual patients in need through an 'import waiver'. Such importation is similar to CU in that it is initiated by the physician on a case-by-case basis; the important difference is that the drug has received reference approval in another jurisdiction.

In the interim period between the initial reference approval and country-specific approval, use of the new drugs for drug-resistant TB could be facilitated in two ways. First, national programs and implementing partners should update their MDR-TB treatment guidelines to incorporate the new drug(s) as soon as there is sufficient evidence to do so. Second, addition of the new drug to the WHO Essential Medicines List would signify international recognition that the drug is important for the indicated condition. Unfortunately, addition of new agents to the Essential Medicines List is a time-consuming process, and will not help make new drugs available to patients in a timely fashion. While neither of these steps leads directly to registration in countries where the drug is needed, such actions would have the potential to facilitate the wide use of new TB drugs. The WHO is currently developing operational materials to guide countries in initiating CU/EAP and formulating policy on the adoption and safe use of proven effective new drugs within TB treatment programs.

PROPOSALS

We propose that the following five steps be taken promptly by national health bodies, international agencies and non-governmental organizations to prevent undue delays in providing access to new TB drugs by patients who could benefit from them:

- 1 National regulations should be updated to ensure the use of second- and third-line drugs meeting

international standards of quality and for new drugs.

- 2 In conjunction with National TB Control Programs, clinical centers that can ensure a high standard of care for programmatic treatment of patients with MDR-TB should be established. These centers should:
 - i Perform quality-assured DST to identify patients who could be eligible for CU/EAP and to enable design of effective regimens
 - ii Have access to and be able to design and provide the most effective companion regimen that will accompany the new agent and be able to provide the necessary adherence and psychosocial support
 - iii Be the preferred implementing facility for CU/EAPs that target patients with pre-XDR- and XDR-TB for CU/EAP with new drug(s)
 - iv Provide comprehensive education to patients to ensure that they are making informed decisions about their treatment.
- 3 National regulations permitting CU and defining required conditions for adequate use and equitable access (e.g., accredited clinical centers, medical committee for CU/EAP, etc.) should be established.
- 4 International agencies and technical partners should support efforts to facilitate access to new drugs by issuing appropriate treatment recommendations and initiating the prequalification process for the new agent.
- 5 Research should be undertaken that aims at elucidating the compatibility of the new drugs with antiretroviral agents and other drugs likely to be co-administered to patients with MDR-TB.

CONCLUSIONS

Since around 1990, with the fight for access to anti-retrovirals under development, there has been 'a shift from preventing harm by protecting patients from risk to actively promoting patients' welfare by providing them earlier and broader access to experimental drugs.'¹⁶ Persons with life-threatening illnesses are willing to assume greater risks in exchange for smaller potential benefits than other groups of patients.^{14,16} Pre-approval drug distribution programs recognize their right to assume such risks. Such access is not accomplished merely by the provision of a drug by the manufacturer; rather, regulatory conditions must be such that patients can receive drugs in a timely manner and use them in a way that maximizes their likelihood of receiving benefit. These conditions do not currently exist in most of the 27 countries that WHO defines as high-burden for MDR-TB.² Countries without a regulatory framework for CU should move quickly to develop such frameworks, and the WHO could give guidance to facilitate such development. A harmonized regulatory pathway should also be con-

sidered for public health pandemics, such as MDR-TB, to expedite access to companion second-line drugs to ensure that CU programs provide the maximum benefit to patients. The African Medicines Regulatory Harmonization Initiative is an example of such an effort.³⁴

It is essential for these countries to first offer adequate MDR-TB diagnosis, *in vitro* DST and management with existing drugs, so that patients benefit from optimal existing treatment and so that addition of new drug classes will provide lasting benefit. This will need to be complemented by efforts to reform the global marketplace to ensure availability of quality assured second- and third-line drugs according to international standards. Such efforts should be a high public health priority in countries with a substantial burden of MDR-TB.¹ For their part, national health bodies, international agencies and non-governmental organizations should outline the circumstances and conditions in which new TB drugs should be used and provide guidance on how to develop the necessary regulations for CU/EAP and licensure in highly affected countries. Finally, it is critical that civil society and patient organizations are engaged in the design and implementation of these programs to ensure that all programs meet the needs of the patients.

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R É S U M É

Au cours de la décennie à venir, plusieurs nouvelles classes d'agents antituberculeux sont susceptibles de devenir disponibles. Garantir un accès rapide à ces médicaments par les patients n'ayant pas d'autres options thérapeutiques est un problème important sur le plan médical et sur le plan de la santé publique. Cet article fait la revue de l'état actuel des programmes « d'usage compassionnel » et « d'accès élargi », et les insuffisances qui limiteront l'accès des patients à ces médicaments. Nous

décrivons une série de cinq étapes qui devront être suivies par les institutions de santé nationales, les agences internationales et les organisations non-gouvernementales pour prévenir des retards inacceptables dans l'accès aux nouveaux médicaments TB pour les patients qui pourraient en bénéficier. En suivant ces étapes, on peut garantir que les patients seront capables de bénéficier de l'accès à ces médicaments tout en minimisant le risque d'apparition de la résistance à ces médicaments.

R E S U M E N

Es posible que en los próximos diez años se encuentren al alcance varias clases nuevas de medicamentos anti-tuberculosos. Procurar el acceso oportuno de los pacientes sin otras opciones de tratamiento a estos medicamentos representa una importante cuestión médica y de salud pública. En el presente artículo se analiza la situación de los programas sobre el 'uso compasivo' y la 'ampliación del acceso' a estos nuevos anti-tuberculosos y se señalan algunas dificultades que limitarán el acceso a los medicamentos. Se describe asimismo una serie de

cinco etapas que habrán de superar los organismos nacionales de salud, los organismos internacionales y las organizaciones no gubernamentales a fin de evitar los retrasos injustificados en el acceso a los nuevos medicamentos anti-tuberculosos por parte de los pacientes que los necesitan. Al seguir estas etapas, se logrará que los pacientes accedan a los beneficios del tratamiento y se disminuirá al mismo tiempo el riesgo de aparición de farmacoresistencia.
