

New Drugs for the Treatment of Tuberculosis: Needs, Challenges, Promise, and Prospects for the Future

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For the first time in 40 years, a portfolio of promising new compounds for the treatment of tuberculosis is on the horizon. The introduction of new drugs in combination treatment for all forms of tuberculosis raises several issues related to patients' access to novel treatments, programmatic feasibility, cost effectiveness, and implications for monitoring and surveillance, particularly with regard to the development of drug resistance. Particular attention should be given to the identification of optimal drug combination(s) for the treatment of all forms of tuberculosis, particularly in high-risk and vulnerable groups, such as human immunodeficiency virus–coinfecting persons and children, and to the rational use of new drugs. Addressing these issues adequately requires the establishment of clear guidelines to assist countries in the development of policies for the proper use of tuberculosis drugs in a way that guarantees access to best treatments for all those in need and avoids inappropriate use of new drugs. After a description of these various challenges, we present activities that will be carried out by the World Health Organization in collaboration with key stakeholders for the development of policy guidelines for optimal treatment of tuberculosis.

A 6-month chemotherapy regimen using a combination of 4 drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months) with cure rates of approximately 90% in human immunodeficiency virus (HIV)–negative patients is the globally accepted standard treatment of drug-susceptible, active tuberculosis [1]. However, poor patient compliance, poor-quality drugs, and irrational prescribing practices increase the risk of selection of drug-resistant (DR) strains of *Mycobacterium tuberculosis*, which are more difficult and more expensive to treat. Recommended regimens for the treatment of

multidrug-resistant (MDR) tuberculosis require at least 20 months of treatment with drugs that are toxic, poorly tolerated, and of limited efficacy, with cure rates in the range of 60%–75% [2]. Tuberculosis/HIV coinfection further complicates the matter. Tuberculosis is the leading cause of death among HIV-infected people in developing countries, and treatment is complex due to interactions between antiretrovirals (ARVs) and anti-tuberculosis drugs and increased risk of adverse effects. Shorter and simpler drug regimens that are safe, well tolerated, effective against drug-susceptible (DS) and DR tuberculosis, appropriate for joint tuberculosis/HIV treatment, and amenable to routine programmatic conditions are needed urgently. This article reviews the needs, challenges, recent advances, and priority operational issues in development of new tuberculosis drugs and shorter treatment regimens for the management of DS and DR tuberculosis and particularly for widespread use in countries with a high tuberculosis burden.

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TUBERCULOSIS DRUGS CURRENTLY IN CLINICAL DEVELOPMENT PHASES

For the first time in 40 years, a portfolio of promising new compounds is on the horizon (Figure 1). Some have the potential to become the cornerstone drugs of future tuberculosis treatment [3, 4]. Eleven new or repurposed tuberculosis drugs are in clinical investigation, 1 in phase 1 (safety and dose ranging), 7 in phase 2 (early bactericidal activity and sputum culture conversion), and 3 in phase 3 (safety and efficacy) trials.

Two phase 3 trials are evaluating the possibility to shorten treatment of DS tuberculosis to 4 months through the inclusion of a third-generation fluoroquinolone, either gatifloxacin or moxifloxacin, to replace ethambutol or isoniazid [5, 6]. Rifapentine (a semisynthetic rifamycin that has a longer half-life than rifampicin) is presently being tested in various clinical studies to evaluate its safety and ability to shorten the duration of therapy for DS tuberculosis. Regimens being studied include rifapentine given at high doses once or twice weekly during the treatment continuation phase together with moxifloxacin substituting for isoniazid during both the intensive and continuation phases, or dosed daily in combination with other first-line drugs. Of note, rifapentine has recently been tested in combination with isoniazid for shorter treatment of latent tuberculosis [7].

Two novel drugs are presently entering into phase 3 trials for the treatment of MDR tuberculosis: TMC-207 (bedaquiline), a novel adenosine triphosphate synthase inhibitor [8], and OPC-67683 (delamanid), a member of the nitroimidazole

family (nitroimido-oxazole subclass) [9]. Both compounds have been successfully evaluated in phase 2b placebo-controlled, double-blind, randomized trials in patients with newly diagnosed MDR tuberculosis, adding either the investigational drug or a placebo to an optimized background regimen of currently recommended drugs [10].

Other compounds have recently moved from phase 1 to phase 2 trials. These include PA-824, another nitroimidazole (nitroimidazo-oxazine subclass) [11]; linezolid, the only approved drug in the oxazolidinone class [12], presently being tested at a dose of 600 mg daily for the treatment of extensively DR tuberculosis in the Republic of Korea; PNU-100480 (sutezolid), a close analogue of linezolid [13]; and SQ-109, a highly modified derivative of ethambutol [14]. Last, AZD5847, a member of the oxazolidinone class, is presently in phase 1 trial but will soon enter in a phase 2 trial in South Africa.

CHALLENGES IN THE DRUG DEVELOPMENT PATHWAY: THE SEARCH FOR OPTIMAL COMBINATION REGIMENS

The discovery of streptomycin, the first effective antituberculosis agent, in 1943 brought much excitement and hope to the world [15]. It was, however, soon observed that *M. tuberculosis* rapidly developed resistance to this drug and stable cure was unattainable with monotherapy. To prevent the development of resistance and produce a stable cure, combination therapy was needed [16, 17]. Since that time, the search for better tuberculosis therapy has been driven by

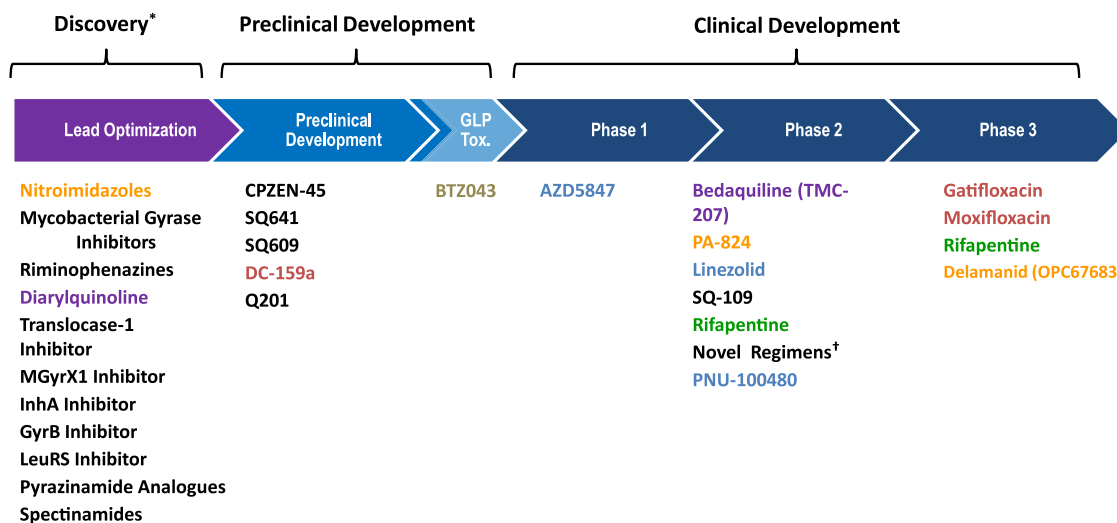


Figure 1. Global tuberculosis drug pipeline. Chemical classes are shown in various colors: fluoroquinolone (red), rifamycin (green), oxazolidinone (blue), nitroimidazole (yellow), diarylquinoline (purple), enothiazinone (tan). *Ongoing projects without a lead compound series can be viewed at <http://www.newtbdugs.org/pipeline-discovery.php>. †Combination regimens: first clinical trial (NC001) of a novel tuberculosis drug regimen testing the 3-drug combination of PA-824, moxifloxacin, and pyrazinamide was initiated in November 2010. Abbreviation: GLP Tox, Good Laboratory Practice Toxicology Study.

Source: Working Group on New Drugs, Stop TB Partnership.

2 intertwined activities: the search for new drugs and the development of efficacious combination regimens [18].

Currently, the standard tuberculosis drug clinical development pathway includes phase 1 safety, tolerance, pharmacokinetic (PK), and dose-ranging studies as well as drug-drug interaction studies to assess the interaction of the new compound with the currently used antituberculosis drugs [4]. These studies are most frequently performed in healthy volunteers. This is followed by studies in tuberculosis patients, assessing the bactericidal activity of the new compound, usually at various doses, compared with either isoniazid or rifampicin or with the standard isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) regimen over 7–14 days (extended early bactericidal activity [EBA] studies) [19] followed by an 8-week drug combination proof-of-concept study (2-month culture conversion studies or serial sputum colony count studies) [20, 21]. Finally, phase 3 pivotal trials are conducted with a long follow-up period to assess clinical and microbiological non-relapsing cure. This process is extremely lengthy and expensive, and if, for selection of a proper combination, new drugs were added to, or substituted into, the current regimen one at a time, it would take 20–30 years to develop a new regimen of 3–4 new drugs [22]. Alternative options are therefore needed to shorten the pathway to identify optimal drug combinations.

Historically, the identification of optimal tuberculosis treatment regimens was carried out by publicly funded institutions with drugs developed and donated by various companies [18]. The situation has changed considerably today. Although new drugs are being developed, only limited efforts have been made so far to define the best combination(s) of drugs (including new drugs) for the treatment of DS and DR tuberculosis. Due to the relatively unattractive market for tuberculosis drugs, sponsors involved in the development of new tuberculosis drugs are unlikely to be willing to support the conduct of large and lengthy trials to identify the optimal combination of drugs, thus potentially leaving this aspect of tuberculosis therapy development unresolved [22]. How studies to identify the best new drug combinations for the treatment of both DS and DR tuberculosis will be conducted, by which mechanism(s), and how these should be funded are questions of extreme importance.

Because the current 6-month standard regimen has 95% efficacy under trial conditions [23], the most appropriate design to test the efficacy of a new regimen for DS tuberculosis is noninferiority. This requires the recruitment of a large number of patients who must be followed closely for a long period of time (usually 12–24 months after treatment) to reliably detect microbiological and clinical cure [6]. Such trials are also expensive, typically costing tens of millions of dollars [24]. This has led drug developers to select the use of randomized superiority designs in MDR tuberculosis treatment trials, which entails testing a new drug against placebo, in addition to an optimized background therapy determined by each patient's

treatment experience and drug sensitivity testing results [25]. This design has the advantages of allowing an equal distribution of key potential confounding factors between study arms and requiring much smaller sample sizes than non-inferiority trials [26]. This route is therefore preferred by pharmaceutical companies developing new drugs for tuberculosis to obtain marketing approval, as it entails lower investments than identification of an optimal treatment combination including their new compound. It has, however, 2 negative consequences: (1) treating MDR tuberculosis patients with a new drug in addition to the existing ones implies that patients will likely receive 6 or 7 drugs for a duration that is usually estimated to be about 20 months in total, and (2) this approach leaves the identification of an optimal combination regimen for the treatment of DS and DR tuberculosis unaddressed.

A new model for tuberculosis drug development proposes that promising new drugs be tested together, rather than sequentially, as follows: Preclinical and full phase 1 safety, tolerability, and PK testing of each individual drug are conducted in parallel with *in vitro* and *in vivo* preclinical evaluation of potential drug combinations to identify optimized candidate regimens (see Figure 2). On the basis of mouse model studies and single-drug phase 1 and early phase 2 (14 day EBA) testing, a candidate combination regimen is developed and advanced into phase 2 EBA testing (so-called combo EBA). If the new combination regimen is found to be promising compared with the control HRZE regimen in terms of early bactericidal activity, it is then advanced into phase 2b 2-month treatment trials for proof of concept both in DS and DR tuberculosis patients. If data are supportive, the new combination regimen is then brought into full phase 3 safety and efficacy testing. This approach is presently being used by the TB Alliance for the development of a novel combination regimen composed of PA824, moxifloxacin, and pyrazinamide that is potentially suitable for MDR (but pyrazinamide-sensitive) tuberculosis as well as DS tuberculosis and has recently been tested in a 14-day combo EBA study vs HRZE as control [27].

Combination With Antiretrovirals

Tuberculosis is the leading cause of death in HIV infection worldwide, accounting for almost one-quarter of all estimated HIV-associated deaths in 2009 [28], so tuberculosis drugs must be compatible with antiretroviral therapy (ART). According to the latest World Health Organization (WHO) recommendation, ART should be initiated as soon as possible during the first 2–8 weeks of tuberculosis treatment in all patients with HIV-associated tuberculosis, regardless of CD4⁺ cell count [29]. Recent studies support initiating ART for those with very low CD4 counts soon after starting tuberculosis therapy (within 2 weeks for those with CD4⁺ cell counts <50) [30–32]. For these reasons, drug-drug interaction studies of new

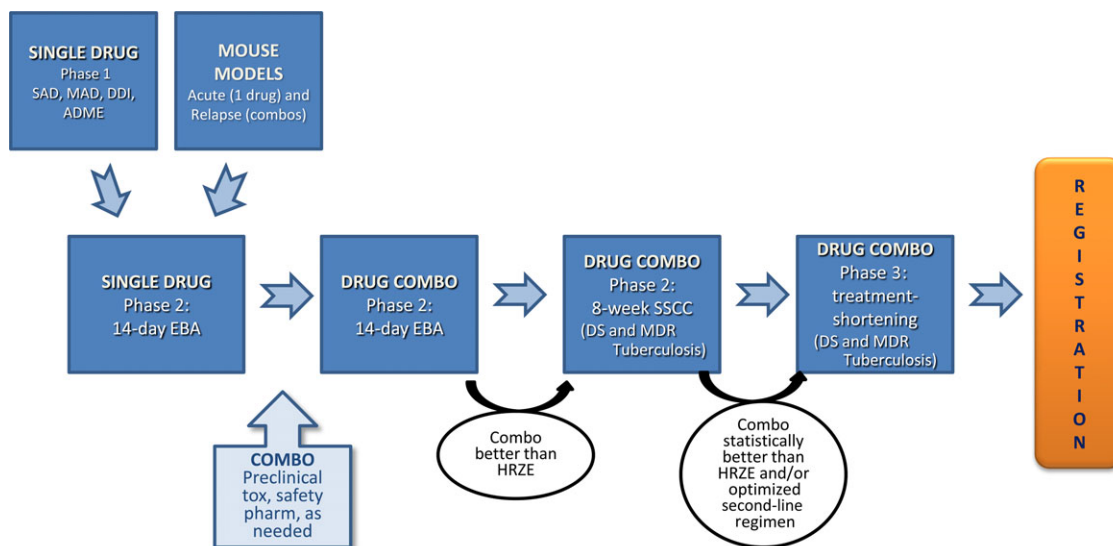


Figure 2. New model for development of drug combination therapy. Abbreviations: ADME, absorption, distribution, metabolism, and excretion; DDI, drug-drug interaction; DS, drug-susceptible; EBA, early bactericidal activity; HRZE, isoniazid, rifampicin, pyrazinamide and ethambutol; MAD, multiple ascending dose; MDR, multidrug-resistant; SAD, single ascending dose; SSCC, serial sputum colony count.

tuberculosis agents and HIV medications should be carried out as early as possible during the drug development process [33]. Of note, this will require anticipation of the continued evolution of the ART arsenal with early studies of well-tolerated, potent ART agents such as integrase inhibitors.

Once drug interaction data are available to guide appropriate dosing of both HIV and tuberculosis agents, participation of people living with HIV should not be deferred until phase 3 studies, as this will delay identification of regimens that do not perform well in HIV infection. Therefore, HIV-infected persons should be included systematically in phase 2 studies to ensure that the new tuberculosis medications can be safely and effectively used in the HIV-infected population [33]. A possible approach is to conduct early combination EBA studies of several tuberculosis drugs in HIV/tuberculosis coinfecting patients with CD4⁺ cell count >200 who can safely defer initiation of ART during the intensive phase of tuberculosis therapy [32, 34]. Subsequent phase 2 studies of promising combinations would then include patients on compatible ART to ensure that commonly used HIV medications can be safely coadministered, and that these regimens perform well in both HIV-infected and HIV-uninfected participants. This approach will ensure that data are available to guide use in HIV/tuberculosis coinfection when new tuberculosis drugs become available.

Issues in Childhood Tuberculosis

The evaluation of antituberculosis treatment in children is difficult [35]. Evidence to support dosing recommendations has been inadequate, and internationally recommended doses of

first-line drugs probably result in suboptimal drug exposure [36]. Even less information exists to guide use of second-line agents. Pediatric drug formulations suitable for high-burden settings must be developed for existing and new drugs, and studies need to be conducted as early as possible to determine the correct dosages of these formulations in children, including HIV-infected children. For these reasons, PK, tolerability, and safety studies should be initiated as soon as possible to identify optimal dosing in children. Conducting separate efficacy trials in children does not appear to be necessary, but sufficient efficacy data could be generated from the above studies. Pediatric tuberculosis drug development, including PK and safety studies in all age groups, and development of child-friendly formulations should be pursued as soon as safety and initial efficacy have been established in adults.

The Way Forward

The challenges above have been recognized by the Bill & Melinda Gates Foundation and the TB Alliance, which, in collaboration with the Critical Path Institute, established the Critical Path to TB Drug Regimens (CPTR) initiative in 2009 [37]. The objective of CPTR is to accelerate the development of new tuberculosis regimens by expediting the process for testing new tuberculosis drugs in combinations before they are individually approved. This broad coalition assembles almost all pharmaceutical companies with compounds currently in clinical trials for tuberculosis as well as a variety of other committed organizations and individuals. Developing a truly novel regimen without going through all the intermediary steps to obtain individual drug approvals separately and only

then beginning to test novel combinations and regimens should substantially reduce the total expenditures needed to make significant progress in the field. This initiative should play a major role in catalyzing the development of optimized drug regimens.

To enable efficient identification of suitable drug combinations, drug developers should investigate the potential for their new compound to be part of a combination regimen through the conduct of drug-drug interaction studies (including standard tuberculosis drugs, ARVs, and other new tuberculosis drugs) at an early stage of development. In addition, providing evidence/support for the use of new compounds (including PK and safety studies) in special populations, such as infants and children, persons living with HIV, and others (elderly persons, diabetic persons, injection drug users, pregnant women), and in different forms of tuberculosis (smear negative, extrapulmonary tuberculosis) should be an integral part of the development plan.

In order to facilitate more rapid use of new drugs and combinations in those special populations, publically funded sponsors such as the National Institute of Allergy and Infectious Diseases will take a lead role for PK/safety and drug-drug interaction studies as needed. Because of resource limitations, trials must be planned among sponsors to avoid redundancy, achieve synergy, and maximize resource use. To achieve this, coordination of phase 2 combination studies among different trial groups is indispensable. Discussions must be held to decide which combinations will be studied and by whom, how to best transition combinations into phase 3, and share relevant pre-clinical, phase 1, and phase 2 trial results. Efforts are now under way to establish a Coordination Forum for these discussions among major nonindustrial clinical research sponsors, which will provide means to coordinate communication and efforts with the pharmaceutical industry and consider potential standardization of methodologies and data to allow comparing and/or combining study results [38]. The activities of this forum will be coordinated with those of the CPTR but with a focus on coordinating phase 2 trial planning.

REGULATORY ASPECTS

With recent activity in antituberculosis drug development, regulatory authorities have updated their guidance for approval of tuberculosis drugs with regard to trial design, definition of endpoints, and optimal posttreatment follow-up period. The urgency of improving MDR tuberculosis treatment has led the US Food and Drug Administration (FDA) to advise that accelerated provisional licensing of such drugs for this indication could be obtained under specific conditions [25, 26]. Most ongoing trials investigating shorter regimens with repurposed drugs for DS tuberculosis are using the noninferiority design (eg, OFLOTUB, REMox, and Rifaquin trials) [22], whereas the evaluation of novel compounds for MDR tuberculosis is based

on superiority trials [25]. The latter has labeling implications: if a drug receives provisional licensure for use in addition to individualized MDR tuberculosis treatment, the question of the number and type of companion drugs to be associated with will not be addressed, generating concern about possible off-label use in DS tuberculosis. This highlights the difficulty of translating the initial approval of a new drug into a subsequent recommendation for use within a specific combination treatment regimen that would be effective and prevent emergence of resistance to new drugs. These issues must be considered and addressed seriously, preferably at early stages of drug development [3]. Some regulatory authorities, such as the FDA, recognize the need to “provide the flexibility needed to rapidly evaluate combination regimens involving new targeted agents in a single development program” [39].

The use of several potential designs in phase 2 and phase 3 trials poses the question of the choice and validity of trial endpoints and their harmonized use for comparability between trials. One criterion for a successful treatment outcome in trials of new regimens is demonstrating stable cure both clinically and microbiologically. Clinical cure is defined as complete resolution of clinical signs and symptoms of tuberculosis that were present at baseline and absence of any new clinical signs and symptoms [40]. Clinical cure is, however, challenging to measure objectively, and the relevance and reliability of clinical scores based on multivariate clinical measurements have not yet been demonstrated. The use of a microbiologic endpoint is preferable as an objective measure of response that is not dependent on clinical outcomes. However, microbiological endpoints are not the same when used in phase 2 or phase 3 trials [25].

The use of early microbiological endpoints in phase 2 studies is based on their surrogacy for treatment outcome. Surrogate endpoints should satisfy the following three criteria: (1) correlation with a definitive clinical endpoint, (2) reproducibility, and (3) clinical/biological plausibility [41]. A perfect surrogate would fully capture the treatment effect on the definitive endpoint, but in practice, most fall short of these criteria while retaining usefulness. In DS tuberculosis, early clinical development relies heavily on culture conversion at 2 months, as proposed by Mitchison on the basis of an observed trial-level correlation with relapse in the series of British Medical Research Council trials [42]. A recent reanalysis of these data indicates that culture conversion at month 3 may outperform conversion at month 2 as a surrogate marker for cure, and there is some evidence of geographical variation [43]. Although considered widely acceptable at present, it is unclear how far this endpoint can be generalized to MDR tuberculosis trials, especially because the definition of culture conversion is more problematic in MDR tuberculosis and the median interval to culture conversion may be prolonged in comparison with DS tuberculosis, often exceeding 2 months [25, 26].

To circumvent the problem of arbitrarily utilizing a single time point for assessment of culture conversion, survival techniques are being increasingly promoted in analysis of tuberculosis trials. Recent studies of quinolone-containing regimens in DS tuberculosis included this approach [5, 20, 44, 45]. The median time to culture conversion is considered useful to suggest superiority of a tested regimen in terms of sterilizing activity. In addition, survival techniques may more accurately capture the underlying rate of sputum sterilization independently of the time points selected, thus facilitating comparisons between different studies and even of treatment regimens with different durations. Applied to culture conversion, survival techniques are expected to be powerful enough to enable phase 2 studies to usefully inform choices of combinations for study in phase 3 trials [25]. Further studies are needed to confirm the role and optimal time point for use of culture conversion as a surrogate endpoint in phase 2b DS and DR tuberculosis trials and to validate the use of time to sputum culture conversion as an indicator of nonrelapsing cure.

Therefore, the key questions become “What requirements are needed for regulators to issue initial approval for drug use?” and “What recommendations can they make for safe and effective drug use?” If conditional approval is issued (as in the case of the accelerated approval by FDA for use of drugs for MDR tuberculosis), what additional information should be required for definite approval? In addition, as regulatory authorities vary from country to country, what should be the common requirements from the various regulatory authorities? Will regulatory authorities request that a trial be conducted in-country before issuing approval? In fact, many tuberculosis-endemic countries lack adequate regulatory capacities for reviewing and approving clinical trials of new drugs or for review and approval of new drugs or regimens. This raises obstacles in the conduct of pivotal licensure trials and approval of new tuberculosis drugs in high-burden countries that would in principle benefit the most from the innovation. High-burden countries with limited regulatory capacity may choose to utilize approval from countries with a well-established regulatory process (eg, FDA, European Medicines Agency) as a default for local approval.

New strategies are clearly needed for establishing efficient regulatory processes for review and approval of new tuberculosis drug regimens by providing adequate advice and technical assistance to national regulatory agencies. Enhanced discussions are needed among regulators, drug developers, trialists, methodologists, clinicians, program officers, public health managers, and funders to agree on evidence required for approval and registration of tuberculosis drugs and to facilitate harmonization of requirements, including endpoints and surrogate outcomes to be used in randomized controlled trials and observational studies. Clear rationale should be provided for the use of companion drugs in trials submitted for regulatory

approval. Capacity building to strengthen regulatory authorities in countries with a high tuberculosis burden and to ensure that newly developed drugs are suitably registered is another urgent need.

INTRODUCTION OF NEW DRUGS IN COUNTRIES: POSTMARKETING AND PROGRAMMATIC ASPECTS

Once approved by regulatory authorities, new tuberculosis drugs would be ready for marketing and use in tuberculosis-endemic countries. The main issue is to ensure that the new drug(s) is used responsibly within clearly established combination regimens to ensure patients' benefit and prevent the development of resistance.

There are several considerations to the introduction of new or repurposed drugs for the treatment of both DS and DR tuberculosis into the market, particularly regarding patients' access to and eligibility for the new treatment, the programmatic feasibility and cost-effectiveness of the newly developed treatments, the use of new drugs as part of fixed-dose combinations, and the implications for monitoring and surveillance of scaled-up use, particularly the development of drug resistance and emergence of uncommon serious adverse events.

Addressing these issues adequately requires the development of clear guidelines to assist countries to issue proper policies for the use of new drugs/regimens and ensure that adequate surveillance of drug use and key outcomes is in place. For countries with a large proportion of private sector providers that detect and treat tuberculosis cases, defining how the new drugs will be introduced and how information on use can be collected will be critical. To ensure appropriate use of new regimens for MDR tuberculosis treatment, it has been suggested that new drugs should be made available to patients only within duly certified and accredited centers of excellence with relevant experience in treating MDR tuberculosis, proven laboratory capacity (drug sensitivity testing, including to novel agents), and drug management and monitoring capacities. Clear criteria and requirements need to be defined for the selection of such centers, and guidelines developed to enhance standardization across centers and countries for cohort monitoring and analysis of resistance, efficacy, and safety data with use of novel combinations/agents. Alternatively, to ensure wider coverage, the use of the drugs could be channeled through tuberculosis control programs. However, because in some countries, only a small subset of MDR tuberculosis patients are treated through tuberculosis control programs, restricting new drugs to these programs might likely not make the drugs available to most of those who need them—although this might be a good incentive to attract more patients to the public health sector. This important issue, which also has ethical implications, needs to be addressed urgently.

Table 1. Key Issues and Next Steps

Drug development
Continue dialogue with the various drug/combination developers to
<ul style="list-style-type: none"> ● Agree on the evidence and data required by WHO to recommend introduction and use of new drugs/regimens for treatment of tuberculosis ● Clarify what methods and design aspects are to be used in phase 2/3 licensure trials for DS and DR tuberculosis (eg, choice of comparator, endpoints) ● Identify additional studies to be conducted in parallel to phase 2/3 trials to generate evidence for combined regimens for DS and DR tuberculosis ● Discuss the evidence needed from special populations (people living with HIV, children) ● Explore options for marketing to identify best strategies for introduction of drugs postapproval ● Make drugs available for preclinical and clinical testing in new combination regimens and development of drug sensitivity assays
Regulatory issues
Continue dialogue with regulators to
<ul style="list-style-type: none"> ● Agree on evidence required for approval and registration of tuberculosis drugs ● Facilitate harmonization of endpoints and surrogate outcomes used in randomized controlled trials and observational studies to facilitate comparison between trials/studies ● Promote passive and active postmarketing activities ● Promote better collaboration between drug regulators and support capacity building to strengthen regulatory authorities in high-tuberculosis-burden countries
Guideline development
<ul style="list-style-type: none"> ● Undertake preparatory work with countries to enable access to approved new drugs through strengthened capacity for diagnosis, drug resistance surveillance, safety monitoring, and in-country pharmacovigilance systems, etc; this may include the development of demonstration sites for initial deployment of new drugs with harmonized methods and surveillance ● Work on potential "accreditation" mechanisms for controlled access to novel drugs ● Produce a WHO guideline framework for introduction of new drugs, describing best use of new drug(s)/regimens for the treatment of tuberculosis in various settings. This will include safe use of the new drug(s) (indications, doses), optimal combination(s), patient selection criteria, treatment monitoring, management of adverse effects, pharmacovigilance, use for special groups, etc
Compassionate use
<ul style="list-style-type: none"> ● Provide guidance to countries on compassionate use (clarification of the various mechanisms and requirements for program access, patient eligibility criteria, need for companion drugs, need for appropriate monitoring and reporting, mechanisms of access, and patient protection issues) ● Advise drug developers on establishment of Expanded Access Programs in countries with a high burden of MDR tuberculosis

Abbreviations: DR, drug resistant; DS, drug susceptible; HIV, human immunodeficiency virus; MDR, multidrug resistant.

Whatever way treatment is being delivered, establishing proper postmarketing surveillance to collect information on safety, use of drugs in special populations (children, pregnant women, HIV-infected individuals), concomitant use with other drugs, and the emergence of resistance, as well as development of risk-management activities, are critical. Agreement should be

reached on preferable postmarketing surveillance methods, including the development of standard case report forms and mechanisms of passive and active recording. National tuberculosis control programs, as well as the private sector in relevant countries, must be included in these efforts to ensure optimal quality and coverage of data collection.

ROLE OF THE WHO IN THE DEVELOPMENT OF GUIDELINES FOR OPTIMAL TREATMENT OF DS AND MDR TUBERCULOSIS

In September 2010, the WHO Strategic and Technical Advisory Group on Tuberculosis recommended that the WHO examine the potential consequences and implications of the introduction of new or repurposed drugs for the treatment of DS and MDR tuberculosis into the market and develop suitable recommendations for their optimal uptake in countries. At a meeting held in June 2011, experts recognized the importance of ensuring equitable access to new drugs for all patients in need worldwide while avoiding emergence of new drug resistance. They stressed the importance of identifying suitable drug combination(s) for treatment of DS and DR tuberculosis as early as possible and the need to agree on standardized methods to be used in the various clinical drug development phases. They encouraged collaboration among drug developers, regulators, and program managers to determine the suitable balance between wide and equitable access to new therapies and ensuring effective and safe use of new drugs in appropriate combinations. They listed activities to be conducted in 4 distinct areas: (1) drug/treatment combination development, (2) regulatory issues, (3) guideline development, and (4) compassionate use (see Table 1).

All the issues outlined above need to be carefully addressed by all concerned parties (including drug developers, research funding agencies, regulatory authorities, and tuberculosis control program managers) so that the WHO can revise the guidelines for the treatment of both DS and DR tuberculosis and develop suitable policy recommendations for the use of new or repurposed drugs in countries. This implies that, in addition to the registration of new drugs by regulatory authorities (opening the market for introduction of the new drug), optimized combinations of drugs are identified for safe, efficacious, and rational treatment. In addition, criteria of affordability and accessibility of the new drugs must be carefully examined.

Based on the aforementioned issues and careful review of all available evidence, the WHO will issue updated policy guidelines for the treatment of DS and/or DR tuberculosis in countries with a high tuberculosis burden, including the best use of new and/or repurposed drugs. The WHO will work with countries to ensure creation of national guidelines to facilitate

the introduction and use of the new drugs/combinations and to prevent irresponsible use.

CONCLUSIONS

A promising new era in tuberculosis drug development has begun. It is now critical to consolidate recent progress and ensure that new drugs/regimens for treatment of all forms of tuberculosis are suitably introduced in countries in a way that guarantees access to best treatments for all those in need and avoids inappropriate use of new drugs. The WHO will need to build evidence-based strategies for postapproval introduction of drugs to ensure affordability and access while preserving drug efficacy. Programmatic implementation should be aligned with ongoing efforts that aim to maximize the efficiency and effectiveness of DS and DR tuberculosis treatment by optimizing drug regimens, advancing point-of-care and other simplified platforms for diagnosis and monitoring, reducing costs, adapting delivery systems, and mobilizing communities.

In an effort to facilitate rational introduction of new tuberculosis drugs into tuberculosis-endemic countries and ensure wide access to optimal treatment, the WHO has initiated a process that includes discussions among and actions from main concerned parties, including drug developers, regulatory authorities, national tuberculosis control program managers, scientists, public health officials, nongovernmental organizations, research agencies, donors, and community representatives. Drug developers must ensure that appropriate studies are being carried out early in the drug development pathway to identify suitable treatment combinations. This includes drug-drug interaction studies of novel compounds with approved tuberculosis agents, as well as interaction with ARVs, and early combination EBA studies. Tuberculosis drug developers should also allow access to new tuberculosis agents prior to approval for preclinical and clinical studies to evaluate promising new combinations of drugs and development of appropriate drug resistance assays. Work is needed with regulatory authorities to ensure expedited evaluation of promising new drugs and combinations and to agree on the evidence required for provisional and full approval of tuberculosis drugs. Further work is needed with a wide variety of constituencies to develop guidelines and requirements for making new drugs available, ensuring wide access and appropriate use for effective treatment and prevention of drug resistance. This will require appropriate postmarketing surveillance of treatment use and outcomes, with adequate information technology support and laboratory capacities to allow rapid identification of tuberculosis disease and drug resistance. Taking these proactive steps now will help to ensure timely and responsible access to the long-awaited new tuberculosis regimens that are on the horizon.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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