

The TB Alliance: overcoming challenges to chart the future course of TB drug development

The Global Alliance for TB Drug Development (TB Alliance) is a not-for-profit organization dedicated to the discovery and development of faster-acting and affordable drugs to fight TB. TB kills nearly 2 million people each year, partly due to the inadequacy of the current treatment. There have been no new drugs registered for TB in more than 40 years, but new partnership models over the past decade have enabled tremendous progress in the pipeline. With 10 clinical compounds now in development globally, the TB Alliance is embarking on a new paradigm of clinical development, one that leverages both new and existing compounds to discover and develop markedly shorter, simpler, faster-acting and less toxic multidrug regimens that can treat both drug-sensitive and multidrug-resistant TB concurrently, dramatically simplifying treatment and facilitating the scale-up of global treatment efforts.

A resilient foe

Tuberculosis is one of humanity's oldest and most resilient plagues. Evidence of TB dates back to mummified tombs of ancient Egypt and has taken the lives of many notable figures throughout history, from Voltaire, to Chopin, to Orwell. Today, TB remains one of the world's leading killers, responsible for 1.7 million deaths and 9.4 million new infections in 2009 alone, according to the WHO [1]. Every country is affected by TB, but the vast majority of TB's health, social and economic impact occurs in the developing world. The resulting dynamic is the perception in wealthy nations that TB has been eradicated, even as the number of new TB cases has increased every year since the WHO began tracking such data in 1990 [2].

The footprint of the global TB epidemic is the footprint of poverty. As such, there is little incentive for pharmaceutical companies to adequately invest in improving the current standard TB treatment regimen, which is nearly half a century old and relatively inexpensive, but unfortunately inadequate to control the epidemic. Current WHO guidelines for treating drug-sensitive TB require patients to take a four-drug regimen (ethambutol, isoniazid, pyrazinamide and rifampicin) for 2 months followed by two of these drugs (isoniazid and rifampicin) for an additional 4 months, totaling a minimum 6-month treatment course. Adherence presents a daunting challenge to individuals and serious burdens to health systems, as the recommended treatments include directly observed therapy administered by healthcare workers – challenges that are exacerbated by the practical

and infrastructural realities of the impoverished communities where TB thrives. As a result, patients often discontinue treatment before achieving cure, leading to the spread of drug-resistant strains of the bacteria that cause TB, *Mycobacterium tuberculosis*, which are far more difficult to treat.

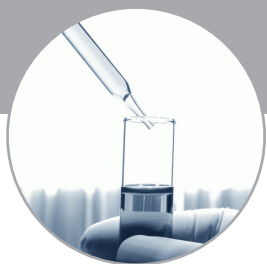
Certainly, yesterday's TB treatment is inadequate to handle today's complex epidemic. The regimen for multidrug-resistant TB (MDR-TB) is typically administered for 2 years or more, is highly complex, expensive and accompanied by severe side effects. Due to these characteristics, just 5% of the world's estimated 440,000 patients who suffer from MDR-TB receive proper treatment [1].

Further diminishing the practical effectiveness of the current TB treatment are its drug–drug interactions with common anti-retroviral treatments for HIV/AIDS. This is particularly problematic because TB and HIV, often called the 'dual epidemic', frequently affect the same individuals, and each makes the other more severe. In TB-endemic countries, immunocompromised HIV-infected individuals are 20-times more likely to develop active TB disease than those not infected with HIV, and TB is the single most common cause of death in HIV/AIDS patients [10].

Without these urgently needed new TB therapies, the TB epidemic will continue to worsen. A revitalized TB drug R&D community, a growing pipeline of promising compounds and an innovative drug-development paradigm offer new promise for the next generation of TB treatments.

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TB Alliance forms

As recently as a decade ago, there were no TB drug clinical candidates in the pipeline. Motivated by the urgent medical and public-health need and an emerging culture of innovation and scientific opportunity, a group of stakeholders came together, spurred and initially funded by the Rockefeller Foundation, and conceived of a not-for-profit organization that would spearhead and coordinate a global effort to discover and develop better, faster-acting, affordable drugs to fight TB. Shortly thereafter, the Global Alliance for TB Drug Development (TB Alliance) was formed in 2000 to fulfill that mission. Today, the TB Alliance operates with an internal staff of approximately 50 and an extensive network of partners and collaborators that spans the globe.

As a not-for-profit product-development partnership, the TB Alliance collaborates with the public, private, academic and philanthropic sectors and operates as a virtual drug R&D organization to contribute to and advance the TB drug pipeline, and stimulate and facilitate global efforts to develop new TB treatments. Using a variety of licensing and partnership agreements, the TB Alliance leverages the expertise and resources of a broad and diverse network of partners while minimizing R&D costs, including overhead and investments in infrastructure.

Since its founding, the TB Alliance has created and advanced the largest TB drug pipeline in history. By offering expertise and cost-sharing development models, it has also catalyzed other organizations to participate in and contribute to TB drug development.

A maturing portfolio

Since the TB Alliance was established, there has been marked growth in interest in developing new TB therapies on the part of previously disengaged for-profit entities. Today, many leading

pharmaceutical companies have partnered with the TB Alliance to discover and develop therapies, and several are leading development programs on their own (FIGURE 1) [1].

The TB Alliance portfolio includes three clinical-stage candidates currently undergoing late-stage testing, one of which, moxifloxacin, is an existing antibiotic undergoing evaluation for a TB indication; the other two, PA-824 and TMC207, are novel chemical entities. Each project is based on a unique partnership model. For example, the TB Alliance partners with Bayer Healthcare, which owns the antibiotic moxifloxacin, to develop this third-generation fluoroquinolone for TB. Together, they are working with University College London and other partners to test moxifloxacin in a large-scale Phase III registration trial. In contrast, the TB Alliance is the sole sponsor of PA-824, which was in-licensed from Chiron (now Novartis), and has taken this drug from early preclinical development into late-stage clinical testing through working with contract research organizations. The TB Alliance is collaborating with Tibotec (a Johnson & Johnson subsidiary) to develop TMC207 and next-generation diarylquinolines. In preclinical development, the TB Alliance has created mini-portfolios with AstraZeneca, GlaxoSmithKline and Novartis Institute for Tropical Diseases, which consist of multiple discovery-stage projects and make efficient use of each partner's relative expertise and resources.

More broadly, the global TB drug portfolio consists of ten clinical-stage compounds (FIGURE 1), some of which are new chemical entities and some repurposed compounds, sponsored in whole or part by organizations that in addition to TB Alliance include AstraZeneca, Bayer Healthcare AG, Otsuka, Pfizer, Tibotec (Johnson & Johnson), Sequella and the OFLOTUB Consortium, which is a network of ten organizations based in Europe and Africa. Two compounds, moxifloxacin and gatifloxacin, are currently undergoing Phase III clinical trials to determine whether they can form the basis for new, shorter TB treatment regimens. There is also a promising earlier-stage pipeline with more than 50 active programs, more than 20 of which are managed by the TB Alliance.

The TB Alliance envisions that with sustained effort, support and political will, the treatment for TB can be reduced from 6 months for drug-sensitive disease or 2 years for multidrug-resistant disease to, ultimately, a 2-week novel treatment for which pre-existing resistance is no longer a complicating factor. However, several waves

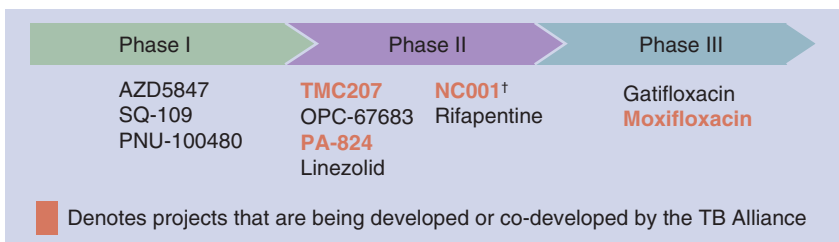
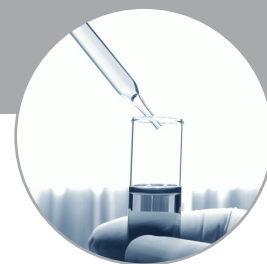


Figure 1. Compounds in clinical development for treatment of active TB.

Before the TB Alliance was established, there were no TB programs in clinical development. Today, the organization is developing or co-developing three clinical compounds as well as the first novel regimen, and has played an important role in galvanizing other organizations to engage in TB R&D.

[†]First clinical trial of a novel TB drug regimen testing the three-drug combination of PA-824, moxifloxacin and pyrazinamide; more information can be found here [104].



of innovation will be needed to achieve this vision, including adopting a novel paradigm for development of multidrug regimens (FIGURE 2).

New model: from drugs to regimens

Tuberculosis drugs must be administered in combination to prevent the development of resistance and ensure adequate efficacy. Historically, as in other therapeutic indications, drug sponsors have focused on improving multidrug combinations by developing one new drug at a time, by substituting or adding the new drug into the existing treatment regimen. Given standard individual drug-development timelines, this approach meant that a completely novel, three- or four-drug combination to treat both drug-sensitive and drug-resistant disease would take a quarter century or longer to develop.

However, after a decade of reinvigorated TB drug R&D efforts, there are now enough novel drug candidates in the pipeline to embark on a new development paradigm that, if successful, will markedly shorten timelines for development of novel TB drug regimens. This new paradigm relies on considering the unit of development to be the multidrug regimen rather than an individual drug, beginning in preclinical development.

Phase I evaluation of safety, tolerability and pharmacokinetic parameters of individual drugs can occur in parallel before promising (based on nonclinical data) multidrug combinations are tested in the clinic in Phase II trials. By developing promising combinations as a unit, drug developers may feasibly register a novel drug regimen in one third to one fourth the time required by the traditional, one-drug-at-a-time paradigm (FIGURE 2).

With support from the Bill & Melinda Gates Foundation and several governmental donors, the TB Alliance is pioneering novel regimen development through a preclinical testing program conducted in collaboration with University Illinois at Chicago (USA) and Johns Hopkins University (USA). Other stakeholders are also contributing: several pharmaceutical companies have voluntarily submitted their TB drug candidates to be tested in combination with one another. In this program, optimized combinations of drugs (experimental compounds or existing, approved drugs, regardless of sponsor) are identified and evaluated in one or more animal models before testing in the clinic (FIGURE 3). When promising regimens are identified, the sponsors of compounds in an identified regimen then work together to progress the regimen

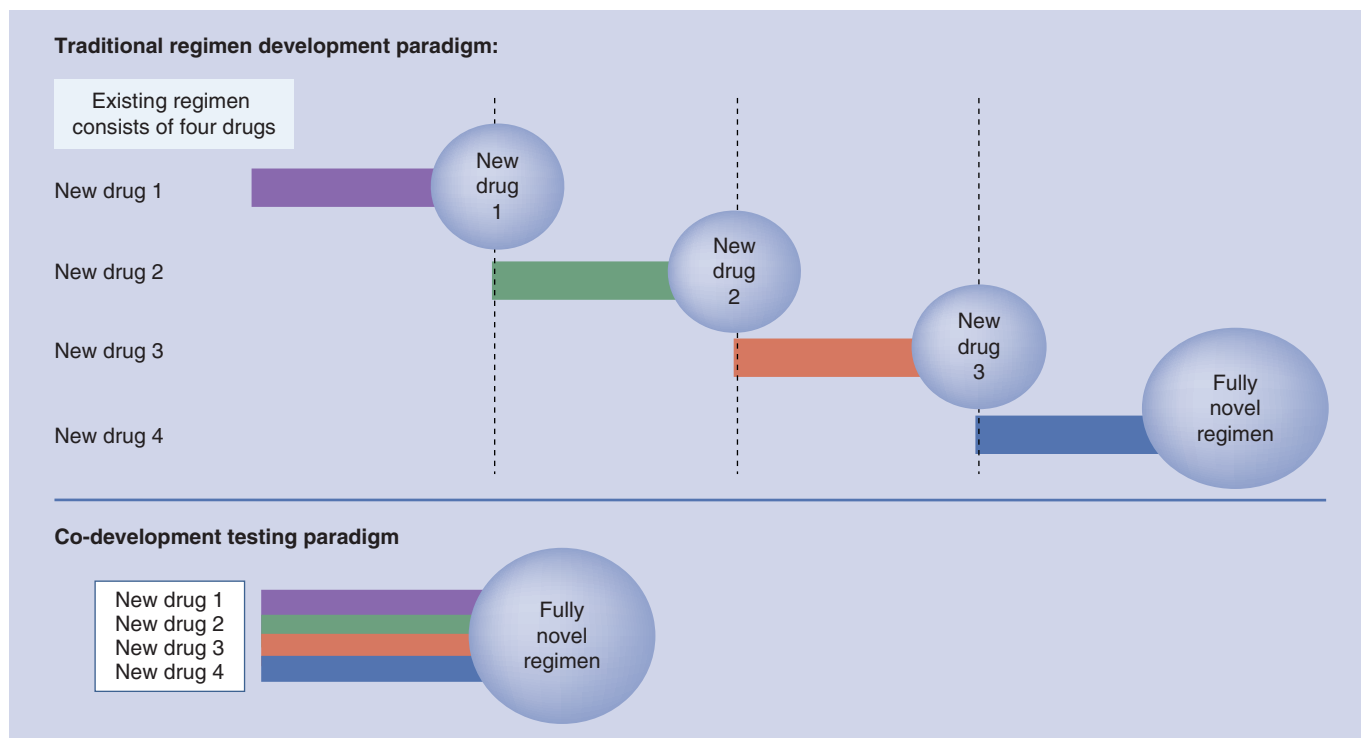
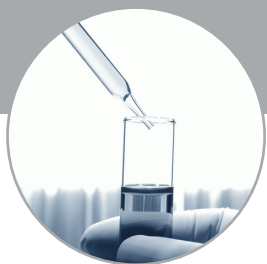


Figure 2. Paradigm shift in development of improved TB therapies. The traditional approach to TB drug development relied on sequential, individual modifications to the existing regimen, which meant it could take decades to develop a novel TB drug regimen. The co-development paradigm allows for the wholesale evolution of TB R&D, enabling novel regimens to be developed in a fraction of the time previously needed.



through clinical trials. The US FDA recently issued draft regulatory guidance consistent with this approach [3].

The first trial of a novel drug combination identified as having potential to substantially shorten treatment of both drug-sensitive disease and MDR-TB entered into a Phase II early bactericidal activity clinical trial (NC001 or Novel Combination 1 [see **FIGURE 1**]) in November 2010. It is the first time that a clinical-development program is aimed at registering a multidrug combination containing more than one previously unapproved TB drug candidate. This new regimen consists of an existing antibiotic not yet approved to treat TB, moxifloxacin; a new chemical entity, PA-824; and one existing, first-line TB drug (pyrazinamide). This study is expected to be completed in 2011.

A model for others

This paradigm of multidrug-regimen development is being championed and facilitated by the Critical Path to TB Drug Regimens (CPTR) initiative. Launched in March 2010 by FDA Commissioner, Margaret Hamburg, CPTR aims to facilitate information sharing and collaborative efforts to tackle a wide array of challenges facing TB drug development. Co-founded by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance, CPTR, with a range of pharmaceutical, civil society and other stakeholder members, aims to speed the introduction of impactful new TB treatments.

The collaborative approach employed by CPTR serves as a model for other fields for

which combination therapy is crucial, such as cancer and hepatitis C. Under the framework of CPTR, drug sponsors share information and work in collaborative ways, while other stakeholders undertake efforts to ensure the proper infrastructure and resources are in place for drug testing. This includes the advancement of a regulatory science framework to support the evaluation of regimens developed under this new model as well as ensuring adequate global capacity to conduct TB regimen trials to the highest regulatory standards [102].

The promise of novel regimens

The introduction of novel drug regimens will offer shorter, safer, cost-effective treatment options to address the global TB burden. This will be particularly dramatic for MDR-TB. The current treatment for MDR-TB must often be administered for 2 years or longer to achieve cure and requires the use of injectable agents, which present usage and storage challenges in resource-poor settings. As such, while the WHO and others have called for the scale-up of MDR-TB therapy, the cost and complexity of current drug regimens make that an infeasible task today.

However, the introduction of new TB drug regimens to which there is no pre-existing resistance will essentially 'erase the line' between MDR-TB and drug-sensitive TB by allowing the vast majority of TB patients to be treated with the same shortened and effective regimen. This will simplify the delivery of TB drugs globally, lessening the burden on both public health infrastructures and patients.

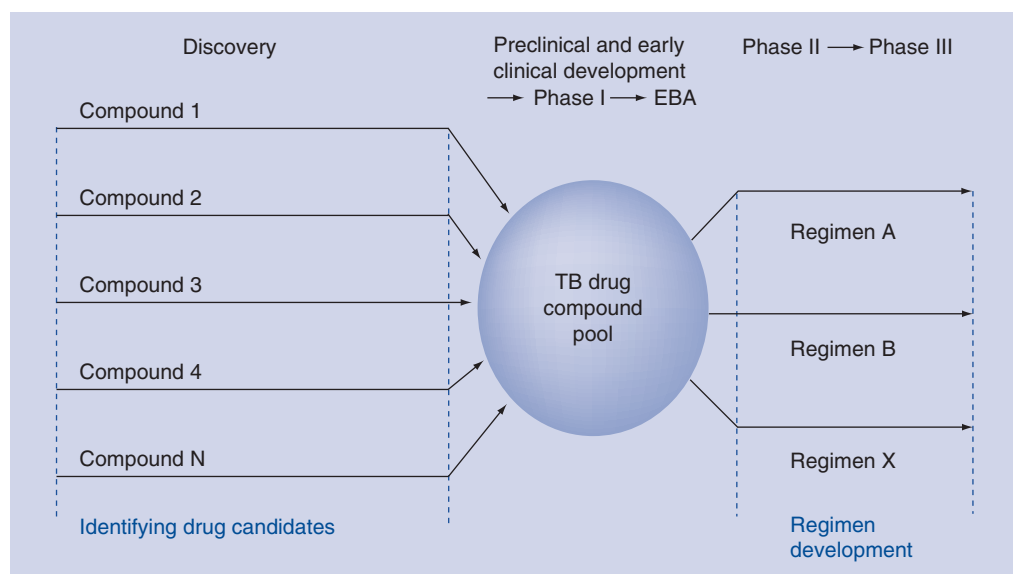
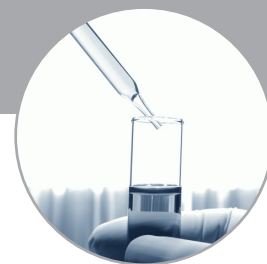


Figure 3. Approach to identifying and developing optimized regimens.



One of the chief benefits of the regimens currently undergoing development is that they are a fraction of the cost of the current WHO-recommended second-line treatments. The cost of the drugs alone that are required to properly treat MDR-TB today are commonly estimated to be U\$9000 per patient [103]. New regimens should also alleviate other associated health-care costs, given that they show promise to reduce treatment time from 2 years to less than 6 months, and are intended to be simple, inexpensive, and orally bioavailable, and, therefore, their introduction would represent a realistic opportunity to scale up treatment programs for drug-resistant TB around the world.

Maximizing impact

Resistance to TB drugs has emerged globally, therefore rapid diagnosis and drug susceptibility testing are essential elements of proper TB care. Advances in TB diagnostics will enable the widest, most effective and responsible use of newly developed TB treatments. The WHO's recent endorsement of the Foundation for Innovative New Diagnostics' and Cepheid's drug-sensitivity and TB diagnostic test, GeneXpert MTB/RIF assay, a rapid, specific and sensitive TB diagnostic that detects *M. tuberculosis* and whether it is resistant to rifampicin, illustrates progress towards

rapid drug-sensitivity testing. It is important to remember that the implementation of improved diagnostics will intensify the demand for new and improved TB treatments, as much as the full impact of new TB drugs depends on the availability of improved diagnostics and drug-sensitivity testing.

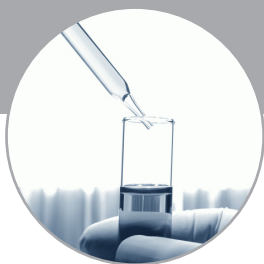
Future perspective

After a near half-century hiatus, exciting developments in TB drug R&D are once again underway. Innovation in TB research, delivery and control, propelled by viable partnership models, has yielded new hope and potential in the fight against TB. A shorter, simpler and affordable TB treatment now seems attainable in the near future, with the first generation of novel TB drug candidates soon to emerge from late-stage trials.

Regimen development, the next wave of innovation, has the potential to speed the development of shorter, novel treatments for both drug-sensitive and MDR-TB. Regimen-based development could yield dramatically shortened timelines to registration for the novel therapies that would simplify TB treatment for both providers and patients, improve treatment completion rates, and thereby slow the emergence of drug resistance and decrease rates of relapse and transmission.

Executive summary

- Current treatments used to treat TB are inadequate to control the global TB epidemic, largely due to the excessive burden adhering to such treatment places on patients and healthcare providers alike.
- Incomplete or improper treatment for TB leads to the development and spread of drug-resistant bacteria. Multidrug-resistant TB is a serious public health threat, with 440,000 cases estimated in 2009. Treatment for multidrug-resistant TB can take nearly 2 years or more, and roughly a third of patients die.
- Established in 2000, the TB Alliance is leading the global effort to develop new and improved TB treatment regimens through a partnership-based model that relies on flexibility and innovative thinking to lower the barriers to entering the TB drug development field.
- Over the past decade, the global portfolio of new TB drug candidates has grown from virtually bare to the largest such portfolio in history.
- The traditional TB drug-development paradigm relies on incremental additions or substitutions of new drug candidates into the existing standard regimen. Each new alternation is tested in long and expensive clinical trials, so that the development of a fully novel TB drug regimen would likely take a quarter century. The TB Alliance is pioneering a new paradigm, which shifts the 'unit of development' from the individual drug to an entire drug regimen and, in doing so, has the potential to dramatically reduce the time needed to develop a novel TB drug regimen by decades. This paradigm has been championed by the Critical Path to New TB Drug Regimens initiative, which is working to speed the introduction of impactful new TB regimens.
- The first Phase II trial testing multiple TB drugs simultaneously, known as NC001, was initiated in 2010 by the TB Alliance, with completion expected in 2011.
- Advances in TB diagnostics must complement advances in TB drug development, enabling the widest, most effective and responsible use of newly developed TB treatments.
- The introduction of the first wave of new, shorter and simpler TB treatment regimens is within our grasp in the near future. Subsequent waves of innovation further improving treatment can be achieved in the longer term with sustained political and financial support from the international donor communities, continued and intensified engagement by the public and private TB drug sponsors, and concerted advocacy on the part of civil society and TB-affected communities around the world.



The development of complementary diagnostic technology would further amplify the impact of improved TB therapies by enabling more patients to begin treatment more quickly, ensuring they receive appropriate drugs, and helping to protect the new drugs from resistance-development. All this promise has emerged from a decade of dedicated effort. However, the fulfillment of all the scientific potential depends on the sustained commitment of R&D partners and the international donor and private philanthropic communities in partnership with policy makers, health advocates, the patient communities and civil society to ensure availability and implementation of novel, improved TB regimens once available.

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Financial & competing interests disclosure

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■ Websites

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- 103 Stop TB Partnership. The Global Drug Facility Product Catalogue, 2011. www.stoptb.org/gdf/drugsupply/drugs_available.asp
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