Critical Path to TB Drug Regimens

CPTR:

A new paradigm for TB drug development

The Critical Path to TB Drug Regimens (CPTR) is a cross-sector initiative that aims to speed the development and introduction of shorter, safer, more effective TB drug therapies. It is a collaboration of leading international pharmaceutical companies, public health experts, civil society organizations, and U.S., European, and other regulatory authorities.

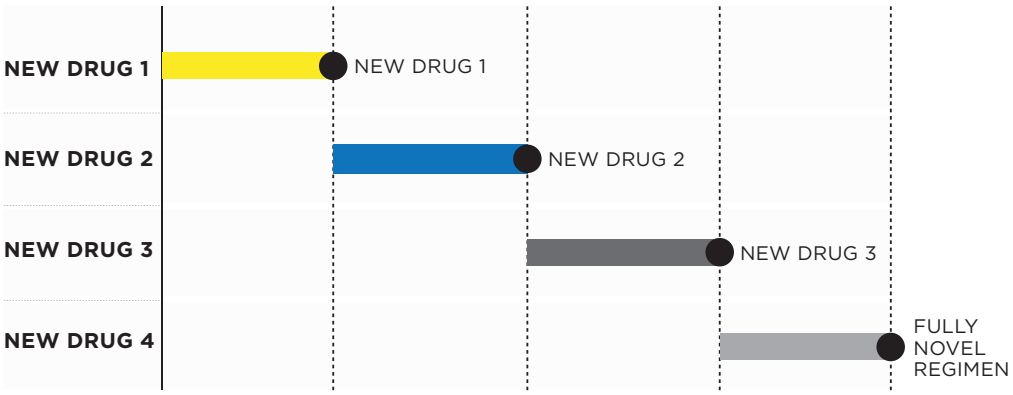
CPTR facilitates partners working together to test promising combinations of individual TB drug candidates from different sponsors early in the pipeline–and identify the best new treatment regimens, regardless of sponsor. The initiative also focuses on developing new regulatory pathways and other tools needed to support regimen development—to overcome the obstacles standing in the way of new TB drugs.

NEW TB DRUG REGIMENS ARE URGENTLY NEEDED

TB and drug-resistant TB are major threats to global health. TB is one of the world's deadliest infectious diseases, and although it is often thought of as a disease of the past, **8.8 million people develop TB each year**, mainly in developing countries. **TB kills 1.4 million people annually**, and it is the largest killer of people living with HIV/AIDS.

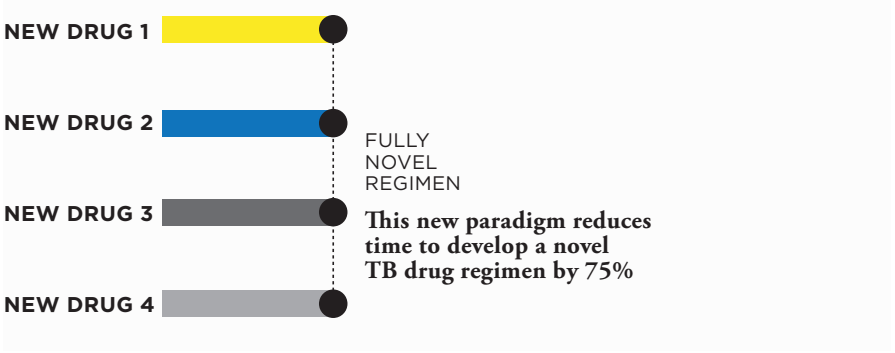
CURRENT REGIMEN DEVELOPMENT PARADIGM:

Existing regimen consists of four drugs



NOVEL COMBINATION TESTING PARADIGM:

Novel regimen development can reduce the time to develop a new TB drug regimen by 75%:



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GLOBAL TB DRUG PIPELINE:

Today there is a promising pipeline of TB drugs and an opportunity to test them together to find the best regimen, regardless of sponsor.

PHASE II	PHASE III	REGISTRATION
LINEZOLID	GATIFLOXACIN	BEDAQUILINE (TMC-207)
SQ-109	MOXIFLOXACIN	
RIFAPENTINE	RIFAPENTINE	
NOVEL REGIMENS (NC-003 TRIAL)	DELAMANID (OPC67683)	
AZD5847		
SUTEZOLID		
PA-824/MOXIFLOXACIN/ PYRAZINAMIDE		

SOURCE: WORKING GROUP FOR NEW TB DRUGS

New TB drug regimens are long overdue. Drugs exist that can treat TB, but today's TB therapies are more than 40 years old and take an unacceptably long time to cure. The current regimen for drug-sensitive TB takes six months or more, and many patients experience side effects. These shortcomings may cause patients to default on their treatment, which can lead to further illness, drug resistance, or even death. Globally, **between 20-30% of patients who start treatment stop before it is complete**.

At the same time, resistance to currently available TB drugs is growing. It is estimated that there are **650,000 cases of drug-resistant TB in the world,** for which the treatment is even more complex and expensive. Treatment takes up to two years, with daily injections for the first six months. The drugs used are more toxic, and they can be up to **475 times more expensive than first-line therapies**. The result is that fewer than 20 percent of patients with drug-resistant TB have access to appropriate treatment, and treatment is successful in only 60% of those with access to quality-assured therapy.

New TB drugs are also needed that can be co-administered with HIV treatments. South Africa, for example—a country with the largest population of people living with HIV/AIDS—**has a 70% HIV/TB co-infection rate**. New TB drugs designed to avoid ARV interactions are essential to address the specific challenges that co-infected patients face.

TRADITIONAL DRUG DEVELOPMENT IS NOT ENOUGH

Speeding development of new TB regimens is a public health imperative. New TB drugs, which have little pre-existing resistance, could treat both drug-sensitive and drug-resistant TB effectively, transforming global TB control efforts.

Due to the resilient nature of the bacterium, successful TB treatment will likely always require multiple drugs. Traditional regimen development meant that each new drug needed to be tested and approved separately, and then substituted—one at a time—into existing combinations. To create a novel treatment, this process would need to be repeated until the drugs in the existing regimen were replaced. Each of these trials lasts six years or longer, which means that a novel TB regimen could take decades to develop using this model. With nearly 4,000 people dying from TB each day and growing numbers of people resistant to the current treatment, this is an unacceptably long wait for those suffering.

We urgently need innovative models that accelerate TB drug development and deliver dramatically improved treatment to TB patients worldwide.

CPTR IS ALREADY DRIVING INNOVATION AND ADVANCING THE FIELD

Since the launch of CPTR in 2010, the initiative has made significant progress:

- It has actively engaged the FDA, which has released updated regulatory guidelines for developing new drug regimens. The FDA continues to work to create a more favorable environment for regimen development. In 2011, CDER head Dr. Janet Woodcock wrote an opinion piece in the *New England Journal of Medicine* expressing her support for "co-development" of therapies for life-threatening diseases such as TB.
- Since CPTR was established, the TB Alliance launched clinical trials of novel combination drug regimens for TB.

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TB studies have highlighted the promise of novel regimens. Results of the first trail were published in 2012.

» CPTR is building new public-private partnerships and participants are thinking creatively about how groups can work together. For example, CPTR has brought a range of stakeholders together to develop an online inventory of clinical trial sites implementing registration-quality trials, including a marketplace for new trial sites to share their capacity and a collaboration space where researchers can discuss new clinical trial concepts for TB. Work is also progressing on efforts to evaluate biomarkers, clinical endpoints, and preclinical science tools for qualification by FDA.

If successful, CPTR could become the gold standard' for rapid, safe and efficient development and testing of new drug combinations to treat TB, as well as in other disease areas where combination testing is a necessity, such as cancer and hepatitis.

CPTR MEETS AN URGENT PUBLIC HEALTH NEED

A range of pharmaceutical companies have signed onto CPTR, pledging to collaborate in new ways to develop combination therapies. Other organizations have also joined. These groups are working with the core CPTR conveners—the TB Alliance, the Bill & Melinda Gates Foundation

CPTR Can Speed TB Drug Development

For the first time ever, there are multiple TB drug candidates from different drug classes in the development pipeline. An unprecedented opportunity exists to test them in combination early, so the most effective novel drug regimens can then be developed.

CPTR Focuses on These Key Areas:

REGIMEN DEVELOPMENT

Today, there is a robust pipeline and the opportunity exists to test the available compounds together, in order to speed novel regimens to people in need. Using the innovative clinical paradigm of regimen development could reduce the time it takes to develop new TB drug combinations by 75%. CPTR, under the Drugs Coalition, brings together several sponsors with clinical TB drug candidates to share information with the goal of developing the most promising novel TB regimens.

CRITICAL PATH TO TB DRUG REGIMENS:

CPTR RESEARCH RESOURCES	REGULATORY SCIENCE (C-PATH)	TB DRUG SUSCEPTIBILITY TESTING	DRUGS COALITION
LED BY THE BILL & MELINDA GATES FOUNDATION	LED BY THE CRITICAL PATH INSTITUTE & PARTNERS	LED BY THE CRITICAL PATH INSTITUTE WITH NIAID	LED BY THE TB ALLIANCE
FOCUS			
• Clinical Trials infrastructure • Stakeholder & Community Engagemtnt • Access & Appropriate Use • Global Regulatory Pathways	• Modeling & Simulation • Preclinical & Clinical Science • Biomarkers & Clinical Endpoints • Data Standards & Integration	• Enabling Science • Assay Development • Surveillance • Impact Assessment/ Modeling	• Drug and Combination Testing & Development

REGULATORY SCIENCE

Under the Regulatory Science Consortium, CPTR partners are promoting the development of new regulatory approaches that support innovative research into TB therapeutics, evaluate new TB drug combinations safely and effectively, and reinforce current guidelines for development of effective drug combinations. Partners are also developing the regulatory science and infrastructure needed to ensure that regulators can effectively evaluate multi-drug combinations. The overarching aim is to generate the evidence necessary for regulatory authorities such as FDA and EMA to officially designate combination testing methods "qualified or fit for use" in TB drug development. The new testing methods will then be made available for CPTR studies and broader drug research.

RESEARCH RESOURCES

CPTR is tackling other challenges facing TB drug development. CPTR works collaboratively with existing partners in the TB field to 1) ensure needed trial capacity is available to develop new TB drug regimens 2) work with traditional funding streams and search for new ones; 3) solicit global regulatory participation and solve regulatory challenges; 4) engage TB stakeholders, including the communities of TB patients and trial participants; and 5) foster access and appropriate use for future drugs regimens.

DRUG SUSCEPTIBILITY TESTING

Treating TB patients with the drugs that the bacteria are susceptible to is integral to improving treatment outcomes, slowing the development of drug-resistance, and the protecting the efficacy of new TB treatments. For these reasons, the development of new TB cures and corresponding diagnostics go hand in hand. CPTR recognizes this need. CPTR partners work to advance the field of drug sensitivity testing both by efforts to better understand the existing drug-resistance landscape and working to enable the development of new diagnostic tools to complement novel drug regimens.

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PARTNERS

Critical Path Institute – collaborate · innovate · accelerate
TB Alliance – Global Alliance for TB Drug Development
Bill & Melinda Gates foundation
Anacor Pharmaceuticals
Abbott
astellas
AstraZeneca
Bayer
CDC – Centers for Disease Control and Prevention
Celgene
Cepheid
EDCTP
Forest Laboratories, Inc.
gsk GlaxoSmithKline
Johnson & Johnson
National Institute of Allergy and Infectious Diseases
NOVARTIS
Otsuka
Pfizer
Reagan - Udall Foundation for the Food and Drug Administration
SANOFI
SEQUELLA Incorporated
TAG Treatment Action Group
VERTEX

Peggy Hamburg, Commissioner of the U.S. FDA, gave a keynote address at the launch of the CPTR Initiative.

"It is time for us to emerge from hibernation. To advance TB innovation and develop regulatory processes that can deliver innovation more quickly to the people who need it most."

and Critical Path Institute – and a broad network of public health experts and civil society organizations to ensure the initiative's success.

CPTR will work closely with regulatory scientists at the FDA, EMA and other agencies to develop the regulatory tools that are needed to support testing of combination drug regimens. CPTR is also actively engaging regulators and key stakeholders in Europe, China, India and some countries in Africa.

SUCCESS WILL REQUIRE ADDITIONAL SUPPORT

Despite all the progress to date, sustainable funding is needed to support clinical trials of new TB regimens and to ensure new treatments reach all those who need them. Key donors have committed initial funds to combination drug trials, but more support is needed to ensure that promising TB regimens can move quickly into late-stage clinical trials. In addition to funding for future Phase III studies, there is a significant need to build clinical trial capacity for research.

HOW TO GET INVOLVED

The CPTR initiative welcomes participation from any company or research organization with a promising TB drug candidate in development, as well as other groups providing the technical expertise or resources to help develop new TB drug regimens.

CPTRinitiative.org