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New Drugs for an Ancient Disease: Objectives and Successes of the Global Alliance for TB Drug Development

Abstract:

Die Tuberkulose (TB) stellt für ärmere Länder und Bevölkerungsgruppen nach wie vor eine massive Bedrohung dar. Seit den 60er Jahren wurde kaum an der Entwicklung von Medikamenten gegen die TB gearbeitet, obwohl dies dringend nötig wäre, um die Unzulänglichkeiten der derzeitigen Behandlungsmethoden zu beseitigen. Neue Medikamente sollten die Behandlungsdauer verkürzen (und damit die Kosten senken, die Verabreichung vereinfachen und die Wahrscheinlichkeit eines Therapieabbruchs verringern), arzneimittelresistente Erregerstämme bekämpfen, mit lebenserhaltenden HIV/AIDS-Therapien verträglich sein und gegen latente TB-Infektionen wirken. Die Global Alliance for TB Drug Development ist eine einzigartige öffentlich-private Partnerschaft für die Entwicklung innovativer, verbesserter Therapien gegen TB.

Introduction

For centuries, tuberculosis (TB) has targeted the most vulnerable populations during their most productive working years, killing millions each year and imposing a devastating economic toll on some of the world's poorest countries. Decades after the discovery of antibiotics to treat the disease, TB is second only to HIV as the leading infectious killer of adults worldwide.

The World Health Organization (WHO) estimates that one third of the world's population is infected with *Mycobacterium tuberculosis* (*M.tb*), the bacillus that causes the disease. Today's TB crisis is fueled by a surge in HIV-*M.tb* co-infection and is compounded by the growing emergence of drug-resistant strains, making the epidemic increasingly difficult to control.

The current TB drug regimen, a product of the best scientific advances of the 1960s, works for active, drug-susceptible TB – as long as patients complete the six to nine-month treatment programme. The problem is that many do not or cannot complete their treatment. The regimen, a four-drug combination, is taken under daily monitoring by healthcare workers, so called Directly Observed Treatment Short Course (DOTS). Patients often feel better after the first two months and, despite the remarkable advances in provision of services over the past few years, many find it difficult to complete the cumbersome treatment.

Poor adherence and improper administration of the existing antibiotics have led to the emergence of multi- and extensively drug resistant TB strains that defy current medicines. In addition, the most important of the first line drugs, rifampin is not compatible with some antiretroviral (ARV) therapies, complicating the treatment of those patients co-infected with TB and HIV.

New, simpler, faster-acting drugs are desperately needed to save the millions of lives needlessly lost to TB. Winning the battle against TB depends upon modernising today's treatment that induces noncompliance, burdens healthcare systems and drains economies.

After a decades-long gap in TB drug development, the Global Alliance for TB Drug Development (TB Alliance) was conceived at a February 2000 meeting in Cape Town, South Africa, where representatives from academia, industry, major development agencies, non-governmental organisations, and donors gathered to discuss the problems of TB treatment. Participants stressed the need for new TB drugs, highlighting the unprecedented scientific opportunities and the economic rationale for developing new medicines.

Today, with the help of scientists, philanthropists, governments and our partners across the globe, the TB Alliance is leading the development of the most comprehensive portfolio of TB drug candidates in history, paving the way for the first new treatments in 40 years. The Alliance is equally committed to seeing new drugs through the regulatory and adoption process, so that the new treatments reach the hands of patients. Specifically, the mission is to accelerate the development of new TB drugs that will:

- Shorten treatment;
- Be effective against both drug-susceptible and drug-resistant strains;
- Be compatible with ARV therapies used for HIV/AIDS;
- Improve treatment of latent infection; and
- Be available and affordable for patients who need them.

Targets for Developing a New Cure

Modernising TB therapy is a medical and moral imperative with direct public health benefits and significant socio-economic returns. Improved TB treatment will save millions of lives by increasing compliance, speeding time to cure, overcoming resistance, and being compatible with HIV/AIDS ARV therapy. The following scientific objectives drive the development of the TB Alliance drug portfolio:

1) Shorten today's burdensome treatment

Although current medicines do exist to treat drug-susceptible TB, the current six to nine-month treatment regimen presents a variety of hurdles in controlling the disease and ultimately saving lives.

Today's treatment course is long and difficult to administer, often leading to non-compliance and the emergence of TB strains that are resistant to first-line — and even second-line — drugs. Reducing the time it takes for patients to finish their medication could vastly improve compliance, saving lives and curbing the threat of deadly drug-resistance.

Aside from the grim health consequences if treatment is not finished, the current regimen is costly to administer. The infrastructure necessary for today's treatment course — with its extensive monitoring requirements — represents the bulk of the cost of treating TB patients. The world spends about $4 billion annually to reach less than half of those with active TB. Reducing the current six to nine-month regimen could dramatically reduce those expenses, making it possible to reach more patients while significantly lightening the enormous burden on healthcare systems in developing countries.

Although the short-term goal is to cut treatment to just two months, ultimately the vision is to develop a TB treatment with duration akin to that required for other common bacterial infections.

2) Treat drug-resistant as well as drug-susceptible disease

Drug-resistant TB is the result of interrupted, erratic or inadequate TB therapy. It develops when the current TB drug regimen is poorly administered, or when patients stop taking their medication before the bacteria are eradicated. Once a drug resistant strain has developed, it can be transmitted directly to others.

Multi-Drug Resistant TB (MDR-TB) is defined by resistance to isoniazid and rifampin, the two most powerful drugs in the current four-drug, first-line regimen. Extensively Drug Resistant TB (XDR-TB), also known as Extremely Drug Resistant TB, is emerging as an even more ominous threat. XDR-TB is defined as MDR-TB with additional resistance to two classes of antibiotics used in second-line treatment: the fluoroquinolones and the aminoglycosides. This makes XDR-TB treatment extremely complicated, with some strains virtually untreatable with current medicines.

The drug candidates in our diverse pipeline are aimed at treating drug-resistant disease, including MDR- and XDR-TB, by attacking novel targets.

3) Compatibility with life-saving HIV/AIDS therapies

TB is the leading infectious killer of people with HIV/AIDS, with an especially high burden in sub-Saharan Africa, where it causes up to half of all AIDS deaths. TB-HIV co-infections are also on the rise in other areas of the world, particularly in Asia and Eastern Europe. As long as HIV/AIDS continues to spread, TB will remain a constant and deadly threat.

ARV therapy is today's most effective, available treatment option for controlling the progression of AIDS. Unfortunately, drug-drug interactions between the current first-line TB regimen and certain commonly used ARVs complicate treatment for co-infected patients. Rifampin, a cornerstone of the current regimen, induces the enzyme cytochrome P450. Cytochrome P450 causes some AIDS drugs to be metabolised too quickly, inhibiting effective ARV therapy. People with HIV/AIDS who contract TB must sometimes change their ARV regimens to avoid this dangerous interaction or delay needed ARV treatment until their TB is under control.

New TB drugs, developed to avoid these drug-drug interactions, are essential to treat the growing number of people dually infected with TB and HIV. A faster, better regimen would also speed time to cure for patients severely weakened by the deadly co-infection. All drug candidates in the TB Alliance development portfolio are being tested for the ability to be administered in conjunction with ARVs for HIV-infected TB patients.

4) Improved treatment of latent TB infection

Latent tuberculosis is defined as *M.tb* infection that has not progressed to active TB disease. People with latent tuberculosis are not infectious, and it is not possible to get TB from someone with latent tuberculosis. However, approximately 10% of those with latent TB but not HIV will go on to develop active TB at a later stage of their life, and this risk increases greatly for those co-infected with HIV. The treatment of latent tuberculosis infection is essential to controlling and eliminating TB by reducing the risk that *M.tb* infection will progress to disease. However, little is known about this phenomenon, and this lack of understanding creates a critical hurdle that must be overcome for the development of successful medicines.

A Revolutionary Concept for TB Drug Development

The TB Alliance pipeline reflects aggressive scouting around the globe, strict selection criteria and meticulous evaluation and oversight once projects are selected. The portfolio

acquisition strategy also leverages the work being done in an increasingly fruitful research arena.

Three distinct approaches fuel the pipeline: identifying the most promising molecular targets that can be inhibited as part of a shortened therapy; researching known classes of antimicrobial drugs that have demonstrated activity against *M.tb* but are not yet optimised to treat TB infection; and expanding the likelihood of discovering a successful drug by investigating analogs of the new drugs that are now in clinical testing, such as the nitroimidazoles and quinolones.

At the clinical stage, all work is geared toward determining the ideal combination of new and existing drugs to shorten therapy. In recent years, the operating strategy for new TB drug development has been to improve therapy by substituting new drugs, one at a time, into the current combination. The success of this strategy is demonstrated in ongoing clinical trials. In late 2007 the TB Alliance and its research partner Bayer Healthcare plan to begin a Phase III trial of moxifloxacin as a substitute for ethambutol or isoniazid to shorten treatment duration by 2 months. At the same time, the TB Alliance is trailblazing a new strategy whereby two or more novel compounds may be incorporated simultaneously into a new regimen, thereby reducing the total time required for approval and registration of a markedly improved new combination. To do so, the Alliance is working with partners and regulatory agencies worldwide, conducting extensive *in vivo* preclinical combination trials, and ensuring the highest level of ethical and medical practices.

Without continued research and new drugs, TB will continue to grow as a global threat, driven by its deadly synergy with HIV/AIDS, complicated by multi-drug resistant strains, and amplified by the consequences of poverty. New, more effective and shorter treatment regimens will speed cure rates and save lives; they will increase productivity, enhance current TB control efforts, and alleviate much of the current burden on healthcare systems. When introduced alongside other advancements, such as diagnostics and vaccines, new drugs will expand the scope of current TB control and redefine public health targets. All of this requires the continuous dedication of scientists and researchers throughout the world, sustainable commitments by governments and philanthropists, and strong political will.