TB TOOLKIT

make medicines affordable
END UNFAIR MONOPOLIES

ITPC
INTERNATIONAL TREATMENT PREPAREDNESS COALITION

ABOUT ITPC

The International Treatment Preparedness Coalition (ITPC) is a worldwide network of community activists unified by our vision of a longer, healthier, more productive life for all people living with HIV (PLHIV). ITPC's mission is to enable communities in need to access optimal HIV treatment. As a grassroots movement based primarily in the Global South, ITPC is the community's voice on HIV treatment and is driven by and committed to the human rights of those most impacted by the HIV epidemic.

ITPC is a global coalition that includes eight regional networks in Africa, Asia, Latin America and the Caribbean, Eastern Europe, and the Middle East. Through its different campaigns, ITPC is committed to providing accurate and timely HIV treatment information that can improve the lives of PLHIV. Many of the tools developed under this program are also intended to be used for advocacy initiatives.

Additional information about ITPC is available at: www.itpcglobal.org

Thank you to Mike Frick, Blessi Kumar and Lindsay McKenna

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ABBREVIATIONS

AIDS	acquired immunodeficiency virus
API	active pharmaceutical ingredient
ART	antiretroviral therapy
ARV	antiretroviral
BCG	bacille Calmette-Guerin
BDQ	bedaquiline
BPaL	bedaquiline, pretomanid and linezolid
CL	compulsory license
DLM	delamanid
DR-TB	drug-resistant tuberculosis
DS-TB	drug susceptible TB
DST	drug susceptibility testing
DTG	dolutegravir
EMA	European Medicines Agency
EML	essential medicines list
ERP	Expert Review Panel
FDA	Food and Drug Authority
FDC	fixed-dose combination
GDF	Global Drug Facility
GPO	Government Pharmaceutical Organization
HIV	Human Immunodeficiency Virus
IP	Intellectual property
J&J	Johnson and Johnson
LTBI	latent TB infection
MDR-TB	Multidrug-resistant TB
MIC	middle-income countries
MPP	Medicines Patent Pool
MSF	Médecins Sans Frontières
NDRA	National Drug Regulatory Authority
PEPFAR	President's Emergency Plan for AIDS Relief
RTD	rapid diagnostic test
RPT	rifapentine
RR	rifampicin resistance
RR-TB	rifampicin-resistant TB
SL-LPA	second-line line probe assays
SRA	stringent regulatory authority
TB	tuberculosis
TB-LAM	TB lipoarabinomannan
TPP	target product profile
TRIPS	Trade-Related Aspects of Intellectual Property Rights
TST	tuberculin skin test
US	United States
US FDA	United States Food and Drug Administration
VL	voluntary license
WHO	World Health Organization
WHO-PQ	World Health Organization Pre-Qualification
XDR-TB	Extensively drug-resistant TB

PART ONE

INTRODUCTION AND PURPOSE

TB: A Threat to Global Public Health

The world has the tools, targets [1] and a plan to eliminate tuberculosis (TB), which is the world's deadliest infectious disease - and the leading cause of death among people living with HIV. In 2018, TB killed 1.4 million people, including 251,000 people who were living with HIV.

This resource was developed to highlight what to fight for – newer TB drugs and diagnostics- why it is important to fight for them; it also contains information for policy briefs and trainings to increase TB diagnostics and treatment literacy.

TB diagnostics and treatment are improving, but they remain complicated. TB is usually curable, but some forms of TB are drug-resistant (DR); these are harder to treat.[2] Although there are newer, less toxic and more effective treatments for DR-TB, many people lack access to them, due to high prices.

Currently, there is no magic bullet for diagnosing and treating all forms of TB simply, quickly, tolerably and effectively. While knowing patent status and strength is essential, there are additional criteria for selecting TB diagnostics and drugs, including products in the pipeline. This resource includes key background information to inform product prioritization:

- an overview of TB epidemiology,
- transmission, prevention, diagnostics, natural history and treatment;
- insight into the development of TB treatment from 'bench to bedside',
- a target product profile for TB treatment,
- information about drug registration and procurement, and
- WHO recommendations for TB prevention, diagnostics and treatment.

While WHO recommendations are the international standard, and a useful framework for identifying priority TB drugs, there are other considerations for selecting target diagnostics and medicines, such as price, registration status, perspectives from people living with TB, healthcare providers and policymakers, as well as information about:

- the national epidemic – how high are the country's burdens of TB and TB/HIV? How common is drug-resistant TB?
- a country's TB policies and guidelines;
- a country's national laboratory capacity and access to TB diagnostics, including testing for drug resistance;
- common co-morbidities among people who have TB, and access to treatment for them;
- how does the country procure TB medicines and diagnostics?
- is the country prepared to transition from Global Fund procurement mechanisms to national processes - without an impact on the affordability, quality and supply of TB medicines and diagnostics?
- what are the prospects for successful intellectual property (IP) interventions in your country?
- what are the possibilities for fostering competition between generics producers to increase access and lower prices in your country?

[1] The End TB Strategy calls for a 90% reduction in TB deaths and an 80% reduction in new TB infections by 2030 and a 95% reduction in TB deaths and a 90% reduction in new TB infections by 2030 (compared to 2015).

[2] Some forms of drug-resistant TB are incurable, underscoring the need for new drugs.

THE WHAT: ABOUT TB

- TB is airborne.
- There is a TB vaccine, recommended for newborns and in places where TB is common; it reduces their risk for serious illness from TB, and may prevent TB infection.

TB TRANSMISSION

TB is an airborne bacterial infection. When a person with untreated TB disease in their throat or lungs sings, speaks, coughs or spits, droplets containing TB bacteria are released into the air. When nearby people inhale these droplets, they may become infected.

TB Prevention: Vaccination with Bacille Calmette-Guerin (BCG)

The BCG vaccine can protect children up to 5 years of age from severe forms of TB outside of the lungs, and it may have a protective effect against TB infection and reactivation. [3] WHO recommends that a single dose of a BCG vaccine be given to at birth to all infants in settings where TB is highly endemic or where there is high risk of TB exposure. In these settings, WHO also recommends BCG vaccination for tuberculin skin test (TST)- negative and unvaccinated children, older persons at risk from occupational exposure and for infants, children, adolescents and adults living with HIV who are receiving antiretroviral therapy. [4]

Although the median global price per dose of BCG in 2015 was $ 0.52 per dose, pricing varies; countries in the Africa region pay more than those in the Europe and Western Pacific regions.

Currently, two suppliers produce 75% of WHO- pre-qualified BCG vaccines. [5]

TB OVERVIEW

- TB is the world's deadliest infectious disease, and the leading cause of death among people living with HIV.
- In 2018, 10 million people fell ill with TB and I.4 million of them died.
- Some forms of TB have become resistant to one or more drugs; they are harder to cure and need treatment that has debilitating, sometimes permanent side effects.
- There is an urgent need for new medicines for DR-TB.

Globally, 10 million people – 90% of them adults - fell ill with TB in 2018, and 1.2 million of them died from it, although TB is curable. People who become ill with drug-susceptible (DS) forms of TB can usually be cured by six months of treatment with a combination of drugs. Some forms of TB are resistant to one or more of the drugs used to treat it – and they are more difficult to cure.

[3] Of note, people who have received BGC may have a false positive reaction to TST; for this reason, blood testing is recommended for BCG-vaccinated people.

[4] WHO. Strategic Advisory Group of Experts Evidence to recommendations framework. BCG vaccination for HIV infected infants. [Online] 2017 [Cited 2019 October 19] Available from: https://www.who.int/immunization/policy/position_papers/bcg_evidence_recommendation_table_hiv.pdf?ua=1

[5] SAGE Working Group on BCG Vaccines; WHO Secretariat. Report on BCG against mycobacterial infections including tuberculosis, leprosy, and other nontuberculous mycobacteria (NTM) infections. [Online] 22 September 2017 [Cited 2019 October 19] Available from: https://www.who.int/immunization/sage/meetings/2017/october/1_BCG_report_revised_version_online.pdf

In 2017, an estimated 558.000 people developed rifampicin resistant (RR)[6] -TB; 82% of this group had multidrug-resistant (MDR)-[7] TB and 8.5% of them had extensively drug-resistant (XDR)-[8] TB. These forms of DR-TB require treatment with second-line drugs, which have debilitating side effects and have only cured 34-55% of people. XDR-TB cannot always be cured by currently available medicines; there is urgent need for new drugs that can safely and effectively cure all forms of TB.

TB NATURAL HISTORY

- Up to a quarter of the world's population has latent TB infection; although they do not feel ill and cannot transmit TB, 5-10% of them will develop active TB disease. In 2018, this happened to 10 million people.
- TB can spread from the lungs throughout the body – which is more likely to happen among people living with HIV.
- People living with HIV are over 20 times more likely to develop active TB- and more likely to die from it.
- ART and LTBI treatment reduce the risk for active TB among people living with HIV.
- TB can be treated in people living with HIV.

LATENT TB INFECTION (LTBI)

An estimated 1.7 billion people – or a quarter of the world's population - have latent TB infection (LTBI). People who have been infected with TB and are well, without signs and symptoms of active TB disease, have latent TB infection (LTBI). Some people with LTBI have a robust immune response that prevents them from developing active TB disease (known as TB reactivation). But over a lifetime, 5-10% of people with LTBI will develop TB reactivation, usually within 18 months of becoming infected. The risk for TB reactivation is much higher among people with weakened immune systems, especially people living with HIV, who are up to 21 times more likely to develop active TB disease.

ACTIVE TB DISEASE

In 2018, an estimated 10 million people developed TB disease worldwide. Because symptoms of active pulmonary TB (coughing, fever, night sweats and fatigue) are initially mild, people are not always diagnosed promptly. Over a year, a person with untreated pulmonary TB disease can transmit it to 10-15 people through close contact.

[6] Rifampicin is one of the two most powerful TB drugs; it is used as part of first-line treatment.

[7] MDR-TB is resistant to isoniazid and rifampicin, the two most powerful TB drugs used in first-line regimens.

[8] XDR-TB is MDR that is also resistant to at least one of the second-line injectable TB drugs and at least one of the fluoroquinolones.

EXTRAPULMONARY TB

TB can spread from the lungs to other parts of the body through the bloodstream; this is known as extrapulmonary TB. Extrapulmonary TB can infect any part of the body except for the hair and nails; it is most commonly found in the lymph nodes, the skin around the lungs (called the pleura), the bones and joints, and the central nervous system. Extrapulmonary TB is more common among people living with HIV, children and elderly people.

Extrapulmonary TB is hard to diagnose, since images and/or samples need to be taken from different sites in the body, but it can be treated with the same medicines used for TB in the lungs.

TB/ HIV Coinfection

People living with HIV who have LTBI are more likely to develop active TB disease - and more likely to die from it than HIV-negative people. In fact, TB is the leading cause of death among people living with HIV. Each illness worsens the other, although HIV is treatable and TB is curable, regardless of HIV status – with the same drugs that are given to HIV-negative people.

WHO recommends antiretroviral therapy (ART) for all infants, children, adolescents and adults living with HIV. Antiretroviral therapy (ART) reduces the risk for TB among people living with HIV, although it remains higher than that among HIV-negative people.

WHO recommends LTBI treatment for all adults, adolescents, children and infants living with HIV (who do not have active TB disease). Adding LTBI treatment to ART further reduces the risk of TB reactivation among people living with HIV.

WHO recommends that people diagnosed with TB/HIV coinfection start TB treatment first and start ART within 8 weeks (or within 2 weeks if CD4 cell count is <50 cells/mm3).

TB TESTING: WHICH TESTS ARE IMPORTANT, AND WHY

- There are specific tests for LTBI, drug-resistant forms of TB, and for TB in people with advanced HIV.

TESTING FOR LTBI

WHO recommends LTBI testing and TB preventive treatment for people at increased risk for developing active TB disease; this includes people of all ages who are living with HIV.

Testing for LTBI is done using either a TST or a blood test. However, only two blood tests, the QuantiFERON®-TB Gold In-Tube and the T-SPOT® TB, are WHO-recommended and each has limitations, including affordability and need for infrastructure.

WHO recommends systematic LTBI testing for the following groups:

- All adults, adolescents, children and infants living with HIV (although it is not required before starting LTBI treatment);
- Infants and children less than age 5 who have had close contact with a person who has active TB disease;
- People on dialysis;
- People being treated for an autoimmune disorder with TNF inhibitors;
- People who are going to undergo organ or blood transplantation;
- Children above age 5, adolescents and adults who have had close contact with a person who has TB, including MDR-TB;
- Prisoners;
- Healthcare workers;
- Homeless people;
- Immigrants from countries where the burden of TB is higher;
- People who use drugs;
- People who have silicosis.

TESTING FOR ACTIVE TB DISEASE

WHO recommends use of Xpert MTB-RIF as the initial diagnostic test for all persons with signs and symptoms of TB.

TB is more difficult to diagnose in people who are living with HIV and in children. Smear microscopy, an examination of phlegm coughed up by a person thought to have TB, is not always reliable and does not distinguish DS-TB from DR-TB. Xpert MTB-RIF is a rapid molecular test; it uses sputum samples to diagnose TB and detect resistance to rifampicin in 2 hours.

Pricing is a barrier to implementation of and access to Cepheid's Xpert MTB-RIF. Although FIND and Unitaid have negotiated prices for low- and middle-income countries, the price for a Gene Xpert machine is $17,000 - $17,500 – and this does not include warranty or calibration, which add thousands of dollars. [9]

[9] See http://www.stoptb.org/global/awards/tbreach/bet.asp and http://www.stoptb.org/assets/documents/gdf/drugsupply/GDFDiagnosticsCatalog.pdf

An agreement between the United States (US) President's Emergency Plan for AIDS Relief (PEPFAR), the US Agency for International Development (USAID) and the Bill and Melinda Gates Foundation lowered the price for a single-test cartridge to $9.98 in 145 countries [10] but it does not cover all upper middle-income countries and it expires in 2022.

TB-LAM Testing

The TB- lipoarabinomannan (LAM) assay is a urine-based, rapid, point-of -care test that can help diagnose TB in people living with HIV. [11]

WHO recommends TB-LAM to help inpatient and outpatient TB diagnoses for people living with HIV who have a low CD4 cell count (≤100 cells/µL) and TB symptoms, or for all people living with HIV who are very ill.

TB is more difficult to diagnose in people living with HIV –especially those with advanced HIV disease (CD 4 count of <200 cells /µL) - since they may have extrapulmonary disease or be too sick to produce sputum.

Since the 2015 WHO recommendation for TB-LAM, research has demonstrated that it increases the rate of TB diagnosis and improves survival among those with a CD4 cell count of <200 cells/µL. Activists are pushing to increase access to TB-LAM testing to prevent deaths from undiagnosed TB among people with advanced HIV disease, who are the most vulnerable to TB-related death.

A new instrument-free rapid test, FujiLAM, further increased TB diagnosis among hospitalized patients living with HIV. Given the recent information on TB-LAM and the promising new testing option, the WHO held a Guideline Development Group meeting in 2019 to update the recommendations for the use of urine LAM assays in people living with HIV.

TESTING FOR TB DRUG RESISTANCE

For confirmed RR-TB or MDR-TB WHO recommends that SL-LPA

People with RR-TB need additional drug susceptibility testing (DST) to see which TB medicines are likely to be effective for them. Pricing is a significant barrier to second-line lineprobe assays (SL-LPA). The equipment that performs MTBDRsl testing ranges from US $ 8,000 to $40,000. FIND has negotiated a price with Hain LifeScience of EURO 7.50 for MTBDRsl strips in 138 countries [12] but the price for laboratory supplies and equipment adds up to US $30 per test. [13]

A range of barriers, including high prices resulting from patent monopolies and quasi-monopolies, are limiting access to WHO-recommended TB diagnostics. Each testing platform requires a significant investment for the machine as well as staff training and it is not possible to switch to better and/ or cheaper tests and reagents from another producer, unless a new machine is purchased. Lack of generic reagents and general compatibility standards across testing platforms help keep a monopoly on TB diagnostic products.

[10] For a list of countries, see page 10: http://www.stoptb.org/assets/documents/gdf/drugsupply/Xpert_info_note.pdf

[11] In combination with Gene Xpert.

[12] The list of countries was not available on FIND's website as of August 2019.

[13] https://www.who.int/tb/publications/factsheet_tb_sllpa.pdf

PART
FOUR

WHAT IS TB TREATMENT - AND WHY NEW DRUGS ARE SO IMPORTANT

- TB is curable with a combination of drugs.
- Without treatment, 45% of HIV-negative people with active TB disease and almost everyone with TB/HIV coinfection will die.
- Over 85% of people with drug-sensitive TB are successfully treated.
- Treatment for DR-TB remains complicated and toxic, and cure rates are lower (39-56%), although new drugs are more effective.
- New drugs are urgently needed- and so is access to them.
- WHO plans to issue consolidated guidelines on treatment for drug-resistant TB in 2020.

TB PREVENTIVE TREATMENT

Treating LTBI reduces the risk of progression to active TB disease, especially for people living with HIV, who are 21 times more likely to develop active TB disease; [14] TB preventive treatment reduces this risk by 60%.

TB preventive treatment is recommended for:

- All adults and adolescents living with HIV who are unlikely to have active TB disease, including during pregnancy and with ART, at any degree of immunosuppression, for people who have been treated for TB in the past, and even if LTBI testing is unavailable;
- Infants (age < 12 months) living with HIV who have had contact with a person who has TB and are unlikely to have active TB, or as recommended by national TB guidelines;
- Children (age ≥ 12 months) living with HIV who are unlikely to have active TB, if they live in settings with high TB transmission;
- All children living with HIV who have successfully completed treatment for active TB disease;
- All children age <5 years who are household contacts of people with TB who do not have active TB, even if LBTI testing is unavailable;
- All children age ≥5 years, adolescents and adults who are household contacts of people with TB who do not have active TB, even if LTBI testing is unavailable;
- People who are starting anti-TNF treatment, dialysis recipients, and people who are preparing to undergo blood or organ transplantation and people with silicosis.

TB preventive treatment should be considered for:

- Selected high-risk household contacts of people with MDR-TB, based on indivudialized risk and clinical judgement;
- Prisoners;
- Healthcare workers,
- Immigrants from countries where the TB burden is higher;
- Homeless people;
- People who use drugs.

[14] Diabetes, malnourishment, tobacco smoking and alcohol consumption are risk factors for development of active TB disease among people with LTBI.

Table 1.
WHO - Recommended TB Preventive Treatment Options - All Settings, Regardless of HIV Status

Regimen	Comments
6 or 9 months of daily isoniazid	Side effects may include clumsiness, numbness and tingling in the hands and feet, yellow skin and eyes, appetite loss, nausea, vomiting, tiredness and weakness.
3 months of weekly rifapentine* plus isoniazid	Side effects may include clumsiness, numbness and tingling in the hands and feet, yellow skin and eyes, appetite loss, nausea, vomiting, tiredness and weakness, blood in the urine, pain in the joints, side, or lower back and swelling in the lower legs and/or feet. Although there are no patents on rifapentine, the high price – due to lack of generic competition[15] - - and limited registration create access barriers.
3 months of daily isoniazid plus rifampicin*	Side effects may include discolored body fluids (red-orange tears, sweat, saliva, urine, stools), clumsiness, numbness and tingling in the hands, and feet, yellow skin and eyes, appetite loss, nausea, vomiting, tiredness and weakness, fever and chills.
Alternatives	
1 month of daily rifapentine* plus isoniazid	Side effects may include clumsiness, numbness and tingling in the hands and feet, yellow skin and eyes, appetite loss, nausea, vomiting, tiredness and weakness, blood in the urine, pain in the joints, side, or lower back and swelling in the lower legs and/or feet.
4 months of daily rifampicin*	Side effects may include discolored body fluids (red-orange tears, sweat, saliva, urine, stools), yellow skin and eyes, appetite loss, nausea, vomiting, tiredness and weakness, fever and chills.

*For people living with HIV, avoid drug-drug interactions between rifampicin/rifapentine and ARVs

WHO LBTI Recommendation for Adults and Adolescents Living With HIV in Settings with High TB Transmission
All adults and adolescents living with HIV (including those who are pregnant), with an unknown or positive LBTI test result and who are unlikely to have active TB disease should receive at least 36 months of daily isoniazid preventive therapy (IPT). Daily IPT should be given whether or not the person is on ART, regardless of the degree of immunosuppression or history of previous TB treatment.

The goal of TB treatment is a cure. Currently, there is no 'pan-TB' regimen for all forms of TB. It is treated with different drugs, for different lengths of time, depending on whether it is drug-sensitive or drug-resistant, according to the extent of drug resistance and a person's response to their treatment.

Activists may prioritize and pursue access to TB drugs that are not WHO-recommended, or drugs that have not yet been approved by a regulatory agency. A TPP can be helpful in making these decisions, as well as consultations with a range of different stakeholders.

[15] As of April 2020, the only WHO pre-qualified rifapentine was produced by Sanofi.

The TPP for TB drugs could include:

- Safety, including for people living with HIV and/or kidney and liver disease and other conditions
- Effectiveness: high cure rate for all forms of TB
- Tolerablity: few – and mild - side effects,
- Potency: a high barrier to resistance; forgiving when doses are occasionally missed
- Simplicity: minimal monitoring needed, once-daily, fixed-dose combination (FDC) or low pill count, no food requirements, temperature stable, two-year shelf life, fixed duration of treatment
- Universal: effective for all forms of TB and in all populations, including children; with hormonal contraceptives, ARVs, opioid agonist therapy and other commonly-used medicines; safe during pregnancy and breast-feeding
- Affordable, for governments and people who must pay out-of-pocket.

A combination of drugs with different mechanisms of action is used to kill TB bacteria over several months, since it dies slowly. Treatment success rates (which include people who finished their treatment and those confirmed as cures) for DS-TB are high (at least 85%), although side effects such as vision loss, fever, weakness, nausea, vomiting, and numbness, tingling or burning sensations in the feet make it difficult for people to complete.

Drug-resistant forms of TB are more likely to be fatal – and harder to cure – than DS-TB. Mortality rates are estimated at 40% and 60% for MDR-TB and XDR-TB, respectively. Treatment success rates among people with MDR-TB who began treatment in 2016 were 56%; the cure rate for XDR-TB was 39% – and treatment involved up to 40 pills each day, many with severe side effects such as permanent hearing loss, nerve damage to the feet and psychosis. Since then, newer drugs – bedaquiline and delamanid - offer great promise to people with DR forms of TB - and higher cure rates. For example, treatment with a regimen including ≥ 6 months of bedaquiline has cured 65.8% of people with either MDR- or XDR-TB, and a clinical trial of a novel regimen (see Box: Pretomanid - a New TB Drug) reported 89% cure rates among people with MDR- and XDR-TB.

Pretomanid- a New TB Drug

On August 14, 2019, the US Food and Drug Administration (US FDA) approved pretomanid, as part of a three-drug, six-month regimen (with bedaquiline and linezolid; BPaL) for MDR- and XDR-TB, based on results from the NIX-TB trial in 109 people; of the 107 who completed treatment, 95 (89%) were cured. Pretomanid was approved under the Limited Population Pathway for Antibacterial and Antifungal Drugs.[16,17] Ongoing trials are assessing pretomanid-containing regimens for DS- and DR-TB. As of December 2019, WHO recommends the BPal regimen only when given under operational research conditions for people with XDR-TB (who have not received more than two weeks of treatment with bedaquiline and linezolid). Although WHO requires more evidence before recommending global programmatic use of BPaL, it may be considered for people without other treatment options, if it is provided in the context of individual consent, adequate counselling on potential benefits and risks, active monitoring and management of adverse events.[18]

Pretomanid was developed by the non-profit TB Alliance, with funding from governments and philanthropists. The TB Alliance licensed it to Mylan in April of 2019. But neither party has disclosed the licensing agreement. Although pretomanid will be priced at $364 for a six-month treatment course, [19] experts from the University of Liverpool and their colleagues have estimated that pretomanid could be produced and sold, profitably, for between US $ 0.36 - $1.14 per day, or $ 65.52 – $ 207.48 per six-month treatment course. [20]

Despite the TB Alliance's assertion that it is "…dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those who need them," [21] It is important to note that in many countries, there are patents on bedaquiline/ pretomanid/ linezolid (and optionally pyrazinamide) compositions, and their use in TB.

High prices have limited access to bedaquiline and delamanid, which are now WHO-recommended as part of combination treatment for DR-TB, [22] forcing people to use TB drugs that can cause permanent deafness, psychosis, kidney damage, and other severe and often debilitating side effects.

[16] Approval of drugs under this pathway relies on studies that may have only answered focused questions about safety and effectiveness in a limited population of patients who have unmet needs, including a lack of available alternative treatments.

[17] TB activists have concerns about the full approval of pretomanid, which is based on a non-randomized, uncontrolled approach and its impact on future regulatory standards. See: Research, Regulatory, and Access Considerations Regarding Pretomanid, at http://www.tbonline.info/media/uploads/documents/tb_cab_pretomanid_nda_considerations_final_05.14.19.pdf

[18] WHO. Rapid Communication: Key Changes to the Treatment of Drug-Resistant Tuberculosis. [Online] December 2019 [Cited 2020 February 10] Available from https://www.who.int/tb/publications/2019/WHO_RapidCommunicationMDRTB2019.pdf?ua=1

[19] MSF Access Campaign. Price Announced for New Lifesaving TB Drug Pretomanid Still Too High. Press release [Online] 29 October 2019 [Cited 2020 February 10] Available from https://msfaccess.org/price-announced-new-lifesaving-tb-drug-pretomanid-still-too-high

[20] Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother [Online]. 2017 Apr 1 [Cited 2019 September 1];72(4):1243-1252. Available from doi: 10.1093/jac/dkw522.

[21] See: https://www.tballiance.org

[22] WHO recommends that bedaquiline should be included in longer regimens for MDR-TB and that delamanid should be added when other MDR-TB drugs cannot be used.

Treating TB and HIV Coinfection

HIV and TB can be treated at the same time, but it is important to avoid interactions between WHO-recommended ARVs and TB drugs (see Table 2), as well as other commonly used medicines. For example, the rifamycin family of antibiotics (rifampicin, rifapentine and rifabutin) interact with many different medicines, including HIV antiretrovirals, proton pump inhibitors, medicines for type 2 diabetes, statins, antifungals, cardiovascular medicines, antihypertensives, psychotropics, hormonal contraception and opioids– among others.[23]

Dolutegravir (DTG) is a WHO-preferred first-line ARV and recommended as part of second-line treatment when non-DTG-based regimens are failing. [24] It can be co-administered with TB treatment. As of 2019, 82 low- and middle-income countries were transitioning to DTG-based HIV treatment. Advocacy for HIV treatment access should include efforts to increase access to DTG-based ART in places where it is not widely available.

Table 2.
Drug Interactions Between WHO-Recommended DR-TB medicines and ARVs

WHO-recommended ARV, by Class	Bedaquiline	Delamanid
HIV protease inhibitors (atazanavir/ ritonavir, darunavir/ ritonavir, lopinavir/ ritonavir)	Potential interaction; more research needed	Potential interaction; more research needed
HIV integrase inhibitors (dolutegravir, raltegravir)	No interaction expected	No interaction expected
HIV nucleoside/ tide reverse transcriptase inhibitors (abacavir, emtricitabine, lamuvidune, tenofovir, zidovudine)	No interaction expected	No interaction expected
HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine)	Do not use with efavirenz; can be used with nevirapine (which is only recommended for neonates)	Do not use with efavirenz or nevirapine

WHO recommendations are evidence-based. It takes time to produce, gather and review evidence about new TB drugs – and the process relies both on pre- approval and post-marketing research. If trials are badly designed, it may be difficult to see how safe and effective drugs are by themselves or in combination. For example, bedaquiline and delamanid – the first new drugs for TB in nearly 50 years- were not studied together until each drug was approved on its own, and questions about the delamanid's effectiveness remain, pending additional data. [25]

[23] See: http://action.lung.org/site/DocServer/Rifamycin_Interactions.pdf?docID=36385

[24] WHO.Update of Recommendations on First- and Second-Line Antiretroviral Regimens. Geneva [Online] July 2019 [Cited 2019 July 30] Available from: https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf?ua=1

[25] For more information, see the WHO position statement on the use of delamanid for multidrug-resistant tuberculosis https://www.who.int/tb/publications/2018/WHOPositionStatementDelamanidUse.pdf?ua=1

Table 3.
WHO TB Treatment Recommendations

Drug-Susceptible TB	Isoniaizid-resistant TB	Isoniaizid-resistant TB
2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin (2HRZE/4HR)	6 months of rifampicin, ethambutol, pyrazinamide and levofloxacin	In December 2019, WHO released a Rapid Communication stating that: "All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones, stand to benefit from effective all-oral treatment regimens, either shorter or longer, implemented under programmatic conditions." [26] For people eligible for shorter treatment, [27] moxifloxacin, clofazimine, ethionamide, pyrazinamide and high-dose isoniziaid for 4-6 months, followed by 5 months of moxifloxacin, clofazimine, pyrazinamide and ethambutol.
		For people who are not eligible for shorter TB treatment, [26] use a combination of medicines for 18-20 months from these groups: Group A (use all 3): levofloxacin *or* moxifloxacin, bedaquiline, linezolid Group B (add one or both): clofazimine, cycloserine/ terizidone Group C (add to complete the regimen and when medicines from Group A and Group B cannot be used): ethambutol, delamanid, pyrazinamide, imipenem–cilastatin *or* meropenem ethionamide *or* prothionamide, p-aminosalicylic acid

*Upcoming WHO Consolidated Guidelines for DR-TB will include use of bedaquiline for more than six months and use of bedaquiline with delamanid.

[26] People with MDR/RR-TB with extensive TB disease, severe extrapulmonary TB, resistance to fluoroquinolones or exposure to second-line TB medicines.

[27] See: https://www.who.int/tb/publications/2019/WHO_RapidCommunicationMDRTB2019.pdf?ua=1

PART FIVE

ACCESS ISSUES AND STRATEGIES

RATIONAL SELECTION

Sometimes national guidelines, essential medicines lists, reimbursement lists, nomenclatures or terms of reference for procurement, and other regulatory lists may include outdated medicines, that are no longer WHO-recommended, or medicines that have a significant budget impact but no advantage over the existing standard of care. It is important for activists to be in close dialogue with relevant state authorities to ensure that only medicines that have scientifically proven clinical effectiveness, safety, and cost-effectiveness are in the regulatory lists. A TPP can be helpful for making these decisions (please see page 11, TPP for TB drugs).

AFFORDABLE PRICES

Although WHO recommendations consider access and affordability, generic DR-TB drugs are not always available or affordable. As examples:

- Intellectual property barriers to BDQ (compound and multiple secondary patents) remain until 2028, although patents on compounds expire in 2023. [28]
  - Multiple patent applications have been filed, and patents have been granted to Johnson and Johnson (J&J) in many middle-income countries where there is a high burden of TB;
  - J&J, the patent holder for BDQ, has not offered a voluntary licensing agreement through Medicines Patent Pool, even for low-income countries.

- Rather than offering affordable pricing to all LMICs, a BDQ donation program [29] sponsored by J&J and USAID was provided to Global Fund-eligible countries; it ended in March 2019.

- The Global Drug Facility (GDF) is a procurement mechanism that does market-shaping and provides technical assistance for implementation of quality-assured, affordable TB drugs and diagnostics to Global-Fund eligible countries The GDF price for BDQ in eligible countries is US $ 400 per treatment course. For more information, see: http://www.stoptb.org/gdf/drugsupply/bedaquiline.asp
  - However, non-GDF countries are subject to tiered pricing for a six-month course of BDQ is $900, $3,000 or $30,000 depending on the economic status and TB burden of the country. [30]

- BDQ has not been registered in all high-burden countries, where it is urgently needed. As of October 2019, BDQ has been registered in the following low- and middle-income countries (those that WHO considers to have high burdens of TB and/or TB/HIV and/or MDR-TB are bolded) Armenia, **Belarus**, **Brazil**, Bulgaria, Burundi, Cameroon, **China**, **Congo – Kinshasa**, **Ethiopia**, **India**, **Indonesia**, Mexico, **Moldova**, Mongolia, **Peru**, **Philippines**, Romania, **Russia**, Rwanda, **South Africa**, **Thailand**, Turkey, Turkmenistan, Uganda, **Ukraine**, and **Uzbekistan**. [31, 32]

[28] Please see Medspal.org for preliminary patent status information. Please note that, in each case, patent status should be verified by conducting a national-level patent search at the national patent office.

[29] Unlike price reductions, donation programs do not create sustainable access to affordable medicines since sponsors can choose to end them at any time. Donations often come with onerous administrative requirements and restrictions, including geographic scope and clinical criteria. In addition, countries may be expected to apply stricter patent protection in return for donations,

[30] See: https://healthgap.org/press/activists-demand-johnson-johnson-drop-the-price-of-vital-tb-medicine-bedaquiline/

TRANSPARENCY OF PRICING INFORMATION

Transparent information on pricing is fundamental to obtaining better prices. In many countries, laws on access to public information exist. [33] Activists could use these laws to find out the latest price for state-procured HCV medicines. Reference prices can be found in several databases, including the Global Fund PQR database [34] and published reports, such as the MSF DR Drugs Under the Microscope.[35]

TARGET PRICES AND PRICE NEGOTIATIONS

To prepare for future pricing negotiations with manufacturers, it is important to determine the optimal target price for a given medicine. Production costs are an important consideration in calculating the target price. Several factors can influence drug prices, such as a high milligram count, complexity of the production process and sales volume. Experts have been tracking the cost of the active pharmaceutical ingredient (API) for key TB drugs, using it to estimate a profitable mass production cost for generic versions of these medicines, including formulation and packaging.

Neither pretomanid nor sutezolid (a TB drug in early development) have reached the market as of October 2019, although pretomanid has been priced at $364 per six-month treatment course.[36] The estimated production cost for profitable generic versions of these drugs are $11-34 and $4-9 per month, respectively.[37] Based on these calculations, it could be possible to profitably mass-produce the 6-month BPaL regimen for between $138 to $360; as of 2015, the cost of a course of MDR-TB treatment – not including novel drugs - ranged from $1800 to $4600.

Table 4.
Estimated Production Costs for Generic WHO-Recommended DR-TB medicines, per month*

bedaquiline	$8–$17
clofazimine	$4-11
delamanid	$5-16
linezolid	$4-9
moxifloxacin	$4–$8

*Treatment duration varies,according to the extent of drug resistance and the response to treatment.

[31] Bedaquiline Country Regulatory Status Overview [Online] Johnson and Johnson. 6 march 2020 [Cited 2020 April 13] Available from https://www.jnj.com/_document/bedaquiline-country-regulatory-status-overview?id=0000016e-0467-db13-a9ef-566f1a520000

[32] Notably absent from this list are the remaining countries considered by WHO to have high burdens of TB and/or TB/HIV and/or MDR-TB: Angola, Azerbaijan, Bangladesh, Central African Republic, Congo, DPR Korea, Kazakhstan, Kenya, Kyrgyzstan, Lesotho, Liberia ,Mozambique, Myanmar (pending), Namibia (pending), Nigeria (pending), Pakistan, PNG, Somalia, Tajiksitan (pending), Tanzania, Viet Nam (pending), Zambia (pending) and Zimbabwe (pending).

[33] https://www.right2info.org/resources/publications/countries-with-ati-laws-1/view

[34] https://public.tableau.com/profile/the.global.fund#!/vizhome/PQRTransactionSummary_V1/TransactionSummary

[35] https://msfaccess.org/dr-tb-drugs-under-microscope-6th-edition

[36] MSF. Price announced for new lifesaving TB drug pretomanid still too high. Press Release [Online] 29 October 2019 [Cited 2020 April 11] Available from https://msfaccess.org/price-announced-new-lifesaving-tb-drug-pretomanid-still-too-high

[37] Gotham D, Fortunak J, Pozniak A, et al. Estimated generic prices for novel treatments for drug-resistant tuberculosis. J Antimicrob Chemother [Online]. 2017 Apr 1 [Cited 2019 September 1];72(4):1243-1252. Available from doi: 10.1093/jac/dkw522.

PATENTS

Since most TB medicines were developed decades ago, generic versions are available – but there are existing patents or patent applications that have already been filed in many countries on newer drugs for DR-TB. Various strategies could be used to overcome granted or pending patents. When patents have been granted, activists may consider filing post-grant patent oppositions or patent invalidations or asking their governments to consider issuing a compulsory license for public non-commercial use. For pending patent application(s), in places where patent laws permit it, activists should contemplate pre-grant opposition(s), third party observation(s) or discussing the scientific arguments against granting patent(s) with their national patent office.

THE CASE OF INDIA

The patent for the bedaquiline base compound was granted and will expire in 2023. There is a pending patent application for bedaquiline fumarate salt, which, if granted, will extend the patent monopoly until 2027. Two patent oppositions [38] were filed against the bedaquiline fumarate salt patent application, one by the Network of Maharashtra People Living With HIV in March 2013, and one by Nandita Venkatesan and Phumeza Tisile (who are TB survivors), in February 2019. The grounds for their oppositions included lack of novelty and inventive step. If successful, these oppositions may effectively reduce the duration of the patent monopoly by four years in India.

Information About Overcoming IP Barriers to Increase Access to TB Diagnostics and Treatment

1. International Centre for Trade and Sustainaible Development, United Nations Conference on Trade and Development, World HealthOrganization. Guidelines for the examination of pharmaceutical patents: developing a public health perspective – A Working Paper [Online] 2006 [Accessed 2020 January 17]. Available from: https://apps.who.int/medicinedocs/documents/s21419en/s21419en.pdf
2. Medicines Patent Pool.MedsPal: the medicines patents and licenses database. [Accessed 2020 January 17]. Available from: https://www.medspal.org/?page=1
3. Médicines Sans Frontières. DR-TB Drugs Under the Microscope, 6th Edition [Online] pages 6-7 2019 [Accessed 2020 January 17]. Available from: https://msfaccess.org/sites/default/files/2019-10/IssueBrief_UTM_6th_Ed_FINAL_web.pdf
4. Unitaid. A Review of the Bedaquiline Patent Landscape: a Scoping Report. [Online] January 2014 [Accessed 2020 January 17]. Available from: http://unitaid.org/assets/TMC_207_Patent_Landscape.pdf
5. United Nations Development Program. Good Practice Guide: Improving Access to Treatment by Utilizing Public Health Flexibilities in the WTO TRIPS Agreement [Online] 2010, [Accessed 2020 January 17]. Available from: https://www.undp.org/content/dam/aplaws/publication/en/publications/poverty-reduction/poverty-website/good-practice-guide-improving-access-to-treatment-by-utilizing-public-health-flexibilities-in-the-wto-trips-agreement/Good%20Practice%20Guide-Improving%20access%20to%20treatment%20by%20utilizing%20public%20health%20flexibilities%20in%20the%20WTO%20TRIPS%20agreement.pdf
6. UN Secretary-General's High-Level Panel on Access to Medicines: Promoting Innovation and Access to Health Technologies. Report. [Online] September 2016 [Accessed 2020 January 17]. Available from: http://www.unsgaccessmeds.org/final-report

[38] See the Patent Opposition Database for more information on these oppositions, at: https://www.patentoppositions.org/en/search?utf8=%E2%9C%93&query=Bedaquiline+%28BDQ%29&facets%5Bdocument_types%5D%5B%5D=patent_opposition

PROCUREMENT STRATEGIES

Countries transitioning from Global Fund support face the 'procurement cliff'- shifting from Global Fund Pooled Procurement Mechanism to national procurement processes for purchasing TB products risk paying higher prices for drugs and diagnostics of unknown quality, and interrupted or delayed supply. [39] To avoid these pitfalls, countries can prepare for national procurement processes.

Country programs often do regional-, national- and district-level 'competitive tendering' to procure medicines. To ensure that this process is truly competitive, and will lead to lower prices, it is important that it is fully transparent, that different regimens are available, and that there are multiple suppliers for each generic product.

Further price reduction could be achieved by strategies to increase the volume of orders (bulk or pooled procurement). These strategies include: avoiding duplication of medicines within same therapeutic categories as much as possible; creating a centralized national procurement service for medicines; combining orders from several treatment facilities; combining orders from different budgets and/or systems (such as those from penitentiary services and from the Ministry of Health's orders for their facilities) or by pooling procurement from different countries, such as by commissioning a procurement agency (United Nations Development Programme, Crown Agents, etc).

GENERIC PRODUCTS – AND COMPETITION

Without competition, patent monopolies allow pharmaceutical corporations to charge whatever the market can bear for their products, keeping them out of reach for millions who need them. However, having only one or two generic products available on the market is not enough to foster competition –generics producers can form a duopoly, by pricing their products almost identically. There is compelling evidence that competition between multiple generics producers lowers the price of medicines. For example, generic competition has enabled significant price reductions for HIV ARVs, making global treatment scale-up possible.

Robust competition is essential for scaling-up access to new drugs for DR-TB treatment, since the more companies that are producing generic drugs, the lower prices can go. Lower prices will enable governments to scale-up treatment without creating budgetary imbalances.

[39] For more information, see Beware the Global Fund Procurement Cliff, at: https//msfaccess.org/beware-global-fund-procurement-cliff

Branded or generic medicines – what is the difference?

Because of patent monopolies, originator pharmaceutical corporations are the only source for certain medicines for at least 20 years. When there are no patent barriers, generics companies can produce their own versions of these medicines.

To enter the market, generic versions of medicines must have the same quality, strength, efficacy and safety as branded medicines. A generic medicine must have the same active ingredient as a branded medicine, and it must reach the same amount in the bloodstream as a branded medicine, from the time a person takes it until it passes out of their body (called bioequivalence). Generic versions of branded medicines must be given at the same dose, and by the same route (tablet, syrup, injection). A survey of 2,070 FDA-approved generic drugs reported that they were therapeutically equivalent to originator products.[40]

Usually, the active pharmaceutical ingredient (API) for originator and generic medicines comes from the same source. Although generic products may have different excipients (ingredients that are used for stability, bioavailability and to enhance overall drug safety or function during storage or use) than branded products, they have the same active ingredient as branded products. Studies of branded vs. generic beta-blockers, [41] glatiramer (used to treat multiple sclerosis), [42] and other medicines for different conditions have reported that effectiveness and tolerability did not differ between versions of these products; globally, millions of people rely on generic versions of HIV antiretrovirals.

PRICE REGULATION

Activists need to be aware of legislation that can create an unfair market for generics manufacturers. For example, governments may decide to regulate medicine prices by limiting their retail mark-up. Instead of a fixed mark-up rate (such as .50 per pack), the mark-up may be a percentage of the medicine's price (such as 25% per peck), which could incentivize pharmacies to promote high-priced branded products to increase their profit, rather than lower-priced generic medicines. Doctors may prescribe medicines using their trade names instead of specifying use of generic versions. Also, unnecessarily burdensome or prolonged registration procedures can delay the market entry of generic products.

REDUCTION OR ELIMINATION OF TAXES AND DUTIES

Various taxes, such as VAT and customs duty, may lead suppliers to increase their prices. This could be addressed by introducing tax exemptions for procuring TB medicines, based on their public health value.

[40] Davit BM, et al. Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration. Ann Pharmacother. [Online] 2009 Oct [Cited 2019 October 17] ;43(10):1583-97. Available from doi: 10.1345/aph.1M141.

[41] Chanchai R, et al. Clinical tolerability of generic versus brand beta blockers in heart failure with reduced left ventricular ejection fraction: a retrospective cohort from heart failure clinic. J Drug Asses [Online] 2018 Jan [Cited 2019 October 17] 11;7(1):8-13. Available from doi: 10.1080/21556660.2018.1423988.

[42] Selmaj K, et al. Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results. Mult Scler. [Online] 2017 Dec [Cited 2019 October 17]; 23(14): 1909–1917. Available from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5700775/

QUALITY

National Drug Regulatory Authorities (NDRAs), which are often called Food and Drug Authorities/Administrations (FDAs), regulate and oversee the development, approval, manufacturing, importing and marketing of medicines to ensure the safety, efficacy and quality of drugs, vaccines, diagnostics and other medical products. Before drugs reach the market, they must secure regulatory approval.

Each NDRA has its own pathways, requirements, procedures and timelines. Many things can cause the 'regulatory lag' of generic medicines, sometimes for years, including:

- Lack of, or limited NDRA capacity and resources
- Delayed and bureaucratic regulatory processes and/or heavy workload
- Data exclusivity, which prevents generics manufacturers from accessing data from originator clinical trials
- Failure among originator companies to prioritize registration in low- and middle-income countries
- In some countries, originator products must be registered before generic versions can be registered to enter the market
- Poor quality dossiers
- Requirement for local clinical trials as a prerequisite for approval

Additional measures can be taken to provide access to TB drugs (and other medicines). The WHO pre-qualification (WHO-PQ) program reviews quality, safety, and efficacy of generic TB drugs that are not SRA-approved. WHO invites manufacturers of eligible medicines (these are recommended by WHO treatment guidelines; and/or are included in, or submitted an application for inclusion in the Essential Medicines List [EML]) to submit an expression of interest for WHO-PQ. Manufacturers must submit a dossier including data on the product's quality, safety, efficacy, which is assessed by an expert panel; their production sites – and any organizations that conducted clinical trials of the product- must be inspected and demonstrate compliance with WHO good manufacturing processes, good clinical practices and good laboratory practices (for more information, see: https://www.who.int/news-room/fact-sheets/detail/prequalification-of-medicines-by-who).

Table 5.
First and Second-Line TB Medicines: Generic Suppliers with WHO-PQ

FIRST-LINE	SUPPLIER
ethambutol/ isoniazid	Cadila Pharmaceuticals, Lupin
ethambutol/ isoniazid/ rifampicin	Lupin, Macleods, Svizera Europe
ethambutol/ isoniazid/ pyrazinamide/ rifampicin	Lupin, Macleods, Micro Labs, Sandoz, Svizera Europe
isoniazid	Antibiotice SA, Cadila Pharmaceuticals, Lupin, Macleods, Micro Labs, Mylan
isoniazid/ rifampicin	Antibiotice SA, Lupin, Macleods, Sandoz, Svizera Europe
isoniazid/ pyrazinamide/ rifampicin	Cipla, Hetero, Macleods
SECOND-LINE	**SUPPLIER**
bedaquiline	None
clofazimine	None
cycloserine	Biocom JSC, Cipla, Dong-A ST CO Ltd, Macleods, Mylan, Strides
delamanid	None
levofloxacin	Cipla, Macleods, Micro Labs, MSN Laboratories Private LTD, PT Kalbe Farma
linezolid	Celltrion, Lupin, Macleods, Micro Labs
moxifloxican	Getz, Hetero, Macleods, Micro Labs, MSN Laboratories Private LTD, Mylan, Sun Pharmaceuticals, Zhejiang Hisun Pharmaceutical Co

Approval by a stringent regulatory authority (SRA), such as the European Medicines Agency and the USFDA can facilitate accelerated NDRA registration of medicines that fulfill public needs – or their export. The USFDA issues tentative approval [43] for generic fixed-dose combinations and co-packaged antiretroviral products used in the President's Emergency Plan for AIDS Relief (PEPFAR), working closely to build capacity among generics manufacturers and prioritizing their applications.

[43] These products must meet the same safety, efficacy and marketing quality standards used for marketing in the US; approval is "tentative" rather than "full" only because they are under patent protection.

Some countries – including Brazil [44] and Thailand - produce their own generic medicines, which must meet national quality standards. Thailand's Government Pharmaceutical Organization (GPO) has been producing generic antiretrovirals for national use since 2003; in 2018, GPO's efavirenz was WHO-prequalified.

WHO has developed a procedure for sharing dossiers with NDRAs, who will work to issue a decision on their registration within 90 days (for more information, see: https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras).

Expert Review Panel (ERP) approval is used to identify products to meet an urgent supply need; these products are not WHO-PQ or approved by a stringent regulatory authority (SRA). To be eligible, dossiers for such products must be accepted by WHO-PQ or an SRA, and there must be evidence of compliance with good manufacturing processes.[45]

Some countries (Armenia, Georgia, Kyrgyzstan, Moldova, Ukraine) have simplified procedures for marketing authorization. In these countries, products that are WHO-prequalified (or approved by FDA, EMA or another SRA), can be available quickly - in less than 30 days in some cases). These procedures help to ensure higher competition on state tenders and quick introduction and uptake of newly available products on the international market.

TB DRUG DEVELOPMENT

In drug development, science, regulation, commerce (and sometimes, people's health needs) overlap. TB drugs– and other medicines – go through a series of steps before they are approved.

Unmet Needs

To improve treatment outcomes and prevent the development of drug resistance, new classes and combinations of TB drugs are needed. But market-driven drug development has failed people with TB. Until recently, drugs were developed one by one, at a lethally slow pace. For example, bedaquiline and delamanid - the first novel TB drugs in nearly 50 years - were not studied together until years after entering the market.

Shorter, less toxic and more effective treatment is still needed for all forms of TB. Although drug-susceptible (DS)- TB is cured in over 80% of people, side effects such as vision loss, fever, weakness, nausea, vomiting, and numbness, tingling or burning sensations in the hands and feet make it difficult to undergo and complete treatment. Drug-resistant (DR) forms of TB are harder to treat, and second-line drugs have more severe side effects.

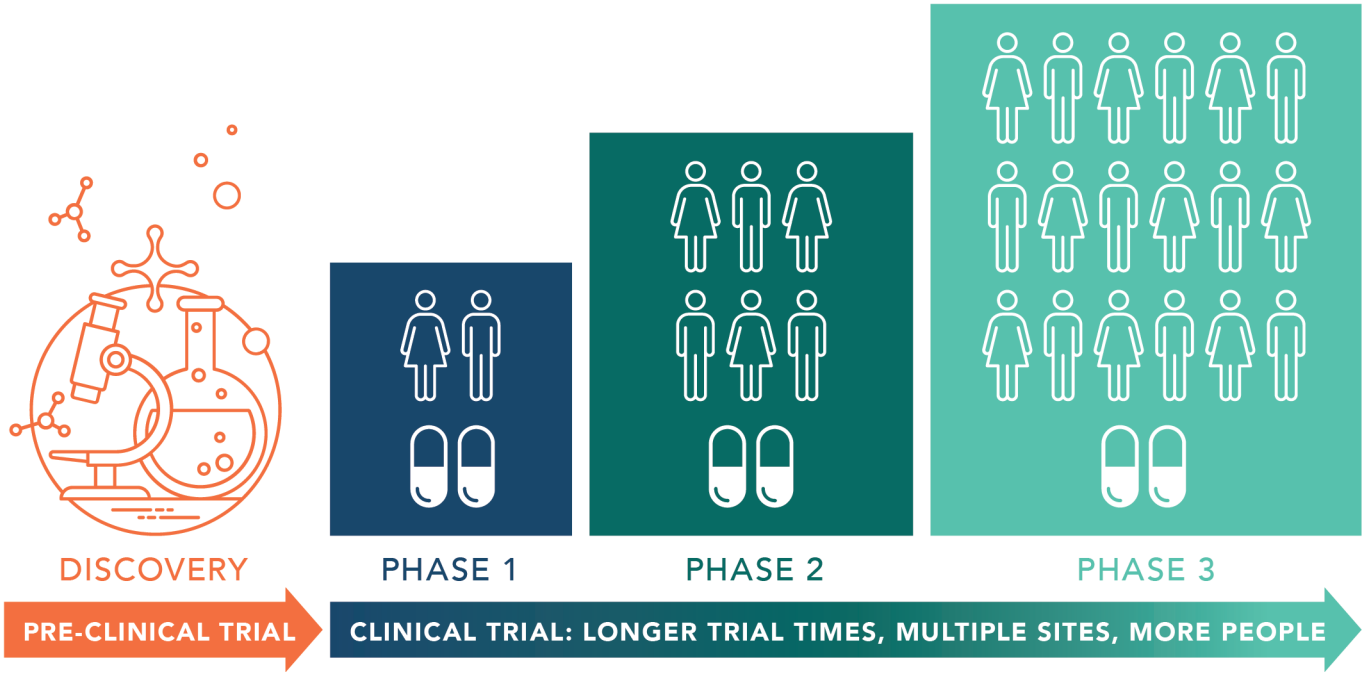
[44] Brazil's 1999 Generic Drug Act requires that generic products demonstrate bioequivalence – meaning that there is no significant difference in bioavailability (the rate and extent of how a generic versus a branded drug is absorbed into the body) and also, that generic and branded drugs become available to act on their intended target over a period of time in the same way, when they are given at the same dose and under the same conditions.

[45] For more information, see: https://extranet.who.int/prequal/sites/default/files/documents/73_ERP_Feb2019.pdf

Unlike HIV, where a significant amount of publicly-funded research has explored how to optimize antiretroviral therapy, TB drug development has been chronically underfunded. This has led to the neglect of certain populations as well as important clinical questions. These unmet needs include:

- Developing a 'pan-TB' regimen that is effective for all forms of TB
- Optimizing TB regimens
- Developing novel drugs and combinations for XDR-TB
- Developing TB drugs and combinations in children (age <12 years);
- Fixed-dose combinations of TB drugs from different pharmaceutical corporations
- Developing long-acting TB drug formulations to further simplify treatment and adherence.

Figure 1. The Drug Development Process



Pre-clinical Trials

Researchers select a target, such as a step in the TB lifecycle, and identify and improve on a lead compound. During this stage, assessments of what the drug does to the body (called pharmacodynamics), what the body does to the drug (called pharmacokinetics), how the drug is absorbed (called bioavaibility), its stability, toxicity, and other characteristics are performed in the laboratory.

Before a drug can be studied in human beings, it must go through trials in at least two species of mammals, which are chosen because of their relevance for assessing risks in humans. Preclinical trials look at the organs a drug passes through, whether it harms any organs or causes cancer, and its impact on reproduction and breast-feeding.[46]

These early stages of drug development are often government-funded, with additional support from foundations. As an example, from 2010 to 2016, the National Institutes of Health contributed over US $100 billion to basic science research which lead to the development of 210 drugs, 84 of them first-in-class.

[46] Despite this precaution, sometimes drugs that are harmful to humans do not cause problems in animals.

An analysis by Treatment Action Group (TAG) was presented at the 50th International Union Against Tuberculosis and Lung Diseases meeting in November 2019. It reported that total public expenditure on the development of bedaquiline far exceed that of the originator company, Johnson & Johnson. Public investment in bedaquiline was 3.1–5.0 times greater than that of the originator (US$455-747 million versus $90-240 million), or 1.6–2.2 ($647-1,201 million versus $292-772 million) when the cost of failures and forgoing other investment opportunities are counted.[47]

Clinical Trials

Clinical trials are experiments in human beings to look at the safety and efficacy of drugs, interventions and treatments for a certain condition. There are four phases of clinical trials.

Phase I

These first-in-human trials are short (weeks to months) and small (20 to 80 people). They begin in healthy volunteers, then may move into people with the given condition, to look at the activity of the drug. Phase I trials look at the safety and tolerability of a drug compared to placebo and at different doses, and a drug's potential for doing short- or long-term harm.

Phase II

These trials are often called 'make it or break it'. They usually include over 100 people, and are conducted at different sites and in different countries, and usually last from months to years, depending on the condition that is being studied. Usually, people with milder forms of the illness, who do not have any comorbidities, are eligible for phase II trials. These trials look at safety, tolerability and efficacy; Phase II and III TB drug trials have looked at treatment regimens, dosing, duration and strategy.

Phase III

Phase III trials are the final step before registration. These trials enroll hundreds to thousands of people, and are performed at multiple sites in different countries. They primarily look at efficacy, safety and adverse events, lasting from months to years. Phase III trials are generally more inclusive, and tend to enroll people with more advanced forms of an illness –a more 'real-life' scenario – than earlier trials, although people with the most urgent need are often left to seek experimental drugs through compassionate use or named patient programs.

Phase IV

These trials are conducted after a drug has been approved. Regulators can require post-marketing studies, including for drugs that received accelerated approval and for pediatrics. Sometimes regulators ask for post-marketing studies because they want longer follow-up, information in certain groups of people who were under-represented in, or excluded from trials (the elderly, women, people from certain countries, ethnic/racial groups, people with other medical conditions or more advanced illness, or to explore different treatment strategies.

[47] Public investments in TB medicine bedaquiline far exceed those of developer Johnson & Johnson, TB Online http://tbonline.info/posts/2019/10/31/public-investments-tb-medicine-bedaquiline-far-exc/#

Pipeline

There is an active pipeline for TB treatment, which includes new, approved, and re-purposed drugs. Phase III trials are focused on regimens rather than single drugs, a paradigm that is most relevant for meeting the needs of people living with tuberculosis. These trials are looking at the least toxic and most effective and concise regimens for different forms of TB, combining new, existing and re-purposed drugs (the new drugs are mainly bedaquiline and pretomanid, with other compounds in earlier stages of development). The ability to access these new regimens may rest on one or two of the medicines in them , or there may be patents on the combination itself.

There has been long-term interest in sutezolid, a drug under development that is similar to linezolid but may be more effective and less toxic; its development has been delayed, and it is currently in Phase I. In January of 2017, the MPP announced that it had entered a voluntary licensing agreement with Johns Hopkins for sutezolid.

STEPS TO INCREASE ACCESS TO OPTIMAL TB DIAGNOSTICS AND TREATMENT

The TB diagnostic and treatment landscape is complex, and likely to remain so in the coming years. In addition to assessing the strength and status of patents, clinical, pragmatic and country-specific factors need to be considered. While WHO guidelines are internationally recognized, promising drugs or regimens may be in the pipeline. Consultations with people living with TB, doctors, researchers, and policymakers can shed light on which products are most important.

To ensure that the procurement process is truly competitive, and will lead to lower prices, it is important for generics producers to easily bring their medicines to a robust market once patents have expired or been removed by use of TRIPS flexibilities. Activists and their organizations have an important role to play by creating demand by:

1. Identifying the optimal treatment and diagnostic products and raising awareness about them among the community of people affected by TB, health professionals and government officials;
2. Empowering effective price negotiations by sharing information about production costs;
3. Helping governments to address patent monopolies for new TB medicines and combinations by requesting compulsory licenses or by filing patent oppositions;
4. Facilitating the marketing authorization process and faster inclusion of the most effective TB drugs in national treatment guidelines, national essential medicines lists, reimbursement lists, procurement nomenclature and/or terms of reference for procurement;
5. Monitoring the transparency, timeliness and efficiency of state procurement and supply chain management for TB diagnostics and medicines, and helping to coordinate stakeholder efforts to lower the risk of, or address stockouts of these products; and
6. Introducing legislative or normative proposals to remove unnecessary regulatory barriers and create mechanisms to improve access to optimal TB diagnostics and treatment.

WHAT ELSE MATTERS?

People living with DR-TB are likely to prefer shorter, less toxic, all oral regimens that do not require them to switch any of the other medications they rely on, such as HIV antiretrovirals.

Doctors may prefer to use familiar products, even if they are no longer recommended - or they may choose the newest medicines (especially if they work closely with representatives from pharmaceutical corporations). Also, some TB drugs may not be used as frequently, since they might only be necessary for certain forms of DR-TB. Prices for such drugs may remain high, since it will not be possible to achieve economies of scale. Policy makers may only be concerned with prices, without knowing which regimens are most effective against DR-TB.

ADVOCACY CONTEXT

Momentum has increased around the possibility of eliminating TB as a threat to global public health. In May of 2014, the World Health Assembly approved and gave full support to the WHO post-2015 Global TB Strategy, which aims to end the global TB epidemic.

Figure 2.
The WHO End TB Strategy

Indicators	Milestones		Targets	
	2020	2025	2030	2035
Reduction in the number of TB deaths (compared with 2015 baseline)	35%	75%	90%	95%
Reduction in the TB incidence rate (compared with 2015 baseline)	20%	50%	80%	90%
Percentage of TB-affected households experiencing catastrophic costs due to TB (2015 baseline is unknown)	0%	0%	0%	0%

Source: WHO Global TB Report, 2018. Available from: https://www.who.int/tb/publications/global_report/en/

RESOURCES

Getting information

Information about TB treatment is often presented at conferences and scientific meetings, in journal articles and conference reports. Reliable sources for TB information include:

Global TB CAB
HIV i-Base
Médecins Sans Frontières Access Campaign
Prescribing information (approved drugs only)
Treatment Action Group
WHO treatment guidelines

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