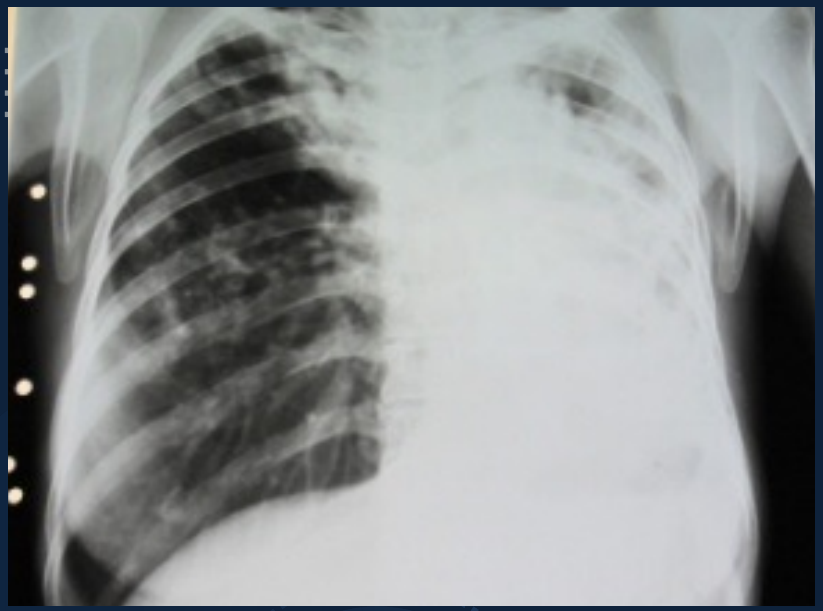
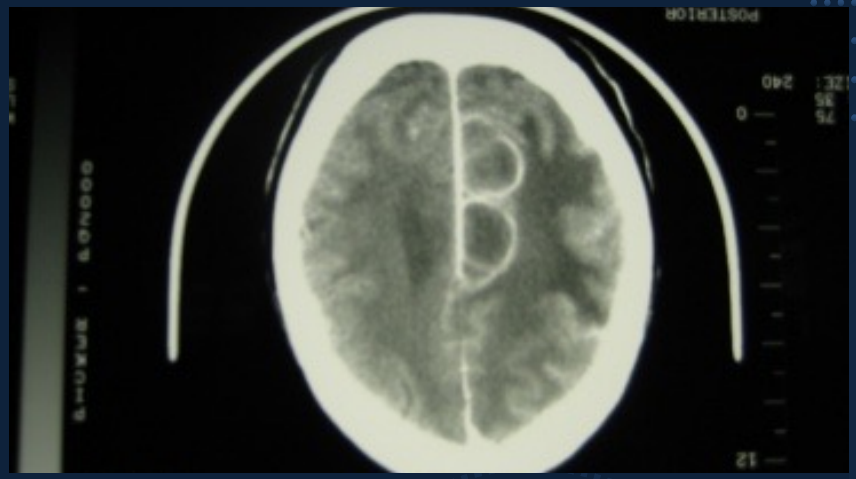




A few key issues in TB

HOPE Conference

January 24, 2023

Rocío Hurtado, MD, DTM & H

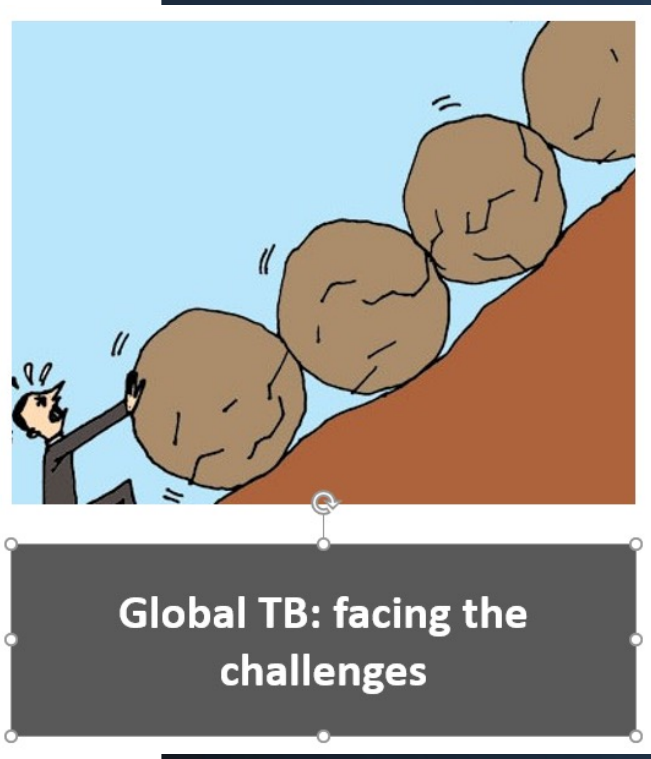
Director, MGH Mycobacterial Center
Infectious Disease Unit, Massachusetts General Hospital
Harvard Medical School
Harvard School of Public Health

Global Health Committee – Ethiopia & Cambodia

Outline

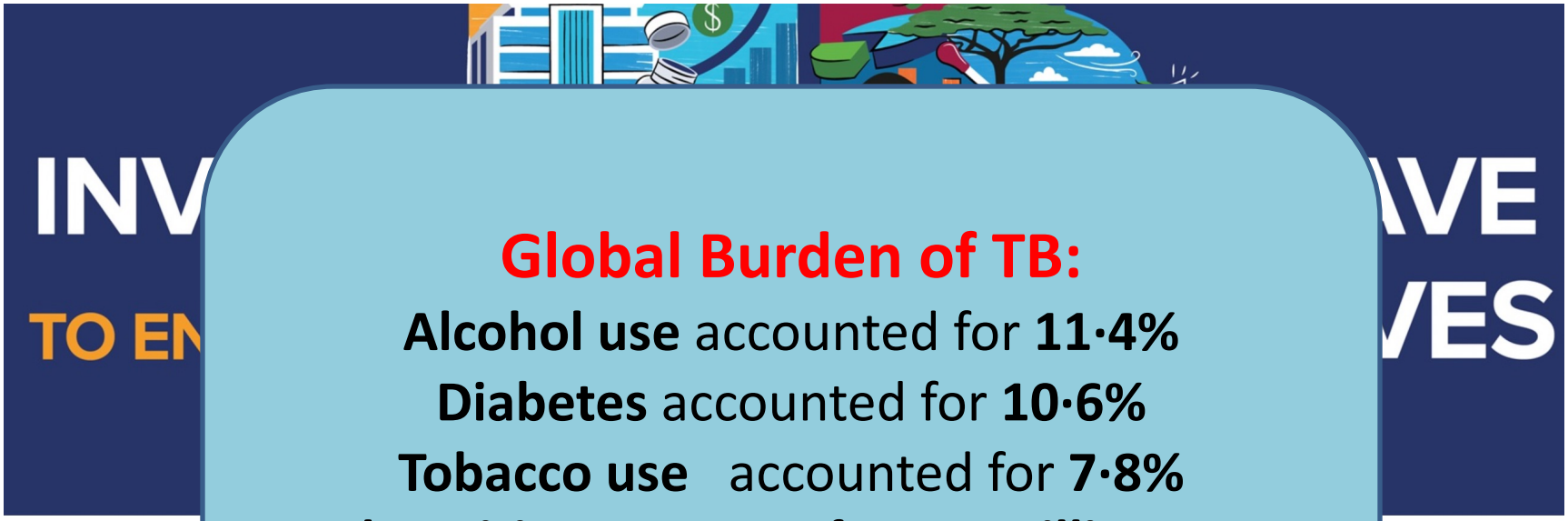
Spotlight on:

- **TB infection screening – antigen tests?**
- **New horizons in TB infection & TB disease treatment:** shorter regimens
- **Open Discussion**



I have no conflicts and no disclosures

TB IS the 2nd LEADING INFECTIOUS DISEASE KILLER IN THE WORLD TODAY



Global Burden of TB:

Alcohol use accounted for **11·4%**

Diabetes accounted for **10·6%**

Tobacco use accounted for **7·8%**

Malnutrition accounts for **2.3 million cases**

Lancet ID 2021: Lancet Infect Dis. 2018 Mar;18(3):261-284. doi: 10.1016/S1473-3099(17)30703-X. Epub 2017 Dec 7.

Global progress in the number of people treated lags behind

what is needed to reach the UN global targets, especially for drug-resistant TB

TB TREATMENT (ALL AGES)

Target:

40 MILLION
2018-2022

19.8 MILLION (50%)
TREATED IN 2018-2020

TB TREATMENT (CHILDREN)

Target:

3.5 MILLION
2018-2022

1.4 MILLION (41%)
TREATED IN 2018-2020

DRUG-RESISTANT TB TREATMENT (ALL AGES)

Target:

1.5 MILLION
2018-2022

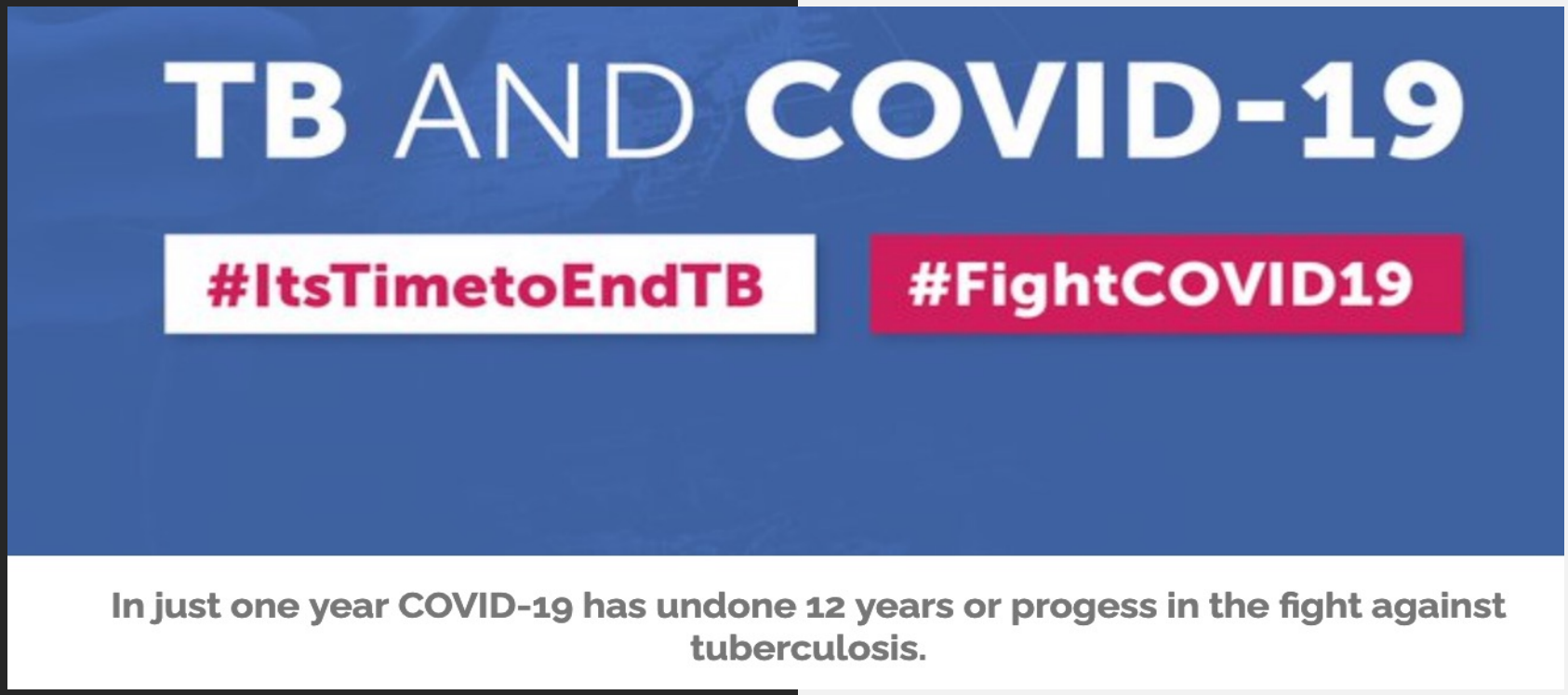
483,000 (32%)
TREATED IN 2018-2020

DRUG-RESISTANT TB TREATMENT IN CHILDREN

Target:

115,000
2018-2022

12,200 (11%)
TREATED IN 2018-2020

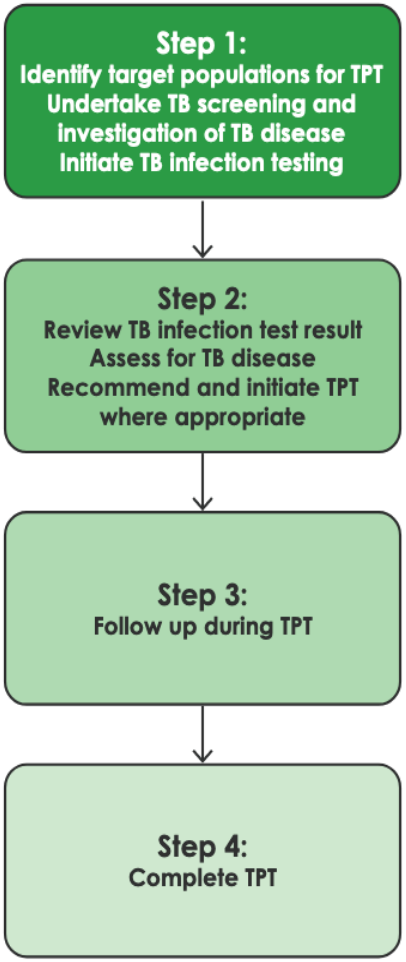


- **TB deaths** have risen for the 1st time in 1 decade
- **TB case detection** down by 18%
- **TB preventive therapy** down by 21%, MDRTB treatment access down by 15%
- **Co-epidemics** – 3-fold higher case fatality rates among TB patients
- The full downstream potential TB in the setting of immunomodulator use is not fully known
- **2% of what is invested in Covid-19 efforts is invested in TB**

Source:

WHO TB report 2022
http://www.stoptb.org/covid19.asp

Simplified TB Cascade of Care for TPT



All health care personnel, in all programmes and all settings, identify target populations for TPT and screen for TB, assessing TB symptoms and preferably using more accurate tools (e.g. CXR) to detect TB disease; those with a positive TB screen are promptly investigated for TB disease. At the same visit, qualified personnel administer skin tests (TST or TBST) or draw samples for IGRA to detect TB infection.

Trained health care personnel read and interpret the TB infection skin test result or obtain the IGRA result. If the test result is positive, they reconfirm that the earlier assessment satisfactorily excluded the likelihood of TB disease, then determine TPT eligibility through clinical evaluation, counsel the patient and initiate TPT, and complete the baseline recording during the same visit.

Trained health care personnel oversee provision of TPT for early identification, recording and reporting of adverse events and follow the patient through TPT completion
Adopting shorter and safer TPT will improve this step.

TPT completion will be facilitated by factors such as ongoing support during TPT and use of a shorter regimen. The final TPT outcome is recorded and reported.

- **TB preventative therapy for high risk groups**
- **cascade of care challenges**
- **70-80% drop off prior to TPT initiation**
- **Among those who receive TPT, only 20% complete rx**

TB infection Diagnosis: WHO September 2022

Target subgroups:

- **HIV co-infection** (regardless of immunosuppression, even if TB infection testing is not available i.e. IGRA or TST)
- **Children <5 years of age who are household contacts** of pts with confirmed TB
- **Children >5, adolescents and adults** who are household contacts of pts with confirmed TB
- Pts with upcoming biologics, end-stage renal disease, transplantation (solid and haematological) and silicosis
- Consider in healthcare works, migrants from high burden settings, prisoners, homeless individuals and people who use drugs.

Source: WHO operational handbook on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva, WHO, 9/2022

Alsdurf H, Hill P, Matteelli A, Getahun H, Menzies D. Lancet Infect

TB Infection Diagnosis – 3 major tools

- **Mantoux skin test, since 1908 (TST/PPD) -- average 37.84 USD**
  - Specificity: affected by BCG and Non-tuberculous mycobacterial (NTM) cross-reactivity
- **Interferon Gamma Release Assays (IGRAs) – average 89.33 USD**
  - more specific tests based on the early secretory antigenic 6 kDa (ESAT-6) protein and culture filtrate protein 10 (CFP-10)
  - blood-based, no return re-evaluation, require more infrastructure and are costly
- **TBSTs: intradermal skin tests: average 5-10 USD**
  - targeting ESAT-6 and CFP-10 proteins now commercially available. WHO now recommending these as an option for TB infection testing.

Impact of BCG & Non-tuberculous Mycobacteria (NTM)

- **If the patient was BCG-vaccinated in infancy**, the false positive TST% (FP-TST) attributed to BCG is:
  - 5-9 mm, then FP-TST_{BCG} = 3.6%
  - 10-14 mm, then FP-TST_{BCG} = 6.0%
  - 15+ mm, then FP-TST_{BCG} = 2.6%

- **If the patient was BCG-vaccinated at > 2 yr of age**, the false positive TST% attributed to BCG is:
  - 5-9 mm, then FP-TST_{BCG}= 25.8%
  - 10-14 mm, then FP-TST_{BCG} = 8.7%
  - 15+ mm, then FP-TST_{BCG} = 7.8%

- **NTM infection effect on TST**: 0.1-2.3%

Source: Farhat M et al. IJTLD 2006 (10): 1192-1204;
http://www.tstin3d.com/en/about.html#calcs

Resource: BCGatlas http://www.bcgatlas.org/

Pros & Cons of TB Testing Globally prior to TPT

- **Pros/Advantages**

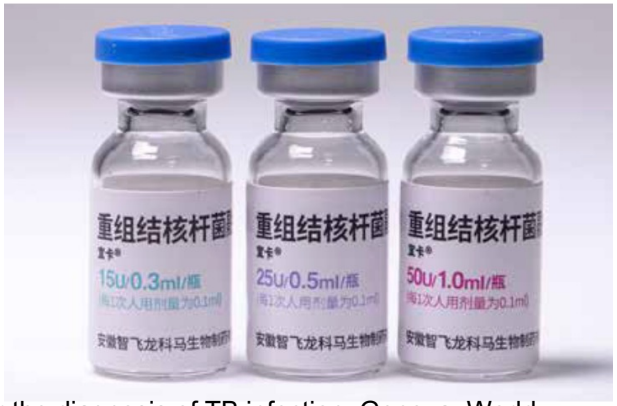
- Identifies most likely to benefit
- Increases TPT benefit/cost ratio
- Good data for testing and treating for several risk groups: TNF recipients, immunosuppressed (transplantation)

- **Cons/Disadvantages**

- Delay in initiation of TPT for very high risk groups
  - HIV, young children
- Cost/discomfort to pts
  - blood draws, return visits (if TST)
- False negatives, indeterminate tests

TBST (antigen skin tests)

- **Cy-TB** (Serum Institute of India)
- **Diaskintest** (Generium, Russian Federation)
- **C-TST** (Anhui Zhifei Longcom, China)



Targets are ESAT-6–CFP-10
Cutoffs >=5

Source: Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection. Geneva: World Health Organization; 2022 (WHO/UCN/TB/2022.1).WHO operational handbook on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva, WHO, 9/2022

MTb antigen-based skin tests (TBST):

- **Diagnostic accuracy:** confirmed for TB infection detection c/t IGRA and TST (16 studies, 3198 pts).
  - Pooled sensitivity 76% in HIV neg and 64% in HIV + and specificity 98%. Difference in specificity was driven among BCG vaccinated
  - When combining all TBST, the pooled agreement with IGRA was 89% (95%CI: 83–93%, 8 studies) in people without TB and 86% (95%CI: 80–90%, 8 studies) in people with TB. The agreement with TST was 59% (95%CI: 45–72%, 16 studies) in people without TB and 88% (95%CI: 82–93%, 13 studies) in people with TB.
- **TBST safety profile similar to TST** (6 studies, 2931 pts).
  - injection site reaction c/t TST 1.05 ((CI 0.7-1.58)
- **TBST found to be cost-effective c/t IGRA and TSTs** (8 studies using Diaskintest used as a representative of the class).
- **TBST acceptable and feasible**
  - similar to TST, yet have the same limitations (need for staff, return visits, etc.).
- **Overall:** appear as sensitive as TST and IGRA yet more specific (similar to IGRA esp if prior BCG).
- **Limitations:** prediction of progression to active disease nor efficacy of TPT could not be evaluated.

Source: Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection. Geneva: World Health Organization; 2022 (WHO/UCN/TB/2022.1).WHO operational handbook on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection. Geneva, WHO, 9/2022; L Gosce, et al. WHO 2022: https://www.ncbi.nlm.nih.gov/books/NBK586679/. Stephen RE, et al. Scientific Reports 2020.

Excluding Active TB disease, some data

PLHIV aged 10 years and older,

- the absence of current cough, fever, weight loss or night sweats:
  - sensitivity of 79%
  - negative predictive value of 97%.. Consider CXR if on ART.

• Infants and children living with HIV,

- the absence of poor weight gain, fever or current cough or a history of contact with a TB patient:
  - sensitivity of 90%
  - negative predictive value of 99%.

• HIV-negative household contacts aged 5 and above and other clinical risk groups:

- the absence of cough of any duration, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath or fatigue had a sensitivity of 73% and a negative predictive value of 99%.

Source: https://tbksp.org/en/node/632; Martinez L, et al... Lancet. 2020;395:973–84. doi:10.1016/ s0140–6736(20)30166–5 Sanchez A, Massari V, Gerhardt G, Espinola AB, Siriwardana M, Camacho LA, et al. X ray screening at entry and systematic screening for the control of tuberculosis in a highly endemic prison. BMC Public Health. 2013;13:983. doi:10.1186/1471–2458–13–983..

The policy to implementation gap

- Priorities: where does the fit in the global scale
- Data gaps
- Implementation gap
  - TBSTs face similar hurdles c/t TST
- Impact of Covid-19 on TB screening services?
  - human resources
  - infrastructure
- Political will
- Discussion

New TB infection and TB treatment Regimens:

the era of shorter regimens?

2022 Global New TB Drug Pipeline[1] Updated 11/3/2022

Discovery | **Preclinical Development** | **Clinical Development**

Lead Optimization → **Early Stage Development** → **GMP / GLP Tox.** → **Phase 1** → **Phase 2** → **Phase 3** → **Regulatory Market Approvals**

Indazole sulfonamides
Diarylthiazoles
DprE1 Inhibitors
Direct InhA Inhibitors
Mtb energy metabolism
Gyrase Inhibitors
Arylsulfonamides
Inhibitors of MmpL3, Translocase-1, ClpC1, PKS13, F-ATP synthase
Oxazolidinones
DnaE1 / Nargenicin analogs

TBD-09, TBD-10 (MK-7762, -3854)
MPL-447*
JSF-3285*
CPZEN-45*
NTB-3119*
MBX-4888A (1810)*
FNDR-10045*, FNDR-20364*

GSK-839*
OTB-658

BVL-GSK098*
GSK-286*
TBAJ-876
TBAJ-587
TBI-223
Macozinone* (PBTZ-169)

Sanfetrinem
Delpazolid
Sutezolid
Sudapyridine (WX-081)
BTZ-043*
TBA-7371*
OPC-167832*
GSK-656* (070)
Telacebec*
Pyrifazimine (TBI-166)
SPR720*
SQ-109*

Results Reported / Expected in 2022/23

TB Practecal
ZeNix
Bedaquiline*
Simplici TB
Delamanid*
(4-month regimen)
Pretomanid*
Truncate TB
(2-month regimens)
STREAM 2

Underline = updates since May 2022

*New chemical class. Known chemical classes for any indication are color coded: rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide, beta-lactam.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound identified: http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: November 2022

TB Alliance, TB Portfolio

PHASE 1

TBAJ-587

TBAJ-587 / Diarylquinoline

TBAJ-876

TBAJ-876

TBI-223

TBI-223 / Oxazolidinone

PHASE 2

BPaMZ/SEM

Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)

Sutezolid

Sutezolid / Oxazolidinone

TBA-7371

TBA-7371 / DprE1 Inhibitor

PHASE 3

SimpliciTB

Bedaquiline / Pretomanid / Moxifloxacin / Pyrazinamide (BPaMZ)

ZeNix

Bedaquiline / Pretomanid / Linezolid (BPaL)

PHASE 4

Pediatric Formulation Development

Pretomanid

Optimized First-Line Drugs in Children >5kg

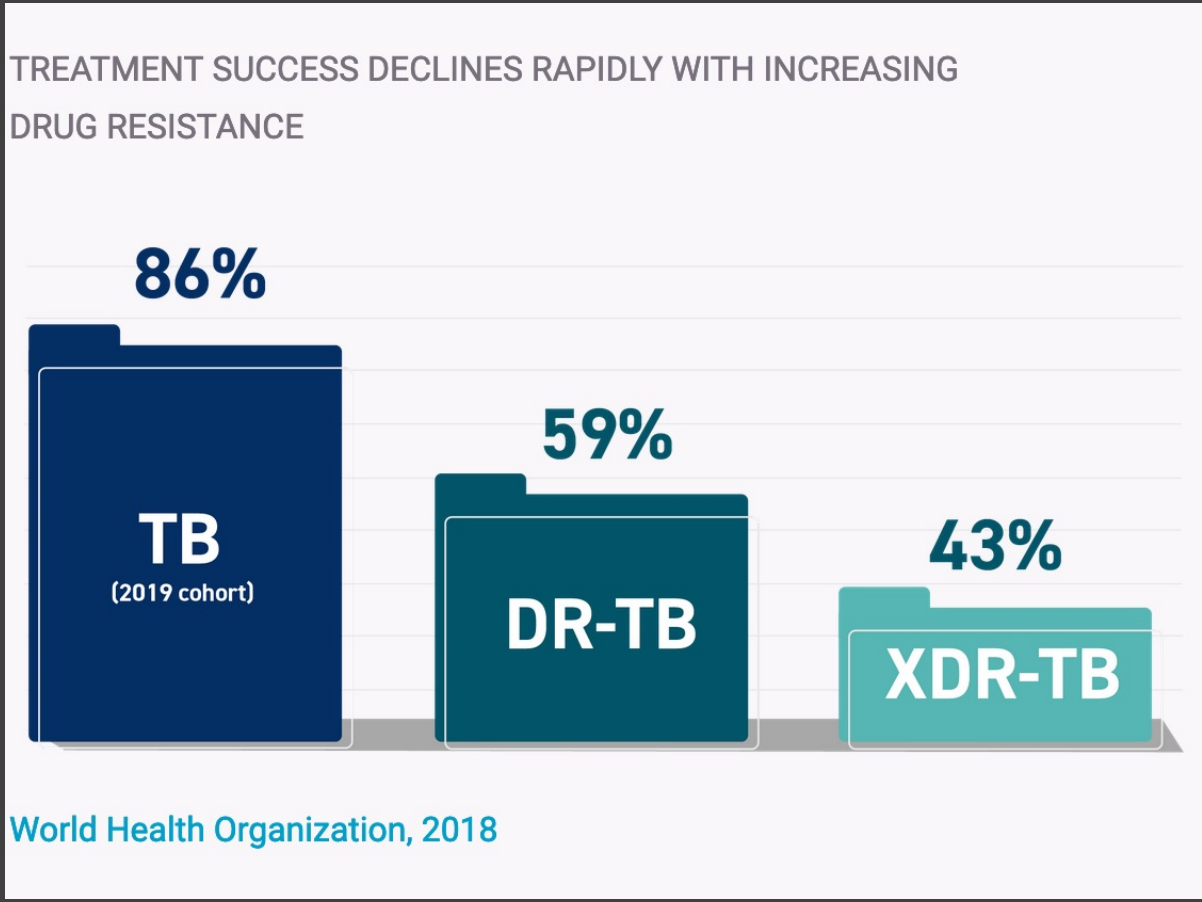
Ethambutol

Pyrazinamide

Isoniazid

https://www.tballiance.org/portfolio

The old mantra:
treat longer if less effective regimens & accept poorer outcomes



MDRTB in the pre-short course era:

The NEW ENGLAND JOURNAL of MEDICINE

Treatment of Highly Drug-Resistant Pulmonary TB

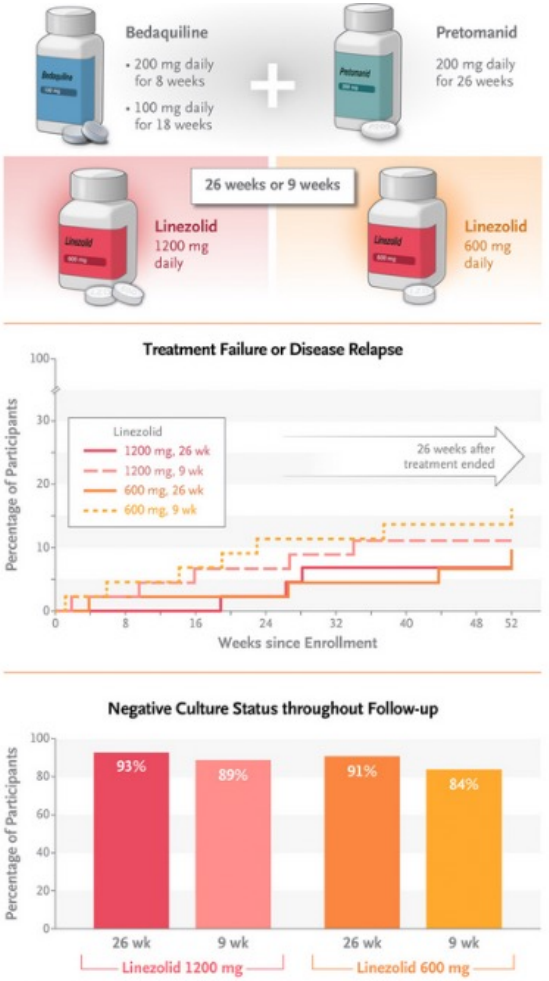
- Nix-TB was not a controlled study
- Recent cohort-comparison study (South Africa, 2021) with prospective f/u comparing patients with XDR-TB and treatment intolerant MDR-TB who received the 6- to 9-month BPaL regimen to patients with XDR-TB who received an 18+ mo. 8-drug (median) bedaquiline and linezolid containing regimen.
- BPaL regimen (6 months) had a more favorable outcome (1.35; P , 0.001) than the 18+ month regimen
- Pretomanid likely accounts for a significant proportion of this difference, though Linezolid doses were higher in BPaL regimen (BID)
  - INT J TUBERC LUNG DIS 2021: 25(6):453–460

Source: F. Conradie et al NEJM 2020

A new era in MDRTB/XDRTB treatment

- **ZeNiX:** BPaL (bedaquiline, pretomanid, linezolid) and **TB Practecal** + Moxi) regimens with successful outcomes in majority of pts (90%+) – 6-9 months
- **In contrast to NTM rx outcomes:**
  - **MAC**: 50-70% culture conversion with 48% microbiologic recurrence
  - **M. abscessus:** <20% culture conversion

ZeNix TB Trial NEJM 2022, 26 weeks: BPaL regimen



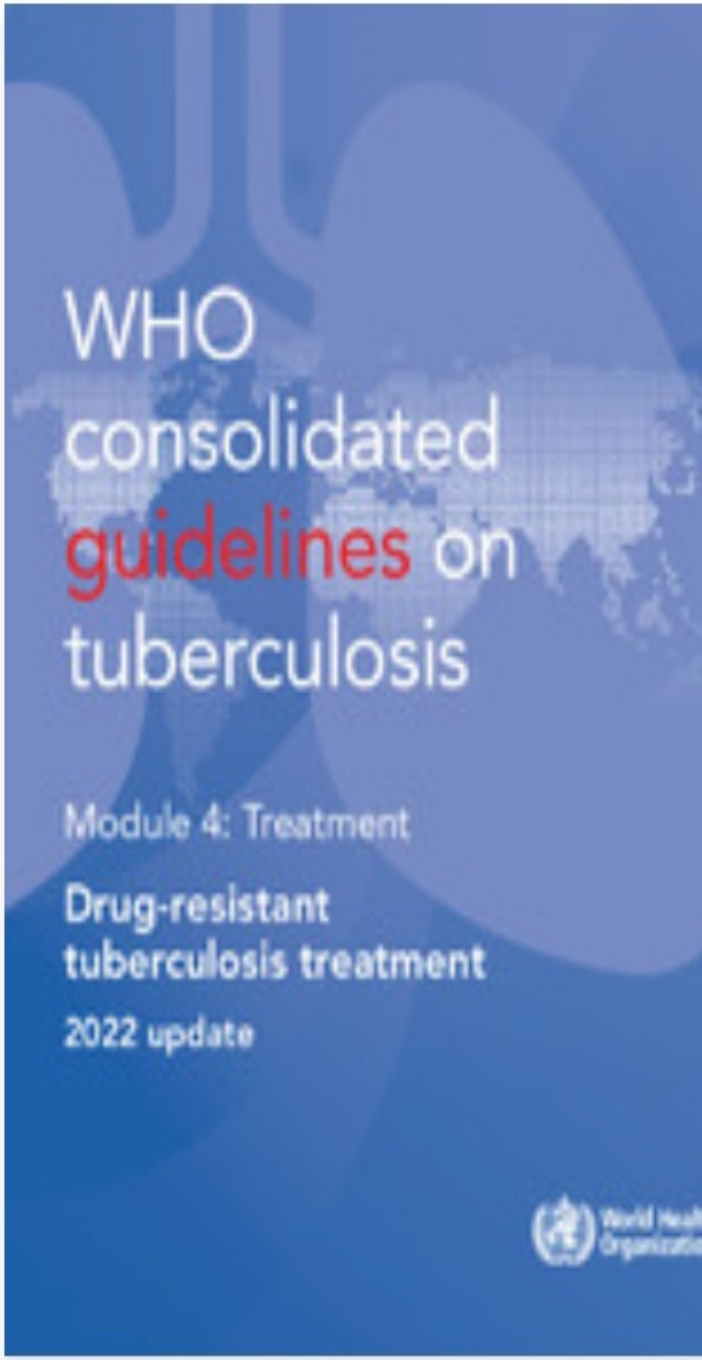
Conradie F et al. N Engl J Med 2022; 387:810-823; N Engl J Med 2019; 380:1201-1213; Meressa D, Hurtado R, Andrews J....Goldfeld AE. Thorax 2015
ps://apps.who.int/iris/bitstream/handle/10665/353743/WHO-UCN-TB-2022.2-eng.pdf?sequence=1

New DR-TB Treatment Guidelines, WHO 2022

Source WHO DRTB Treatment, 2022
https://apps.who.int/iris/rest/bitstreams/1485675/retrieve

Table A. List of recommendations in the 2022 update, where (a) is a new recommendation based on review of the new evidence and (b) is a reprinted recommendation where no new evidence was available or searched for the review.

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*
3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*



What about shorter regimens for TB infection or DS-TB?

- **TB Infection: LTBI**
  - Shorter course regimens
  - 3-HP (12 weeks of weekly Isoniazid + rifapentine)
  - 1-HP (1 month of Isoniazid + Rifapentine)

- **DS-TB Treatment:**
  - Moxi-rifapentine based regimens
  - Other combinations on the horizon?

TPT (Latent TB Treatment): WHO, 2020 update

	6H	3HP	3HR	4R	1HP	H + B6 + CPT (Q-TIB)
Medicines	Isoniazid	Isoniazid + rifapentine	Isoniazid + rifampicin	Rifampicin	Isoniazid + rifapentine	Isoniazid + pyridoxine + cotrimoxazole (only for those living with HIV)
Duration (months)	6	3	3	4	1	6
Interval	Daily	Weekly	Daily	Daily	Daily	Daily
Doses	182	12	84	120	28	182
Pill burden per dose (total number of pills for average adult)[a]	1 (182)	9 singles (108) 3 with FDC (36)	3 (252)	2 (240)	5 (140)	1 (182)
Cost for a full treatment (unless otherwise specified)[5] ***(51)***	US$ 3.50	Rifapentine US$ 17 for singles US$ 15 for FDC Isoniazid US$ 1–2 3HP FDC US$ 15 (expected to become available in mid-2020)	US$ 10.60 (for 12–15 kg child)	US$ 24	Rifapentine and isoniazid US$ 27 for singles US$ 26 for FDC + rifapentine single	US$ 12
Children	All ages; child-friendly (dispersible) formulation available; preferred in HIV+ children on LPV-RTV, NVP, or DTG	≥ 2 years; no child-friendly formulation available	All ages; child-friendly (dispersible) formulation available and recommended up to 25 kg weight	All ages; no child-friendly formulation available, no formulation available for infants < 8 kg weight	> 12 years; no rifapentine dosing available until 13 years of age	All ages; need to split scored adult tablet, lower dose pills suitable for children not available)

WHO Operational Handbook, module 1. TB prevention. 2020.

BRIEF-TB Trial: INH + rifapentine daily x 1 month non inferior to 9 months of INH

Phase III trial in HIV + pts, 3000 pts recruited (10 countries) randomized to 9 months of INH vs 1 month of daily INH + rifapentine.

- Median CD4 470 and 50% on ART; 21% has + TST or IGRA
- **1 month of daily INH + rifapentine was non-inferior to 9 months of INH (in pts with CD4 >250)**, had fewer adverse events and had higher completion rates
  - Rifamycin resistance (1) in each arm 1 case of INH-R in the INH arm. (S Swindells et al. NEJM 2019)
- **2021 Study** using this regimen with Bictegravir-based ART:
  - Significant decreased concentrations of Bictegravir during therapy
    - J Int AIDS Soc . 2021 Nov;24(11):e25844. doi: 10.1002/jia2.25844.
- **This regimen is not yet endorsed by the CDC as an LTBI treatment regimen**.
- **Children & Adolescents in Pakistan**: Prospective Cohort of 678 contacts ages 2-19 --of active PTB – 94% completion rate, 1 case of TB. Safety/feasibility study.
  - Lancet Child Adolesc Health 2021 May;5(5):350-356

TB treatment: 1st shorter TB regimen in > 40 years?

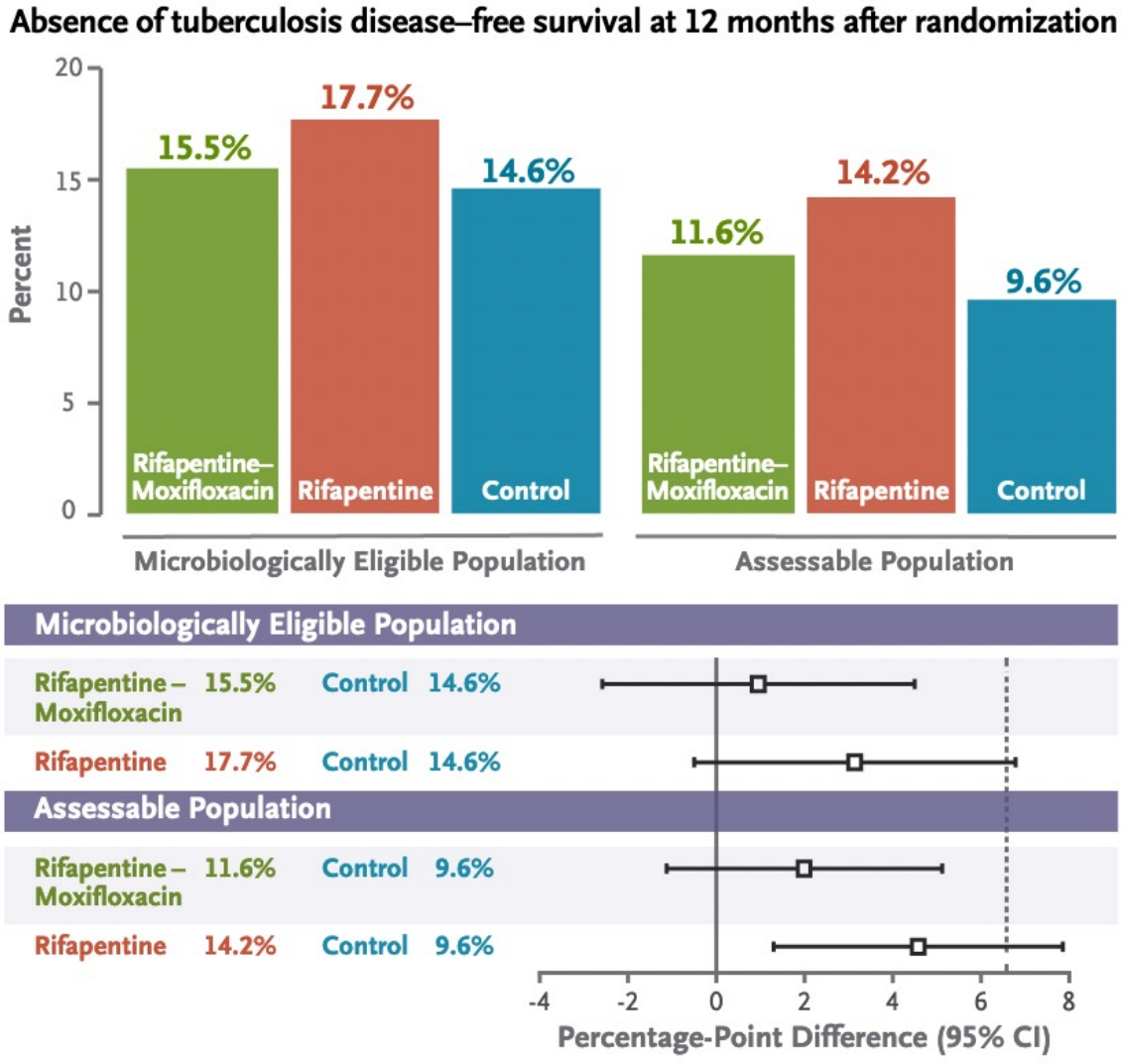
- Prior quinolone trials failed to show non-inferiority to short course chemotherapy (SCC)
- **TBTC31/A5349** -- "*Rifapentine (RFP)-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial*"
- ***2517 participants:***
  - ***34 sites**, 13 countries (29% women, 8% HIV+, included ages 12+, median age 31) **randomized 1:1:1***
  - *Standard SCC ("RIPE")*
  - *17 wks **RFP + moxi**+INH+PZA*
  - *Vs 17 wks of **RFP**+INH+PZA+ EMB*

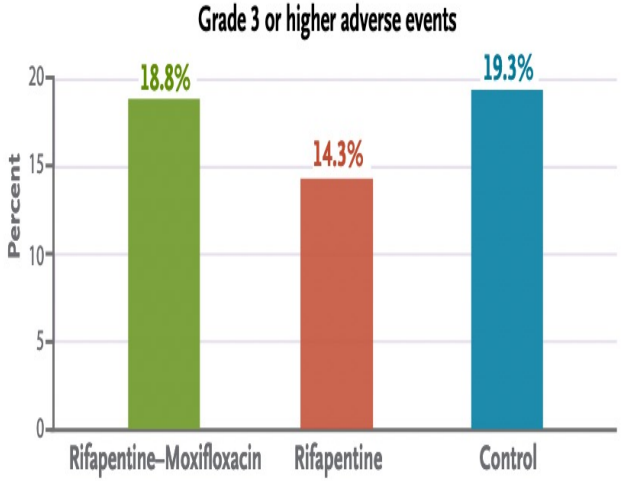
Source: S. Dorman et al. NEJM 2021

Rifapentine + Moxiflox based regimens: 4 months

- **Primary endpoint:** TB disease-free survival at 12 months
- **Primary safety endpoint:** proportion of participants with grade 3 or higher AE during study drug rx
- **Rifapentine + moxi group was found to be non-inferior to control group**, yet not the rifapentine-alone group
- **Investigational regimens were slightly better tolerated than the control regimen**, 92.1%, 95.3%, and 93.2% in the control, rifapentine-only, and rifapentine-moxifloxacin groups, respectively, completed study treatment.
- **All-cause mortality during treatment and follow-up was similar across the arms**, 1.3%, 1.4%, and 1.5% in the control, rifapentine- only, and rifapentine-moxifloxacin groups, respectively.

Source: Dorman S, et al. NEJM 2021





Dorman S. et al. NEJM 2021

A 4-MONTH REGIMEN CONTAINING RFP+MOXI WAS NON INFERIOR IN EFFICACY AND SIMILAR IN SAFETY AND PREMATURE DISCONTINUATION COMPARED TO STANDARD SHORT-COURSE TB THERAPY.

WHO 2022: 4 month regimen

Treatment of DS-TB using 4-month regimens

6. **Patients aged 12 years or older with pulmonary DS-TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM).**
   (Conditional recommendation, moderate certainty of evidence) – **new recommendation**
7. **In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of multidrug- or rifampicin-resistant TB [MDR/RR-TB]), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.**
   (Strong recommendation, moderate certainty of evidence) – **new recommendation**

ELIGIBILITY: Adults and children aged 12 years or older with a body weight of more than 40 kg and affected by
pulmonary DS-TB are eligible for this regimen, including those who are also HIV-positive with a CD4 count of more than 100 cells/mm3 and patients with diabetes.

The following **EXCLUSIONS:**

- patients weighing less than 40 kg;
- patients with severe extrapulmonary TB (e.g. tuberculous meningitis, disseminated TB, osteoarticular
  TB or abdominal TB);
- PLHIV with a CD4 count of less than 100 cells/mm3;
- children and adolescents aged under 12 years; and
- pregnant, breastfeeding and postpartum women.

Source: WHO operational handbook on tuberculosis Module 4: Treatment – drug-susceptible tuberculosis treatment. Geneva:
World Health Organization; 2022.

What about other trials in DS-TB?

- **The Holy Grail:** ultra-short, safe, rifamycin-free regimen for DS-TB
  - would improve completion rates
  - minimize drug drug interactions
- S31/A5349 (and TRUNCATE-TB) demonstrated potential for treatment shortening in DS-TB
- Most planned or ongoing TB trials still include rifamycins for at least 3 months.

Ongoing/Planned Phase 2b/2C/3 trials

All except SimpliciTB contain a rifamycin
All except TRUNCATE-TB are > 8 weeks
None are testing BCZD

Trial Name	Sponsor	Drug/Regimen	Duration	Comparator	Phase	N	Site
APT Study NCT02256696	Johns Hopkins University	Pa, H, RIF, Z Pa, H, RBT, Z	3 months	HRZE	2b	91/183	South Africa
TRUNCATE-TB NCT03474198	University of London	RPT, H, Z, LFX, LZD H, Z, E, BDQ, LZD	2 months	HRZE	2 /3	400/900	4 countries
SimpliciTB (NC-008) NCT03338621	TB Alliance	BDQ, Pa, MFX, PZA	4 months	HRZE	2c	455	10 countries
CLO-FAST (A5362) NCT04311502	ACTG/ NIAID	RPT, CFZ, PZA, INH, EMB	3 months	HRZE	2c	185	Multi-country
RIFASHORT NCT02581527	University of London	RIF 1200/1800, INH, PZA, EMB	4 months	HRZE	3	625/654	6 countries
Trial 323-201-00006 NCT05221502	Otsuka, Gates	BDQ, DLM, OPC-167832 (10, 30 or 90mg)	4 months	HRZE	2b/c	120	South Africa (8 sites)

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

TB Trials: shortened rx for DSTB (plus 7 others)

Study Name	Experimental Arms [Control]	For Treatment of	Number of Participants	Phase	Status [Est. Completion Date]
Active; Drug-Sensitive TB					
SimpliciTB NCT03338621	4BPaMZ [2HRZE/4HR] 6BPaMZ [none] *B_{200} daily for first 8 weeks then B_{100} daily	DS-TB MDR-TB	455	IIc	Fully enrolled [Feb 2022]
TRUNCATE-TB NCT03474198	$2HR_{Hd}ZELz_{600}$ $2HR_{Hd}ZEC$ $2HP_{1200}ZLz_{600}Lx$ $2HZELz_{600}B$ [2HRZE/4HR]	DS-TB	900	II/III	Fully enrolled [Mar 2022]
RIFASHORT NCT02581527	$2HR_{1200}ZE/2HR_{1200}$ $2HR_{1800}ZE/2HR_{1800}$ [2HRZE/4HR]	DS-TB	654	III	Fully enrolled [Apr 2022]
APT NCT02256696	2PaRbHZ/1PaRbH 2PaRHZ/1PaRH [2HRZE/1HR]	DS-TB	150	IIb	Fully enrolled [Apr 2022] *Preliminary results at Union 2021[21]
A5362 / CLO-FAST NCT04311502	2CHPZE/1CHPZ [2HRZE/4HR] *C_{300} daily for first 2 weeks then C_{100} daily	DS-TB	185	IIc	Recruiting [Nov 2022]
SUDOCU NCT03959566	$3BDMStz_{600}/3HR$ $3BDMStz_{1200}/3HR$ $3BDMStz_{600\ BID}/3HR$ $3BDMStz_{800\ BID}/3HR$ [3BDM//3HR]	DS-TB	75	IIb	Recruiting [May 2022]
DECODE NCT04550832	$4BDMDzd_{400}$ $4BDMDzd_{800}$ $4BDMDzd_{1200}$	DS-TB	75	IIb	Recruiting [Jan 2023]

Source: Treatment Action Group https://www.treatmentactiongroup.org/wp-content/uploads/2021/11/pipeline_TB_Treatment_2021_final.pdf

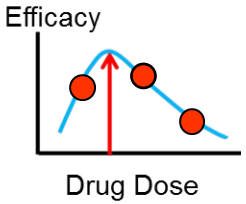
PRESCIENT*: A Phase IIc, Open-Label, Randomized Controlled Trial of Ultra-Short Course BDQ, CFZ, PZA and DLM versus Standard Therapy for DS-TB

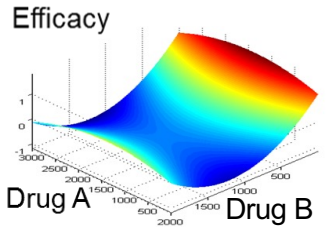
*Parabolic Response Surface Derived Regimen for Treatment Shortening in TB

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Pre-Clinical and Clinical Evidence

- Regimen was selected using parabolic response surface (PRS) platform approach, which identifies optimal drug combinations at optimal doses





- PRS Regimen V (CFZ, BDQ, PZA, DLM) in mice rapidly sterilizes the lung and achieves relapse-free cure in 3 weeks vs. 20 weeks for the standard regimen (RZHE)
- Extrapolated to Humans: Cure in ~5 weeks
- Individual drugs in the regimen have demonstrated bactericidal activity alone and in combination, both in pre-clinical and human studies.

Clemens et al. PLoS One 2019

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Clinical safety

- All drugs in the experimental regimen are widely used in DR-TB treatment, often in combination
- Hepatotoxicity uncommon with BDQ and DLM in clinical trials and programmatic settings
  - endTB observational study (n = 2300): ≥ Grade 3 hepatitis in 5.5%
- CFZ, BDQ and DLM prolong the QTc interval
  - A5343 trial: no ≥ Grade 3 events with BDQ/DLM
  - endTB observational study (n = 2296): only 2.7% experienced any QTcF ≥500 ms or ΔQTcF >60 ms with serious arrythmia
- CFZ tolerability
  - Meta-analysis of MDR-TB cohort studies (n = 602) treated with CFZ adverse drug reactions requiring discontinuation of CFZ in 0.1%

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Study Rationale / Hypothesis

Rationale

- Proof of concept for PRS approach for regimen design
- If the BCZD regimen is found be effective in this phase 2c study, it will pave the way for a future phase 3 study

Hypothesis

An 8-week regimen of BDQ-CFZ-PZA-DLM (BCZD) will demonstrate superior microbiologic efficacy (time to liquid culture conversion during the first 8 weeks of treatment) relative to standard of care (6 months of RHZE)

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Eligibility criteria

Inclusion criteria

- Smear positive, pulmonary TB
- At least 18 years of age
- No RIF/INH resistance
- PLWH: CD4 ≥200 and on ART or planning ART by week 8
- Lab values at screening
  - ALT ≤3 times the upper limit of normal (ULN)
  - Total bilirubin ≤2.5 times ULN
  - CrCl ≤2 times ULN
  - Potassium ≥3.5 mEq/L and ≤5.5 mEq/L
  - Hemoglobin ≥7.0 g/dL; ANC ≥650/mm^3; Platelet count ≥50,000/mm^3

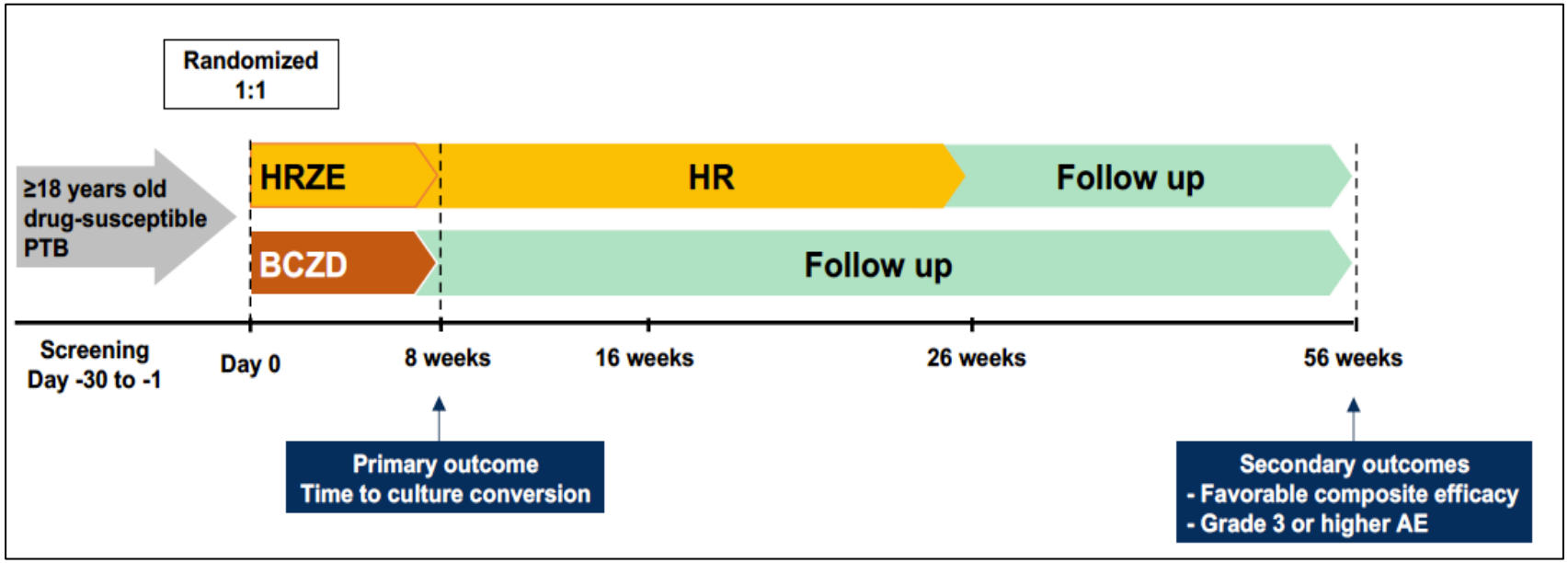
Exclusion criteria

- More than 3 days of treatment for current TB episode
- Extrapulmonary TB
- Pregnant or breast-feeding
- Weight <30 kg
- Use of drug known to severely prolong the QTc interval
- Use of NNRTI/PIs
- QTcF interval >450 ms for men or >470 ms for women

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Study Design

Phase IIc, open-label, multi-center RCT
1:1 randomization stratified by presence of lung cavitation and HIV status



Participants with evidence of poor clinical response, positive AFB smear, or positive MTb cultures at week 8 or later will be referred for standard therapy
Adherence will be monitored with DOT/EAMD

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Outcome evaluations

Primary outcome

- Time to stable liquid culture conversion through 8 weeks of follow-up
- HR of culture conversion through 8 weeks of follow-up estimated by a Cox-proportional hazards model

Key secondary outcome (safety)

- Occurrence of Grade 3 or higher adverse event through 56 weeks

Key secondary outcome (clinical outcome)

- Difference in cumulative probability of having a favorable outcome at 56 weeks after TB therapy initiation

Slides courtesy of Dr. Serena Koenig (BWH & GHESKIO)

Shorter TB Regimens

- **Additional areas of study:**
  - special populations
  - EPTB
  - exclusion of quinolone resistance?
  - monitoring strategies in RLS
  - implementation in the field
  - longer term f/u
  - and more

Open Discussion