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CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

STATE-OF-THE-ART

TB regimens for Treatment & Prevention

Annual Workshop on Advanced Clinical Care-AIDS (AWACC)
19 October 2023

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UNAIDS
CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy
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Overview of Presentation

- **Rationale for new TB treatment and prevention strategies**
- **Drug development pipeline**
- **Clinical trial pipeline of new TB regimens**
  - Results from phase II and III Clinical trials for TB
  - New Regimen for treatment of DS-TB vs DR-TB vs EPTB
  - New Regimen(s) for TB Prevention
- **Summary and conclusions**

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TB remains the top infectious killer worldwide

GLOBAL TB REPORT 2022

THE COVID-19 PANDEMIC HAS REVERSED YEARS OF PROGRESS MADE IN THE FIGHT TO END TB

For the first time in over a decade→ TB deaths have increased

1.6 MILLION TB DEATHS
INCLUDING 187 000 TB DEATHS AMONG PEOPLE WITH HIV

TB is the top infectious killer worldwide
TB is also the leading cause of death among people with HIV and a major cause of antimicrobial resistance related deaths

DR-TB remains a public health crisis with gaps in detection and treatment
Only 1 in 3 needing treatment were enrolled on it

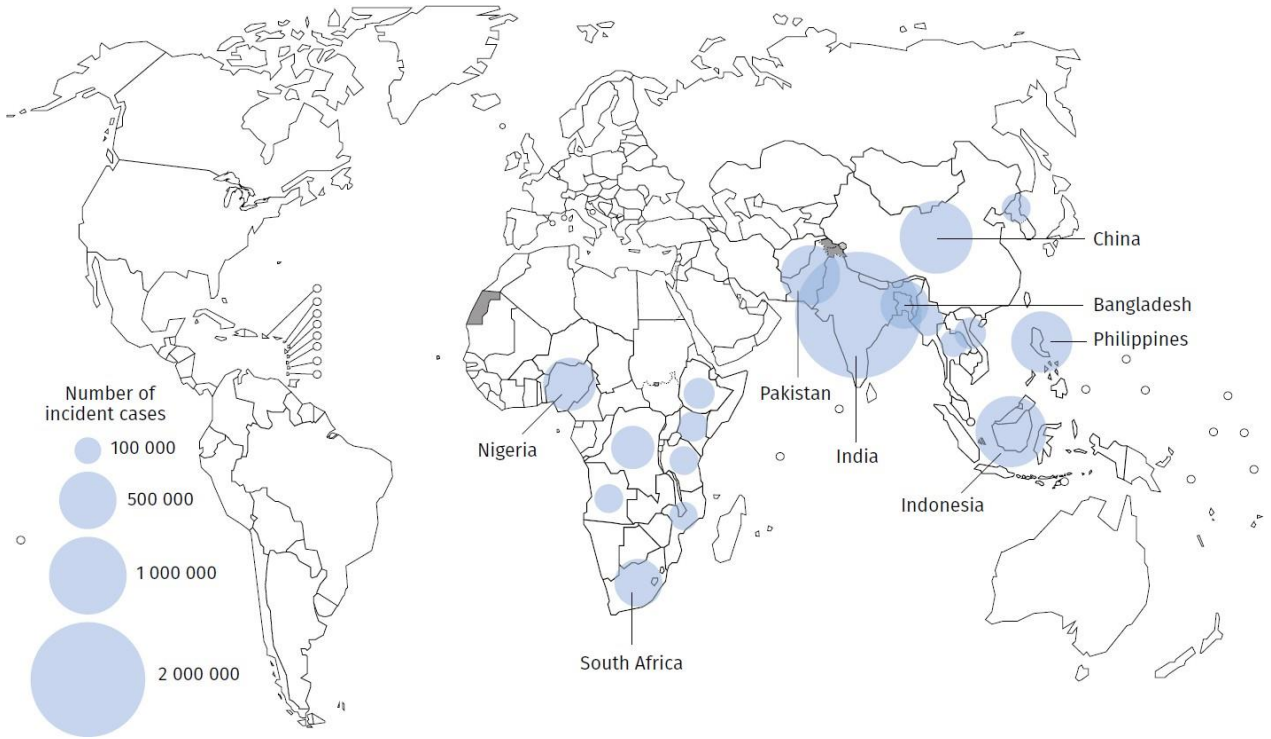
More than 66 million lives saved since 2000

Colliding epidemics of TB & COVID-19

- Global reduction in finding, treating and preventing TB→ 4.5% increase in TB incidence
- 5.8% increase in TB mortality→ **100 000 additional TB deaths in 2021 alone**

Source: Global TB Report 2022

Eight countries account for 66% of the global TB burden



HIV Rank	Prop of Global TB Burden	Country
2nd	26%	India
4th	8.5%	China
5th	8.4%	Indonesia
7th	6%	Philippines
6th	5.8%	Pakistan
3rd	4.6%	Nigeria
8th	3.6%	Bangladesh
1st	3.3%	South Africa

- 6.7% of all incident cases of TB occurred in PLWHA
- Co-infection highest in SSA, exceeding 50%
- 59% HIV co-infection rate among notified TB cases in SA

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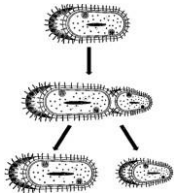
New TB drugs and drug classes

 Impacts Bacterial Replication	 Longer half life for treatment shortening	 Prevents emergence of drug resistance	 Overcome pre-existing drug resistance
 Fewer side effects	 More patient satisfaction	 Simple supply management	 Reduced transmission
 Lower cost	 More lives Saved	 Better outcomes	 Reduced health system burden

- Six new drugs advanced to next phase development
- Treatment simplification for improved adherence→ fewer less-severe side effects → improved quality of life
- However, threat of acquired resistance to new agents persists!!!

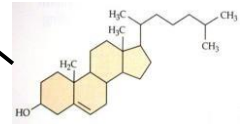
TB Drug Development Pipeline

- Phase 3 → Post market use
- Phase 2
- Phase 1
- GMP/GLP toxicology
- Early development

Nitroimidazoles
Inhibit cell wall synthesis & cell respiration
- Pretomanid*
- Delamanid*

Riminophenazine
Disrupts plasma membrane and involved in intracellular acidification
- Pyrifazimine (like clofazimine)

Cholesterol catabolism Inhibitor (BETA LACTAMS):
Inhibits cholesterol catabolism
- GSK2556286*
- Sanfetrinem

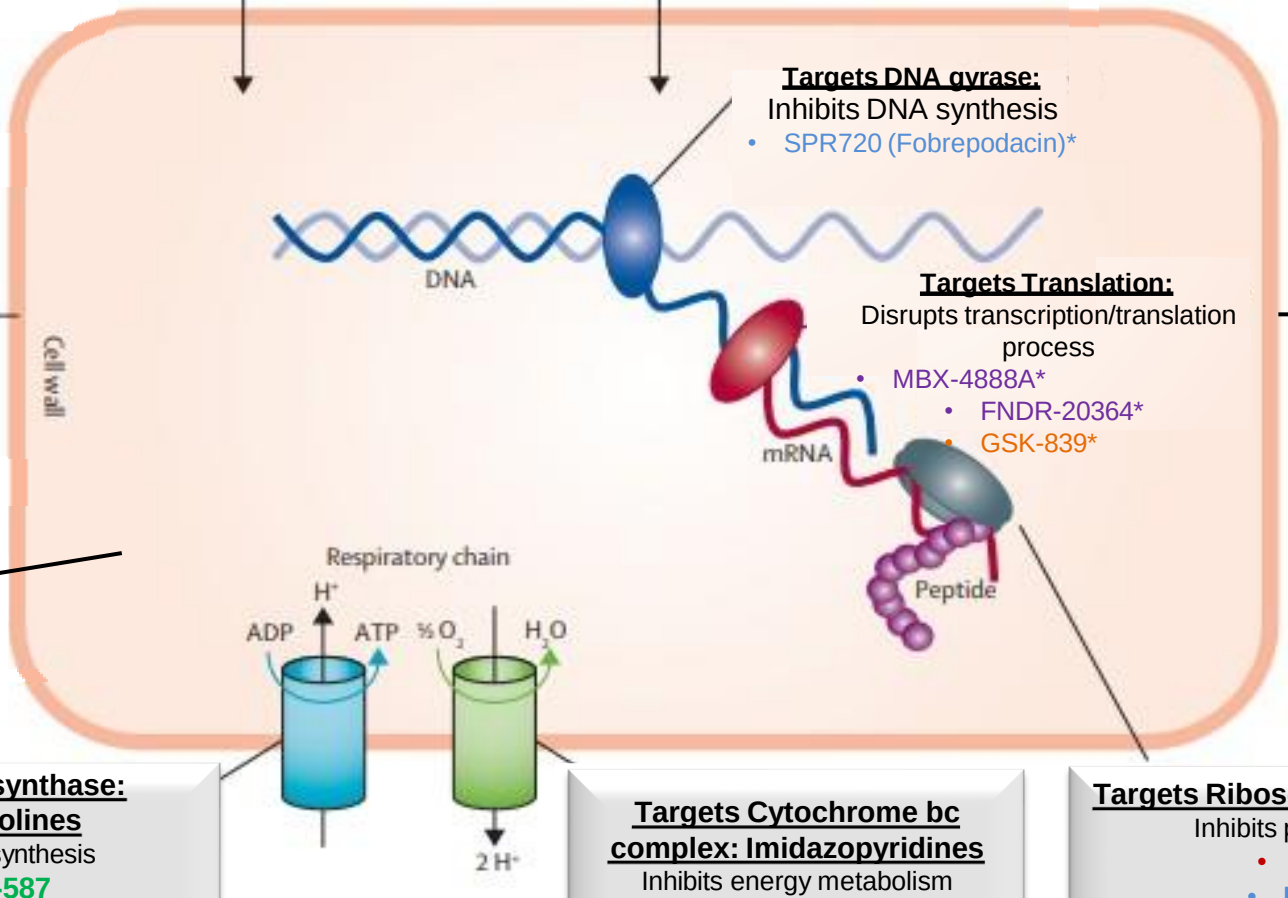


InhA: isoniazid
Inhibit cell wall synthesis

Targets Cell wall: DprE1 Inhibitors: Inhibits cell wall synthesis
- BTZ-043*
- PBTZ-169 (macozinone)*
- OPC-167832*
- TBA-7371*

Targets DNA gyrase:
Inhibits DNA synthesis
- SPR720 (Fobrepodacin)*

Multiple Targets:
Inhibits cell wall synthesis
- SQ109
- Several products in lead optimization development



Targets Translation:
Disrupts transcription/translation process
- MBX-4888A*
- FNDR-20364*
- GSK-839*

Targets Leucyl tRNA synthetase: Inhibits protein synthesis
- GSK-3036656*

Targets Outer capsule components:
- JSF-3285*
- FNDR-20081*
- BVL-GSK098*

Targets ATP-synthase: Diarylquinolines
Inhibits ATP synthesis
- TBAJ-587
- TBAJ-876
- Sudapyridine
- Bedaquiline*
- FNDR-10045*

Targets Cytochrome bc complex: Imidazopyridines
Inhibits energy metabolism
- Talacebe (Q203)
- TB-47*

Targets Ribosome: Oxazolidinones
Inhibits protein synthesis
- Linezolid
- Delpazolid
- Sutezolid
- TBI-223
- OTB-658

Source: Adapted from Zumla, A.I. et al., Lancet ID, 2014

TB Clinical Trials Evaluating Novel Regimen/Strategy

Type of TB	Title & Description	Status	Phase
Treatment of DS-TB	**TBTC-31: Four-Month Rifapentine Regimen with or without MXF**	**Completed Dec 2021**	**III**
	CLO-FAST: Cfz + Rifapentine	**Early termination**	**II**
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TBTC-31: Four-Month Rifapentine-Moxifloxacin Regimen for DS-TB

- Phase III RCT of 2516 DS-TB participants
  - **Control: 2HRZE/4HR**
  - **RPT Arm: 2HPZE/2HP**
  - **RPT/MOXI: 2HPZM/2HPM**
- Primary Endpoint: TB free survival @ 12 months
- Proportion with unfavourable outcomes (positive cultures @/after week 17 or at last visit, died, withdrawn, LTFU, post-treatment TB death

H=INH; R=Rif; Z=PZA; E=Etham; P=Rifap; M=Moxi

A

Primary: adjusted for HIV and cavitation — Primary: unadjusted
Secondary: adjusted for HIV and cavitation — Secondary: unadjusted

Analysis Population	Rifapentine–Moxifloxacin	Control	Percentage-Point Difference (95% CI)
	% (no. with unfavorable outcome/total no.)		
Intention to treat	21.3 (181/849)	20.9 (173/829)	0.4 (−3.5 to 4.3)
			0.5 (−3.5 to 4.4)
Microbiologically eligible	15.5 (123/791)	14.6 (112/768)	1.0 (−2.6 to 4.5)
			1.0 (−2.6 to 4.5)
Assessable	11.6 (88/756)	9.6 (70/726)	2.0 (−1.1 to 5.1)
			2.0 (−1.1 to 5.1)
Per-protocol 75%	6.1 (43/706)	3.1 (21/673)	3.0 (0.8 to 5.2)
			3.0 (0.8 to 5.2)
Per-protocol 95%	5.8 (37/641)	2.7 (15/563)	3.1 (0.9 to 5.3)
			3.1 (0.9 to 5.4)

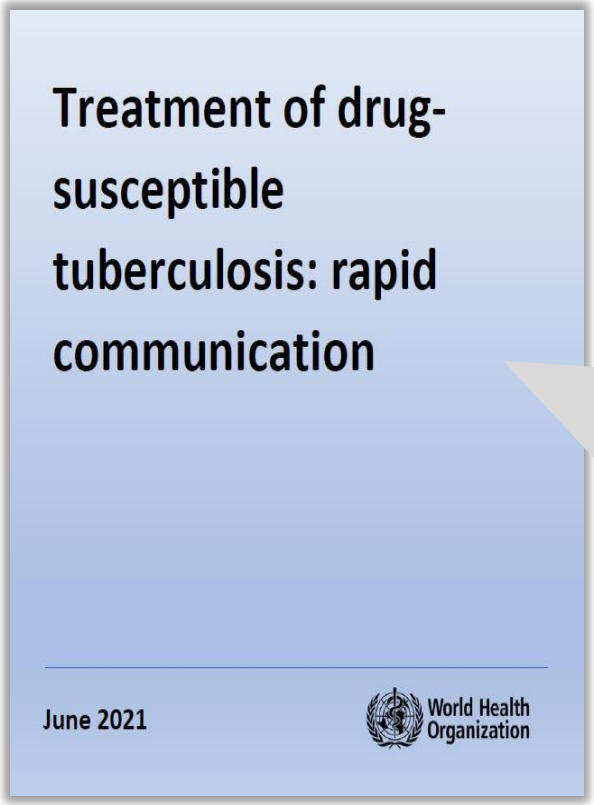
−4 −2 0 2 4 6 8 10

Rifapentine–Moxifloxacin Better — Control Better

Main Findings:

- **RPT-MOX non-inferior to standard 6-month regimen - similar efficacy performance**(15.5% vs. 14.6% with unfavourable outcomes)
- **Similar safety performance -** rates of Grade 3 or higher adverse events across all groups

WHO endorses RPT-MOX 4-month regimen as alternate Rx for DS TB



Conclusions/Summary

The available evidence reviewed by the GDG on the 4-month regimen for treatment of drug-susceptible pulmonary TB supports the use of this regimen as a possible alternative to the current standard 6-month regimen. The shorter regimen has showed similar performance to the current standard regimen, both in terms of efficacy and safety. The 4-month regimen, which is shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system. However, implementation and uptake of the new regimen in the short to medium term will be more feasible if the cost of rifapentine is reduced and availability improved. It will also require rigorous antibacterial stewardship to ensure the appropriate use of the first-line regimen given that it contains moxifloxacin, an antibiotic usually used for the treatment of drug-resistant TB.

Not recommended (no data exists): weight < 40kg; EPTB; HIV infected with CD4 count < 100 cell/mm^3 & those not on EFV containing ART; pregnant, breastfeeding & postpartum women

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TRUNCATE-TB: Shorter DS-TB Regimen Using Novel Drugs

Strategy of initial minimum duration Rx to cure most TB patients, extended Rx for persistent clinical disease, & post-Rx monitoring for relapse

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Nicholas I. Paton, M.D., Christopher Cousins, M.B., Ch.B., Celina Suresh, B.Sc., Erlina Burhan, M.D., Ka Lip Chew, F.R.C.P.A., Victoria B. Dalay, M.D., Qingshu Lu, Ph.D., Tutik Kusmiati, M.D., Vincent M. Balanag, M.D., Shu Ling Lee, B.Sc., Rovina Ruslami, Ph.D., Yogesh Pokharkar, M.Sc., et al., for the TRUNCATE-TB Trial Team*

Table 2. Primary Efficacy Outcome.*

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezo vs. Standard Treat
			Adjusted Difference (97.5% CI)†		Adjusted Diffe (97.5% C
Intention-to-treat population‡					
Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)§	7 (3.9)	21 (11.4)	7.4 (1.7 to 13.2)	11 (5.8)	0.8 (−3.4 to 5.1)
Death before wk 96	2 (1.1)	5 (2.7)	—	1 (0.5)	—
Ongoing treatment at wk 96	2 (1.1)	8 (4.3)	—	5 (2.6)	—
Active disease at wk 96¶	1 (0.6)	4 (2.2)	—	3 (1.6)	—
Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen	2 (1.1)	3 (1.6)	—	1 (0.5)	—
Participant-centered outcomes					
Total treatment time through wk 96 — days‡					
Total duration of treatment	180.2±37.9	105.7±80.1	−74.5 (−87.4 to −61.6)	84.8±65.3	−95.3 (−106.2 to −84.5)
Total qualifying treatment time	177.3±35.6	101.6±74.9	−75.7 (−87.7 to −63.6)	83.8±64.2	−93.5 (−104.0 to −82.9)
Safety outcomes					
Adverse events through wk 96 — no. (%)					
Any grade 3 or 4 adverse event	29 (16.0)	32 (17.4)	1.4 (−6.4 to 9.2)	30 (15.9)	−0.2 (−7.9 to 7.4)
Any serious adverse event	11 (6.1)	18 (9.8)	3.7 (−2.1 to 9.7)	14 (7.4)	1.3 (−4.2 to 6.9)
Death††	3 (1.7)	5 (2.7)	1.1 (−2.4 to 4.8)	1 (0.5)	−1.1 (−4.3 to 1.5)

- Adaptive, open-label trial
- n=674 RIF-S PTB, 96 weeks follow-up
- Standard Rx group: 24 weeks of RIF & INH with PZA & EMB for first 8 weeks *n=181*
- 4 intervention arms*:* **RIF^{high}+LZD; RIF^{high}+CFZ; RIFAP+BDQ & BDQ+LZD (in combination with H, Z, E)**
- Primary outcome: death, ongoing Rx or active TB

Findings:

- Occurrence of primary-outcome event: SOC arm 3.9%-
  - ➢ vs RIF^{high}+LZD arm: 11.4% (noninferiority not met)
  - ➢ vs **BDQ+LZD arm: 5.8%** (noninferiority met)
- Mean total Rx duration:
  - ➢ 180 days standard-Rx group vs 106 days RIF^{high}+LZD arm vs **85 days BDQ+LZD arm**
- Grade 3 or 4 AEs & SAEs → similar across three groups

- 8-week BDQ+LZD regimen→ noninferior to standard Rx with Shorter total Rx duration with no evident safety concerns
- BDQ & CFZ long t½→ risk of monotherapy & emergent resistance

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New All Oral DR TB Regimen

NEJM

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

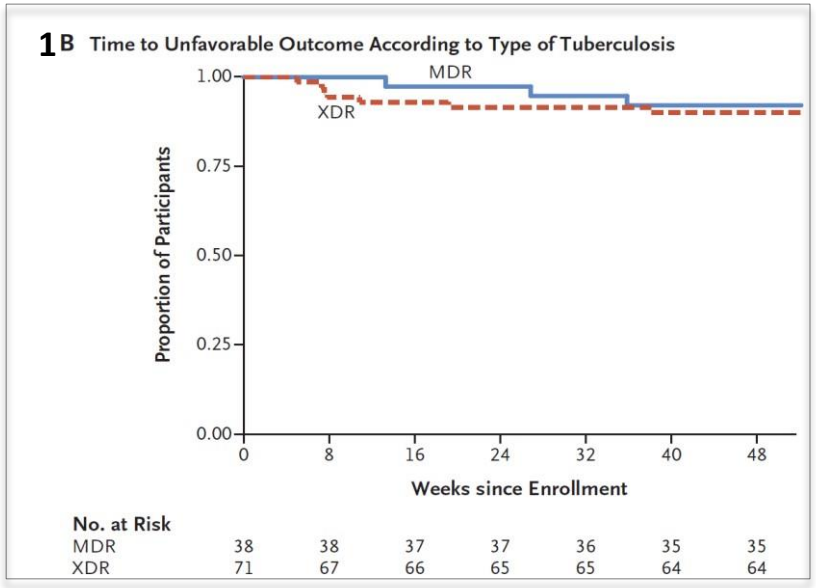
Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. Mc Genevieve H. Wills, M.Sc., Anna Bateson, Ph.D., Robert Hunt, B.Sc., Christo Van Ni Mengchun Li, M.D., Morounfolu Olugbosi, M.D., and Melvin Spigelman, M.D., for the Nix-

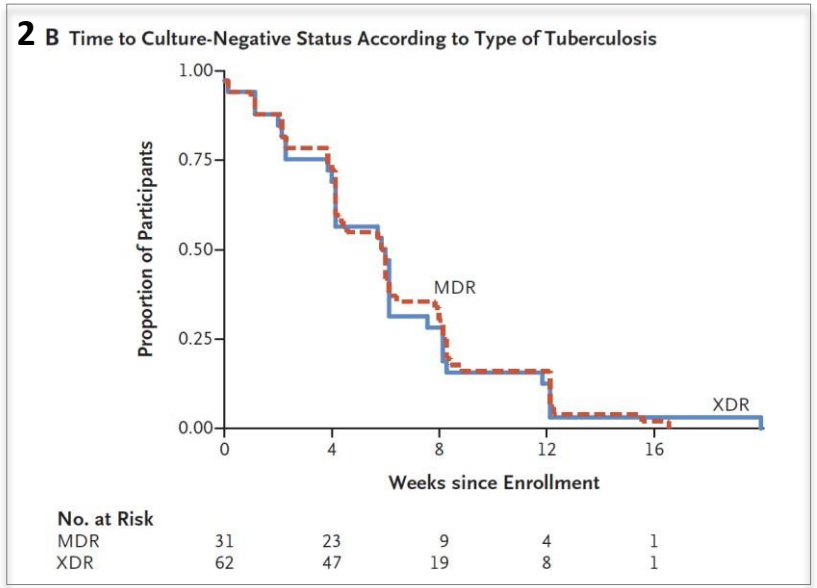
Nix-TB open label single arm study in 109 patients at three South African sites

Aim: To evaluate safety and efficacy of BPaL = bedaquiline (400mg OD for 2 weeks + 200mg 3 weekly for 24 weeks) + pretomanid (200mg daily for 26 weeks) + linezolid (1200 mg for 26 weeks)

Eligibility: Patients with extensively drug-resistant TB (XDR-TB) or treatment intolerant /non-responsive MDR TB

Primary end point: Incidence of unfavourable outcomes: treatment failure (bacteriologic or clinical) or relapse 6 months post treatment completion





- **Figure 1b & Figure 2b:** Irrespective of resistance type, similar time to unfavourable outcomes by 48 weeks and time to culture-negative status
- **Efficacy and safety outcomes at end of treatment (109 patients assessed at 6 months)**
  - 98 patients (90%) had a favourable outcomes (treatment failure [bacteriologic or clinical] or disease relapse), Six patients died
  - Linezolid associated peripheral neuropathy, experienced by 81%, and myelosuppression by 48%
    - common, but manageable, requiring linezolid dose reductions and/or interruptions (ZeNIX study)
- **After 24 months of follow-up, 90% of patients with DR-TB survived and remained healthy**

ORIGINAL ARTICLE

Bedaquiline–Pretomanid–Linezolid Regimens for Drug-Resistant Tuberculosis

F. Conradie, T.R. Bagdasaryan, S. Borisov, P. Howell, L. Mikiashvili, N. Ngubane, A. Samoilova, S. Skornykova, E. Tudor, E. Variava, P. Yablonskiy, D. Everitt, G.H. Wills, E. Sun, M. Olugbosi, E. Egizi, M. Li, A. Holsta, J. Timm, A. Bateson, A.M. Crook, S.M. Fabiane, R. Hunt, T.D. McHugh, C.D. Tweed, S. Foraida, C.M. Mendel, and M. Spigelman, for the ZeNix Trial Team*

Efficacy of Various Doses and Duration of LZD in 181 participants

Primary Endpoint

- Incidence of bacteriologic failure, relapse or clinical failure at 6 months after the end of treatment

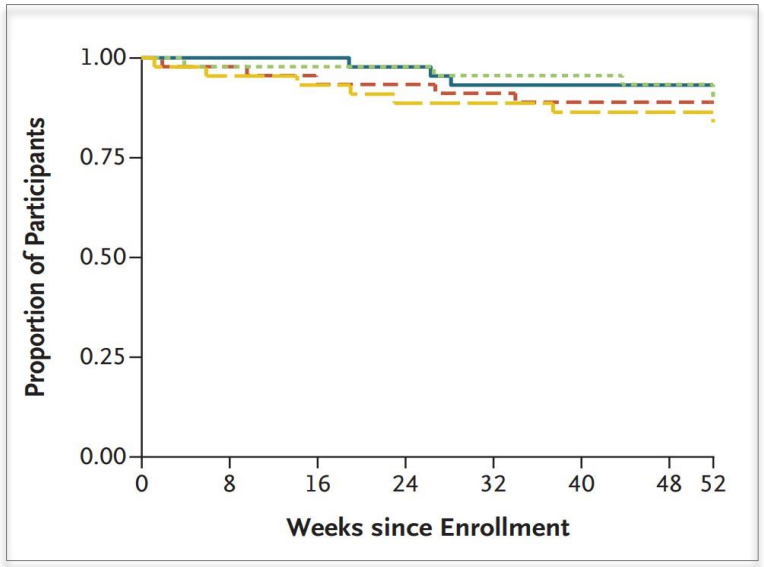


Figure 2A: Time to Unfavourable Outcome, Modified ITT Population

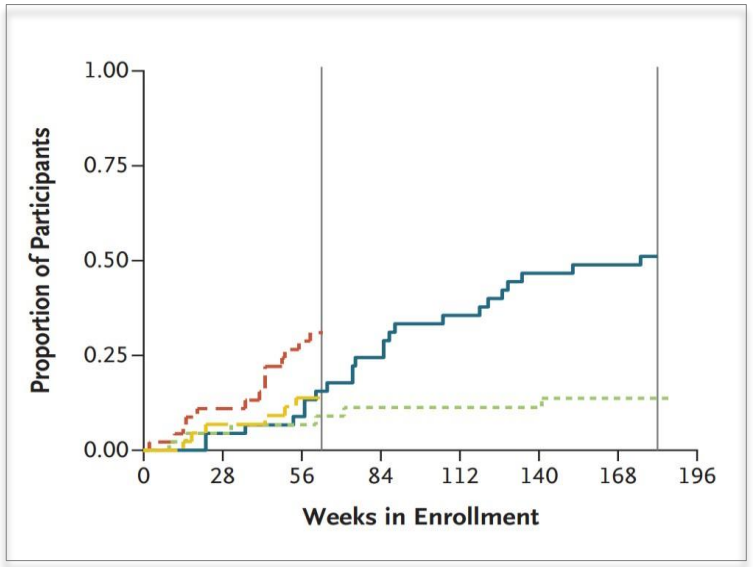


Figure 2B: Time to LZD Dose Modification, ITT Population

ZeNix	LZD 1200mg 26 weeks (N=45) n (%)	LZD 1200mg 9 weeks (N=46) n (%)	LZD 600mg 26 weeks (N=45) n (%)	LZD 600mg 9 weeks (N=45) n (%)	Total (N=181) n (%)
Favourable	**41 (93.2%)**	**40 (88.9%)**	**40 (90.9%)**	**37 (84.1%)**	**158 (89.3%)**

- Similar rates of favourable outcomes across all 4 arms
- Overall 600mg LZD for 26 weeks favoured → low incidence of adverse events→ fewer LZD dose modifications

6-month Regimen for DR-TB

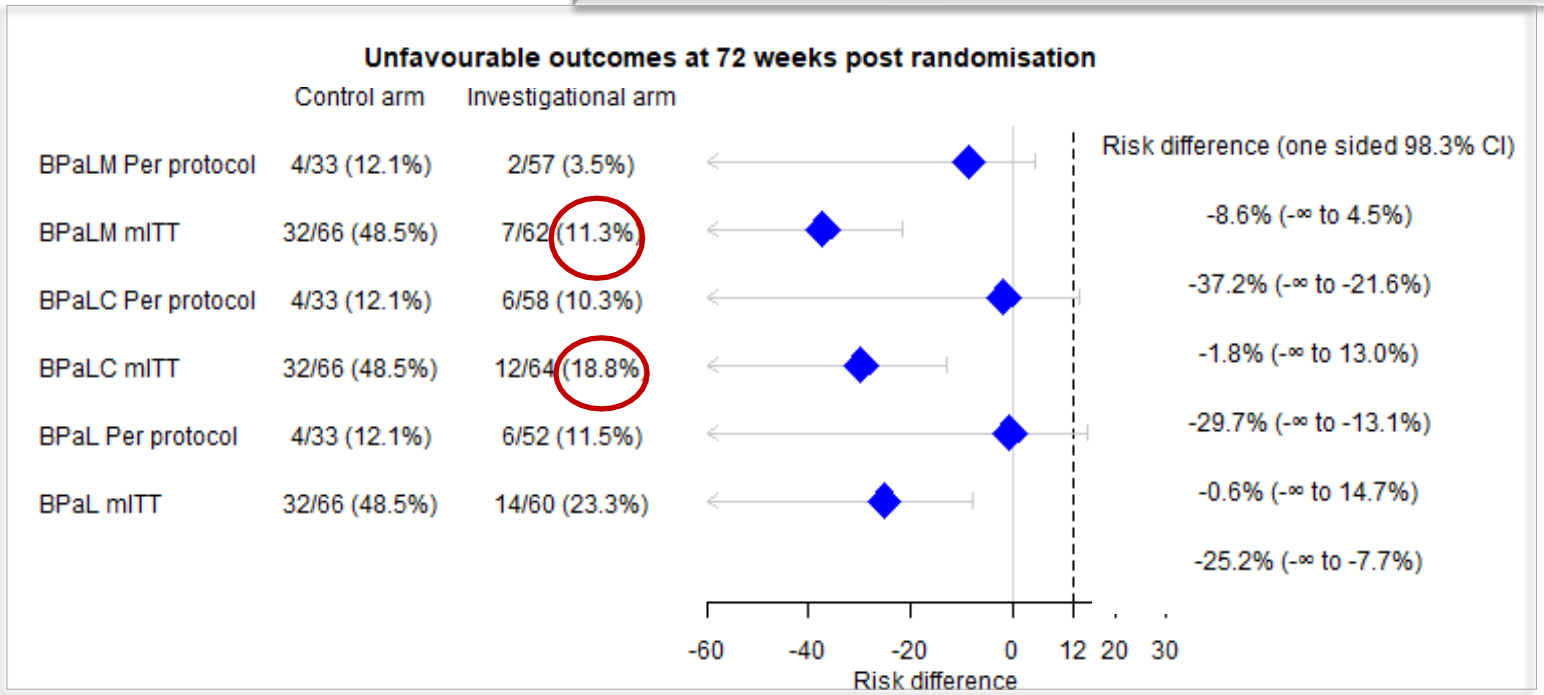
TB Practecal
Innovating MDR-TB Treatment

STUDY PROTOCOL Open Access

TB-PRACTECAL: study protocol for a randomised, controlled, open-label, phase II–III trial to evaluate the safety and efficacy of regimens containing bedaquiline and pretomanid for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis

Catherine Berry[1*], Philipp du Cros[1,2], Katherine Fielding[3], Suzanne Gajewski[4], Emil Kazounis[1], Timothy D. McHugh[5], Corinne Merle[6], Ilaria Motta[1], David A. J. Moore[7] and Bern-Thomas Nyang'wa[8]

- Open label phase II/III non-inferiority, evaluating safety & efficacy of 24-week oral regimens (BDQ+PA+LZD with CFZ or Moxi) compared to WHO SOC regimen for RR TB in patients > 15 years
- Primary Endpoint: Percent unfavourable outcomes at 72 weeks post-randomisation



- Proportion of patients without an unfavourable outcome 89% in BPaLM arm vs 52% in control arm-findings held for 108-weeks post-randomisation
- Safety Outcomes
  - Unfavourable outcomes driven by higher rates of treatment discontinuation in control arms
- Deaths: 1 in BPaLC arm, 2 in Control, none in BPaLM/ BPaL arms
- SAE or new grade 3/higher AEs:
  - 58.9% for the Control
  - 21.7% for BPaL
  - 31.9% for BPaLC
  - 19.4% for BPaLM

BPaLM: Shorter, less toxic and more efficacious regimen offering improved outcomes in RR TB patients

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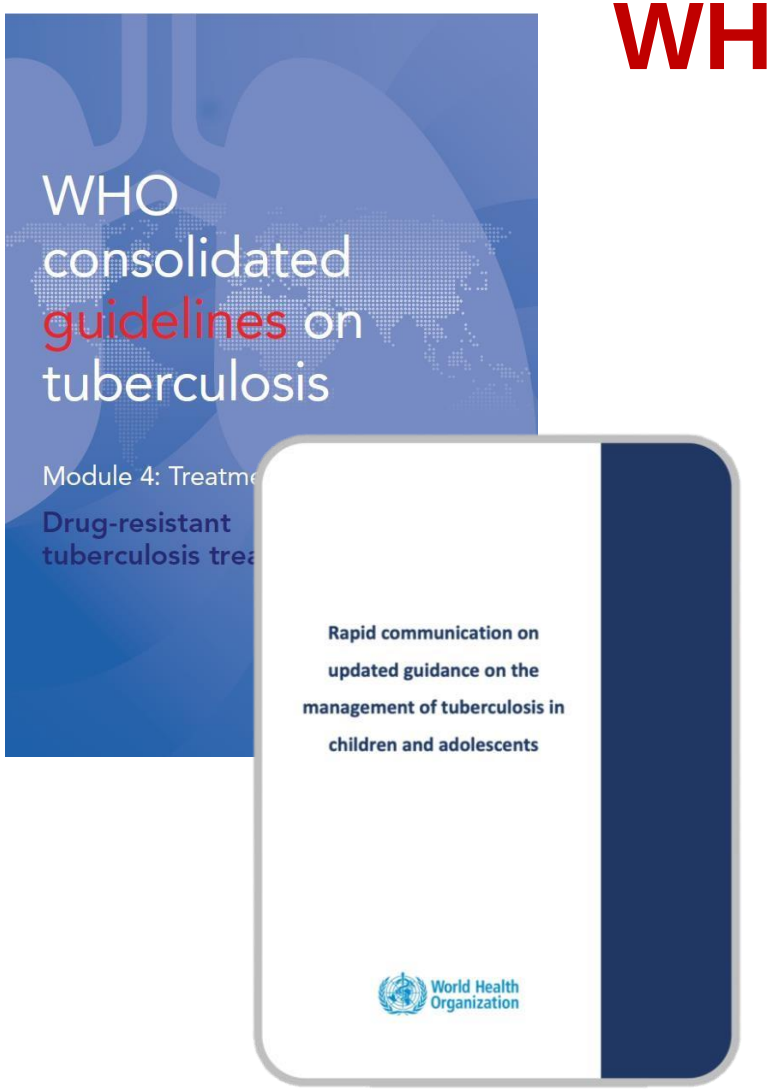
WHO Rapid Communication



All patients with MDR/RR-TB, including those with additional resistance to fluoroquinolones → can benefit from all-oral treatment regimens

- **6-month BPaLM or BPaL**
  - may be used programmatically in place of 9-month or longer (>18 months) regimens, in patients (aged ≥15 years) who have not had previous exposure to (defined as >1 month exposure)
  - Can be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones
  - Drug susceptibility testing (DST) for FQs strongly encouraged but should not delay treatment initiation.
- **9-month, all-oral, bedaquiline-containing regimen**
  - Preferred over the longer (>18 months) regimen in adults and children without previous exposure to second-line treatment (including bedaquiline), without fluoroquinolone resistance and with no extensive pulmonary TB disease or severe extrapulmonary TB.
  - In these regimens, 2 months of linezolid (600 mg) can be used as an alternative to 4 months of ethionamide.
  - DST for ruling out fluoroquinolone resistance is required before treatment initiation.
- **Patients with extensive DR-TB**
  - Not eligible for or have failed shorter treatment regimens will benefit from an individualized longer regimen designed using the priority grouping of medicines recommended in current WHO guidelines

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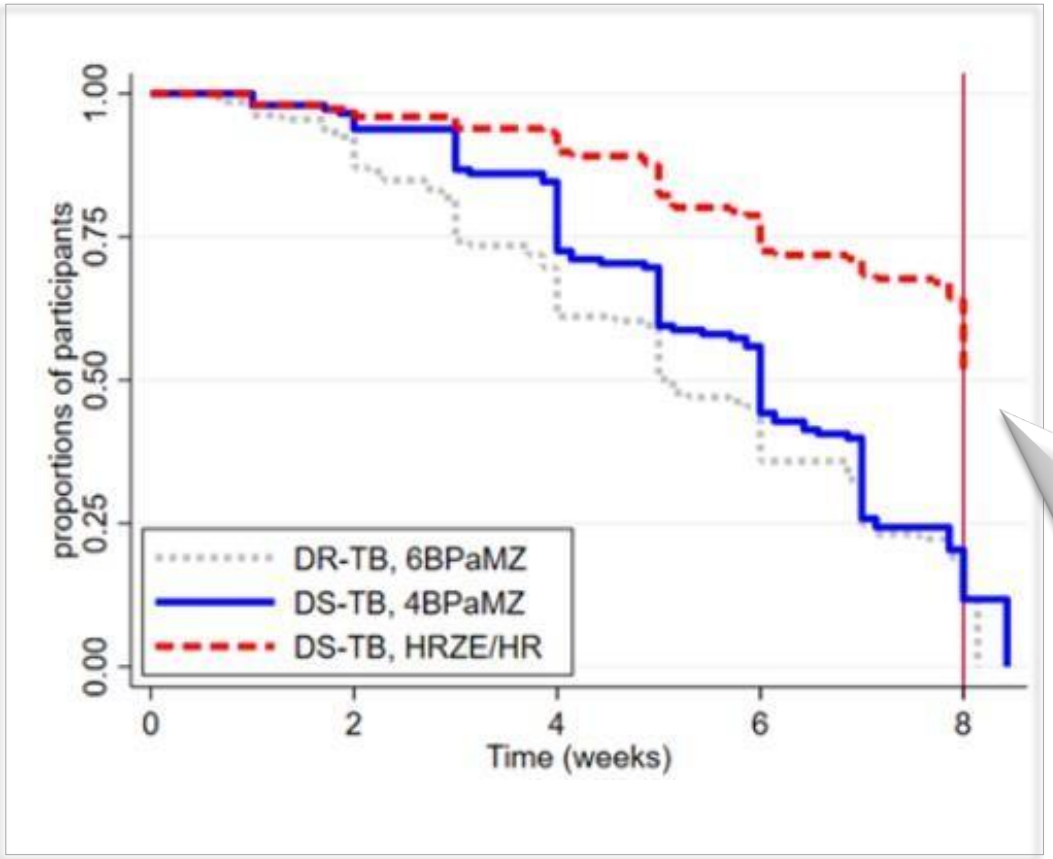
Pan Regimen: 4-month for DS-TB or 6-months for DR-TB Treatment



- Phase 3 multicountry, open-label safety & efficacy study
- DS-TB n=303: 4-months BPaMZ or 6-months HRZE
- DR-TB n=152: 6-months BPaMZ
- Primary endpoint: time to culture negative status through 8 weeks

Findings:

- @ week 8→Culture negative outcomes:
  - DS-TB 47% HRZE vs 84% 4BPaMZ arm; HR 2.9 (95% CI 2.2 – 4.0)
  - DR-TB 86% 6BPaMZ arm
- BPaMZ had hepatotoxicity-related Rx discontinuations:
  - 0% HRZE arm
  - 7% 4BPaMZ arm
  - 6% 6BPaMZ arm

BPaMZ has high efficacy & Rx shortening potential but hepatic toxicity hindered Rx completion in 6-7% of patients

Tuberculous Meningitis (TBM)

- **Two ongoing trials**

1. **HARVEST Study:** Phase III **H**igh Dose Oral **R**ifampicin to Impro**VE S**urvival from Adult **T**BM: A Double-blinded RCT: 440 HIV infected and uninfected patients from SA, Uganda, Indonesia
2. **IMAGINE TBM: I**mproved **M**anagement With **A**ntimicrobial **AG**ents **I**soniazid rifampici**N** Lin**E**zolid for **TBM**
   - Phase II, Randomized, Open-Label Trial of Six-Month High-Dose Rifampicin, High-Dose Isoniazid, Linezolid, and Pyrazinamide Versus a Standard Nine-Month Regimen for the Treatment of Adults and Adolescents With Tuberculous Meningitis

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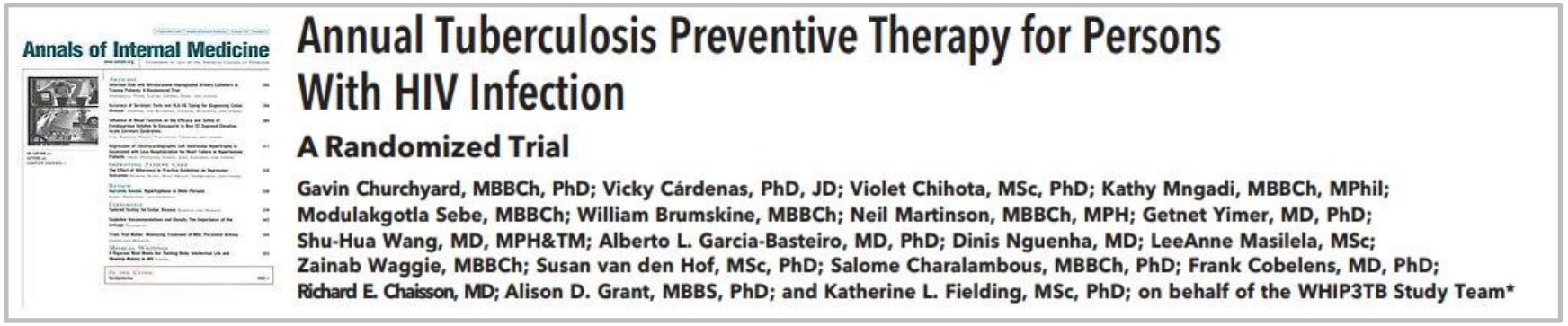
TB Clinical Trials Evaluating Novel Regimen/Strategy

Type of TB	Title & Description	Status	Phase
Treatment of DS-TB	**TBTC-31:** Four-Month Rifapentine Regimen with or without MXF	Completed Dec 2021	III
	CLO-FAST: Cfz + Rifapentine	Early termination	II
	TRUNCATE-TB: BDQ + LZD	Completed	II/III
Treatment of DR-TB	**STREAM I:** 9-month Bangladesh regimen vs. SOC	Recruitment complete	III
	STREAM II: Comparison of 6- & 9-month BDQ regimens to SOC & Bangladesh (confirmatory)	Begin enrolling 2016: multisite	III
	NEXT: 6–9-month all-oral regimen containing BDQ	Completed Dec 2020	T: II; MDR-TB: III
	Nix-TB: BDQ, pretomanid, and linezolid in patients with XDR-TB 6-9 months	Completed Dec 2020	III
	ZeNix: LZD + BDQ & PA for XDR, Pre-XDR or Intolerant MDR TB	Completed Dec 2021	III
	TB-PRACTECAL: short, all-oral regimen incl BDQ & PA in MDR- & XDR-TB	Completed	II/III
Pan Regimen (DS/DR-TB)	**GATB NC-005:** Combinations of BDQ, MFX, PA- 824, & PZA for 8 weeks	Completed Dec 2019	II B
	SimpliciTB: BPaMZ	Completed Dec 2021	III
Prevention of DS-TB	**WHIP3TB : 3HP vs Periodic 3HP vs 6H in PLWH**	**Completed Dec 2019**	**III**
	BRIEF-TB: Rifapentine-Isoniazid Evaluation for TB Prevention	**Completed Dec 2021**	**III**
Prevention in DR-TB	**PHOENIX:** 6 months daily DLM vs. INH, prevention in MDR contacts	Currently recruiting in SA	III

TPT Frequency: Weekly vs Daily, Once off vs Annual



Annals of Internal Medicine

Annual Tuberculosis Preventive Therapy for Persons With HIV Infection

A Randomized Trial

Gavin Churchyard, MBBCh, PhD; Vicky Cárdenas, PhD, JD; Violet Chihota, MSc, PhD; Kathy Mngadi, MBBCh, MPhil; Modulakgotla Sebe, MBBCh; William Brumskine, MBBCh; Neil Martinson, MBBCh, MPH; Getnet Yimer, MD, PhD; Shu-Hua Wang, MD, MPH&TM; Alberto L. Garcia-Basteiro, MD, PhD; Dinis Nguenha, MD; LeeAnne Masilela, MSc; Zainab Waggie, MBBCh; Susan van den Hof, MSc, PhD; Salome Charalambous, MBBCh, PhD; Frank Cobelens, MD, PhD; Richard E. Chaisson, MD; Alison D. Grant, MBBS, PhD; and Katherine L. Fielding, MSc, PhD; on behalf of the WHIP3TB Study Team*

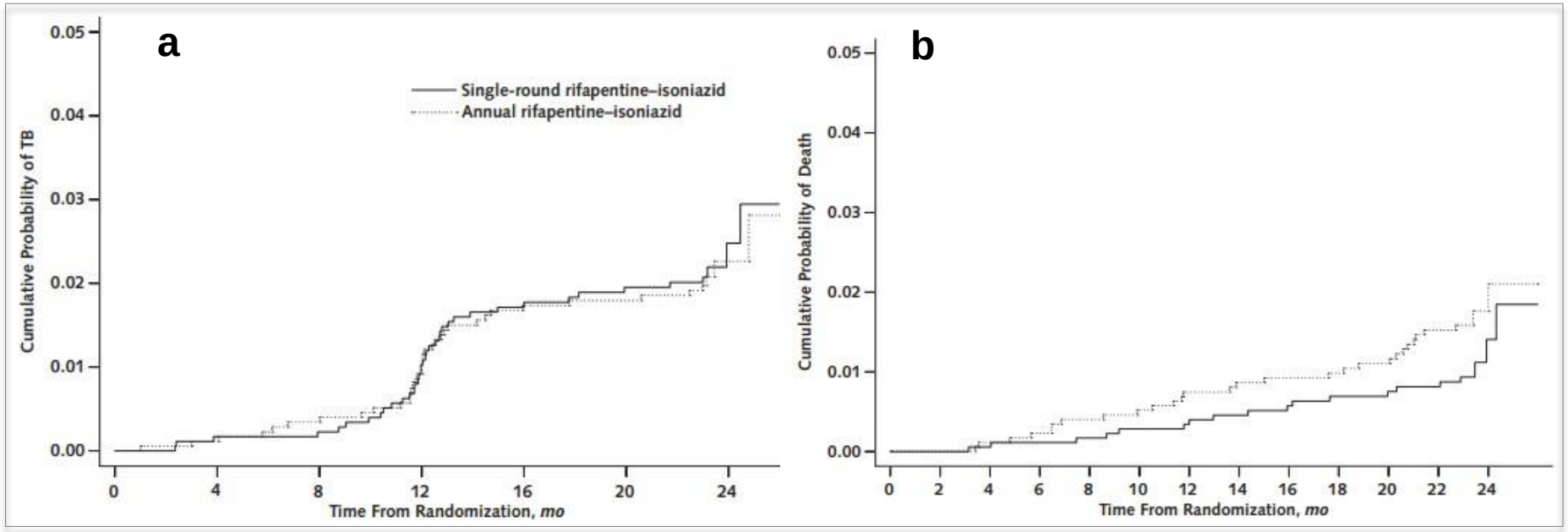


Figure 2: Kaplan-Meier curves depicting a) incidence of TB and b) mortality from months by annual and single-round Rifapentine-INH groups

- WHIP3TB RCT Assessed weekly high dose INH with Rifapentine given once off or annually for 2 years vs daily isoniazid for 6 months in 4047 PLWHA in 3 sites in SSA
- Primary endpoints: incidence of active TB over 24 months & TPT completion rates

Findings

- TB incidence similar across the groups:
  - 1.21 vs 1.26 per 100 p-years: [HR: 0.96 [CI, 0.61 to 1.50]
- TPT completion rates: 90.4% vs 50.5% in Rifapentine & INH VS INH only groups
  - risk ratio, 1.78 [95% CI, 1.61 to 1.95]

Single dose of weekly Rif & INH for 3 months provides protection against TB

- NO repeat annual administration required, as no additional benefit observed

Source: Churchyard *et al.* (2021)

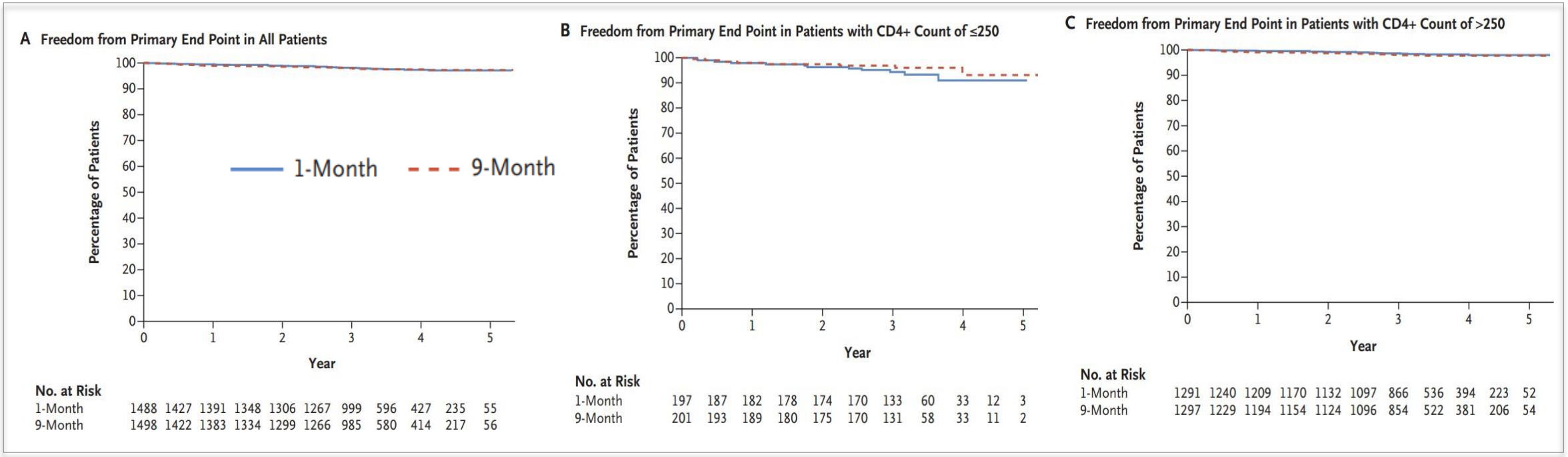
TPT Shortening in PLWHA: BRIEF TB Study

NEJM

One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis

S. Swindells, R. Ramchandani, A. Gupta, C.A. Benson, J. Leon-Cruz, N. Mwelase, M.A. Jean Juste, J.R. Lama, J. Valencia, A. Omoz-Oarhe, K. Supparatpinyo, G. Masheto, L. Mohapi, R.O. da Silva Escada, S. Mawlana, P. Banda, P. Severe, J. Hakim, C. Kanyama, D. Langat, L. Moran, J. Andersen, C.V. Fletcher, E. Nuermberger, and R.E. Chaisson, for the BRIEF TB/A5279 Study Team*

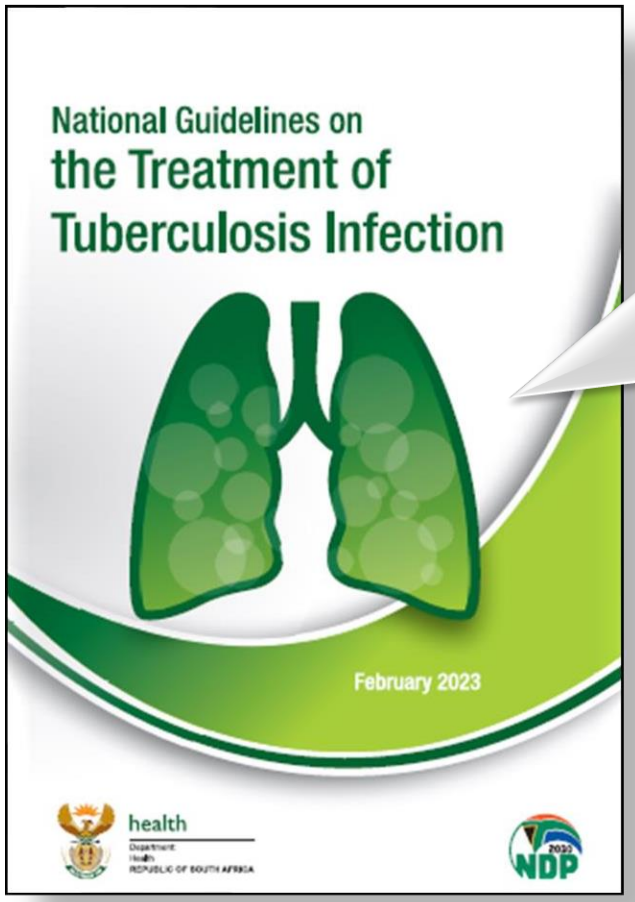
- Phase 3 RCT compared efficacy & safety of 1-month INH and Rifapentine vs 9-months INH in 3000 PLWHA followed up for 3.3 years
- Endpoint: Death or active TB diagnosis



- Similar incidence rates of TB→ 1HP no worse than 9H for TB prevention in PLWHA
- AE rates similar across both groups.
- Higher 1HP completion rates: 97% vs 90%

Source: Swindells *et al.,* (2019)

SA TPT Guidelines for PLHIV



- 12H preferred in adults, adolescents & children ≥25kg *initiating* dolutegravir-containing ART regimen
  - ➢ 6H preferred in children <25kg initiating dolutegravir-containing ART regimen
- 3HP preferred in virally suppressed PLHIV already receiving dolutegravir
- Universal 3HP in all PLHIV once favourable DTG PK data available from DOLPHIN-2, DOLPHIN-kids and TBTC Study 35 trials

Source: National Guidelines on the Treatment of Tuberculosis Infection, 2023

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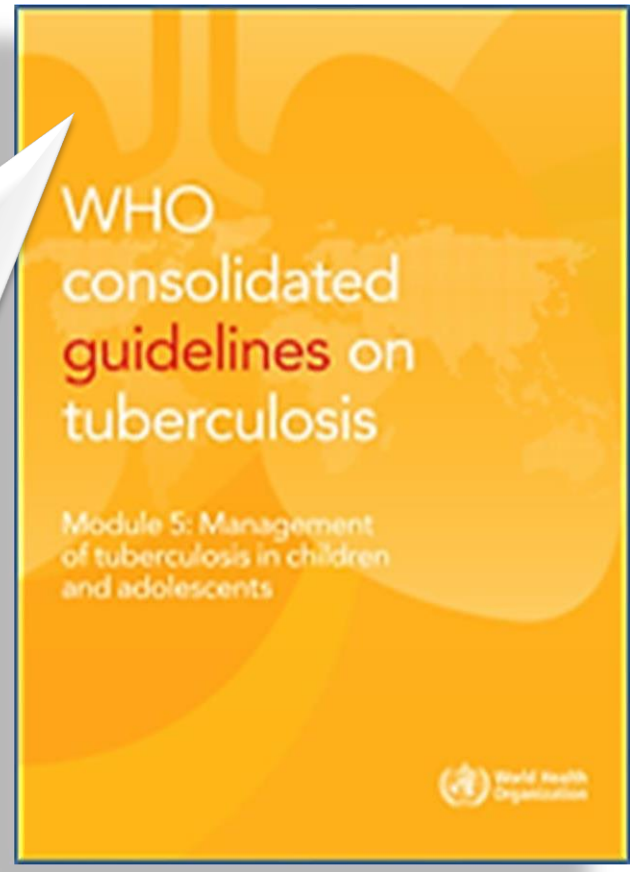
Guideline Updates: Paediatric DS-TB Treatment

Treatment of drug-susceptible TB

In children and adolescents aged between 3 months and 16 years with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

*(**NEW**: strong recommendation, moderate certainty of evidence)*

- *Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern.*
- *Children and adolescents who do not meet the criteria for non-severe TB should receive the standard 6-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.*
- *The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV[6], or of isoniazid resistance[7].*



Source: World Health Organization, 2022

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Adult & Paediatric MDR-TB Prevention Studies

Tuberculosis prevention in children: a prospective community-based study in South Africa

Anna M. Mandalakas[1], Anneke C. Hesseling[2], Alexander Kay[1,3], Karen Du Preez[2], Leonardo Martinez[4], Lena Ronge[2], Andrew DiNardo[1], Christoph Lange[5,6,7] and H. Lester Kirchner[1,8]

- Prospective community cohort study in WC among ⩽15 years of age
- Enrolled 966 children, median age 5 yrs, 70% with TB exposure within 3 months
- **82% of those receiving IPT were less likely to develop TB**
- Risk of incident TB: increased in <5 years, living with HIV, positive *M.tb* specific immune response, recent TB exposure

Levofloxacin versus placebo for the treatment of latent tuberculosis among contacts of patients with multidrug-resistant tuberculosis (the VQUIN MDR trial): a protocol for a randomised controlled trial

Greg J Fox[1, 2], Cam Binh Nguyen[2], Thu Anh Nguyen[2], Phuong Thuy Tran[2], Ben J Marais[3, 4], Steve M Graham[5, 6], Binh Hoa Nguyen[7], Kavi Velen[2, 3], David W Dowdy[8], Paul Mason[9], Warwick J Britton[3, 10], Marcel A Behr[11, 12], Andrea Benedetti[13], Dick Menzies[12], Viet Nhung Nguyen[7], Guy B Marks[2, 14]

- Phase III, blinded RCT in Vietnam
- Enrolling high risk high-risk HHC"s of index MDR-TB patients
- **Levofloxacin or placebo**
- Endpoint: bacteriologically confirmed TB over 30 months

Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP)

James A. Seddon[1,2*], Anthony J. Garcia-Prats[2], Susan E. Purchase[2], Muhammad Osman[2], Anne-Marie Demers[2], Graeme Hoddinott[2], Angela M. Crook[3], Ellen Owen-Powell[3], Margaret J. Thomason[3], Anna Turkova[3], Diana M. Gibb[3], Lee Fairlie[4], Neil Martinson[5], H. Simon Schaaf[2] and Anneke C. Hesseling[2*]

- Phase 3 RCT in SA currently underway
- 1556 < 5 yr contacts of MDR TB patients
- **Levofloxacin 15-20 mg/kg vs placebo x 6 months**
- Endpoint: Incident TB disease or death at 12 months

Protecting Households on Exposure to Newly Diagnosed MDR-TB (PHOENIx) A 5300 B Study

- Phase III, open label RCT in 12 countries
- Enrolling high risk high-risk HHC"s of index MDR-TB patients
- **Delamanid vs isoniazid for 26 weeks**
- Endpoint: efficacy and safety in preventing active TB over 96 weeks

Summary & Conclusion

- Despite past gains in TB prevention, detection, and treatment, TB mortality is rising globally, and TB incidence remains unacceptably high.
  - Unlikely to achieve SDGs & End TB Strategy targets
- Multiple new TB drugs and regimens undergoing development or investigation
- Guidelines now offer shorter regimen for DS-TB & DR-TB in adults & children with promise of better efficacy, reduced patient burden however toxicity concerns exist
- Several studies in adults and children studying novel, short, all-oral regimens:
  - Shortening and simplifying DR-TB & DS-TB treatment
  - Shortening and simplifying DR-TB & DS-TB prevention
  - Improving outcomes in EPTB
- ***TB Treatment and Prevention Goal: TB Free world!***

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MCQ 1: TB Drug Development Pipeline

Which of the following statements are **TRUE** regarding the *TB Drug Development Pipeline*:

a) Six new drugs have advanced to the next stage of development

b) Novel drugs eliminates the risk of TB drug-resistance

c) Search underway for new drugs & compounds that overcome preexisting drug-resistance

d) Sutezolid is a new drug in the same class as linezolid

e) None of the above

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MCQ 2: 4-Month DS-TB Regimen

Which of the following statements are **TRUE** regarding the 4-Month DS-TB regimen in adults:

a) Rifapentine replaces Rifampicin & Moxifloxacin replaces Ethambutol

b) The intensive phase & continuation phase of TB Rx are each 2 months

c) 4-month new regimen performs with the same efficacy & safety as the standard 6-month regimen

d) Not recommended (no data exists): weight < 40kg; EPTB; HIV infected with CD4 count < 100 cell/mm^3 & those not on EFV containing ART; pregnant, breastfeeding & postpartum women

e) All of the above

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MCQ 3: TPT Shortening

Indicate whether the following statements are *True* or *False*:

a) Single dose of weekly Rifapentine & INH for 3 months provided similar protection against TB as 6 months daily oral INH

b) Additional TB prevention benefit observed with repeat annual administration of single dose of weekly Rifapentine & INH for 3 months

c) 1-month of INH & Rifapentine had similar efficacy & safety of 9-months daily INH in TB prevention

d) 3HP preferred in virally suppressed PLHIV already receiving dolutegravir

e) 3HP recommended for adults, adolescents & children ≥25kg initiating dolutegravir-containing ART regimen in SA

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Indicate whether the following statements are ***True*** or ***False***:

a) Single dose of weekly Rifapentine & INH for 3 months provided similar protection against TB as 6 months daily oral INH **T**

b) Additional TB prevention benefit observed with repeat annual administration of single dose of weekly Rifapentine & INH for 3 months **F**

c) 1-month of INH & Rifapentine had similar efficacy & safety of 9-months daily INH in TB prevention **T**

d) 3HP preferred in virally suppressed PLHIV already receiving dolutegravir **T**

e) 3HP recommended for adults, adolescents & children ≥25kg initiating dolutegravir-containing ART regimen in SA **F**

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