New Directions: An Introduction to Patient Tailored Treatment

Barbara Seaworth, MD

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Has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this activity

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World TB Day 2026

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Co-Medical Director
Heartland National TB Center

Disclosures

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Objectives

Explain ways to tailor diagnosis and care to the individual

- Where we are now?
- What are new approaches we may be using in future?

Examine several new treatment trials and how they may improve health outcomes

- Duration of therapy

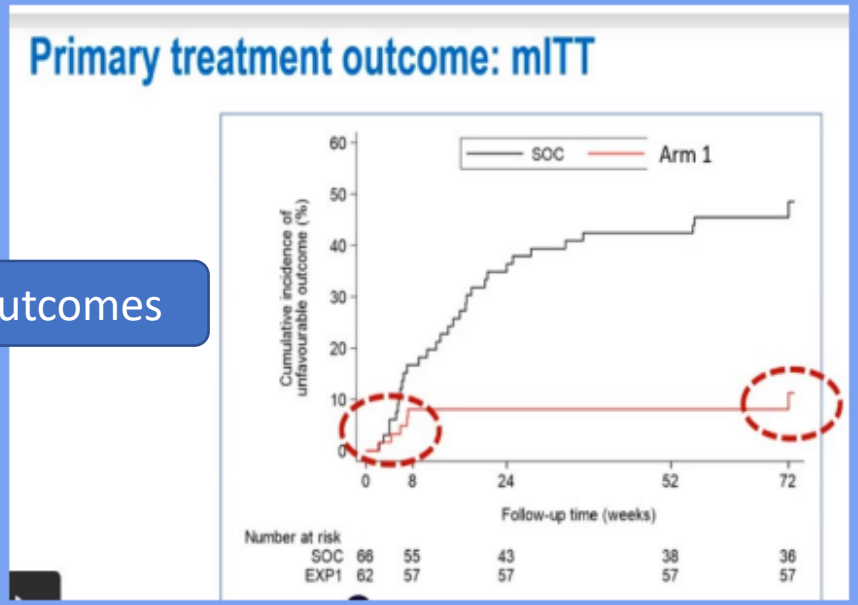
Things will likely become a bit more complicated but lead to more patient centered care and better outcomes

Treatment Shortening

TB-PRACTECAL - Efficacy

- Arm 1: BPaLM: 89% favorable
- Arm 2: BPaLC: 81% favorable
- Arm 3: BPaL(modified): 77% favorable
- Arm 4: SOC: 52% favorable

Cumulative incidence of unfavorable outcomes



Bedaquiline, delamanid, linezolid, and clofazimine for rifampicin-resistant and fluoroquinolone-resistant tuberculosis (endTB-Q): an open-label, multicentre, stratified, non-inferiority, randomised, controlled, phase 3 trial

Lorenzo Guglielmetti*, Uzma Khan*, Gustavo E Velásquez*, Maelenn Gouillou, Muhammad Hammad Ali, Samreen Amjad, Farees Kamal, Amanzhan Abubakirov, Elisa Ardizzoni, Elisabeth Baudin, Sagit Bektassov, Catherine Berry, Maryline Bonnet, Vijay Chavan, Sylvine Coutisson, Zhanna Dakenova, Bouke Catherine de Jong, Luong Van Dinh, Gabriella Ferlazzo, Ohanna Kirakosyan, Nathalie Lachenal, Leonid Lecca, Helen Mdlleron, Kwabisha Kunda Mikanda, Sergio Mucching-Toscano, Wim Mulders, Hebah Mushtaque, Payam Nahid, Dong Van Nguyen, Nhung Viet Nguyen, Lawrence Oyewusi, Ilaria Motta, Samiran Panda, Sandip Patil, Thuong Huu Pham, Dat Thuong Phan, Ha Thi Thu Phan, Patrick PJ Phillips, Jimena Ruiz, Praharshinie Rupasinghe, Naseem Salahuddin, Epifanio Sanchez-Garavito, Kwonjune J Seung, Meseret Tamirat Asfaw, Dante Vargas Vasquez, Michael L Rich*, Francis Varaine*, Carole D Mitnick*, for the endTB-Q Clinical Trial Team†

Lancet Resp Med 2025:13

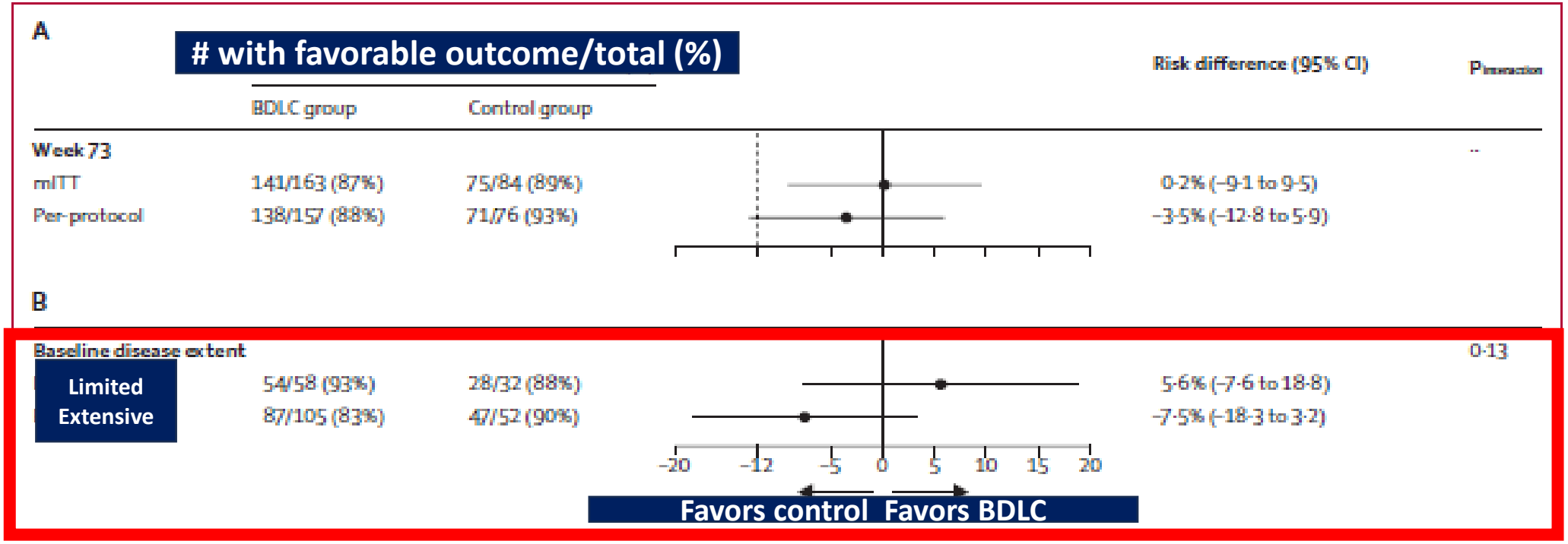
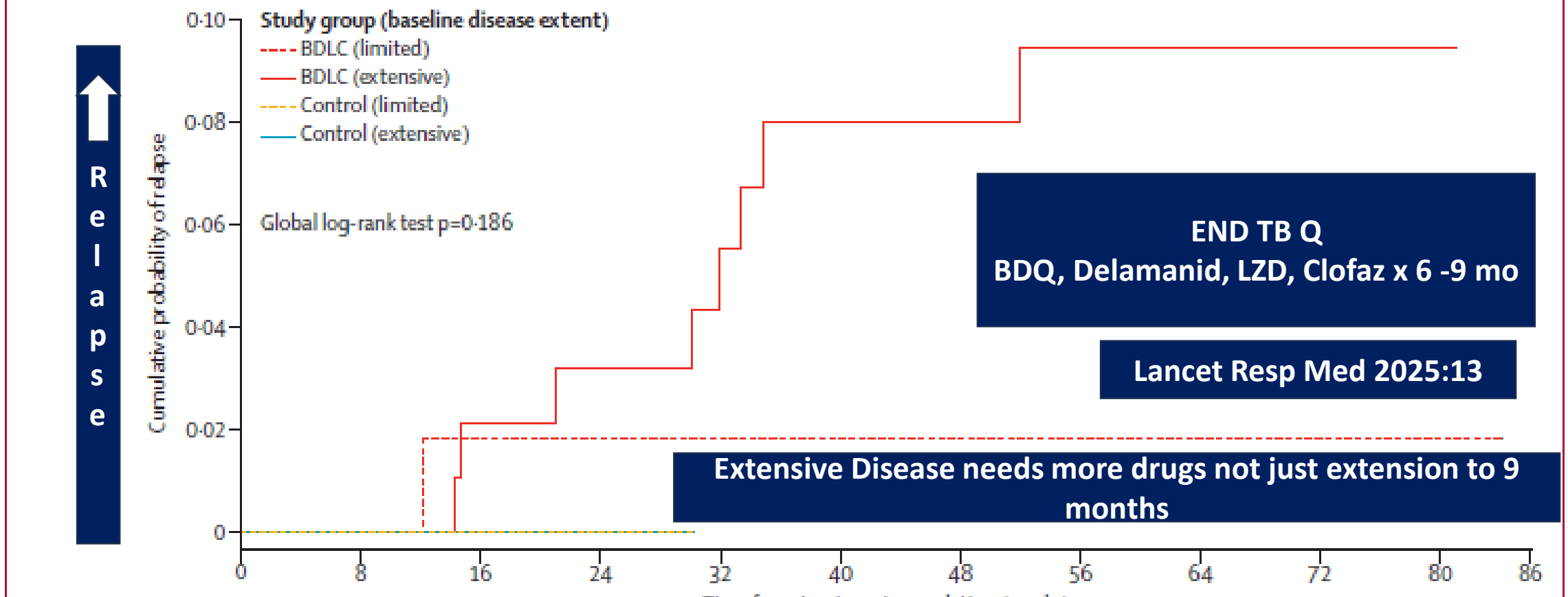


Figure 2: Primary efficacy analysis at week 73 between the BDLC and control groups

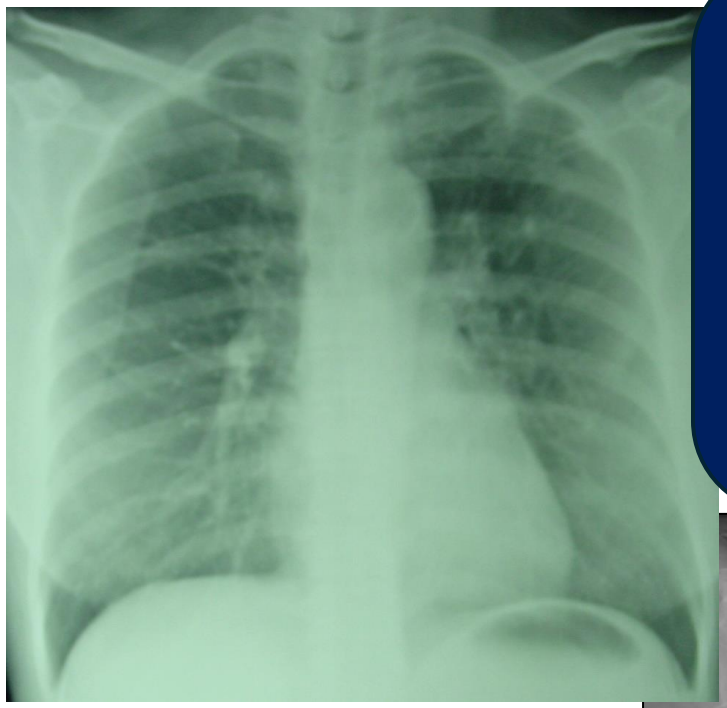
(A) Forest plot of primary efficacy analysis at week 73 in the mITT and per-protocol populations, adjusted by stratification factors. The non-inferiority margin of −12% is shown by the dashed vertical line. (B) Forest plot at week 73 of the risk difference in the prespecified subgroup analysis, stratified by baseline tuberculosis disease extent. Favourable outcome was defined as two consecutive, negative cultures including one between weeks 65 and 73; or favourable bacteriological, radiological, and clinical evolution) at week 73 after randomisation. BDLC=bedaquiline, delamanid, linezolid, and clofazimine. mITT=modified intention-to-treat.

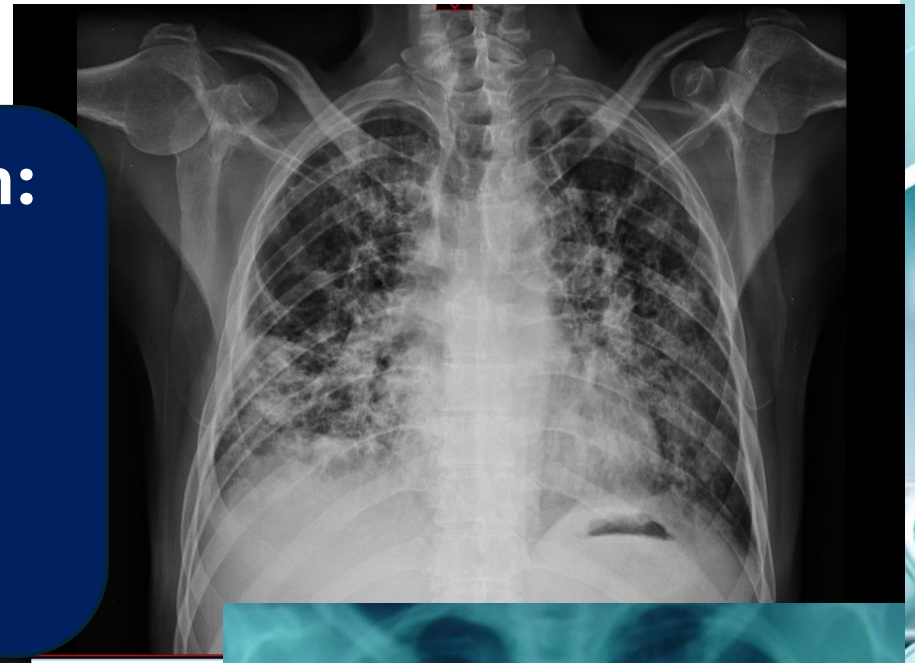


Number at risk (relapses)												
BDLC (limited)	56	55	54	54	51	51	47	42	40	27	15	0
	(0)	(1)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
BDLC (extensive)	94	94	92	90	78	71	68	61	31	6	2	0
	(0)	(2)	(1)	(2)	(2)	(0)	(1)	(0)	(0)	(0)	(0)	(0)
Control (limited)	27	24	22	15	0	0	0	0	0	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Control (extensive)	46	37	35	21	0	0	0	0	0	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)

Figure 3: Kaplan–Meier plot of time to relapse (from treatment completion) by baseline extent of tuberculosis disease in the mITT population

One size for everyone?





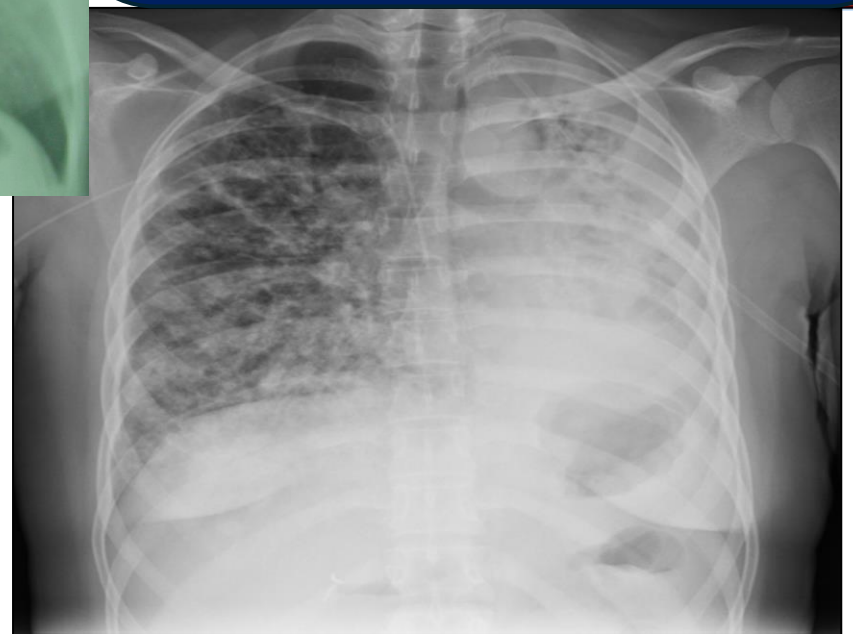
Standard Duration:

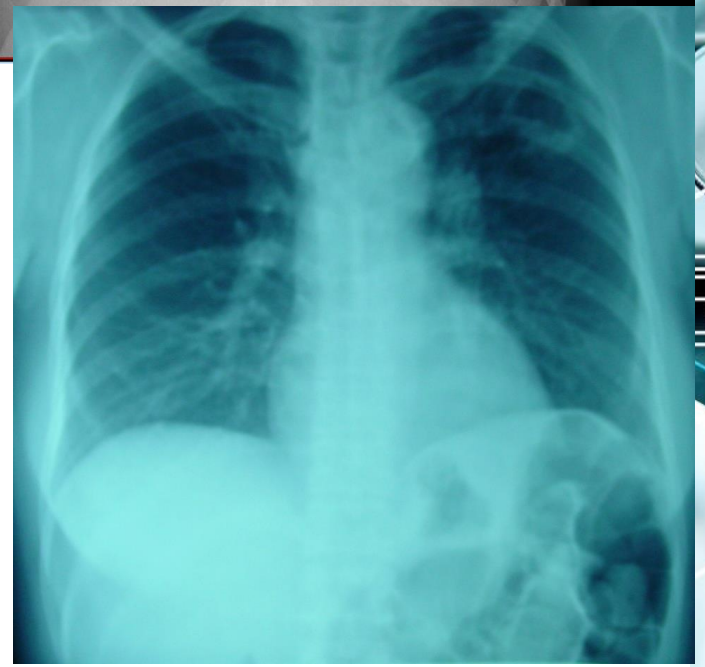
6 months RIPE (Drug Sen TB)

6 months RPE + moxi (INH R)

6 months BPAL (MDR TB)

6 months BPALM (MDR TB)





Remember to Ask:
What does the TB Community Want?

- **Safety**

Efficacy

- **Tolerability**
  - Pill burden, side effects

Time

Shorter Treatment Duration

“Home Time”

One Size Does Not Fit All

Public Health Action Sept 2023, Makone et al

How can we give each person what they really need?

TO GET THERE WE NEED to IDENTIFY

Disease **phenotypes** –define the extent and type of TB

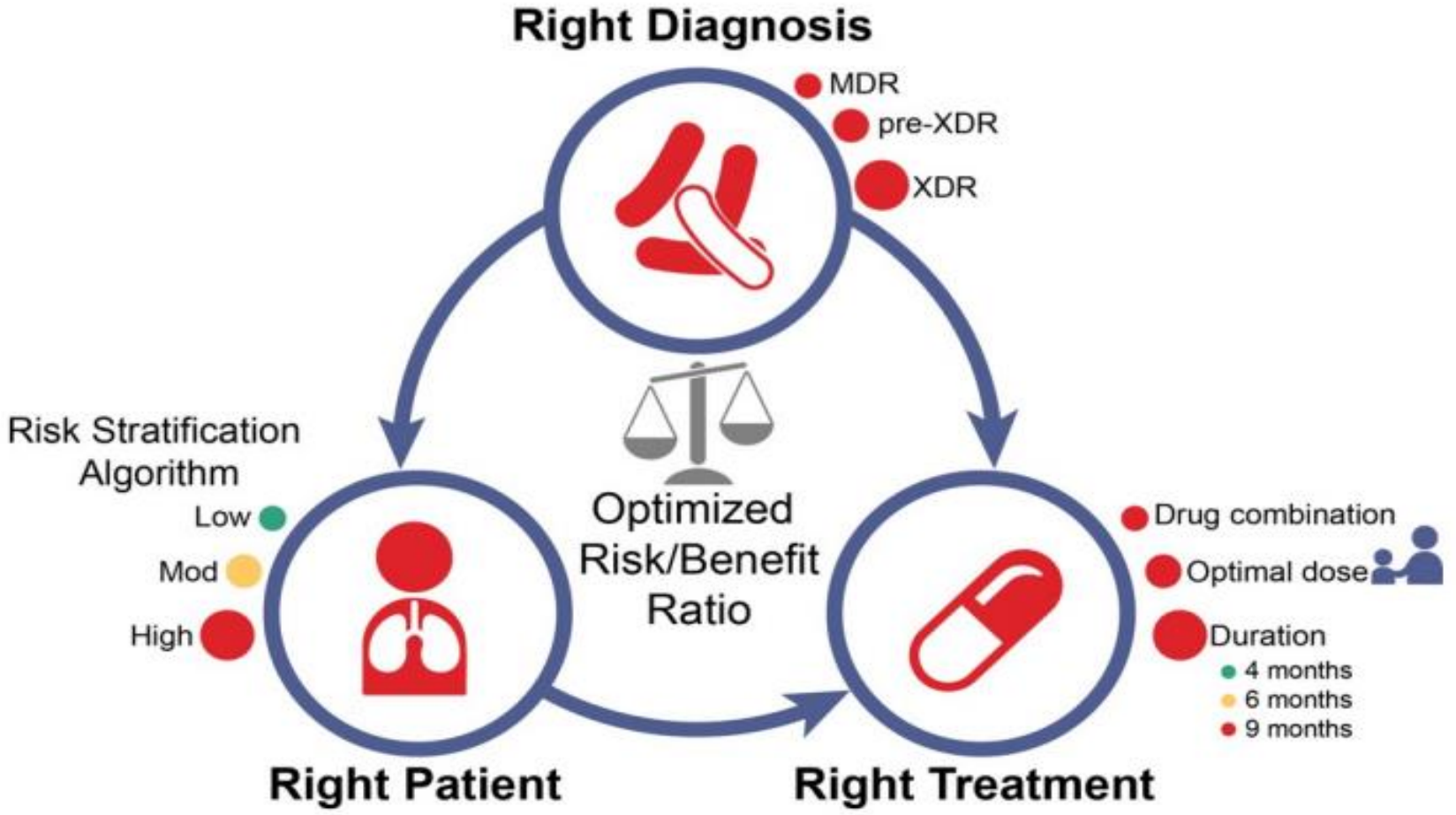
Assessing immune response
(**endotypes**)

Host directed therapies (HDT)

Look at long term health not just microbiological cure

Stratified Care – Precision Medicine

Giving each patient what they need



With gratitude to Dr. Rada Savic for sharing her work a number of subsequent slides are hers or from her publications.

ORIGINAL ARTICLE

Precision-Enhancing Risk Stratification Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials

Marjorie Z. Imperial[1,2], Patrick P. J. Phillips[2,3], Payam Nahid[2,3], and Radojka M. Savic[1,2,3]

- Goal: **Develop risk stratification tool** to assign optimal treatment duration for each patient

- Risk score successfully grouped participants into
  - **low, moderate and high-risk**
  - Requiring treatment durations of 4, 6 and > 6 months to **reach 93% target cure**

- **Four-month regimens were noninferior to the standard 6-month regimen in the low-risk group**

Am J Resp Crit Care Med Nov 2021

Table 1: Summary of main outcomes from 4-month treatment trials

Trial	Regimen	N	Failure *n (%)*	Relapse *n (%)*	Favourable *n (%)*
ReMOX [21]	2RHZM/2RHM	568	4 (1)	46 (8)	436 (77)
	2REZM/2RM	551	1 (1)	64 (12)	419 (76)
	Control	555	3 (1)	13 (2)	468 (84)
RIFAQUIN [22]	2RMZE/2PM	165	2 (1)	19 (12)	135 (82)
	Control	163	2 (1)	4 (2)	155 (95)
OFLOTUB [23]	2RHZG/2RHG	694	12 (2)	101 (15)	548 (79)
	Control	662	16 (2)	47 (7)	548 (83)
S31 [16]	2HPZM/2HPM	791	34 (4.3)		668 (85)
	2HPZ/2HP	784	63 (8.0)		645 (82)
	Control	768	11 (1.4)		656 (85)
RIFASHORT [24]	$2R_{1200}HZE/2R_{1200}H$	186	9 (4.8)		167 (89.8)
	$2R_{1800}$ HZE/$2R_{1800}H$	186	9 (4.8)		161 (86.6)
	Control	187	2 (1.1)		174 (93)

R, rifampicin at a dose of 10mg/kg; H, isoniazid; Z, pyrazinamide; M, moxifloxacin; E, ethambutol; G, gatifloxacin; P, rifapentine; R_{1200}, rifampicin at a dose of 1200mg once daily; R_{1800}, rifampicin at a dose of 1800mg once daily.

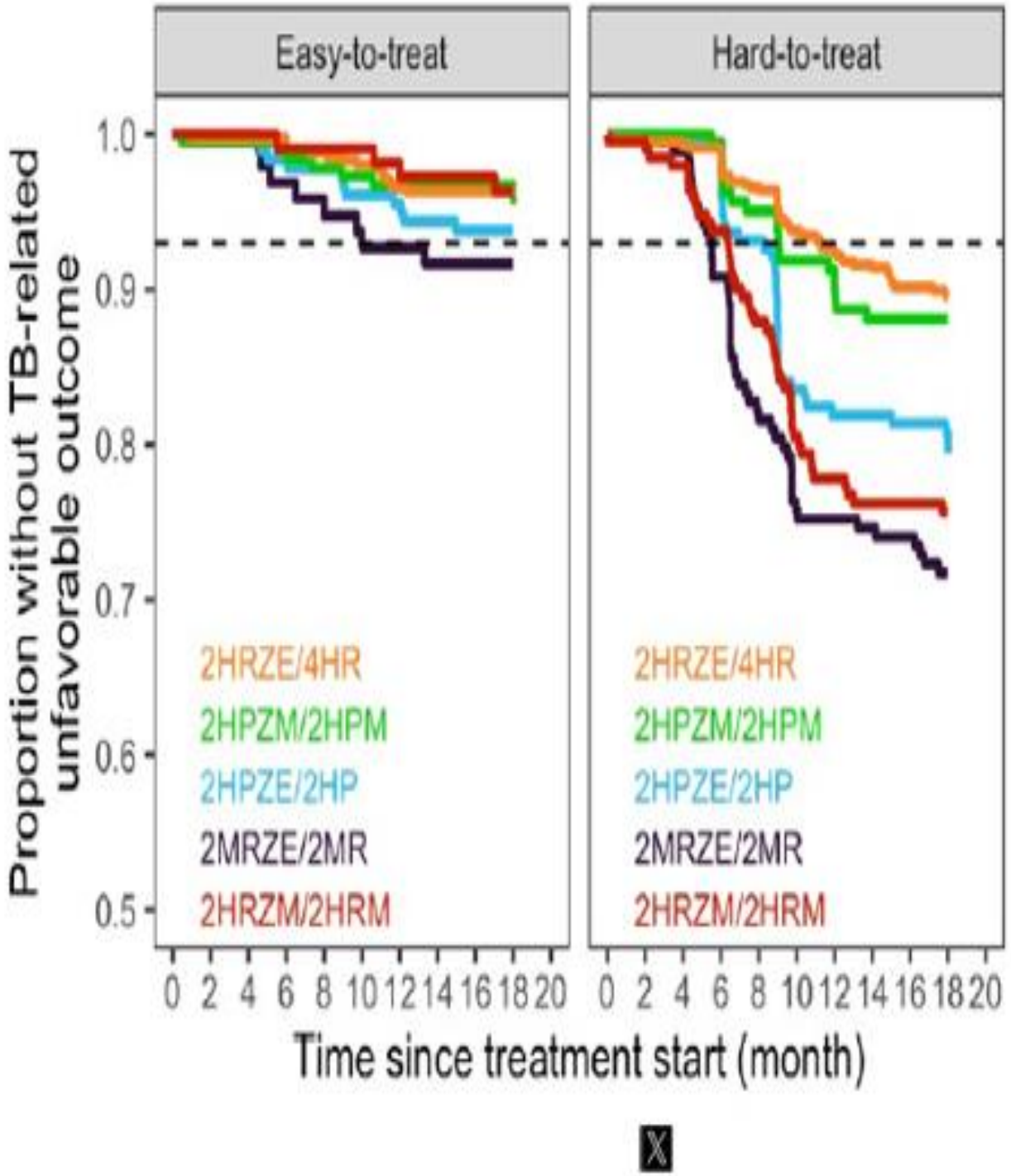
ARTICLES
https://doi.org/10.1038/s41591-018-0224-2
Nov 2018
nature medicine
OPEN
Corrected: Publisher Correction

A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis

Imperial et al

- Using pooled patient level data identified populations eligible for 4-month treatment by:
  - Analysis of 3,405 participants
    - OFLOTUB, RIFAQUIN and REMox TB which evaluated 4 months with a later generation FQN regimen or a standard regimen
    - Control RIPE x 2months; RI x 4 months
- **Identification of hard-to-treat phenotypes**
- Assessing impact of adherence and dosing strategy

Lessons from the DS Phase 3 Clinical Trials to shorten treatment duration to 4 months



Control

Successful 4-month regimen

Failed

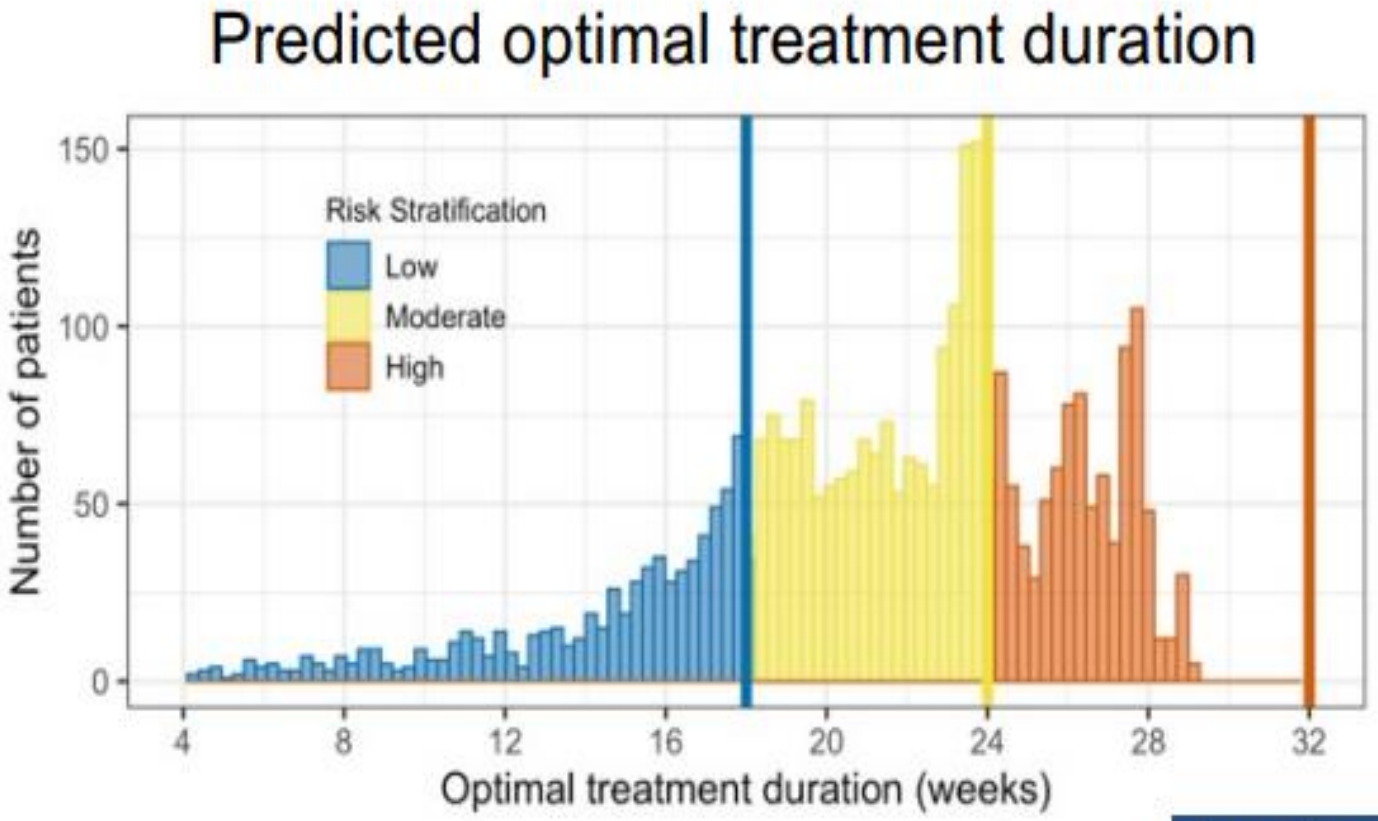
Failed

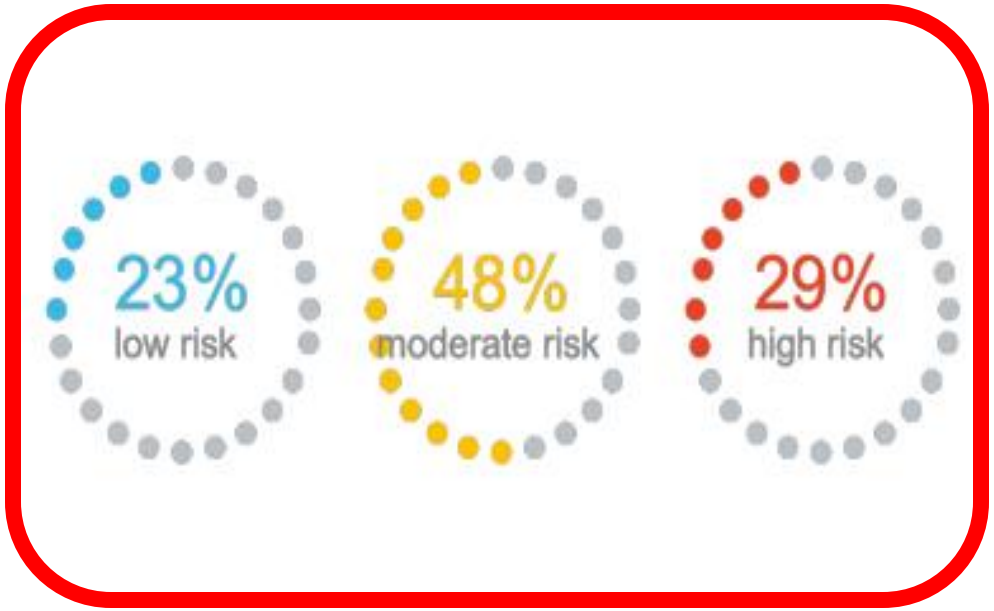
Failed

Phase 3 clinical trials failed because of inadequate response
In hard-to-treat patients

(Imperial et al. 2018)

OPTIMAL DURATION FOR HRZE





American Journal of Respiratory and Critical Care Medicine

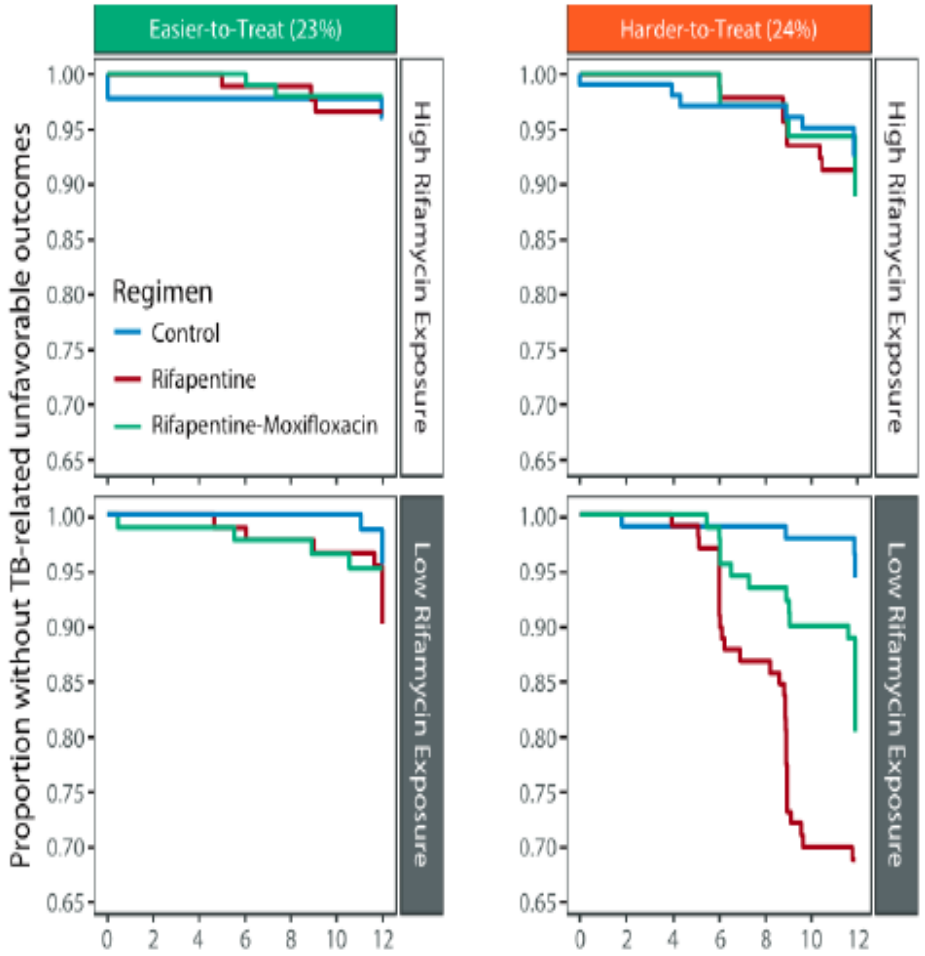
Home > American Journal of Respiratory and Critical Care Medicine > List of Issues > Volume 204, Issue 9

Precision-Enhancing Risk Stratification Tools for Selecting Optimal Treatment Durations in Tuberculosis Clinical Trials

Marjorie Z. Imperial [1,2], Patrick P. J. Phillips [2,3], Payam Nahid [2,3], and Radojka M. Savic [1,2,3]
+ Author Affiliations

UCSF

MORE INTENSIVE TREATMENT CAN OVERCOME PHENOTYPE EFFECT
MORE INTENSIVE = HIGHER EXPOSURE



nature communications

Article

https://doi.org/10.1038/s41467-024-53273-7

Risk-stratified treatment for drug-susceptible pulmonary tuberculosis

Received: 14 May 2024

Accepted: 30 September 2024

Published online: 30 October 2024

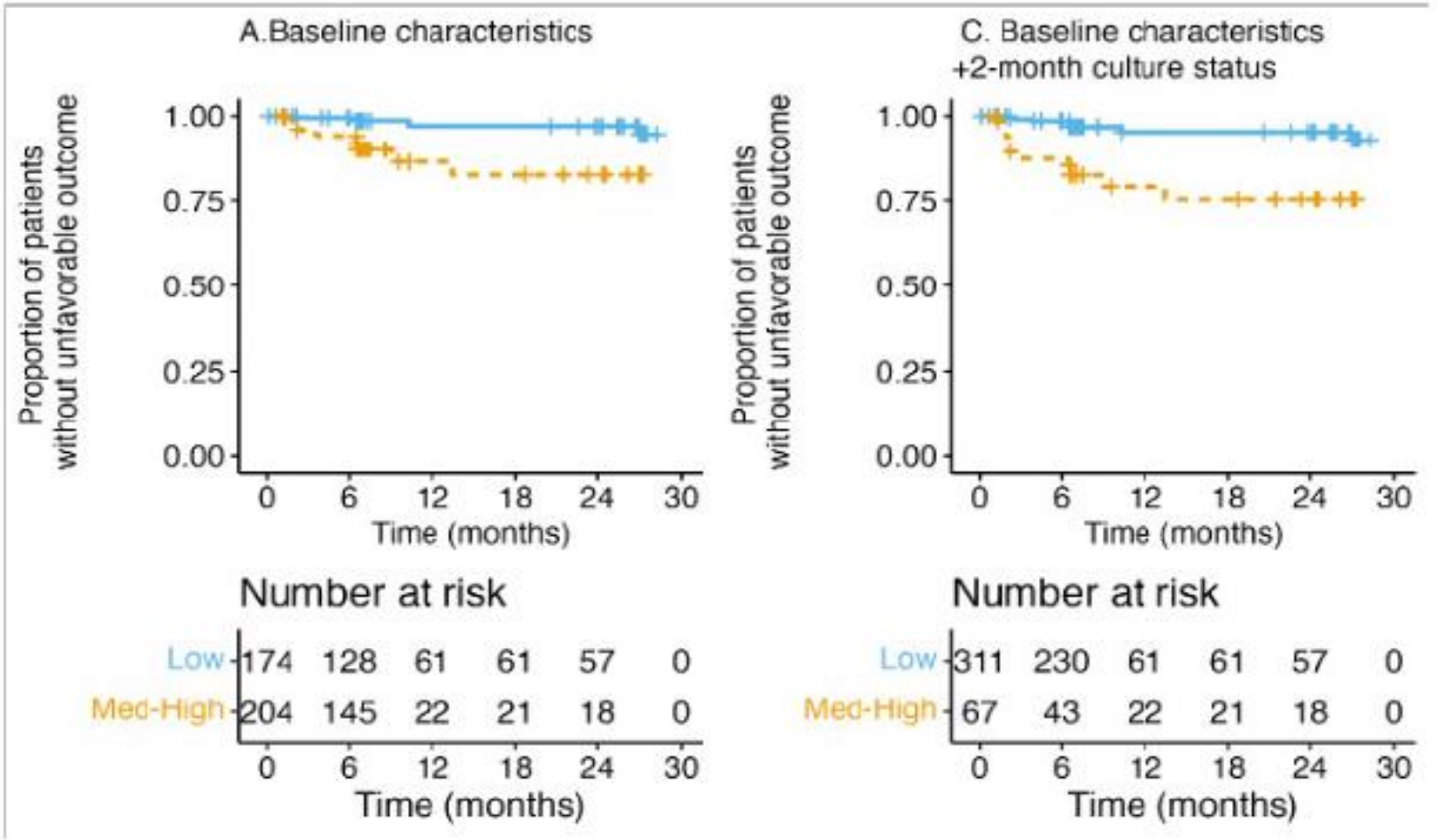
Check for updates

Vincent K. Chang[1,2], Marjorie Z. Imperial[1,2], Patrick P. J. Phillips[2,3], Gustavo E. Velásquez[2,4], Payam Nahid[2,3], Andrew Vernon[5], Ekaterina V. Kurbatova[5], Susan Swindells[6], Richard E. Chaisson[7], Susan E. Dorman[8], John L. Johnson[9,10], Marc Weiner[11], Erin E. Sizemore[5], William Whitworth[5], Wendy Carr[5], Kia E. Bryant[5], Deron Burton[5], Kelly E. Dooley[12], Melissa Engle[11], Pheona Nsubuga[10], Andreas H. Diacon[13], Nguyen Viet Nhung[14,15], Rodney Dawson[16], Radojka M. Savic[1,2] ✉, AIDS Clinical Trial Group* & Tuberculosis Trials Consortium*

Disease phenotypes defined by:
Xpert CT and
Disease extent on CXR

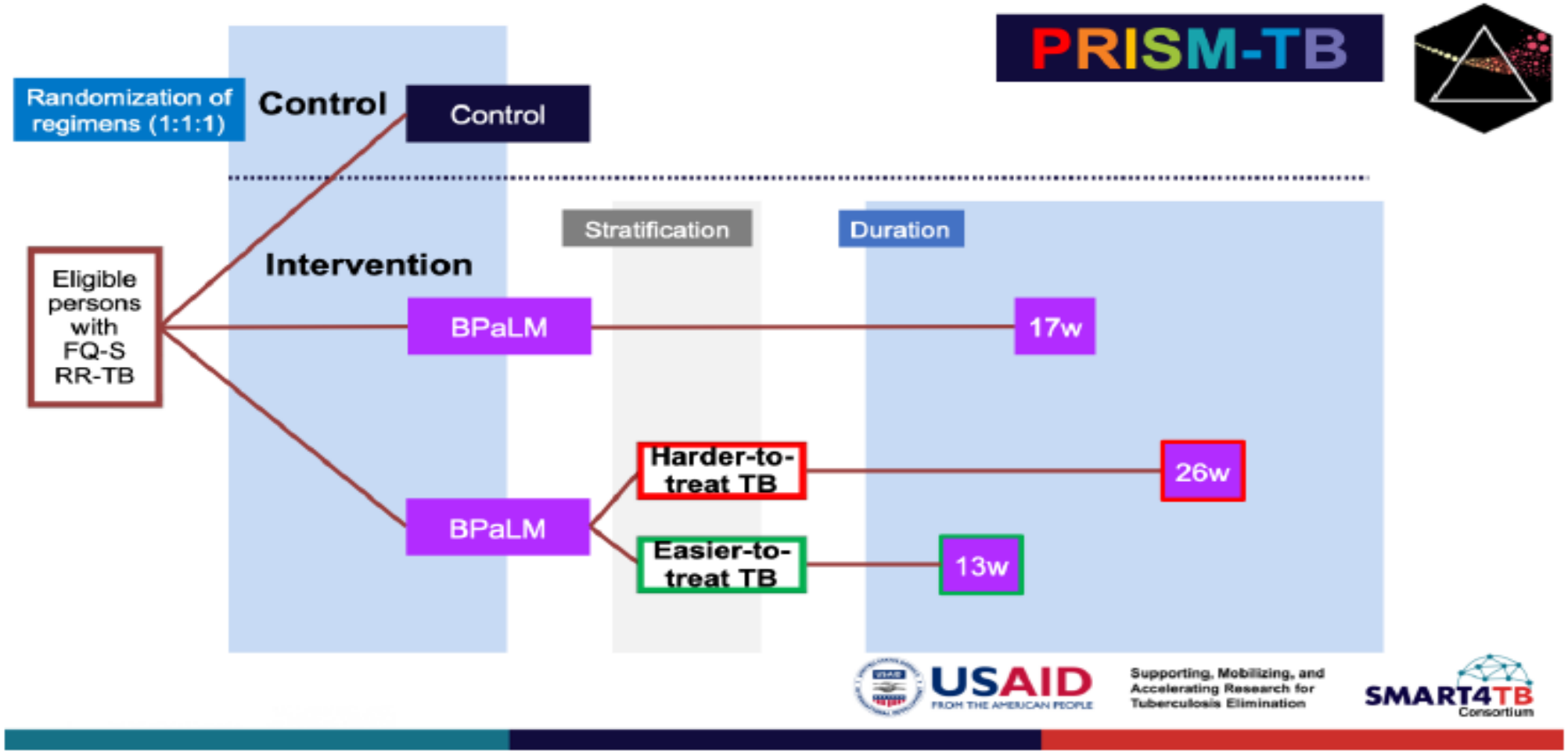
TREATMENT OUTCOMES IN DR - CLINICAL TRIALS
NIX, ZENIX, TB PRACTECAL

Low risk patients do best with BPaL and BPaLM
High risk patients may need treatment > 6 months



worldlunghealth.org

RISK STRATIFIED MEDICINE IN CLINICAL TRIALS



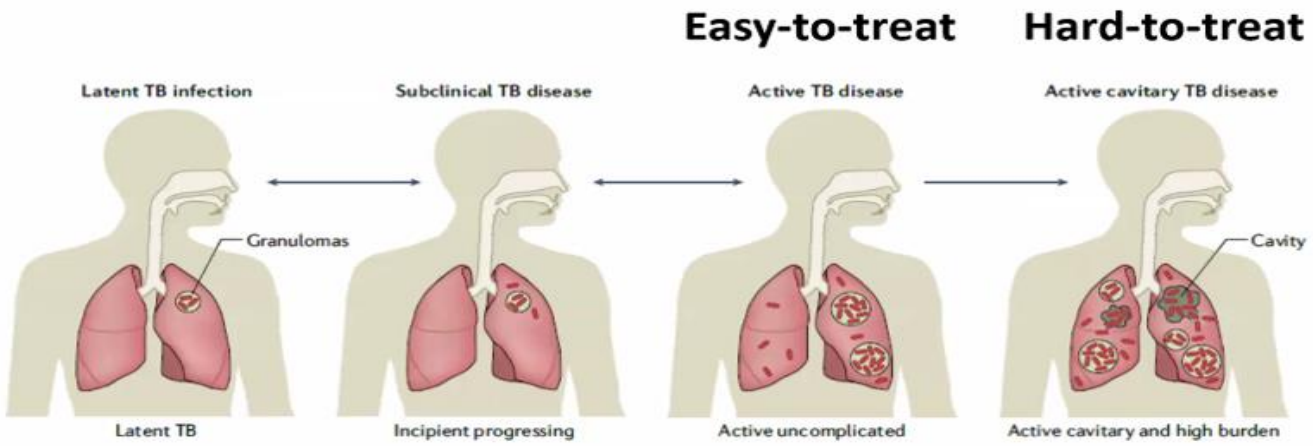
PReDiCTR goal: Derisk transition from preclinical to human studies
Learn from failures and successes

1. Mouse models: "easy-to-treat" versus "hard to treat"
2. Lesional pharmacokinetics (PK) & pharmacodynamics (PD)
3. Pathogen burden and health during treatment: CFU & RS ratio

Tool #1

Easy-to-treat versus hard-to-treat mice

- Patients with cavities & high bacillary burden drive trial outcomes



Lesion Coverage: Do steady state concentrations reach $cMBC_{50}$ or $cMBC_{90}$ in caseum?

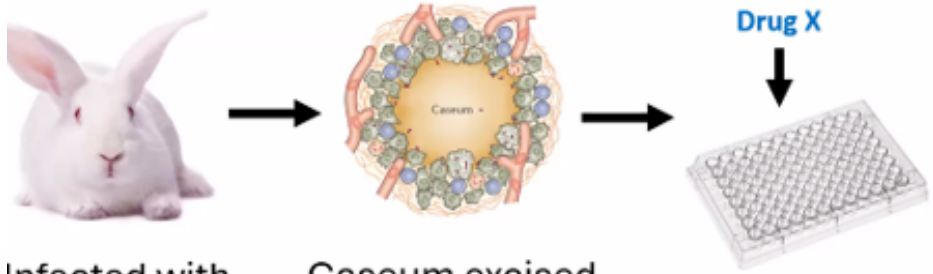
Tool #2

Lesional PD

1. Does drug have intrinsic potency against caseum *Mtb* phenotypes?

***Ex vivo* caseum model**

Activity against non-replicating, metabolically quiescent *Mtb*

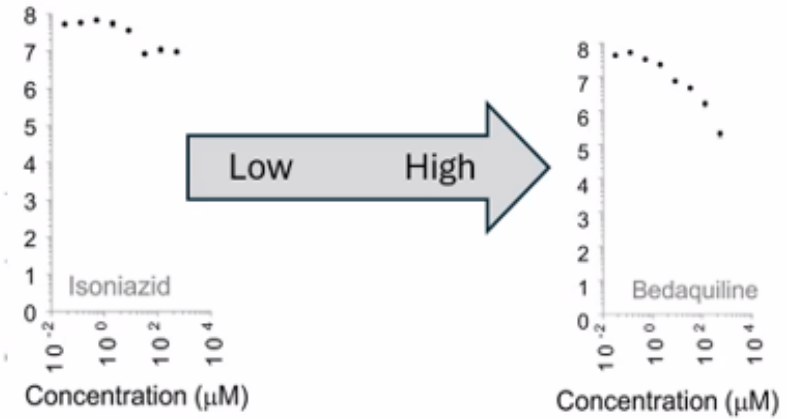


Infected with *Mtb* HN878v

Caseum excised & aliquoted

Sarathy, et al. "Extreme Drug Tolerance of Mycobacterium Tuberculosis in Caseum." *Antimicrob Agents Chemother* 62, no. 2 (2018).

Concentration -Response



$cMBC_{50}$ and $cMBC_{50}$

Drug concentration that kills 50% or 90% of *Mtb* in caseum

Tools to quantitate bacterial growth and health of MTB bacilli in a patient

Tool #3

Evaluate pathogen burden & health during treatment

- CFU — Colony Forming Units
  - Burden of *Mtb* capable of growth on solid agar plates
- RS ratio
  - Ongoing ribosomal RNA synthesis, a measure of "pathogen health"

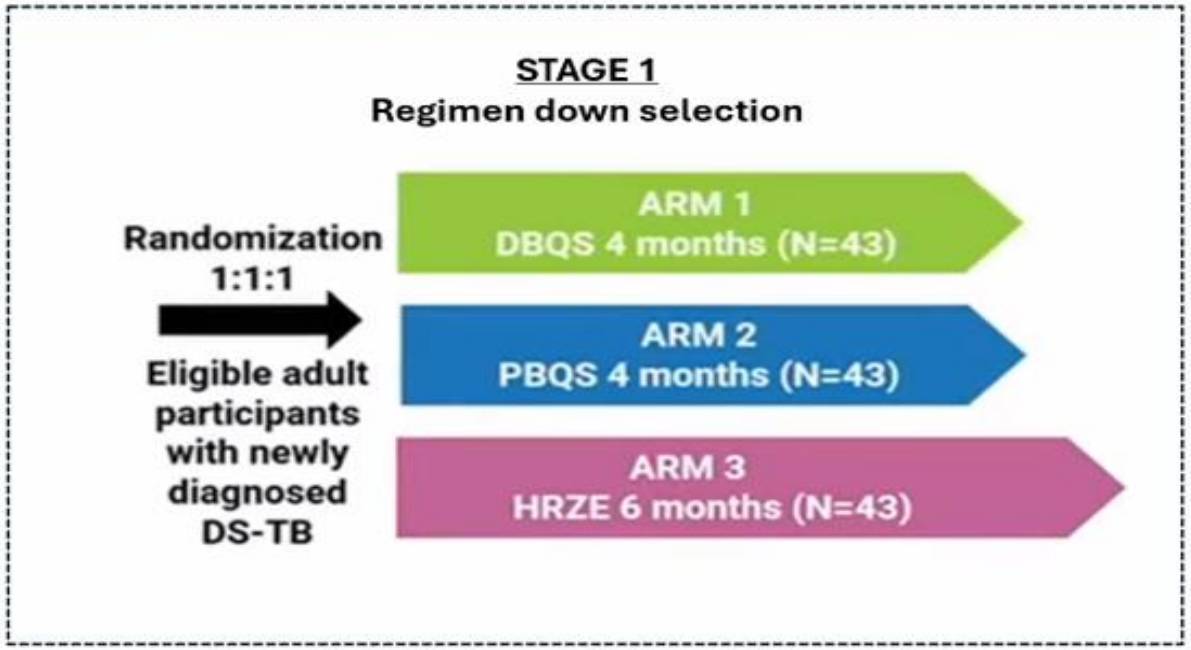
Consortium for Applied MICROBIAL METRICS

WHY did the XBQU Trial Fail?

PAN-TB XBQU trial

2-stage, Phase 2b/c to identify 3-month or less regimen

bedaquiline (B),
quabodepistat(Q),
sutezolid (U)
+
pretomanid (Pa)
or
delamanid (D)



From David Holtzman (Gates MRI) presentation at TB Science meeting November 2025

Drug Penetration into a Lesion is Critical to Overall Success
Lesional Liability

Stopped early due to lack of efficacy to shorten therapy

PAN-TB XBQU trial

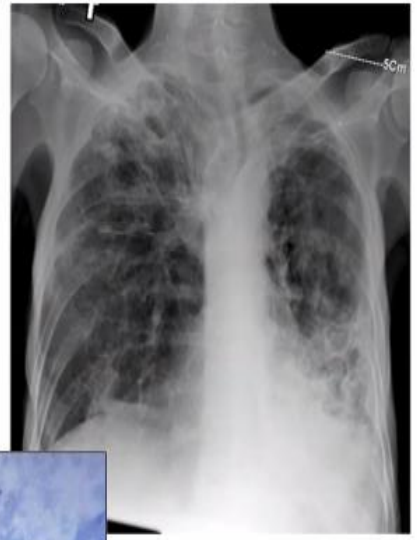
Hard-to-treat population

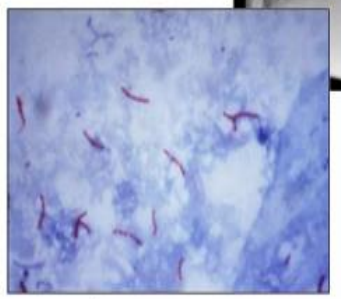
61% of mITT participants had:

- ≥2+ smear grade

  and

- Radiographically advanced disease
  - bilateral cavitation, cavity ≥4cm or ≥2 lung zones involved





Back-translation of XBQU

Why do regimens have varying lesional liability?

Lower liability — Higher liability

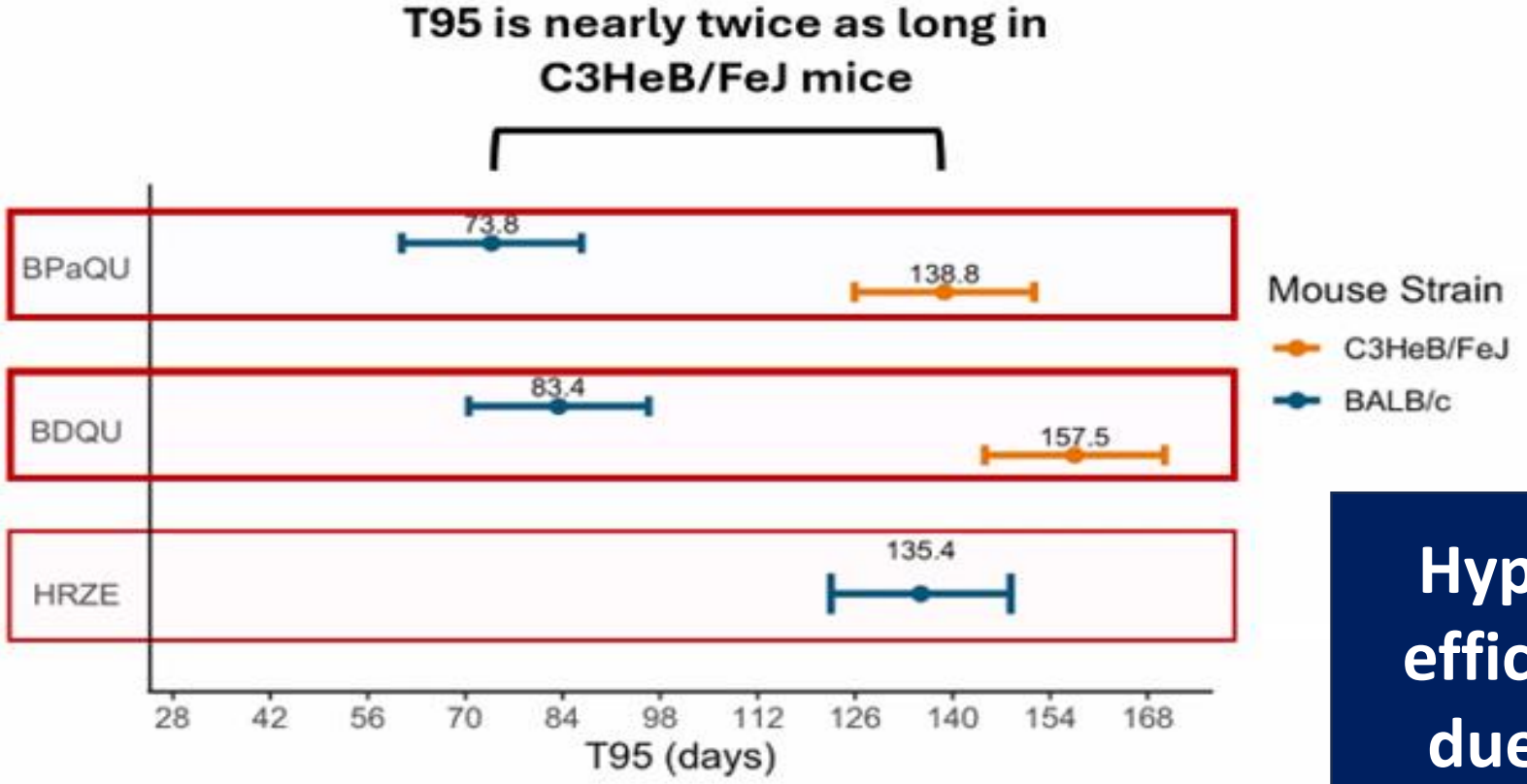
BPaMZ ← 2-drug substitution MZ vs QU → PaBQU

Adding DRIP plus sustezolid

XBQU regimens

Lower efficacy in hard-to-treat mice

C3HeB/FeJ



"Lesional Liability"
Low efficacy in C3HeB/FeJ relative to BALB/c mice

Hypothesis is that limited efficacy in complex lesions due to inadequate lesion coverage leads to under performance of XBQU

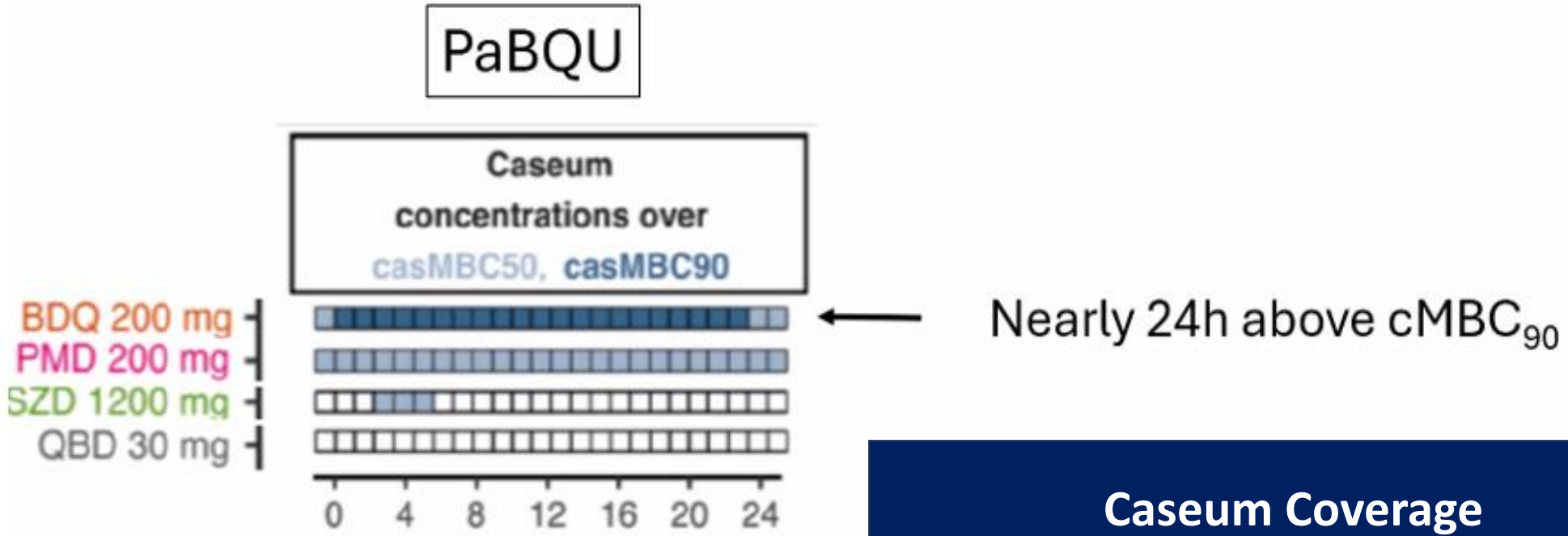
BPaMZ

Intrinsic activity of drugs against caseum *Mtb* phenotypes

Drug	$cMBC_{50}$ (µM)	$cMBC_{90}$ (µM)
moxifloxacin	0.125	1.6
bedaquiline M2	1.1	4
sutezolid	1.4	16
bedaquiline	2.1	4.7
pretomanid	3	70
sutezolid M1	12	44
pyrazinamide	800	8196
quabodepistat	>512	>512

Integrating PK

Lesion coverage at steady state



Caseum Coverage

PMD good coverage but only at MBC 50
SZD limited coverage and only at MBC50
QBD no coverage

TB Alliance Research Agenda

Roadmap to next transformational treatment paradigms

Sorfequiline/SPaL

- NC-009
- Phase 3 study
- Registration

ONE MONTH
Oral/LAI Regimen development

Long-acting injectables (LAI) technology

LAI Development:
- Sorfequiline
- Pretomanid
- TBAJ-587
- Telacebec
- Others

Sorfequiline or TBAJ-587 1-shot treatment for Latent TB

ORAL REGIMEN OF
SPaL(X)
Given for 30 days
No pre-existing resistance

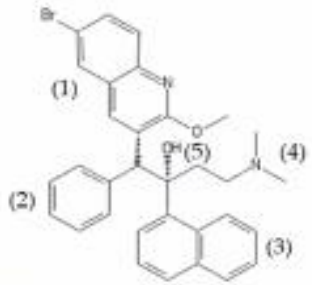
1 month

SINGLE INJECTION OF
SPa(X)
Therapeutic for 3+ months

X = additional TB drug with oral/LAI formulations, e.g., TBD11 from GMRI

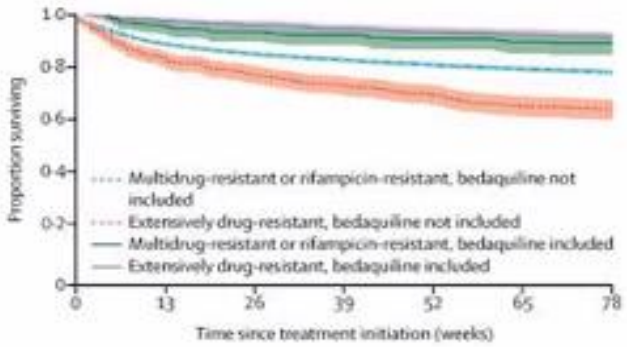
What is sorfequiline and why it is important

BDQ

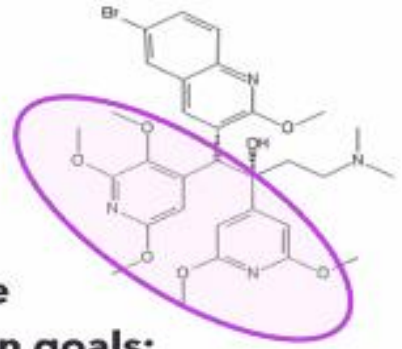


Bedaquiline (BDQ)

- First-in-class diarylquinoline (DARQ)
- Novel mechanism of action
- QT prolongation

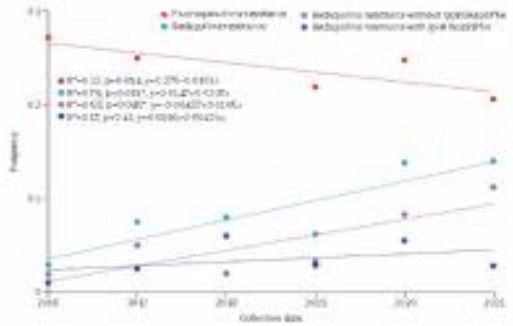


SFQ



Sorfequiline (SFQ) design goals:

- Increase potency
- Reduce/eliminate QT effect



10x greater potency compared with BDQ

- Potential to shorter treatment duration
- Lower likelihood of resistance emerging
- Activity against BDQ-resistant strains

No QT prolongation observed in preclinical or clinical studies

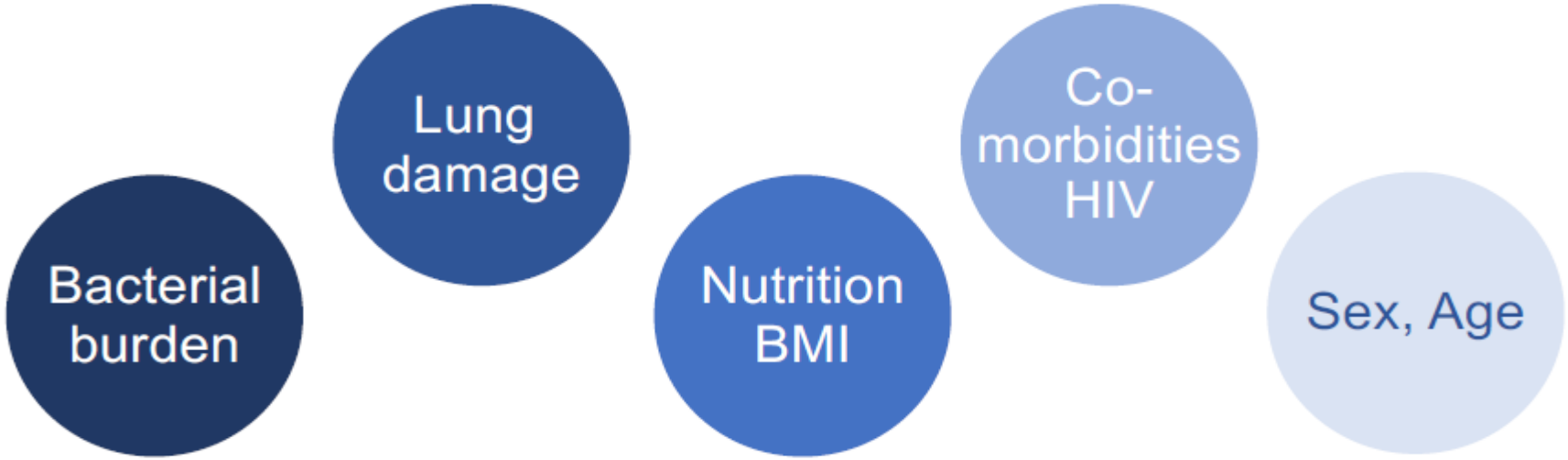
Bedaquiline Resistance developing faster than initially projected; 10+ % in many areas

We have maximized treatment shortening with drugs, disease phenotypes and regimens…

Cure of TB disease does not equal health.

- **WHAT NEXT?**
- Use defined disease phenotypes to study:
  - Underlying host immune defense and response to MTB
  - Target specific immune (endotype) with appropriate host directed therapy

FEATURES DETERMINING RISK SCORES AND STRATIFICATION



Factors other than bacterial burden impact outcomes

UCSF

Med

CellPress

Understanding the patient's endotype will likely allow specific HDT targeted to the patient's immune response (immune suppression or immune restoration)

Perspective

Tuberculosis endotypes to guide stratified host-directed therapy

Andrew R. DiNardo,[1,*] Tomoki Nishiguchi,[1] Sandra L. Grimm,[2,3] Larry S. Schlesinger,[4] Edward A. Graviss,[5] Jeffrey D. Cirillo,[6] Cristian Coarfa,[2,3] Anna M. Mandalakas,[1] Jan Heyckendorf,[7,8,9] Stefan H.E. Kaufmann,[10,11,12] Christoph Lange,[7,8,9] Mihai G. Netea,[13,14] and Reinout Van Crevel[13,*]

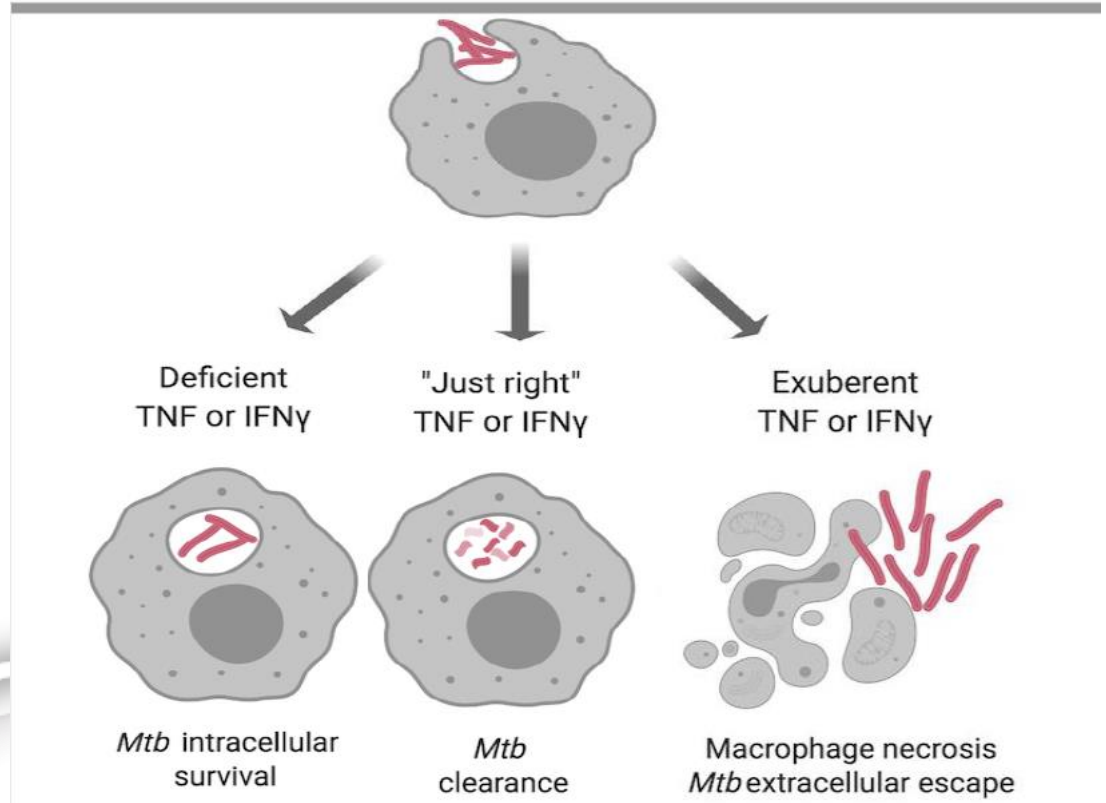
2021

TB Endotypes

Distinct molecular profiles, with specific metabolic, epigenetic, transcriptional, and immune phenotypes.

Characterized by either immunodeficiency or pathologic excessive inflammation.

Both TNF and IFN ɣ have narrow therapeutic window

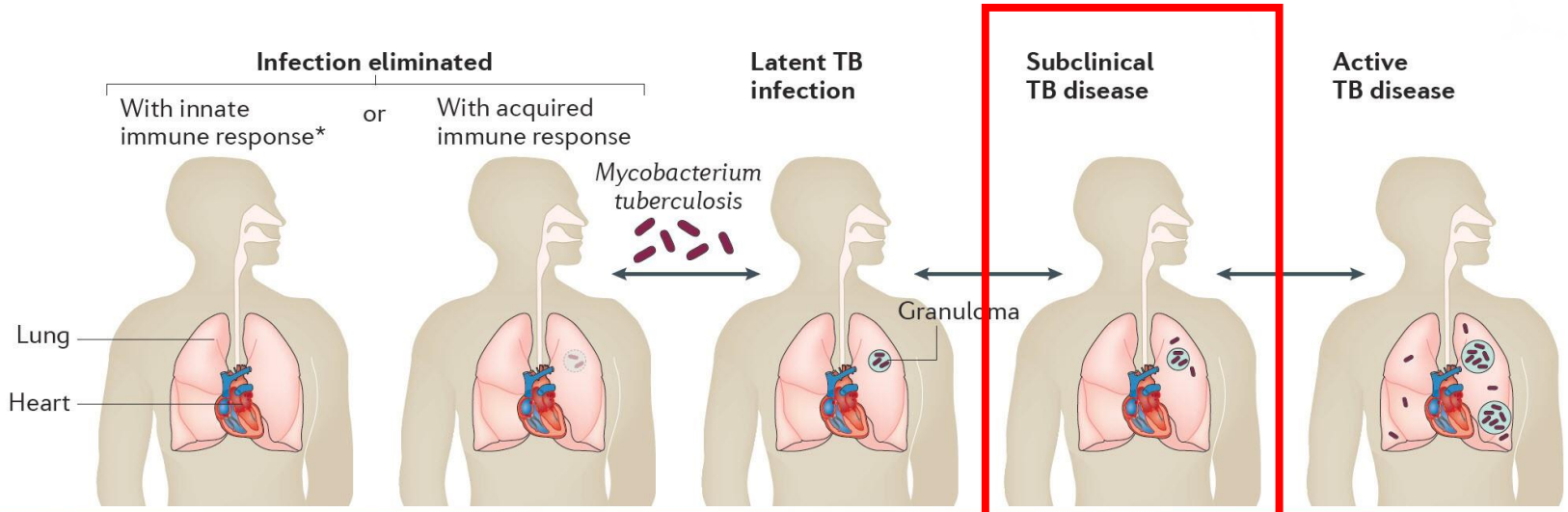


No single immune correlate of protection yet identified

What is protective in some can be harmful in others

Tuberculosis Spectrum of Disease

We may be missing up to 50% of TB patients



TST	Negative	Positive	Positive	Positive	Usually positive
IGRA	Negative	Positive	Positive	Positive	Usually positive
Culture	Negative	Negative	Negative	Intermittently positive	Positive
Sputum smear	Negative	Negative	Negative	Usually negative	Positive or negative
Infectious	No	No	No	Sporadically	Yes
Symptoms	None	None	None	Mild or none	Mild to severe
Preferred treatment	None	None	Preventive therapy	Multidrug therapy	Multidrug therapy

Biomarkers may assist with earlier diagnosis but not yet ready for prime time

Host protein biomarkers distinguish asymptomatic TB in an active case finding study.

Pedersen JL et al; IJTLD Open 2025

- Participants recruited from a nested study within active TB case finding study in Vietnam
  - **TB disease** (positive Xpert and culture or an abnormal CXR c/w TB)
  - **LTBI** (negative Xpert but positive QFT Gold)
  - **Controls**
- Most asymptomatic or had only one symptom
- Screened with 9 Protein panel
  - **IP-10 and IL-6 significantly elevated in individuals with clinical TB** compared to both healthy controls and the TBI cohort
  - IP-10 most effective single marker with **specificity of 95.5% but sensitivity of only 32.9%**
- **Suggests measurable changes at transcriptional level are present in early TB Disease and are associated with the inflammatory response to TB Disease rather than LTBI**

Post tuberculous Lung Disease

Clinical and Transcriptomic Risk Factors for Post TB lung disease in a cohort of Kenyan Adults
Zifodya et al; Am J Respir Crit Care Med Feb 2026

- Prospective, observational cohort study; adults with newly Dx TB
- Post TB lung disease defined as abnormal spirometry at month 12
  - 6 months after completion of 6 months of standard TB treatment
  - PTLD patients had more cough and dyspnea
  - Prior TB more common
- PTLD found in **50.2%**
  - **29%** Restrictive (FVC < 5^{th} %, FEV1/FVC > 5^{th}%)
  - **21%** Obstructive (FEV1/FVC < 5^{th} %)

Clinical and Transcriptomic Risk Factors for Post TB Lung Disease (PTLD) in a cohort of Kenyan Adults

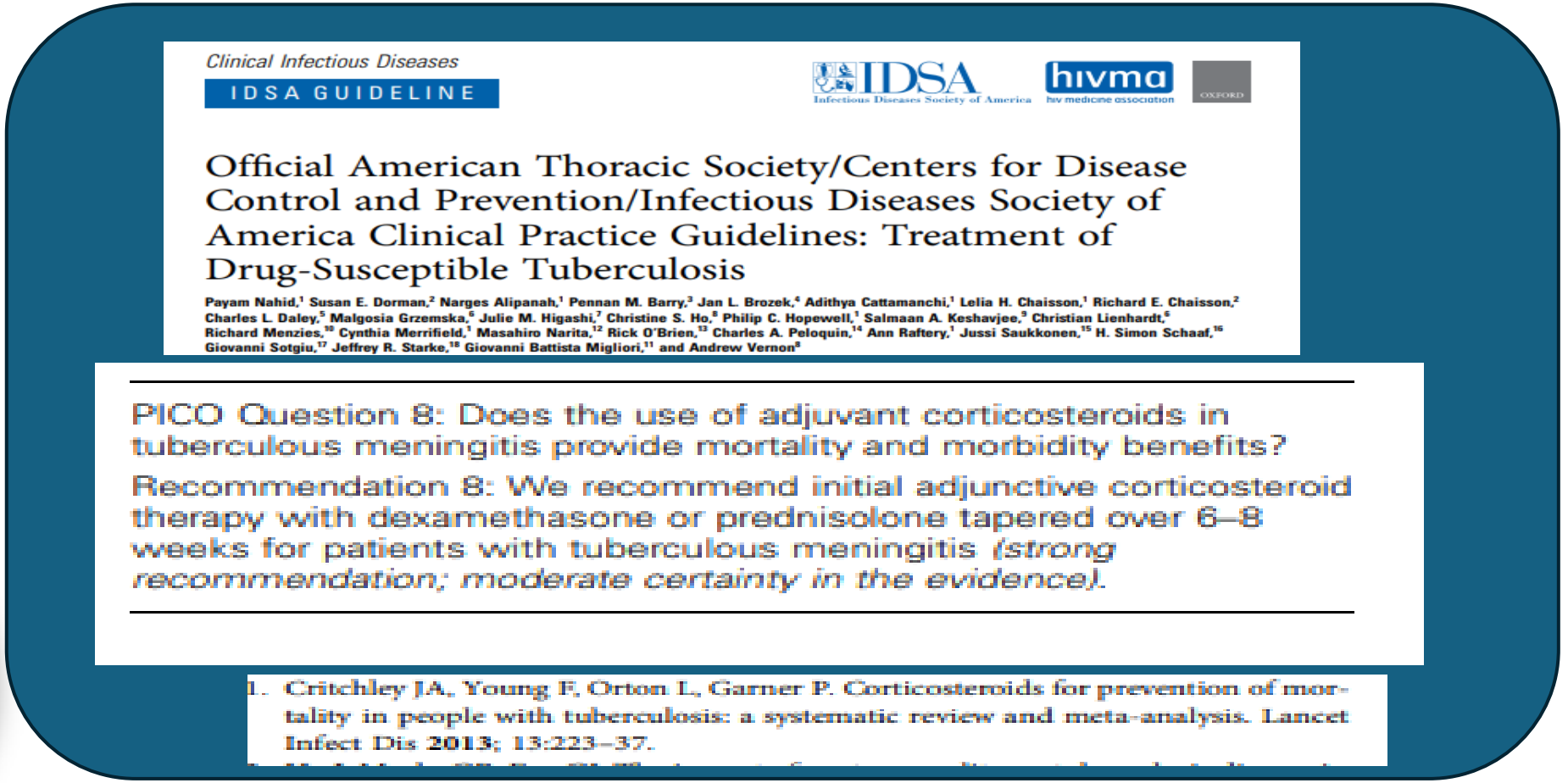
Zifodya et al; Am J Respir Crit Care Med Feb 2026

- Post TB lung disease defined as abnormal spirometry at month 12
  - 6 months after completion of 6 months of standard TB treatment
  - PTLD patients had more cough and dyspnea
  - Prior TB more common (adjusted odds ratio): aOR 3.2
  - Increasing number of CXR quadrants involved at TB Dx: aOR 2.0

- Novel differential gene expression at TB diagnosis and after completion of treatment
  - **Restrictive PTLD**: **early inflammation and immune activation** which mitigated at treatment completion
  - **Obstructive PTLD** no differential gene expression at diagnosis but **ongoing inflammation and differential gene expression present at 6-month visit**

Recommended Host Directed Therapy in TB

- ART in HIV TB
- Adjuvant steroid therapy in TB meningitis



Clinical Infectious Diseases

IDSA GUIDELINE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

PICO Question 8: Does the use of adjuvant corticosteroids in tuberculous meningitis provide mortality and morbidity benefits?

Recommendation 8: We recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks for patients with tuberculous meningitis *(strong recommendation; moderate certainty in the evidence).*

1. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis **2013**; 13:223–37.

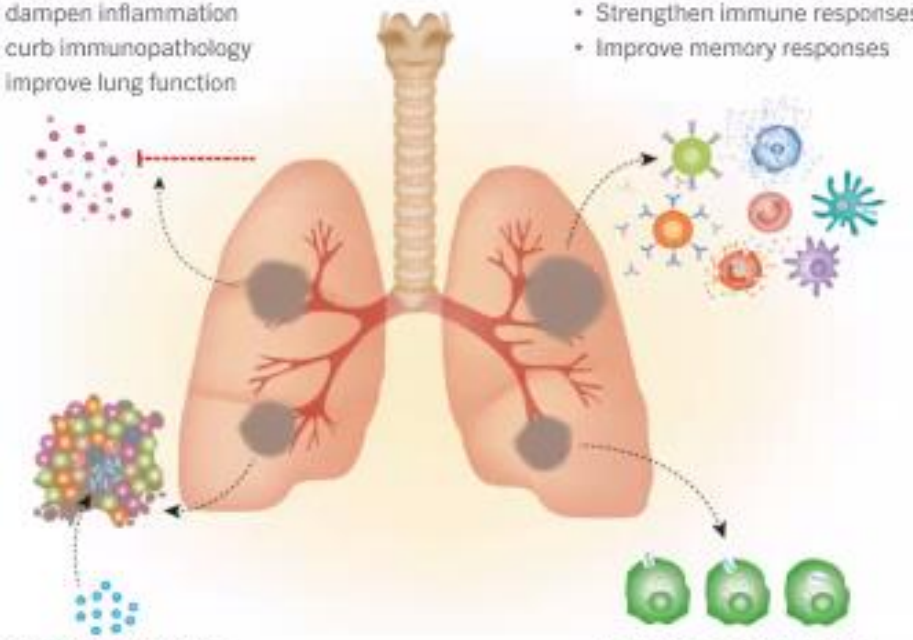
OUR VISION

Exploit novel host directed therapies to achieve treatment shortening

TB Alliance

Target inflammatory mediators:
- dampen inflammation
- curb immunopathology
- improve lung function

Enhance immune response
- Strengthen immune responses
- Improve memory responses



Disrupt structure to improve drug penetration

Enhance macrophage bactericidal mechanisms

Synergy with ongoing GSK partnership (iPSC and GWAS platform for HPI discovery)

GOAL

LONG TERM

Utilize immunotherapy potential to achieve cure in less than 1 month

NEAR FUTURE

Identifying 1-2 novel adjunctive therapies with demonstrated potential for treatment shortening to enter pre-clinical development in the context of TBA novel regimen

Roadmap to next transformational treatment paradigms

Sorfequiline/SPaL

- **NC-009**
- **Phase 3 study**
- **Registration**

ONE MONTH
Oral/LAI Regimen development

1 month

ORAL REGIMEN OF
SPaL(X)
Given for 30 days
No pre-existing resistance

SINGLE INJECTION OF
SPa(X)
Therapeutic for 3+ months

Long-acting injectables (LAI) technology

LAI Development:
- Sorfequiline
- Pretomanid
- TBAJ-587
- Telacebec
- Others

Sorfequiline or TBAJ-587 1-shot treatment for Latent TB

X = additional TB drug with oral/LAI formulations, e.g., TBD11 from GMRI