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Controlling Tuberculosis: The Impact of of Adherence on Treatment and Drug Development

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Disclosures:

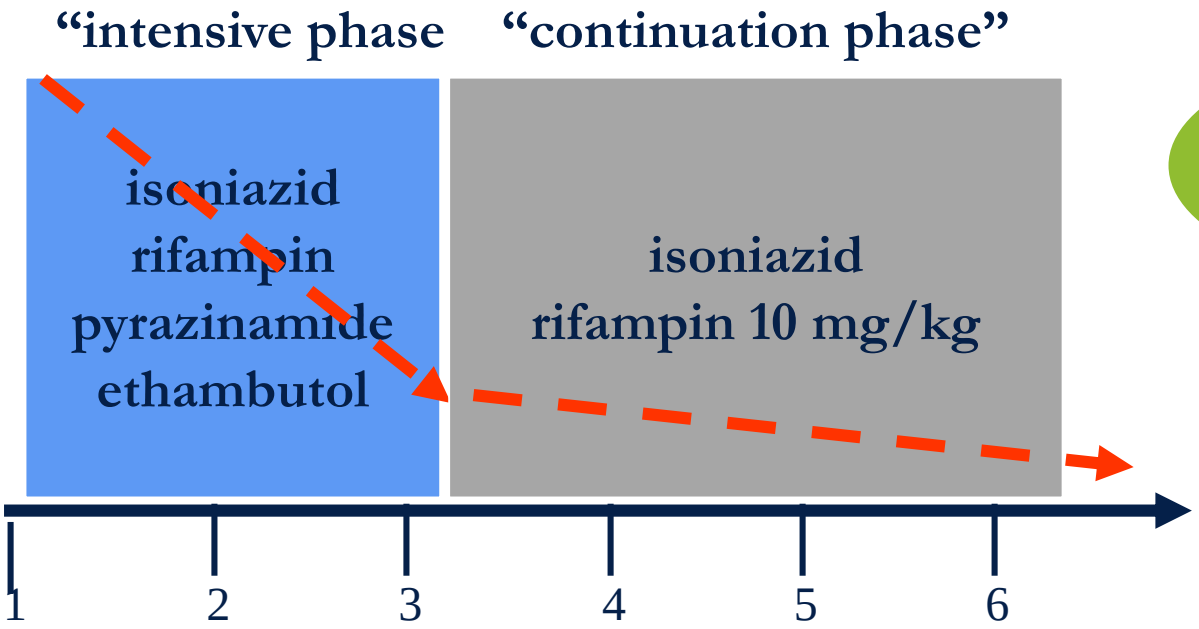
- I receive funding from BMGF, NIH, UNITAID and CDC for TB-related research
- I serve as a paid consultant for WHO on various task forces related to TB Therapeutics and treatment guidelines
- I serve as a Scientific Advisor to TB Alliance, NGO
- I serve as a Scientific Advisor to Sanofi Aventis on TB Therapeutics
- I serve on Core Science Groups for TB Therapeutics in CDC and ACTG (NIH funded) Consortia

Tuberculosis: Global Scourge

- Infectious disease that kills most people in the world
- 9.4 million cases, 1.8 million deaths/year
- Most common cause of death in HIV-infected patients
- 1/3 of the world's population latently infected
- Resistance is substantial (DR, MDR, XDR)

Current TB treatment (50 years old)

- Drug sensitive TB is treated for at least **6 months** with 50-year-old drugs
- MDR-TB requires **9-24 months** of highly toxic, poorly efficacious drugs

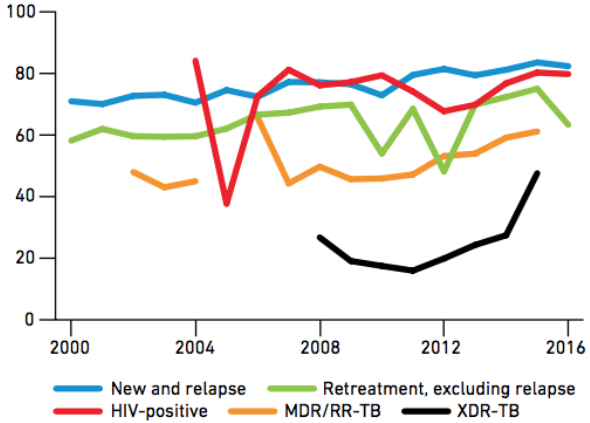


Controlled Settings
90-95%

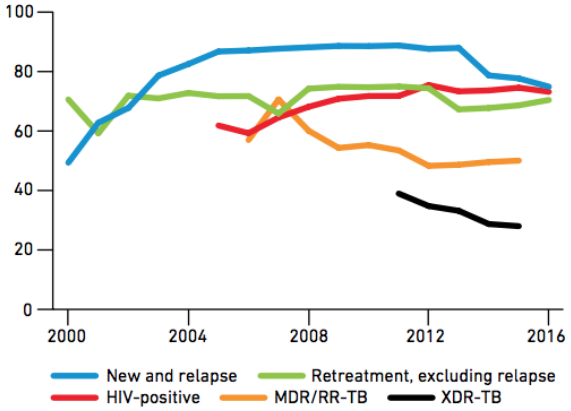
Treatment success globally

Treatment success rates (%)

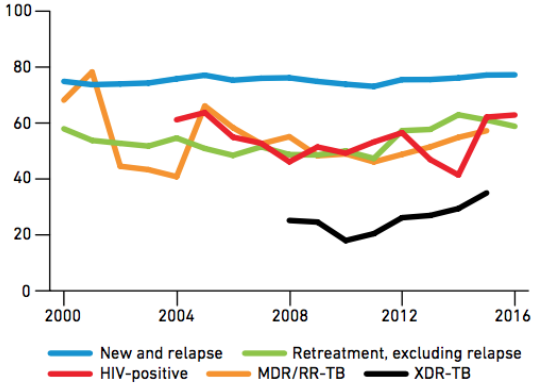
Africa



South-East Asia



Europe



WHO 2018 Global Report

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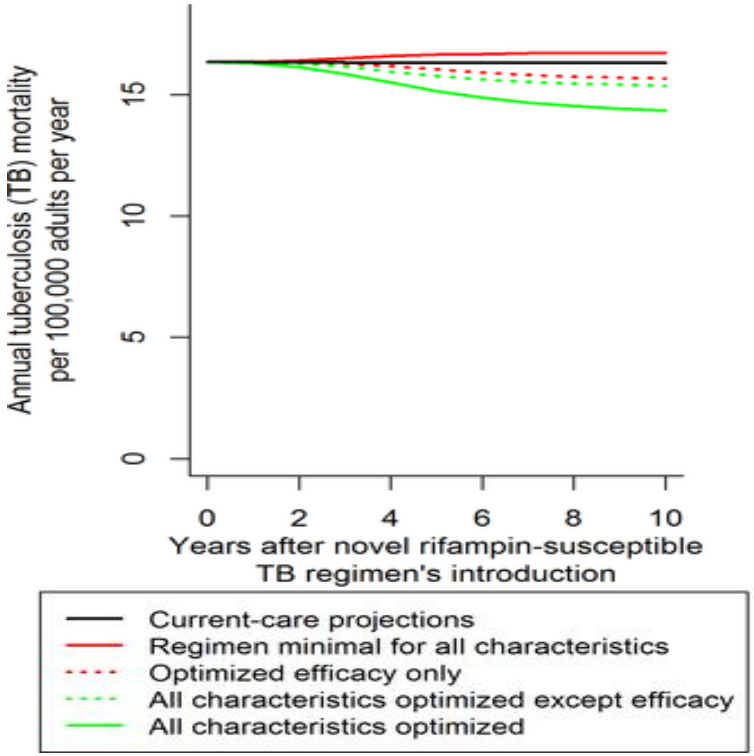
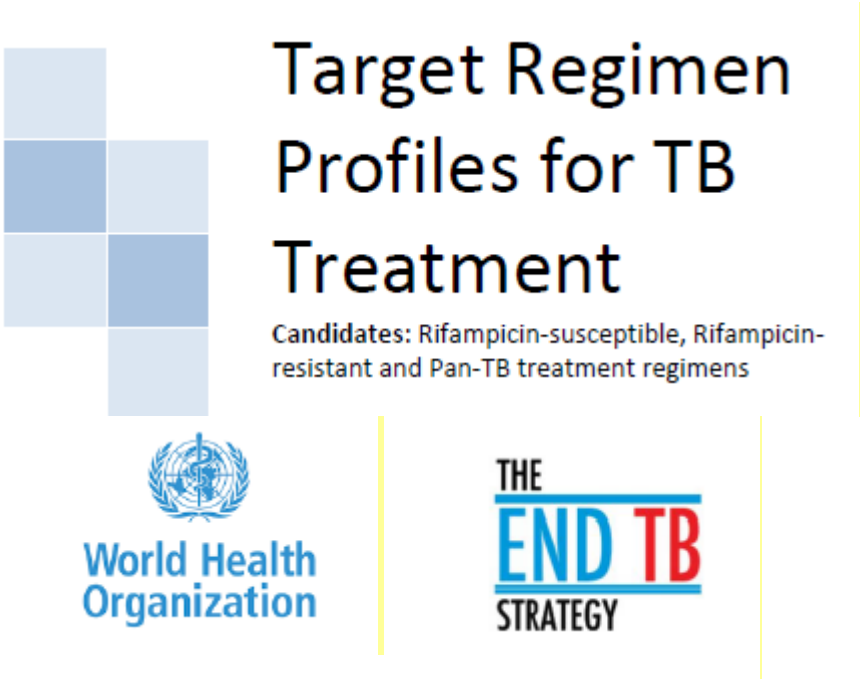
Priority-Setting for Novel Drug Regimens to Treat TB An Epidemiologic Model.

Regimen characteristic	Values modeled for novel RS TB regimen
Efficacy	• Minimal: 94% • Intermediate: 97% • Optimistic: 99%
Barrier to resistance	• Minimal: 5% • Intermediate: 0.8% • Optimistic: 0%
Preexisting novel-regimen resistance	• Minimal: 10% • Intermediate: 3% • Optimistic: 0%
Medical contraindications	• Minimal: 11% • Intermediate: 5% • Optimistic: 0%
Duration	• Minimal: 6 mo • Intermediate: 4 mo • Optimistic: 2 mo
Tolerability/ease of adherence	• Minimal: 0% • Intermediate: 25% • Optimistic: 50%



Emily A. Kendall Sourya Shrestha Ted Cohen Eric Nuermberger Kelly E. Dooley Lice Gonzalez-Angulo Gavin J. Churchyard Payam Nahid Michael L. Rich Cathy Bansbach Thomas Forissier Christian Lienhardt David W. Dowdy (2017) Priority-Setting for Novel Drug Regimens to Treat Tuberculosis: An Epidemiologic Model. PLOS Medicine 14(1): 2017

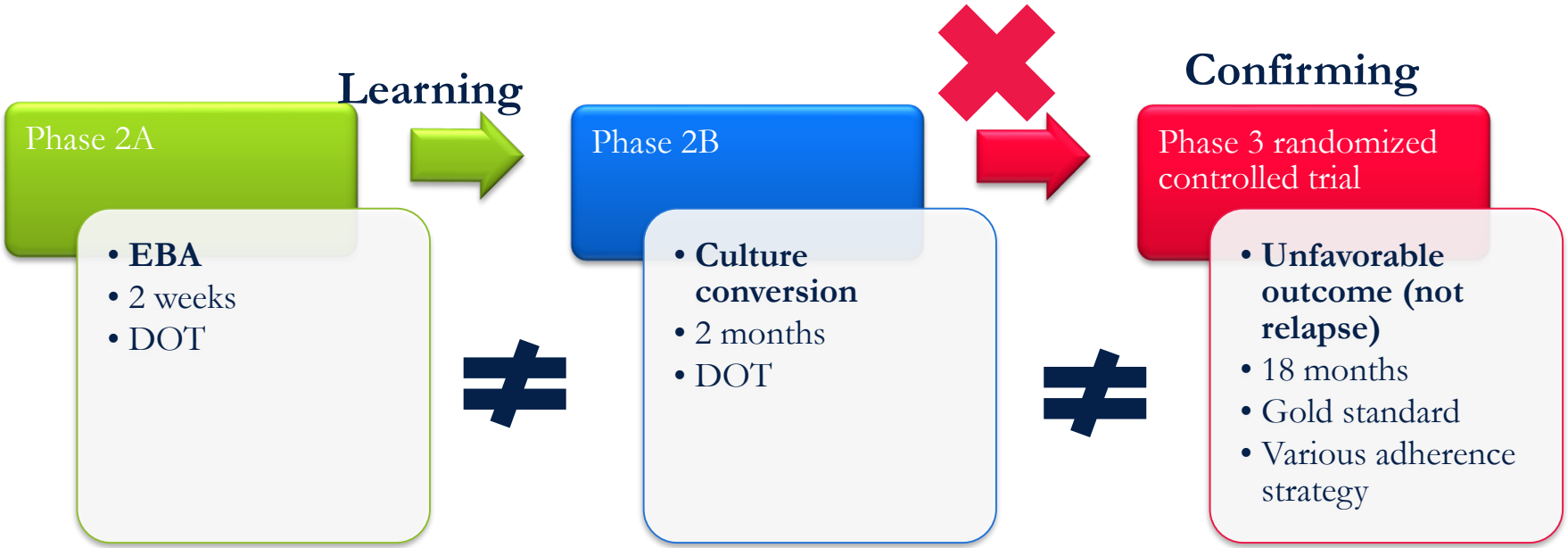
Target Regimen Profile- Drug-Sensitive TB



Priority attributes

- 2-4 month duration
- ≥95% cure rate
- No requirement for lab testing for safety
- No drug interactions with first-line HIV drugs
- High barrier to emergence of resistance

Treatment Shortening Trials



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ORIGINAL ARTICLES

Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis

S.H. Gillespie and Others

Free Full Text | Comments

One approach to improving tuberculosis therapy is to shorten the duration from 6 months to 4 months. In this trial in over 1900 patients with smear-positive tuberculosis, **two 4-month moxifloxacin-based regimens did not perform** as well as the standard 6-month regimen.

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

C.S. Merle and Others

Free Full Text

Shortening treatment regimens for tuberculosis may help control the disease. In this trial, patients with tuberculosis in sub-Saharan Africa received either a 4-month gatifloxacin-based regimen or the standard 6-month regimen. The gatifloxacin regimen **was less effective**.

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

A. Jindani and Others

Free Full Text | CME

In this report from sub-Saharan Africa, a 4-month regimen of moxifloxacin and rifapentine for pulmonary **tuberculosis was not as beneficial as two 6-month regimens**, and the benefits of a 6-month regimen based on rifapentine were similar to those of the standard 6-month regimen.

> 10 years
> $ 100M

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TB-ReFLECT: TB Re-Analysis of FluoroquinoLone Clinical Trials

World Health Organization

Critical Path to TB Drug Regimens

BILL & MELINDA GATES foundation

- Individual Level Patient Meta Analysis (n=3709)
- Aimed to:
  - Identify **patient groups eligible for 4 month treatment**
  - Profile **"hard-to-treat" patient populations**
  - Identify **drug-specific** factors predicted of unfavorable response
  - To provide data-driven evidence for immediate impact on TB treatment implementation
- Findings validated in an independent dataset (Johnson, et al., TBRU trial)

Imperial MZ, et al, A patient-level pooled analysis of treatment-shortening regimens for drug-susceptible pulmonary tuberculosis., Nat Med. 2018 Nov;24(11):1708-1715.

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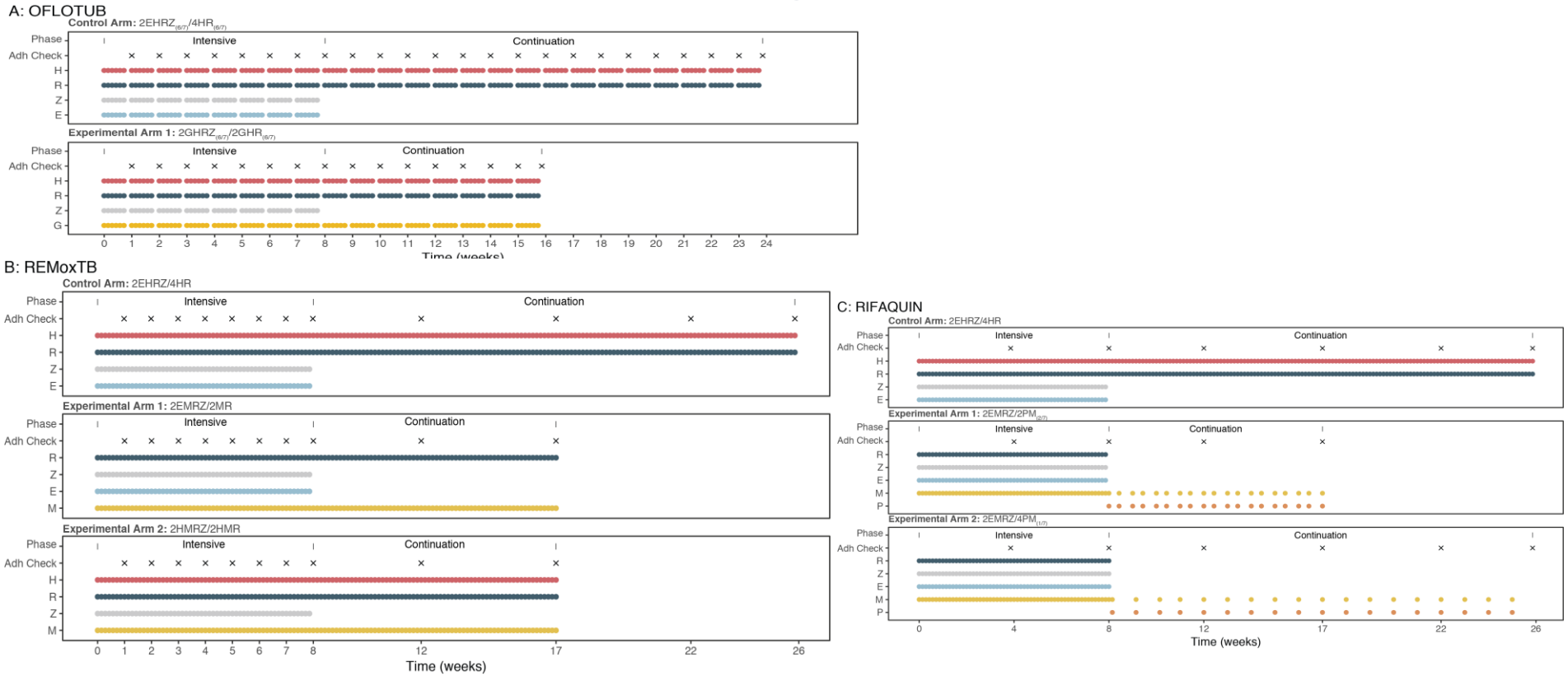
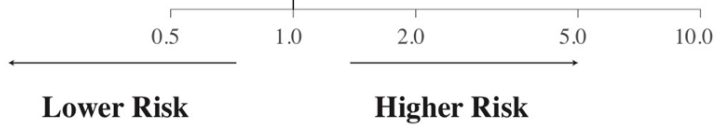
Trials and Adherence Designs



Standard-of-Care, Adherence impact

Baseline characteristics, on treatment culture status, and adherence

Variable	No.unfavorable outcomes/ No. of study participants (%)	Hazard Ratio (95% CI)
Adherence		
100%	70/824 (8)	Reference
> 90 and < 100%	23/192 (12)	1.8 (1.1 – 3.0)
<=90%	9/30 (30)	5.4 (2.5 – 11.5)
HIV status		
Negative	75/884 (8)	Reference
Positive	27/162 (17)	3.0 (1.8 – 5.0)
Month 4 culture status		
Negative	84/951 (9)	Reference
Positive	18/95 (19)	2.4 (1.4 – 4.3)
Month 2 culture status		
Negative	62/800 (8)	Reference
Positive	40/246 (16)	2.1 (1.4 – 3.3)
Sex		
Female	21/304 (7)	Reference
Male	81/742 (11)	1.9 (1.1 – 3.1)



4-Month Regimens, Adherence impact

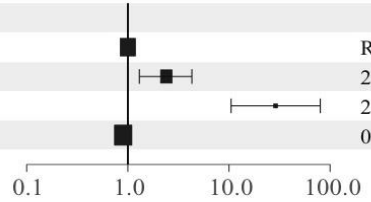
Baseline characteristics, on treatment culture status, and adherence

Variable	No.unfavorable outcomes/ No. of study participants (%)	Hazard Ratio (95% CI)
Adherence		
100%	238/1348 (18)	Reference
> 90 and < 100%	64/288 (22)	1.4 (1.0 – 1.9)
<=90%	15/32 (47)	5.7 (3.3 – 9.9)
Month 2 culture status		
Negative	212/1357 (16)	Reference
Positive	105/311 (34)	2.2 (1.7 – 2.9)
Sex		
Male	64/492 (13)	Reference
Male	253/1176 (22)	1.6 (1.2 – 2.1)
Smear grade		
Smear 0+ or 1+	53/388 (14)	Reference
Smear 2+	72/430 (17)	1.2 (0.8 – 1.7)
Smear 3+	192/850 (23)	1.6 (1.2 – 2.3)
HIV status		
Negative	270/1463 (18)	Reference
Positive	47/205 (23)	1.5 (1.1 – 2.0)
BMI (per 5 kg/m2 decrease)	†	1.4 (1.1 – 1.7)
Age (per 10 years increase)	†	1.1 (1.0 – 1.2)

Adherence and 6/7 vs 7/7 Pill Counts

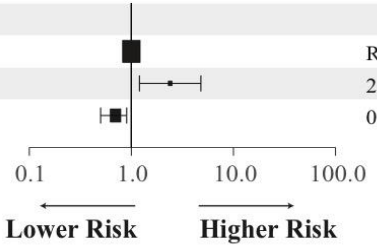
A. REMoxTB and RIFAQUIN analysis (7/7 doses per week)

Variable	No. Unfavorable Outcomes/ No. Study Participants (%)	Hazard Ratio (95% CI)
Total doses		
182 (7/7 doses per week)	26/452 (6)	Reference
156–181	22/217 (10)	2.4 (1.3 – 4.3)
112–155	13/18 (72)	28.9 (10.5 – 80.0)
Treatment Duration (per week)	*	0.9 (0.8 – 1.1)

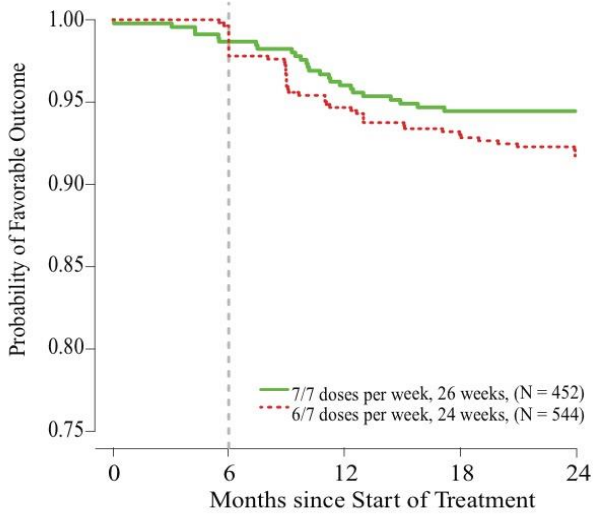


B. OFLOTUB analysis (6/7 doses per week)

Variable	No. Unfavorable Outcomes/ No. Study Participants (%)	Hazard Ratio (95% CI)
Total doses		
144 (6/7 doses per week)	50/533 (9)	Reference
112–143	13/65 (20)	2.4 (1.2 – 4.8)
Treatment Duration (per week)	*	0.7 (0.5 – 0.9)



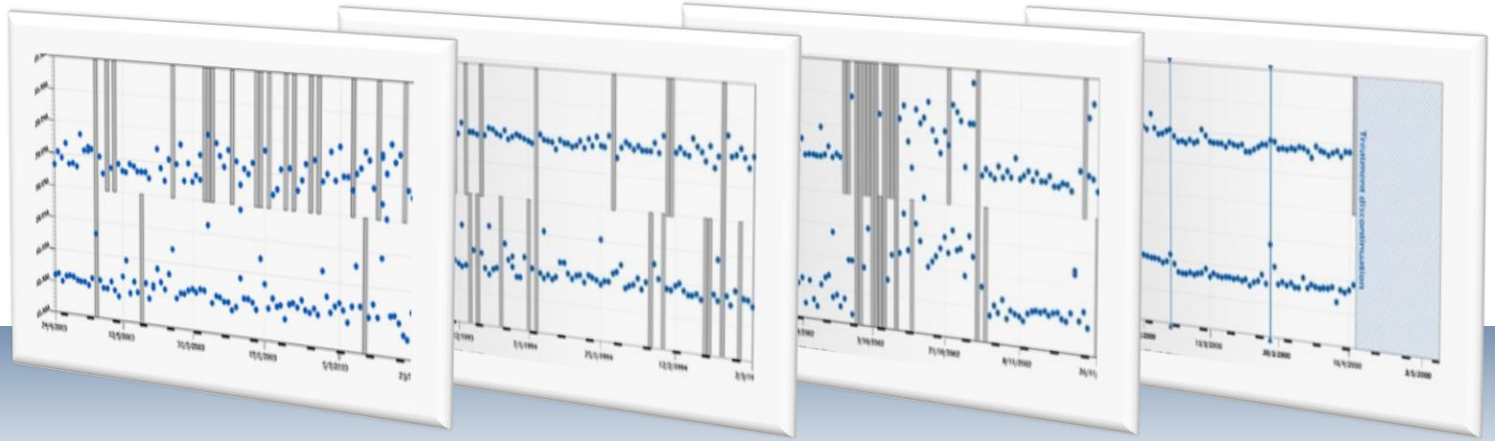
C. Kaplan Meier estimates



IN ADHERENCE, PATTERNS and TIMING MATTER

Very different health outcomes are possible, indeed likely

Each of the 4 patients took 75% of prescribed doses during a 3-month period



Problem with Evening Dose

Sporadic Dosing

Drug Holiday

Early Discontinuation

Slide Courtesy of T Blaschke and B. Vrijens

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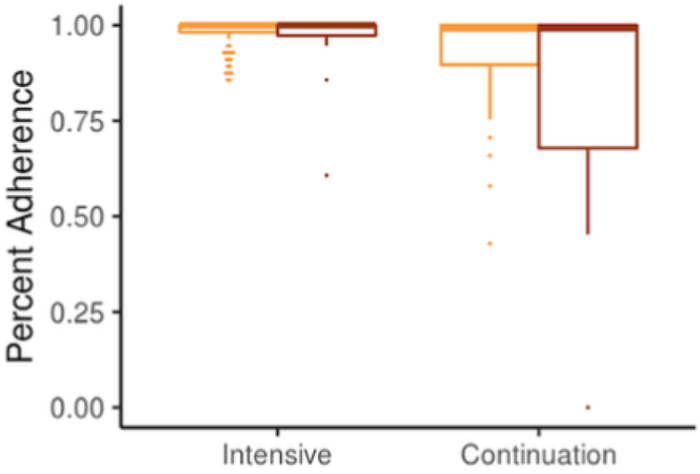
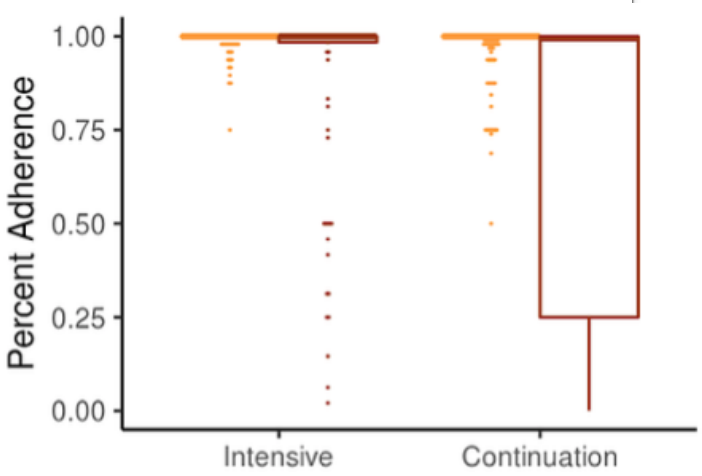
Adherence in Continuation Phase, SOC

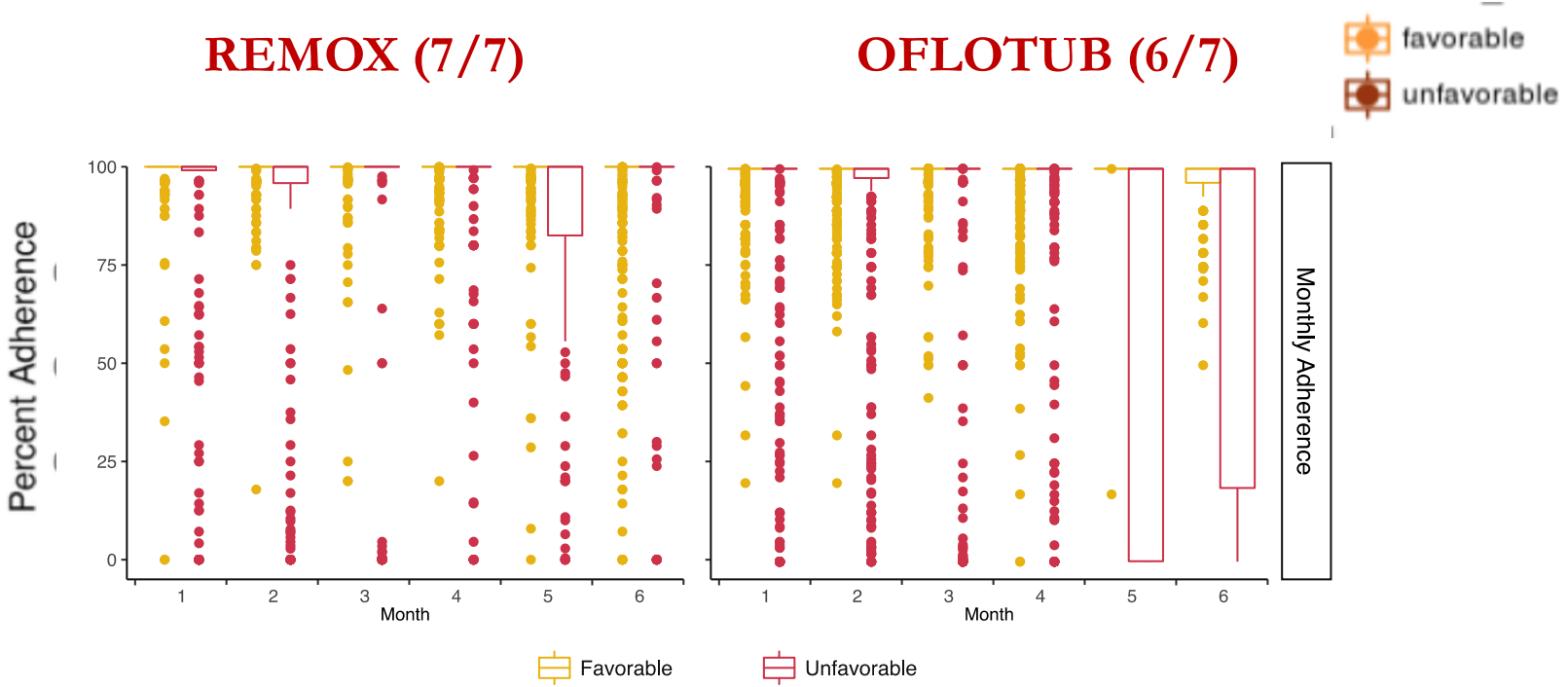
REMOX (7/7)



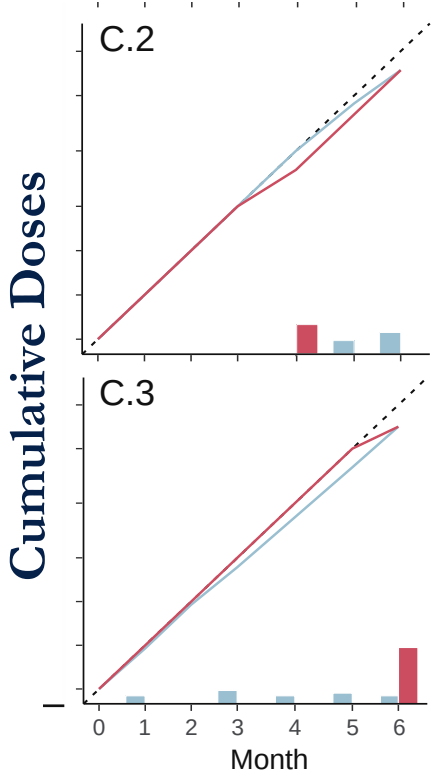
OFLOTUB (6/7)

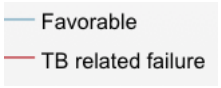


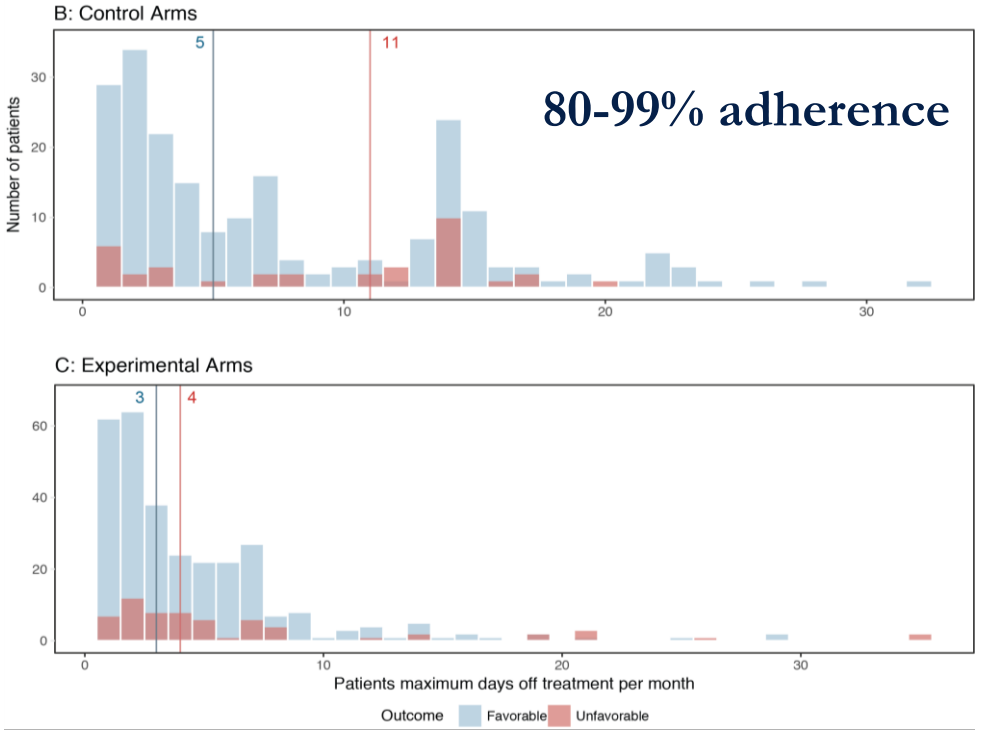
Monthly Adherence, SOC



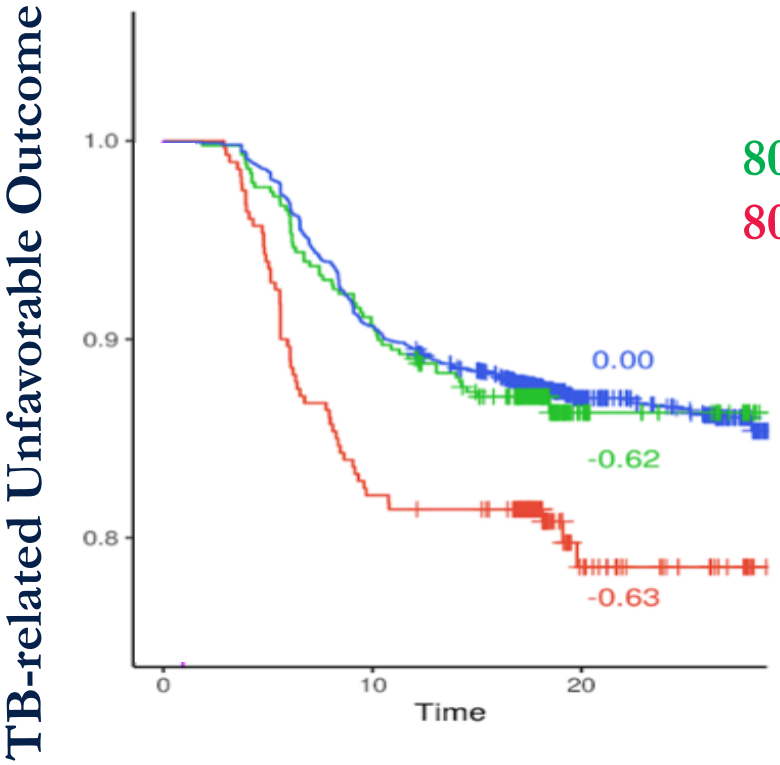
Distribution of Monthly Missed Doses in Nonadherent patients: Non-random patterns drive the treatment failure







Non-random Patterns Drive the Treatment Failure

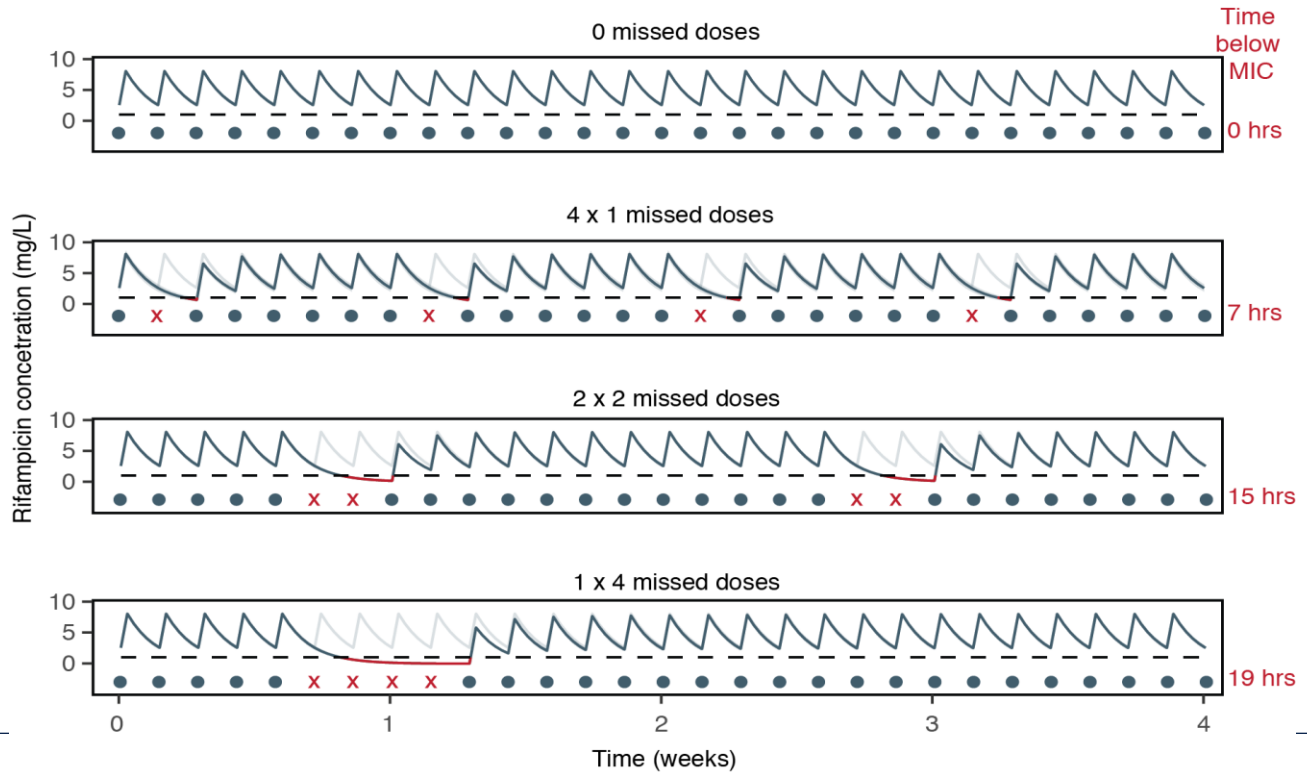


100 % Adherence

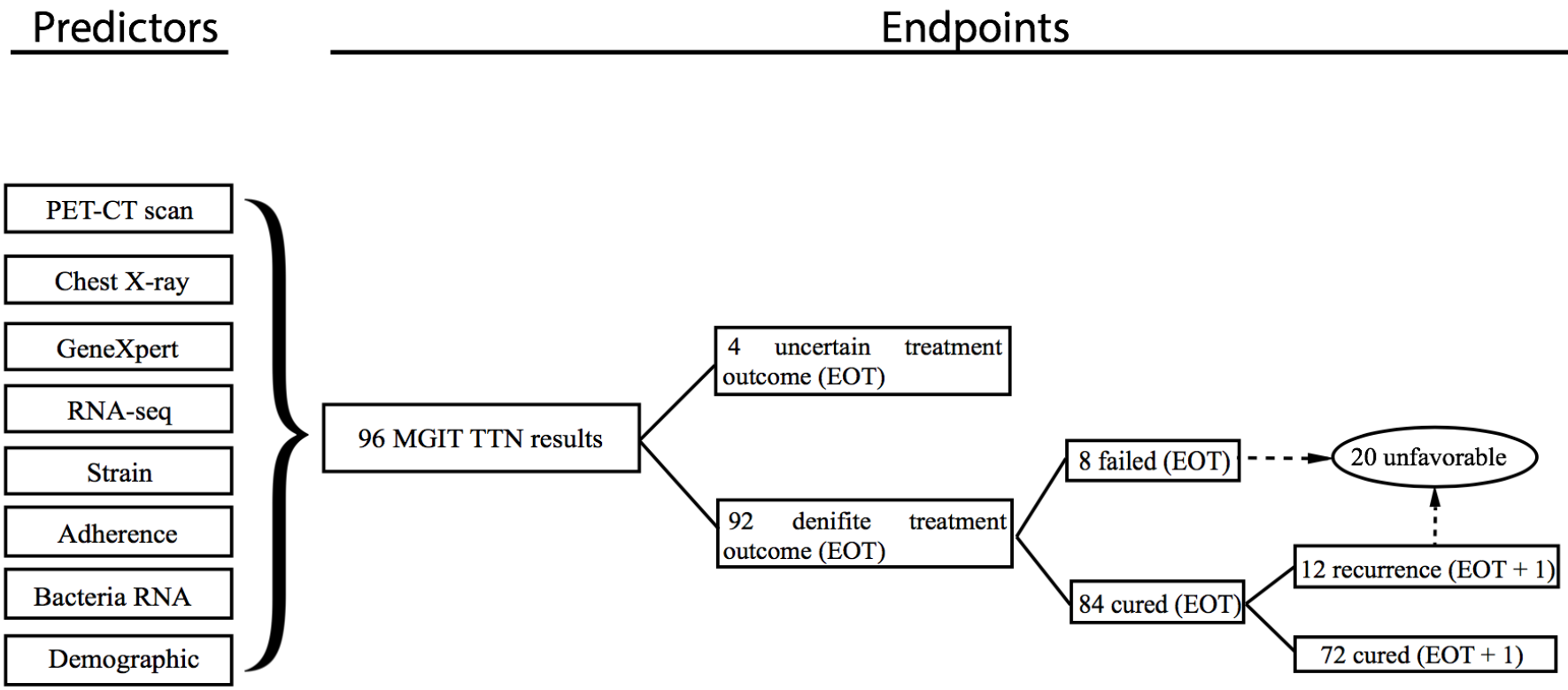
80-99% Adherence and Random patterns

80-99% Adherence and Non-Random patterns

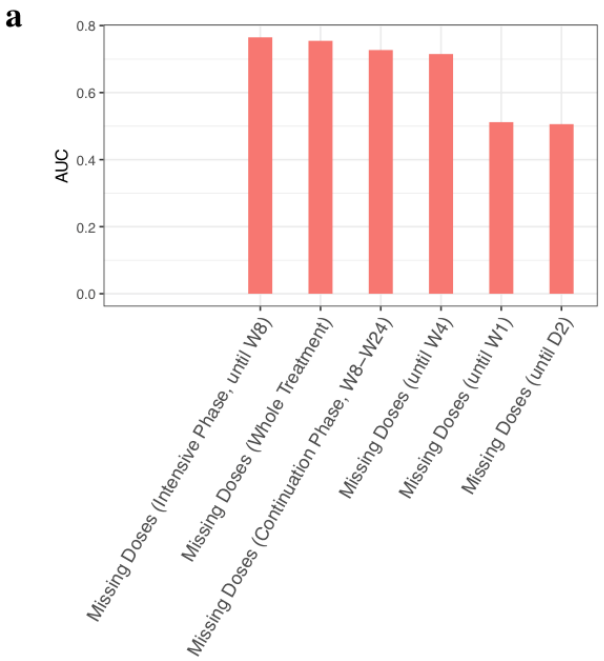
Pharmacological Rationale for Impact of Clustering of Missed Doses

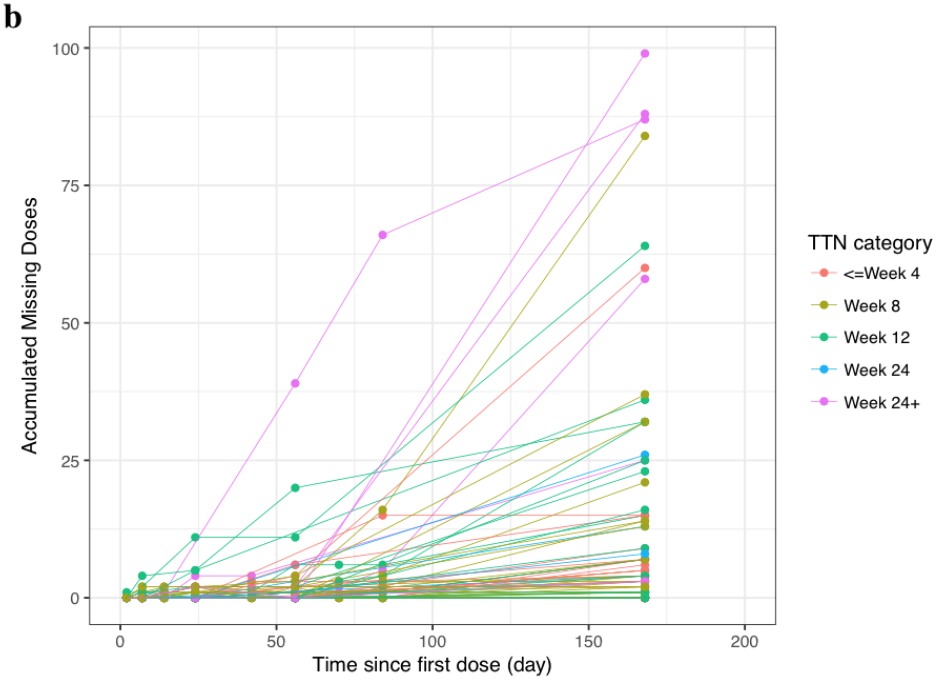


Catalysis Biomarker Study

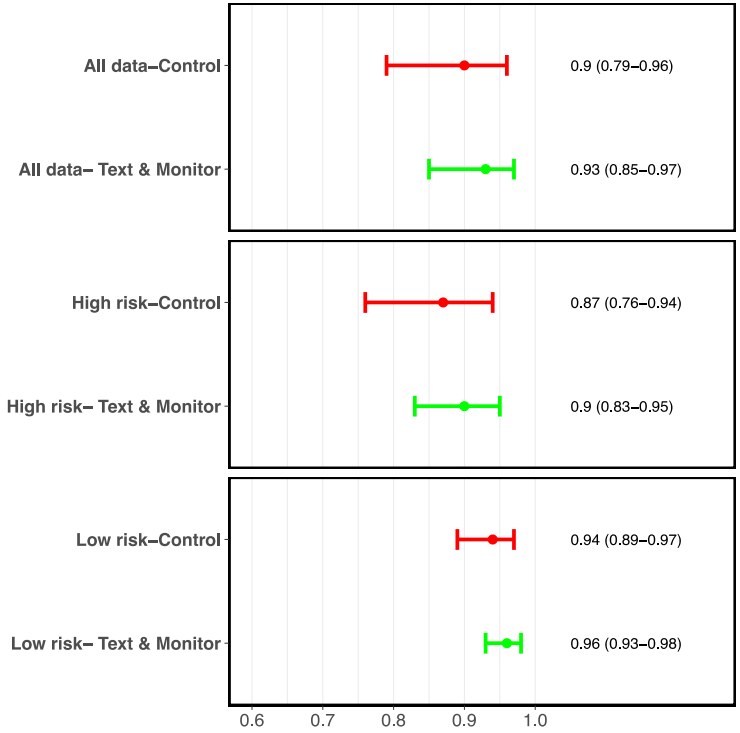


Adherence one of the best "biomarkers" of treatment failure





Hard-to-Treat Patients Benefit Most from Adherence Interventions



All patients

Hard-to-Treat patients

Easy-to-Treat patients

Control (No intervention):
% Adherence= 77.4%*

Text & Medication Monitor Intervention:
%Adherence= 88.6%*

*Data from Lui et. al, PLOS Med, 2015

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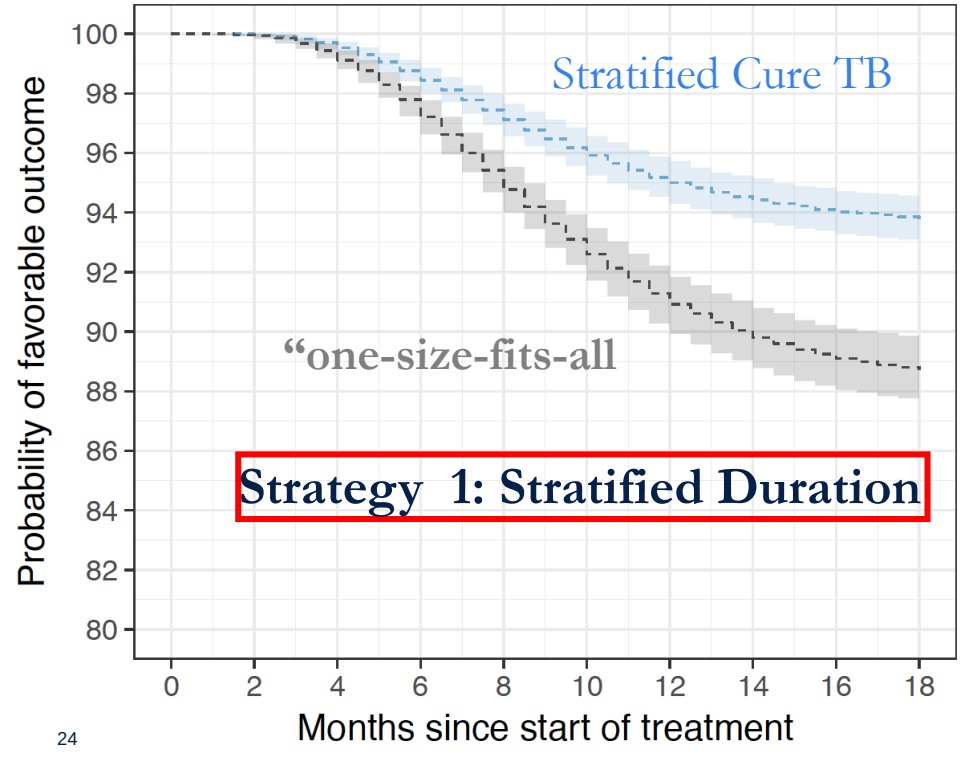
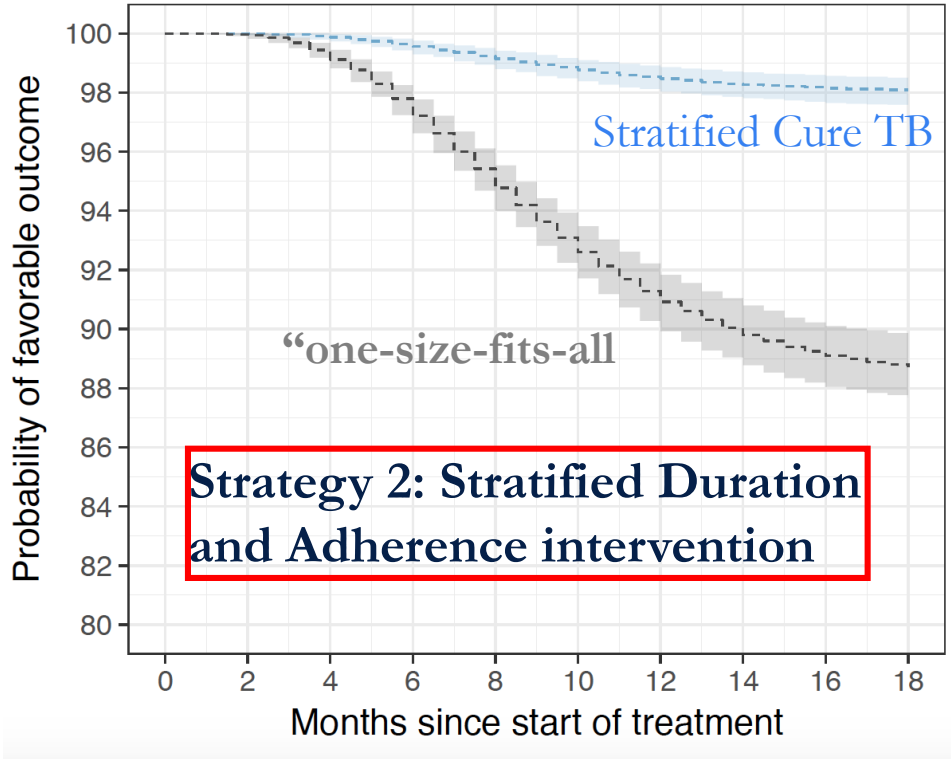
Cure TB Strategy with Adherence Intervention:

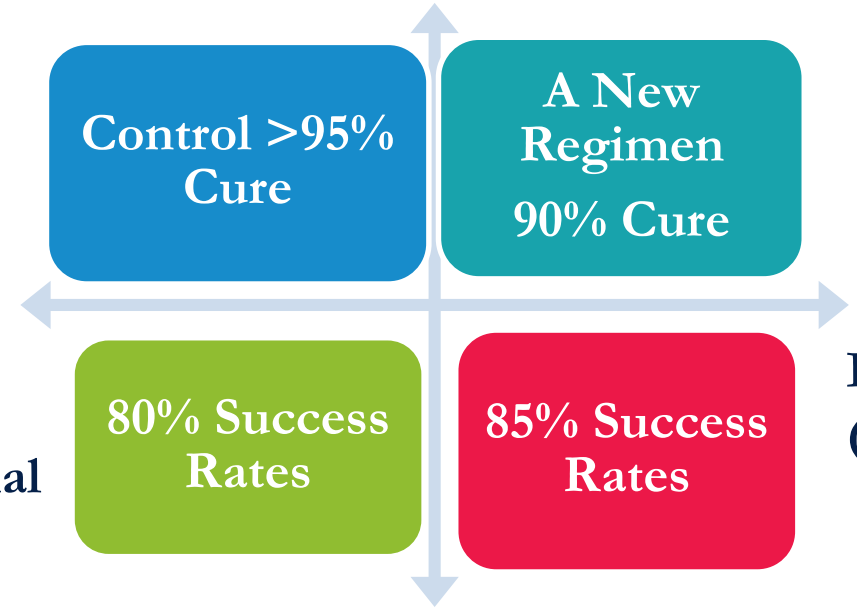
Clinical Trial Simulations, Pragmatic Trial with Adherence Intervention





Adherence and Forgiveness as Determinants of Efficacy vs Effectiveness and Clinical Trial Success

Randomized Clinical Trial



Efficacy

Implementation, Pragmatic Clinical Trial

Effectiveness (Regimens with drugs with long half-life)

Summary

- Partial- or non-adherence is the rule, rather than the exception, in clinical trials and in the field
- HRZE is unforgiving regimen requiring large resources for optimizing adherence, but performing excellent in the trials
- The gap between efficacy and effectiveness is much larger than for the unforgiving drug versus a ‘forgiving” drug
- Forgiveness of the drug should be factored in non-inferiority margin
- We will learn great deal from dosing history data collected with new devices

Data Contributors:

- TB Alliance
- St. George's, University of London
- WHO
- Case Western

TB ReFLECT steering committee:

- Christian LIENHARDT
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- David HERMAN
- Katherine FIELDING
- Patrick PHILLIPS
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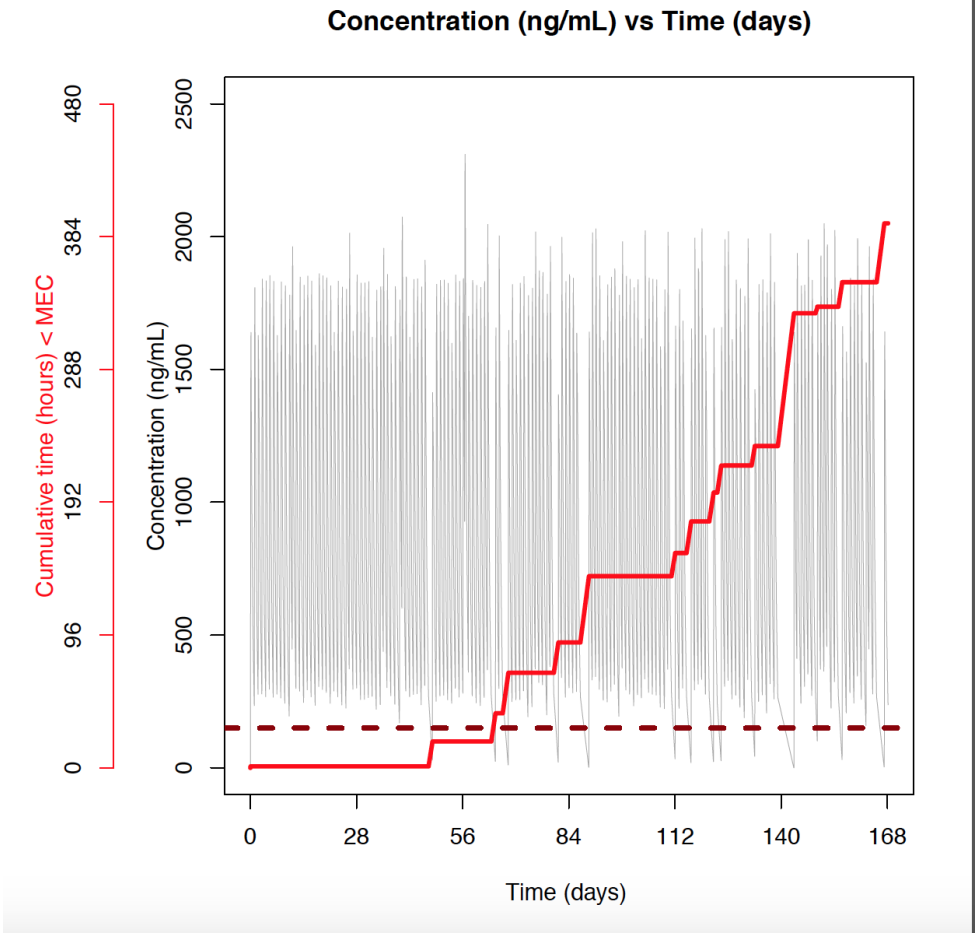
- Jill WINTER



RM Savic[1,2], A Barrail-Tran[3,4], X Duval[1], G Nembot[1], X Panhard[1], D Descamps[5], C Verstuyft[6], B Vrijens[7], A-M Taburet[3], C Goujard[8], F Mentré[1] and the ANRS 134–COPHAR 3 Study Group

Clin Pharmacol Ther. 2012 Nov; 92(5): 575–583

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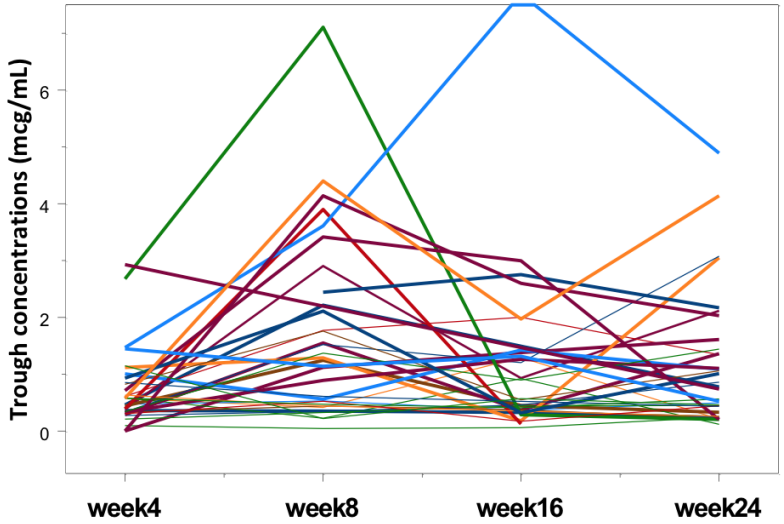
Value of PK in context of missing adherence data

- Minimal if no dosing history data
- Biased interpretation of exposure/res

- Up to 10 fold variation within a patient assuming full adherence
- With correct dosing histories: no significant variation

Atazanavir PK "steady-state" troughs

✓ Additional trough samples at week 8, 16, 24



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