Tuberculosis Trials Consortium (TBTC): CDC Experience

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Clinical Research Branch, DTBE

FDA Public Workshop

Development of New Tuberculosis Treatment Regimens--Scientific and Clinical Trial Design Considerations

July 19, 2017

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Division of Tuberculosis Elimination

Disclaimer

Opinions herein are those of the author, and do not reflect an official position of the Centers for Disease Control and Prevention

Conflict of Interest statement

I have no direct financial interest in any of the products about which I will speak. I do not receive consultation fees from commercial firms. I work with a federally funded TB clinical trials group. Some of their studies have received some funding or other support from commercial firms, including the manufacturers of Rifapentine and Moxifloxacin.

Andrew Vernon, MD, MHS

Content of presentation:

1. Overview of TBTC
2. TBTC approaches to its research
3. Specific considerations on role of individual drugs
4. Examples from TBTC work
5. Other networks

1. Overview of TBTC

The TB Trials Consortium (TBTC)

- Initially funded 1993-94 to conduct one trial (Study 22)
- Re-organized in 1997, modeled on NIAID's HIV trials groups (CPCRA, ACTG)
- Housed in the Clinical Research Branch (CRB) of CDC's Division of TB Elimination
- Since 1995, TBTC has enrolled ~16,000 participants in TB trials

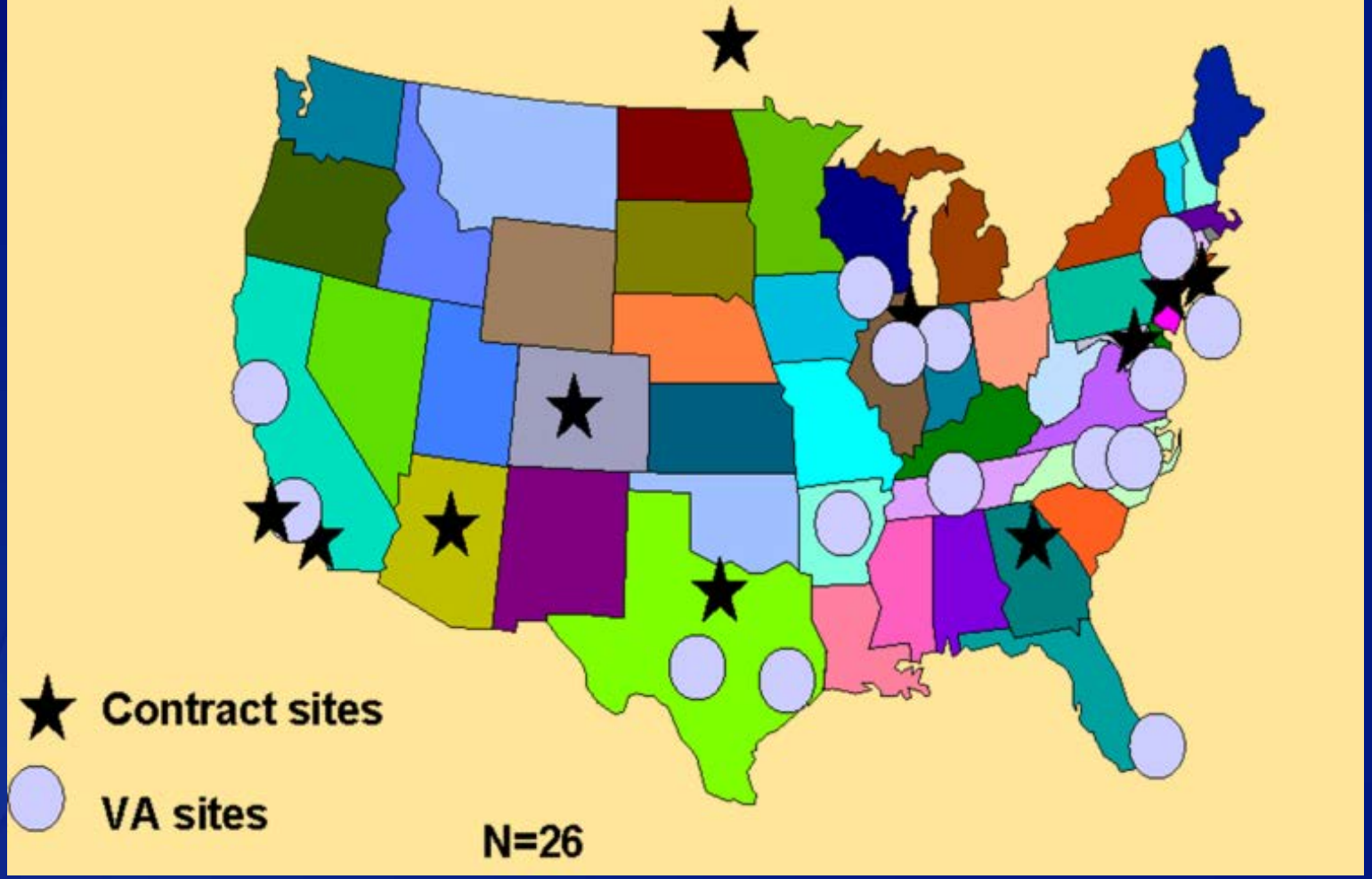
Public Health Rep. 2001;116 Suppl 1:41-9

TBTC mission, as stated in its By Laws, is:

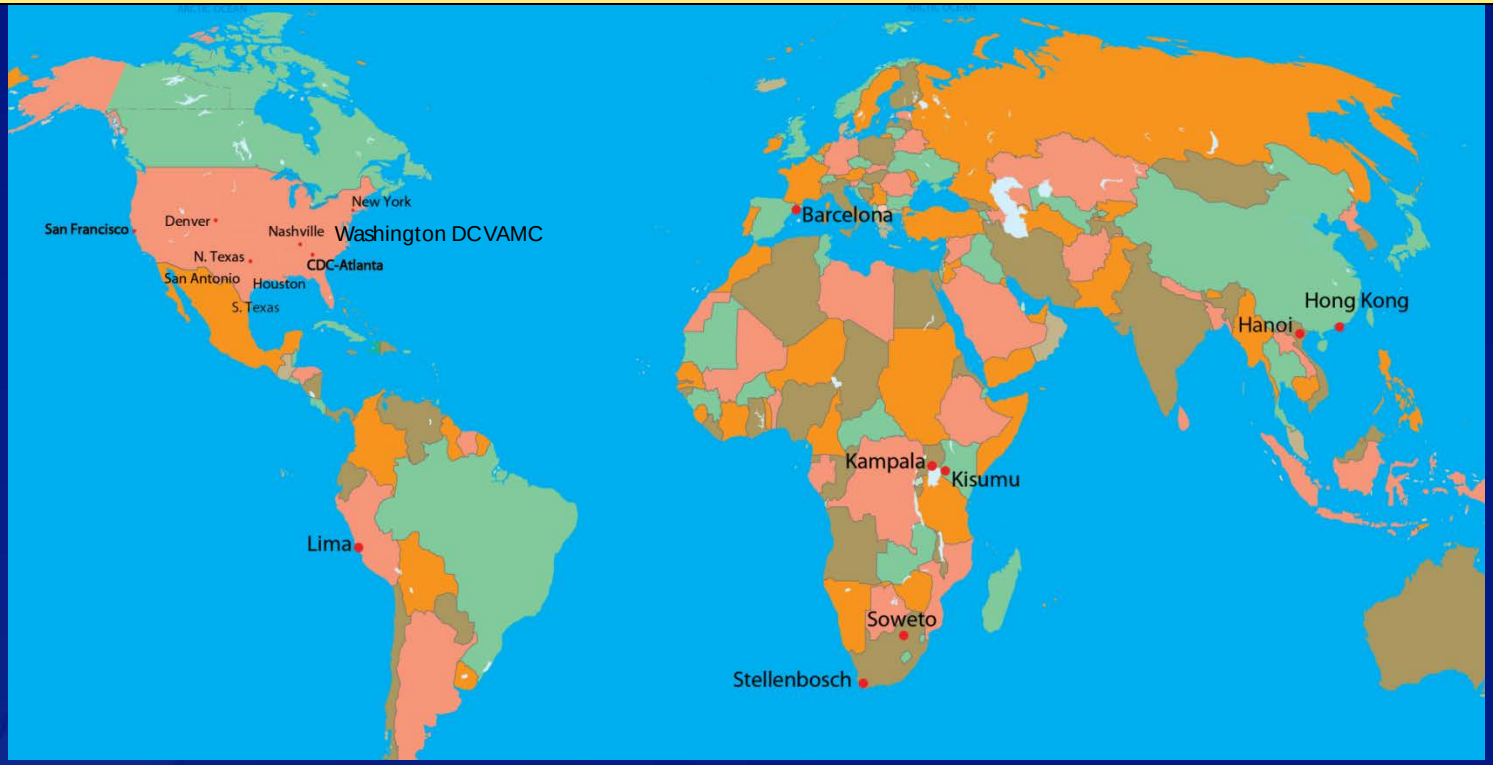
"… to conduct programmatically relevant clinical, laboratory, and epidemiologic research concerning the diagnosis, clinical management, and prevention of tuberculosis infection and disease."

Public Health Rep. 2001;116 Suppl 1:41-9

Distribution of Study 22 Clinical Sites (1993-1999)



CDC TB Trials Consortium 2013-2019



8 international & 8 U.S. sites enrolling (+ Washington DC VAMC collaboration*)

*Washington DC VAMC provides administrative support and coordinates activity at 6 domestic and international sites

TBTC Studies 1995-2008

Phase	Study #: Topic of study
3	Study 22/22PK: Once weekly HP in continuation phase
3	Study 23/23PK$_{A,B,C}$: Intermittent Rifabutin therapy in HIV-TB
3	Study 24 : Intermittent therapy for INH-resistant TB
D	NAA : Biomarkers of response to therapy
2	Study$_{C}$ 25/25PK : Dose escalation for OW Rifapentine
3	Study$_{CA}$ 26/+multiple SS : Once weekly 3HP for LTBI
2b	Study$_{C}$ 27/27PK : Moxifloxacin vs Ethambutol phase 2
2b	Study$_{C}$ 28/28PK : Moxifloxacin vs Isoniazid phase 2

Subscript C indicates collaboration Subscript A indicates ACTG

TBTC Studies 2009-2017

Phase	Study #: Topic of study
2b	Study$_{C}$ 29/29X/29PK/29B : Dose finding for daily Rifapentine
2b	Study$_{C}$ 30/30PK : Low dose linezolid in MDR-TB
3	Study$_{CA}$ 31: 4mo daily high-dose RPT for TB disease
2b	Study$_{C}$ 32 : Dose optimization for levofloxacin in MDR-TB
4	Study$_{C}$ 33 : 3HP for LTBI by DOT vs self-administration
D	Study$_{CA}$ 34 : Gene Xpert for TB diagnosis
D	Study 36/36A$_{C}$: Platform study for DS TB; CTB2 biobank

Subscript C indicates collaboration Subscript A indicates ACTG

TBTC Studies: 2015→

Phase	Study	Currently	Topic
D	Study 36	Ongoing	Platform study for DS TB; observational; biomarkers
2b	Study 32	Analysis	Dose optimization Levo MDR
3	Study 31/31PK$_C$	1,059 enrolled (17Jul17)	4mo daily Rifapentine regimen
PK	Study 35	Q1-2018	Rifapentine PK infants & young children
3	Study 37	Q1-2018	6 week daily RPT for LTBI

http://www.cdc.gov/tb/topic/research/tbtc/projects.htm

2. TBTC approach to its research

TBTC Organization

Steering Committee

Exec. Affairs Group

Core Science

Implementation & Quality

Publications & Presentations

Advocacy & External Relations

Working Groups

Biomarkers

Hepatotoxicity

Protocol Teams

Diagnostics

Pharmacokinetics

MDR

Microbiology

Points emphasized in TBTC Evaluations

2007 External review

Targeted phase 2 trials → phase 3 trials

Collaboration with pharma/NIH

Regulatory standards

Biobanking activities

Explicit targets and linkages

Seek additional funding

2012 Scientific retreat

DS TB Treatment shortening

LTBI treatment shortening

Key related domains:

- HIV-TB, ART DDIs
- PK/PD for guidance

Pediatric TB

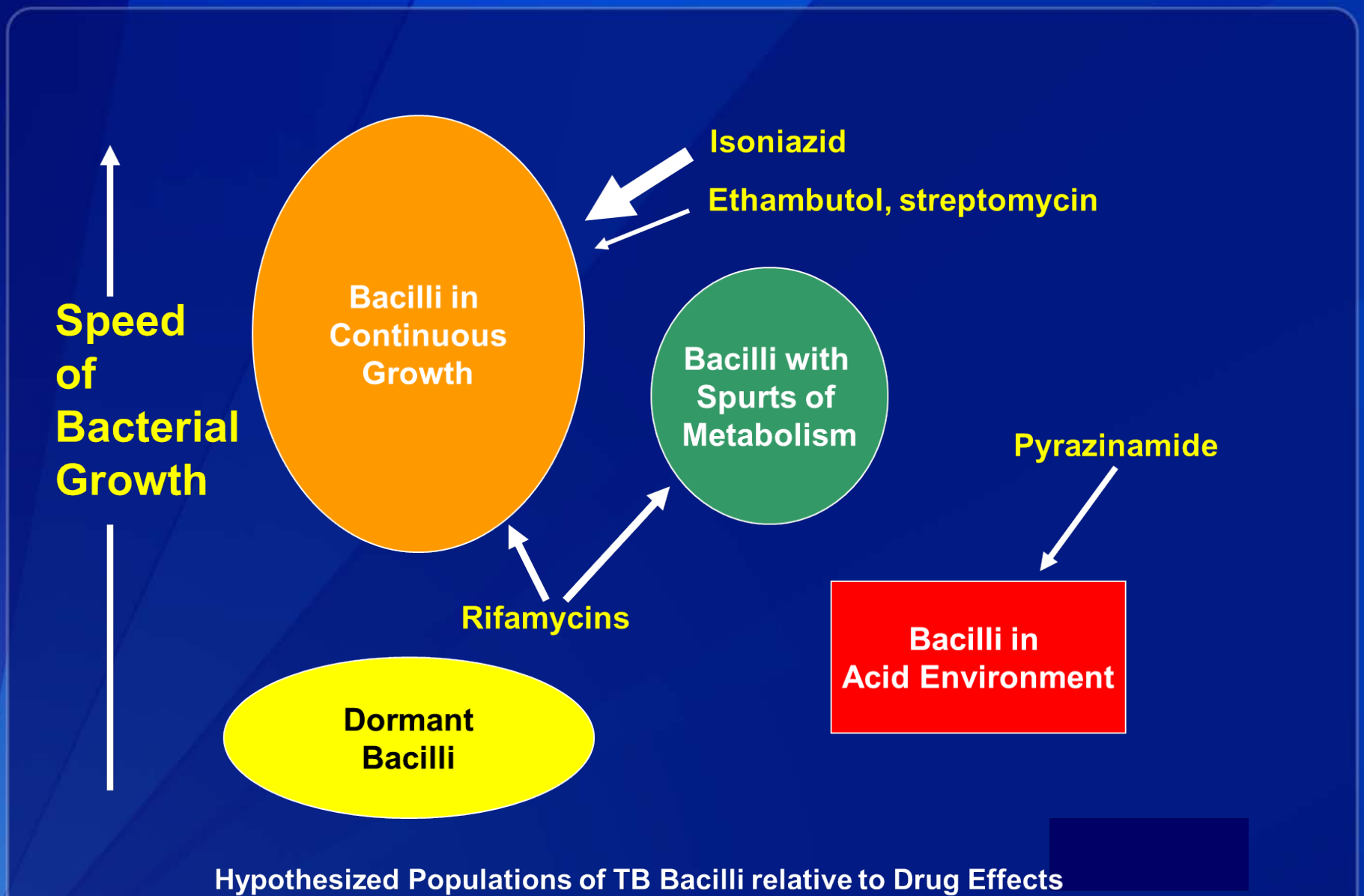
Drug resistant TB

Biomarkers

Comments on the approach

- Studies are "programmatically relevant": expected to drive guidelines, and to establish clinical excellence in program settings
- Core Science chairs emphasize importance of a robust "phase 2 engine" to identify promising regimens; CRUSH TB work group addresses this need; MRC statisticians and others have emphasized importance of phase 2 with proposal for novel phase 2c approaches
- We pay close attention to murine results; every TBTC meeting now invites a report from the "Murine TBTC" at Hopkins

3. Specific considerations on role of individual drugs



Hypothesized Populations of TB Bacilli relative to Drug Effects

Mitchison DA: Chest, 1979; IJTLD 1998

The Action of Anti-Tuberculosis Drugs

Extent of Activity	Early bactericidal activity	Sterilizing activity	Prevention of ADR activity
High	**Isoniazid (H)**	**Rifampin (R)**	**Isoniazid (H)**
		Pyrazinamide (Z)	Rifampin (R)
	Ethambutol (E)		
	Rifampin (R)	Isoniazid (H)	Ethambutol (E)
			Streptomycin (S)
	Streptomycin (S)	Streptomycin (S)	
	Pyrazinamide (Z)	Thiacetazone (T)	Pyrazinamide (Z)
Low	Thiacetazone (T)	Ethambutol (E)	Thiacetazone (T)

Mitchison DA. Tubercle 1985; 66:219-25

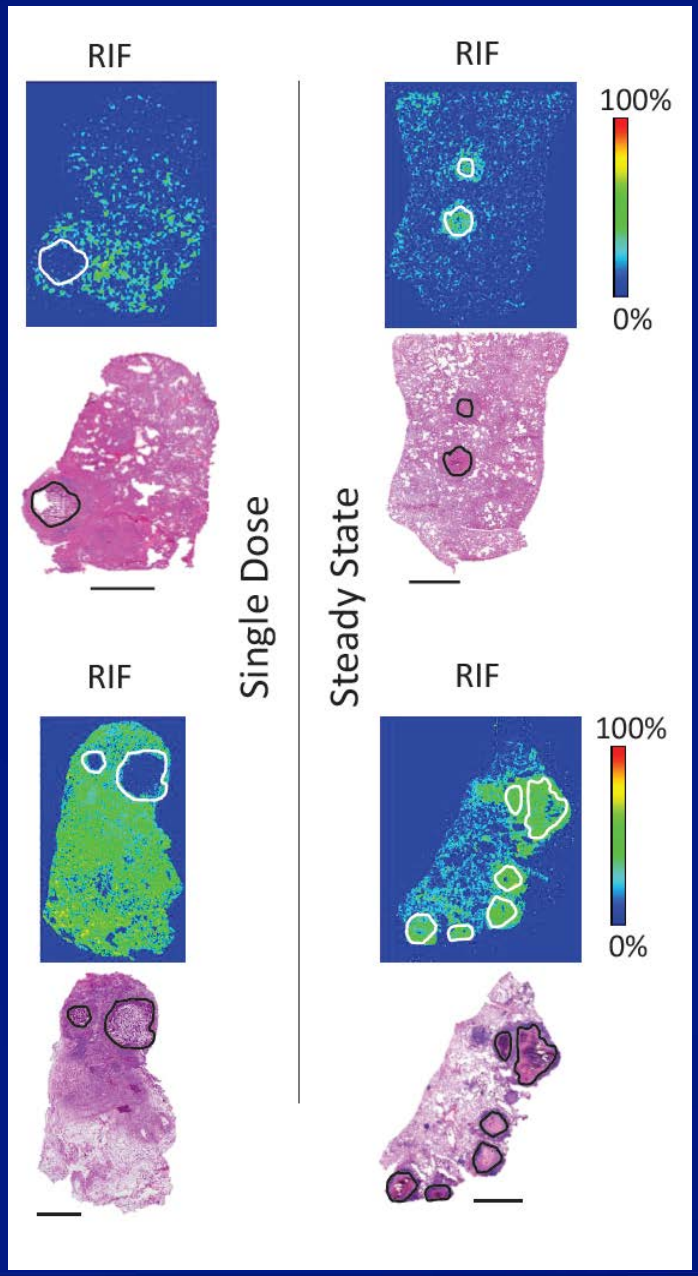
nature medicine

The association between sterilizing activity and drug distribution into tuberculosis lesions

Brendan Prideaux[1], Laura E Via[2], Matthew D Zimmerman[1], Seokyong Eum[3], Jansy Sarathy[1], Paul O'Brien[1], Chao Chen[1], Firat Kaya[1], Danielle M Weiner[2], Pei-Yu Chen[1], Taeksun Song[3], Myungsun Lee[3], Tae Sun Shim[4], Jeong Su Cho[5], Wooshik Kim[6], Sang Nae Cho[7], Kenneth N Olivier[8], Clifton E Barry III[2,9] & Véronique Dartois[1]

Individual drugs may penetrate into different compartments at different rates , to different degrees, over different time frames, and by entry into different compartment components (e.g., cells vs necrotic caseum).

Prideaux B, et al., 2015

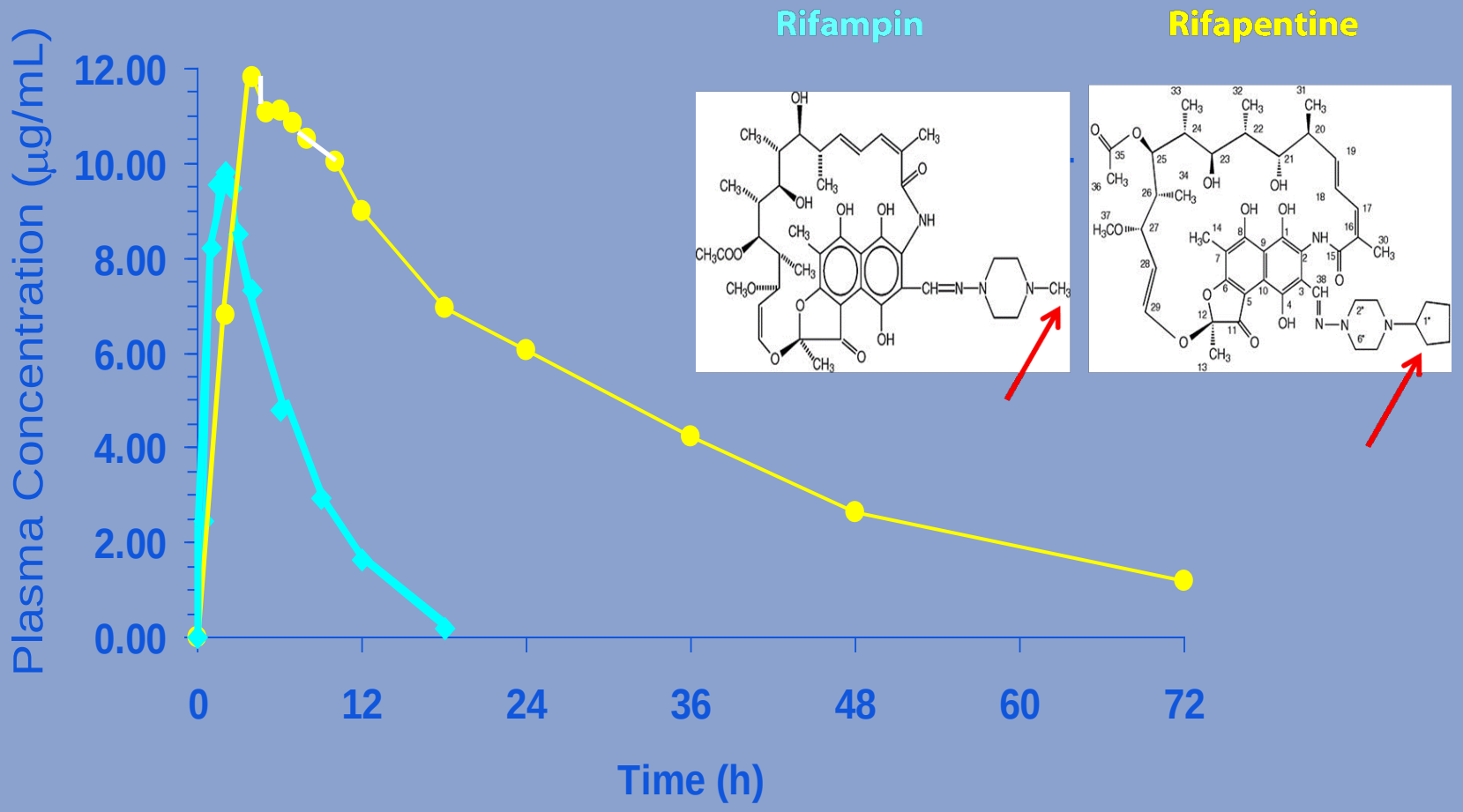


4. Two examples from TBTC work

a. The 3HP LTBI Regimen

b. The 4mo Regimen for TB disease:
2 mo culture, FQ trials, & high dose RPT

Plasma Rifapentine and Rifampin Concentration-Time Profiles



Study 22 in 1995-2001: relapse rates varied substantially in patient subgroups. In patients with both cavitation and positive sputum culture at 2 months, rates of relapse were 22% in the RPT arm, and 21% in the RIF arm. With neither, the rates were 1.9% and 1.7%.


Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial

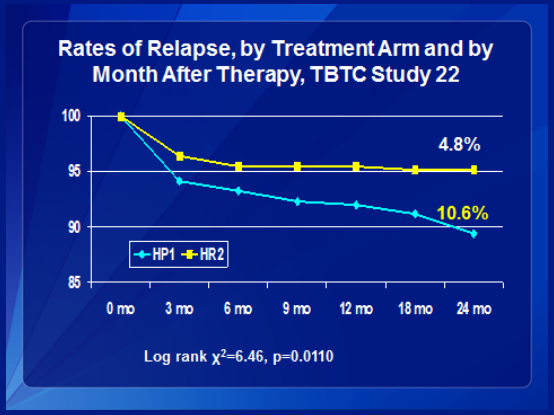


TABLE 11. Percentage of culture-positive relapse* by continuation phase regimen, radiographic status, and 2-month sputum culture: USPHS Study 22

Continuation phase, INH–RIF twice weekly†			Continuation phase, INH–RPT once weekly†		
	Culture-positive at 2 months			Culture-positive at 2 months	
Cavity	Yes	No	Cavity	Yes	No
Yes	20.8 (48)‡	4.7 (150)	Yes	22.2 (72)	9.1 (154)
No	5.9 (17)	1.7 (181)	No	11.8 (17)	1.9 (162)

(1) TBTC investigators reasoned that the group of patients who were cured with a continuation phase of once-weekly INH+Rifapentine were paucibacillary, and thus similar to persons with LTBI.
(2) Murine data supported this logic.
(3) It was thought that LTBI patients were likely to have even lower bacillary loads, and that increasing the dose of Rifapentine from 600mg to 900mg would further strengthen the combination against LTBI.
(4) British experience, and the Uganda PT trial, with 3 months of H-RIF suggested that a 3-month once weekly LTBI regimen was reasonable.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diana Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

ABSTRACT

BACKGROUND

Treatment of latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.

METHODS

We conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil, and Spain and followed for 33 months. The primary end point was confirmed tuberculosis, and the noninferiority margin was 0.75%.

RESULTS

In the modified intention-to-treat analysis, tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the isoniazid-only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid-only group (P<0.001). Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the combination-therapy group and 3.7% in the isoniazid-only group (P=0.009). Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7%, respectively (P<0.001).

CONCLUSIONS

The use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate. Long-term safety monitoring will be important. (Funded by the Centers for Disease Control and Prevention; PREVENT TB ClinicalTrials.gov number, NCT00023452.)

From the Vanderbilt University School of Medicine, Nashville (T.R.S., A.K.); the Centers for Disease Control and Prevention, Atlanta (M.E.V., A.S.B., N.S., E.B.-S., L.B.); the Washington DC Veterans Affairs Medical Center and George Washington University — both in Washington, DC (F.G.); the Johns Hopkins University School of Medicine, Baltimore (J.H., R.E.C.); Family Health International and Duke University — both in Durham, NC (C.D.H.); Montreal Chest Institute, McGill University, Montreal (D.M.); the University of North Texas Health Science Center at Fort Worth, Fort Worth (S.E.W.); the South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio — both in San Antonio (M.W.); and the South Texas Consortium, Harlingen (D.W.); the Federal University of Rio de Janeiro, Rio de Janeiro (M.B.C.); and Boston University School of Medicine, Boston (C.R.H.). Address reprint requests to Dr. Sterling at A2209 Medical Center North, 1161 21st Ave. S., Nashville, TN 37232, or at timothy.sterling@vanderbilt.edu.

Drs. Horsburgh and Chaisson contributed equally to this article.

*Investigators participating in the PREVENT TB study are listed in the Supplementary Appendix, available at NEJM.org.

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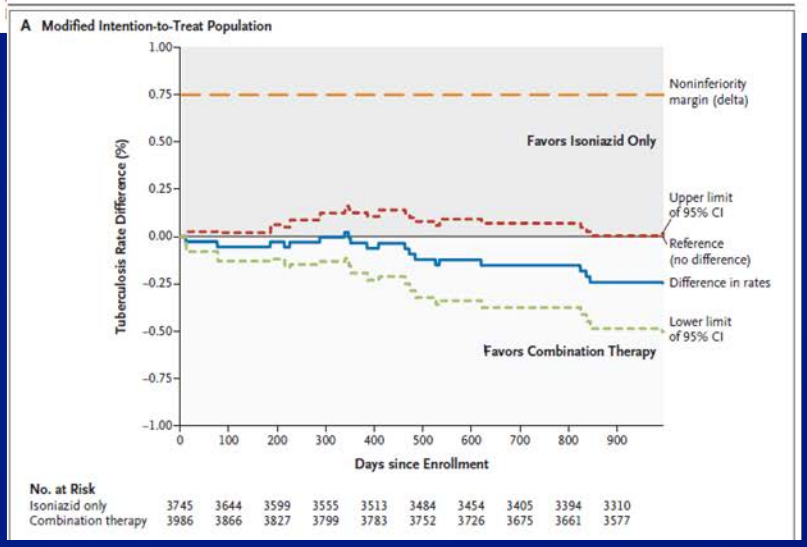
Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 48
December 9, 2011

Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection

Preventing tuberculosis (TB) by treating latent *Mycobacterium tuberculosis* infection (LTBI) is a cornerstone of the U.S. strategy for TB elimination (*1*,*2*). Three randomized controlled trials have shown that a new combination regimen of isoniazid (INH) and rifapentine (RPT) administered weekly for 12 weeks as directly observed therapy (DOT) is as effective for preventing TB as other regimens and is more likely to be completed than the U.S. standard regimen of 9 months of INH daily without DOT (*2*–*5*). This report provides CDC recommendations for using the INH-RPT regimen. The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients aged ≥12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB). The new regimen also has a long plasma half-life enables infrequent dosing, which can increase DOT convenience and thus adherence. Most RIF-resistant isolates also are resistant to RPT.

Methods

In April 2011, CDC convened a panel of 23 consultants, each of whom had demonstrated TB-specific expertise in at least one of the following: diagnosis, treatment, prevention, nursing case management, public health programs, surveillance, epidemiology, clinical research, pulmonology, infectious diseases, pediatrics, mycobacteriology, health communication and education, migrant worker health, patient advocacy, and health economics. The panel reviewed findings from all three INH-RPT clinical trials that had been completed (*3*–*5*),



MAJOR ARTICLE

Flu-like and Other Systemic Drug Reactions Among Persons Receiving Weekly Rifapentine Plus Isoniazid or Daily Isoniazid for Treatment of Latent Tuberculosis Infection in the PREVENT Tuberculosis Study

Timothy R. Sterling,[1,a] Ruth N. Moro,[2,3,a] Andrey S. Borisov,[2] Elizabeth Phillips,[1,4] Gillian Shepherd,[5] Newton Franklin Adkinson,[6] Stephen Weis,[7] Christine Ho,[2] and Margarita Elsa Villarino[2]; for the Tuberculosis Trials Consortium

[1]Vanderbilt University School of Medicine, Nashville, Tennessee; [2]Centers for Disease Control and Prevention, and [3]CDC Foundation, Research Collaboration, Atlanta, Georgia; [4]Institute for Immunology and Infectious Diseases, Murdoch University, Perth, Australia; [5]New York-Presbyterian Hospital/Weill Cornell Medical Center, New York; [6]Johns Hopkins University School of Medicine, Baltimore, Maryland; and[7]University of North Texas Health Science Center at Ft. Worth

“Given the similarity of published reports of flu-like syndrome associated with rifampin and the reactions seen in this study, and given the 9-fold greater frequency of such reactions in the 3HP arm, one might think rifapentine the more likely cause of these symptoms than isoniazid. However, rifapentine was better tolerated than isoniazid on rechallenge. In a recent multicenter randomized clinical trial of intermittent continuation-phase therapy after 2 months of daily therapy (Rifaquin), participants received 900 mg rifapentine twice-weekly or 1200 mg rifapentine once-weekly, both in combination with moxifloxacin (not isoniazid). There were no reports of possible hypersensitivity or flu-like syndrome, but it is possible that the lack of flu-like syndrome was due to the regimens or the populations studied.”

Sterling et al., CID 2016

Safety and Pharmacokinetics of Escalating Daily Doses of the Antituberculosis Drug Rifapentine in Healthy Volunteers

KE Dooley[1,2], EE Bliven-Sizemore[3], M Weiner[4], Y Lu[1], EL Nuermberger[2], WC Hubbard[1], EJ Fuchs[1], MT Melia[2], WJ Burman[5] and SE Dorman[2]

Dooley et al, Clin Pharm Therap 2012

AAC Journals.ASM.org

Novel Dosing Strategies Increase Exposures of the Potent Antituberculosis Drug Rifapentine but Are Poorly Tolerated in Healthy Volunteers

Kelly E. Dooley,[a] Radojka M. Savic,[b] Jeong-Gun Park,[c] Yoninah Cramer,[c] Richard Hafner,[d] Evelyn Hogg,[e] Jennifer Janik,[f] Mark A. Marzinke,[a] Kristine Patterson,[g] Constance A. Benson,[h] Laura Hovind,[f] Susan E. Dorman,[a] David W. Haas,[i] ACTG A5311 Study Team

Dooley et al., AAC, 2015

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Early Termination of a PK Study Between Dolutegravir and Weekly Isoniazid/Rifapentine

Kristina M. Brooks[1], Alice K. Pau[2], Jomy M. George[1], Anela Kellogg[3], Mary McLaughlin[2], Maryellen McManus[1], Colleen Hadigan[2], Joseph A. Kovacs[1], and Parag Kumar[1]

[1]National Institutes of Health (NIH) Clinic Center (CC), Bethesda, MD, USA [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD, USA
[3]Clinical Monitoring Research Program, Frederick National Laboratory for Cancer Research, Leidos Biomedical Research, Inc., Frederick, MD, USA

NIH Clinical Center — Advancing Personalized Healthcare

NIH National Institute of Allergy and Infectious Diseases

Background

- Once-weekly isoniazid (INH) with rifapentine (RPT) (wHP) is a 3-month treatment regimen for latent tuberculosis infection (LTBI). This regimen is of interest in the HIV-infected population due to its shortened treatment duration vs. other LTBI regimens.
- Drug interaction data between antiretroviral (ARV) medications and wHP are limited. RPT can induce CYP and UGT enzymes similarly to other rifamycins, which could lead to decreased ARV drug exposure and subsequent treatment failure.
- Coadministration of wHP with raltegravir- or efavirenz-containing ARV regimens is included in both the DHHS and IAS-USA HIV treatment guidelines based on available PK data with RPT. The IAS-USA guidelines also recommend coadministration with dolutegravir (DTG), which is based on extrapolation of PK data with rifampin and the assumption that twice-daily DTG dosing will be necessary to overcome induction by RPT.

Study Objective

- To characterize the effects of wHP on the pharmacokinetics (PK) of DTG, an ARV agent recommended in 1st-line treatment regimens for HIV-infected adults.

Methods

Study Design

- This was an open-label, intrasubject drug-drug interaction study to evaluate the steady-state PK of DTG with wHP in HIV-negative healthy volunteers (n=10)
- This study was approved by the NIAID IRB (ClinicalTrials.gov identifier NCT02771249)

Figure 1. Study Schematic

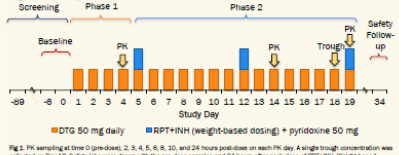


Fig 1. PK sampling at time 0 (pre-dose), 2, 3, 4, 5, 6, 8, 10, and 24 hours post-dose on each PK day. A single trough concentration was collected on Day 18. Safety labs were drawn with the pre-dose samples and 24 hours after each dose of RPT+INH. Weight-based dosing of RPT and INH was as follows: RPT = 750 mg if <50 kg and 900 mg if >50 kg; INH = 15 mg/kg, max dose 900 mg.

Eligibility Criteria

- Inclusion: healthy adult volunteers as determined by medical history, physical exam, and screening labs; age 18-65 years, weight 45-120 kg, BMI 18-30; negative for HIV, TB, and hepatitis A/B/C infection; no alcohol consumption while on study
- Exclusion: known hypersensitivity to study medications; concomitant prescription, OTC, herbal, or holistic medications within 5 half-lives of study medications (exceptions for intermittent use of OTC analgesics on non-PK days)

Analytical & Statistical Methods

- DTG plasma concentrations were determined using a UPLC method with fluorescence detection. RPT, 25-desacetyl-RPT, and INH concentrations were determined with previously described HPLC-MS/MS methods (Peloquin CA, et al. *Int J Tuberc Lung Dis* 1999;3:703).
- PK parameters for DTG, RPT, 25-desacetyl-RPT, and INH were determined using non-compartmental methods (Phoenix WinNonlin, v6.4). DTG PK parameters were compared between set PK time points to generate geometric mean ratios (GMR) with 90% CIs. P-values were calculated using 2-tailed paired t-tests.
- Symptom and safety laboratory assessments were graded according to the Division of AIDS AE table (November 2014, v2.0).
- Cytokine assays were performed with plasma samples from PK and follow-up safety visits. Cytokines examined included: IFN-Ɣ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α (V-PLEX® Proinflammatory Panel 1, Meso Scale Discovery®, Rockville, MD). Other inflammatory markers included sCD14 (R&D Systems, Minneapolis, MN), SCD163 (Aviscera Bioscience, Santa Clara, CA), and CRP (Meso Scale Discovery®, Rockville, MD).

Results

Study Population

- Four subjects were enrolled before study termination:
  - 3 males (2 white, 1 African American), 1 female (Hispanic)
  - Median age 43 years (range 21-46), weight 77.2 kg (range 74.1-95.8)
  - Subject 3 voluntarily withdrew prior to Day 19

Safety Results

- This study was terminated early due to the development of flu-like syndrome and transaminase elevations (Grade 2-4) in 2 subjects, with symptom onset ~8-10 hours after the last doses of DTG, RPT, and INH on Study Day 19 (Figure 2).
- Subject 1: experienced N/V, headache, and fever (max 39.1°C) for ~24 hrs after onset. A left-shift in the WBC differential also occurred.
  - Symptoms resolved by 72 hrs post-dose, at which point he developed transaminase elevations
- Subject 4: experienced N/V, fever (max 39.5°C), and was hospitalized for orthostatic hypotension (97/50 supine, HR 97; BP 79/51 standing, HR 80), which required IV fluid resuscitation. A left-shift in her WBC differential also occurred.
  - Transaminase elevations developed ~24 hrs post-dose
  - Acute symptoms resolved by 72 hrs post-dose
- Other reported AEs: diarrhea and nausea (grade 1) with DTG alone in subject 1, and headache (grade 1) in subject 3 after the 1st and 2nd HP doses.

Table 1. Summary of Major AEs in Subjects 1 & 4

Adverse Events	Highest Grade	
	Subject 1	Subject 4
Flu-like syndrome		
Nausea	2	1
Vomiting	1	1
Headache	1	1
Dizziness/lightheadedness	1	2
Tachycardia	1	1
Fever	1	3
Chills	0	2
Orthostatic hypotension	0	3
Rash	0	1
Lab abnormalities		
Absolute lymphocyte decrease	4	4
ALT elevation	2	3
AST elevation	2	4
Direct bilirubin elevation	3	3

Safety Results

Figure 2. Lab Trends in Subjects 1 & 4 during the Study Period

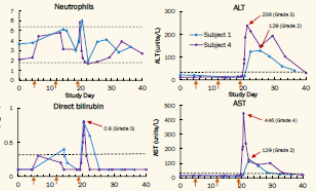


Fig 2. Orange arrows = administration of wHP; dashed line = reference range. Left shifts (top left) were observed in both subjects following the development of flu-like syndrome. Transaminase elevations (right) developed 24-72 hours after the final doses of DTG, RPT, and INH, and took 2-3 weeks to resolve. Transient increases in direct bilirubin (bottom left) were observed after the 1st and 2nd doses of wHP.

Figure 3. Select Inflammatory Markers in Subjects 1 & 4 during the Study Period

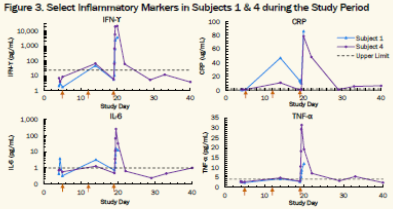


Fig 3. Orange arrows = administration of wHP. Postdose elevations of inflammatory markers revealed transient increases in IFN-γ, CRP, IL-6, and TNF-α after the 2nd doses of HP, with significant increases in all markers during the flu-like syndrome events after the 3rd HP dose.

PK Results

Figure 4. RPT, 25-desacetyl RPT, and INH Plasma Concentration vs. Time Curves by Subject on Day 19

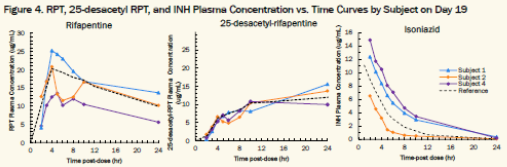


Fig 4. RPT, 25-desacetyl-RPT, and INH levels were examined following the development of flu-like syndrome in subjects completing all doses of study medications. Exposure to RPT (left) and its active metabolite (middle) were similar to reference PK data in healthy volunteers across all subjects, with subjects 1 & 4 having the highest and lowest exposures, respectively. INH exposure (right) was ~67-92% higher in subjects 1 & 4 than available reference PK data in healthy volunteers and LTBI patients. Reference data was estimated from published references using Plot Digitizer (v2) and plotted for comparison (Dooley et al. Antimicrob Agents Chemother 2008; 52: 4087-4042. Weiner M, et al. Am J Respir Crit Care Med 2003;167(10):1341-7. Weiner M, et al. Am J Respir Crit Care Med 2004;169(11):1191-7).

PK Results

Figure 5. DTG Plasma Concentration vs. Time Curves by Subject

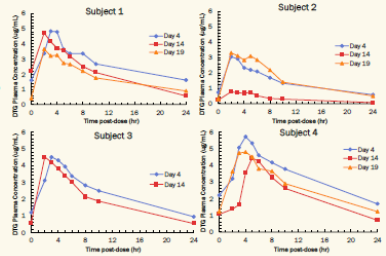


Figure 6. Steady-state DTG C_T Levels[a] throughout the Study

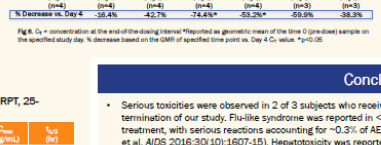


Fig 6. C_T = concentration at the end-of-the-dosing interval [a]Reported as geometric mean of the time 0 (pre-dose) sample on the specified study day. % decrease based on the GMR of specified time point vs. Day 4 C_T value. *p<0.05

Table 3. Individual & Summary DTG PK Parameters with GMR Comparisons vs. Day 4 (DTG Alone)

Subject	C_{max} (ug/mL)	$AUC_{24,ss}$ (h*ug/mL)	$t_{1/2}$ (hr)	CL_{ss}/F (L/h)	Vz/F (L)
DTG Alone (Day 4)					
1	4.8	64.1	17.3	0.78	19.5
2	3.1	33.0	8.7	1.51	21.3
3	4.5	55.2	11.1	0.91	14.5
4	5.7	77.8	12.0	0.64	11.1
Geo Mean	4.4	54.9	12.2	0.91	16.1
DTG 2 days after the 2nd dose of HP (Day 14)					
1	4.7	48.4	7.8	1.01	11.1
2	0.8	7.3	6.4	6.83	63.0
3	4.5	44.3	7.7	1.13	12.5
4	4.4	48.4	7.2	1.03	10.8
Geo Mean	2.9	29.7	7.2	1.69	17.5
DTG with the 3rd dose of HP (Day 19)					
1	3.7	43.1	12.2	1.16	20.5
2	3.3	38.5	8.8	1.37	17.1
4	4.8	63.5	11.0	0.79	12.5
Geo Mean	3.9	46.4	10.5	1.08	16.3
Day 14 vs. 4					
GMR (90% CI)	0.86 (0.31, 1.43)	0.54 (0.27, 1.10)	0.59* (0.46, 0.76)	1.85 (0.81, 3.77)	1.09 (0.44, 2.50)
Day 19 vs. 4					
GMR (90% CI)	0.88 (0.65, 1.20)	0.85 (0.55, 1.29)	0.83 (0.65, 1.06)	1.18 (0.77, 1.80)	0.94 (0.73, 1.32)

*p<0.05
Individual PK data reported as geometric means
Key: C_{max} = maximum (peak) concentration; $AUC_{24,ss}$ = area-under-the-concentration-time curve from time 0–24 hr, Vss/F = apparent volume of distribution at steady-state, CLss/F= apparent oral clearance at steady state; $t_{1/2}$ = elimination half-life

Table 2. PK Parameters of RPT, 25-desacetyl-RPT, and INH

Subject	$AUC_{24,ss}$ (ug*hr/mL)	C_{max} (ug/mL)	$t_{1/2}$ (hr)
RPT			
1	378.2	25.4	n/a
2	317.8	21.0	n/a
4	205.0	13.8	n/a
25-desacetyl-RPT			
1	217.9	15.6	n/a
2	214.1	13.7	n/a
4	199.1	10.9	n/a
INH			
1	79.9	12.4	4.8
2	25.2	6.5	3.9
4	91.8	14.9	5.2

Key: 25-desacetyl-RPT = 25-desacetyl-rifapentine (active metabolite); $AUC_{24,ss}$ = area-under-the-concentration-time curve from 0–24 hrs; C_{max} = maximum concentration; $t_{1/2}$ = elimination half-life
*$t_{1/2}$ not reported as sampling only available through 24 hours post-dose

Conclusions

- Serious toxicities were observed in 2 of 3 subjects who received 3 doses of wHP with once daily DTG, resulting in early termination of our study. Flu-like syndrome was reported in <4% of subjects in clinical trials receiving wHP alone for LTBI treatment, with serious reactions accounting for ~0.3% of AEs (Sterling T, et al. *Clin Infect Dis* 2015; 61(4):527-35. Sterling T, et al. *AIDS* 2016;30(10):1607-15). Hepatotoxicity was reported in ~0.4-1% of patients in these studies.
- Limited PK data from these subjects revealed decreased DTG exposure and C_T values following initiation of wHP. Exposure to RPT and its metabolite were similar to reference PK data for all subjects. INH exposure was higher than expected in the 2 subjects that developed flu-like syndrome.
- The mechanisms behind the reactions observed in these subjects are unknown. Cytokine assays revealed increases in a number of inflammatory markers, including CRP, TNF-α, IL-6, and most notably IFN-Ɣ, a proinflammatory cytokine that is primarily produced by lymphocytes.
- Additional investigations are in progress, including pharmacogenetic testing for acetylator status and screening for anti-INH and anti-RPT antibodies. These efforts may help provide additional insight into the mechanism of these toxicities.

Acknowledgements, Funding & Disclosures

The study team would like to thank our study participants, our Safety Monitoring Committee (Preston Holley, MD; Mary Wright, MD; and Frank Maldarelli, MD, PhD); Charles Peloquin, PharmD and the Infectious Disease PK Laboratory at the University of Florida for measuring RPT and INH levels; and Adam Rupert, MT (ASCP) at the Frederick National Laboratory for Cancer Research for performing the cytokine assays.
Funding for this study was provided by the NIH CC Pharmacy Department and NIAID Intramural Research Programs.
The presenting author of this presentation has nothing to disclose. The content of the publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

4. Two examples from TBTC work

a. The 3HP LTBI Regimen

b. The 4mo Regimen for TB disease:
2 mo culture, FQ trials, & high dose RPT—
"are we rushing in the wrong way?"

Correspondence

ASSESSMENT OF NEW STERILIZING DRUGS FOR TREATING PULMONARY TUBERCULOSIS BY CULTURE AT 2 MONTHS

To the Editor:

The current tuberculosis epidemic, associated with the spread of HIV infection, and the occurrence of multiply-resistant tubercle bacilli has led to pressure for the rapid development of new antituberculosis drugs. Where the new drug may be supposed, on the basis for instance of animal experiments, to have useful

the culture results at 1, 2, and 3 months related to relapse rates, usually at 2 years after the end of chemotherapy, in 7 studies. These studies explored regimens where single drugs (R or Z) were added either to a basic streptomycin (S) and isoniazid (H) regimen (study 1) or to the other drug combinations (studies 2–5) or where a non-sterilizing drug ethambutol (E) replaces Z (studies 6, 7). There was a good correlation between the culture results and the relapse rates, usually best with the 2-month cultures. In study 2, only culture results are given because the regimens com-

TABLE 1

CULTURE RESULTS AT 1, 2 AND 3 MONTHS AFTER THE START OF CHEMOTHERAPY RELATED TO THE SUBSEQUENT RELAPSE RATE

			Percent Patients				
			Culture Negative at Month				
Study	Regimen	No. of Patients at 2 Months	1	2	3	Relapse after Chemotherapy	Reference
1	6SH	154	19	49	81	29	1, 2
	6SHZ	150	27	66	91	11	
	6SHR	148	27	69	94	2	
		χ^2[2]	3.1	15.3	14.7		
2	6SHR	169	34	70	95		3,4
	6HR	173	23	64	96	—	
	2SHRZ/4TH or SHZ_2	347	35	82	—	—	
		χ^2[2]	7.9	20.3	—		
3	2SHR/TH	194	34	75	91	13	5, 6
	2SHRZ/TH	179	40	87	93	6	5, 6
		χ^2 [1]	1.6	7.0	0.2		
4	2SHRZ/4HR	146	38	77	97		7, 8
	2EHRZ/4HR	141	35	77	99	1.6	
	2EHR/7HR	157	29	64	88		
		p	NS	< 0.01	< 0.0001		

"In conclusion, there is good evidence that culture conversion at about 2 months is a reliable measure of the sterilizing activity of drugs and can be used, for instance in the development of new rifamycins, as an indicator of efficacy long before the ultimate relapse rates are known."

Effect of the addition of pyrazinamide on two-month culture conversion rate in randomized trials

S – streptomycin, H – isoniazid, R – rifampin, Z – pyrazinamide, E – ethambutol

Regimen (reference)	N	2-month sputum culture conversion rate	Difference
SH [28]	112	49%	
SHZ	153	66%	17%
SHR [29]	171	70%	
SHRZ	338	82%	12%
SHR [30]	159	75%	
SHRZ	156	87%	12%
SHR [31]	143	88%	
SHRZ	174	95%	7%
SHRE	168	81%	14%
$S_3H_3R_3Z_3$ [32]	151	90%	
$S_3H_3R_3E_3$	166	76%	14%
Average difference			12.7%

W. Burman et al.
TBTC S27 protocol

OPEN ACCESS Freely available online

PLOS ONE

Month 2 Culture Status and Treatment Duration as Predictors of Tuberculosis Relapse Risk in a Meta-Regression Model

Robert S. Wallis*, Cunshan Wang, Daniel Meyer, Neal Thomas

Specialty Care, Pfizer, Groton, Connecticut, United States of America

Abstract

Background: New drugs and regimens with the potential to transform tuberculosis treatment are presently in early stage clinical trials.

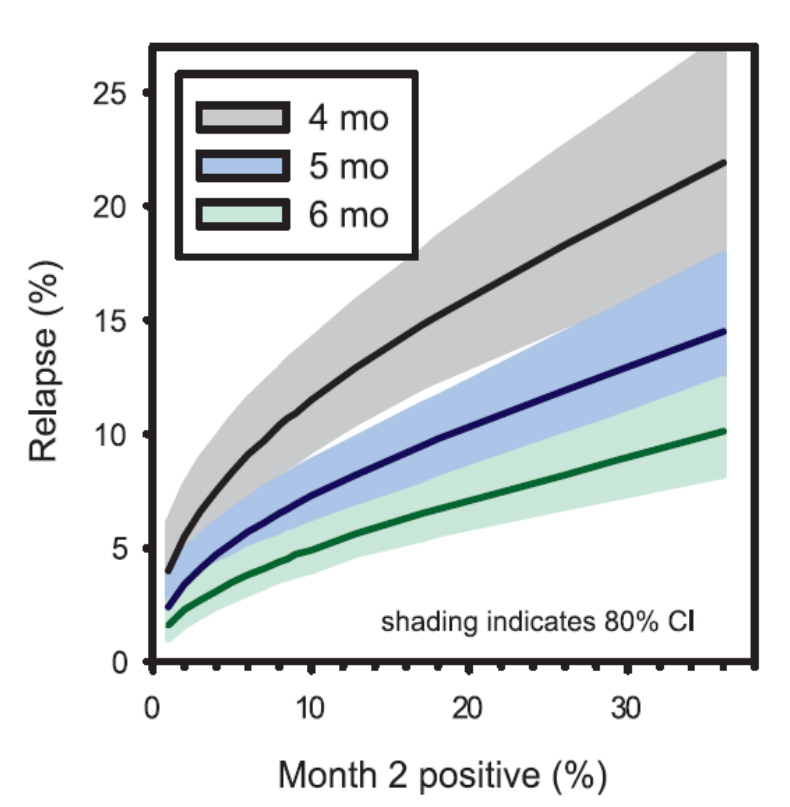
Objective: The goal of the present study was to infer the required duration of these treatments.

PLOS ONE

RESEARCH ARTICLE

Month 2 Culture Status and Treatment Duration as Predictors of Recurrence in Pulmonary Tuberculosis: Model Validation and Update

Robert S. Wallis[1]*, Thomas Peppard[2], David Hermann[2]



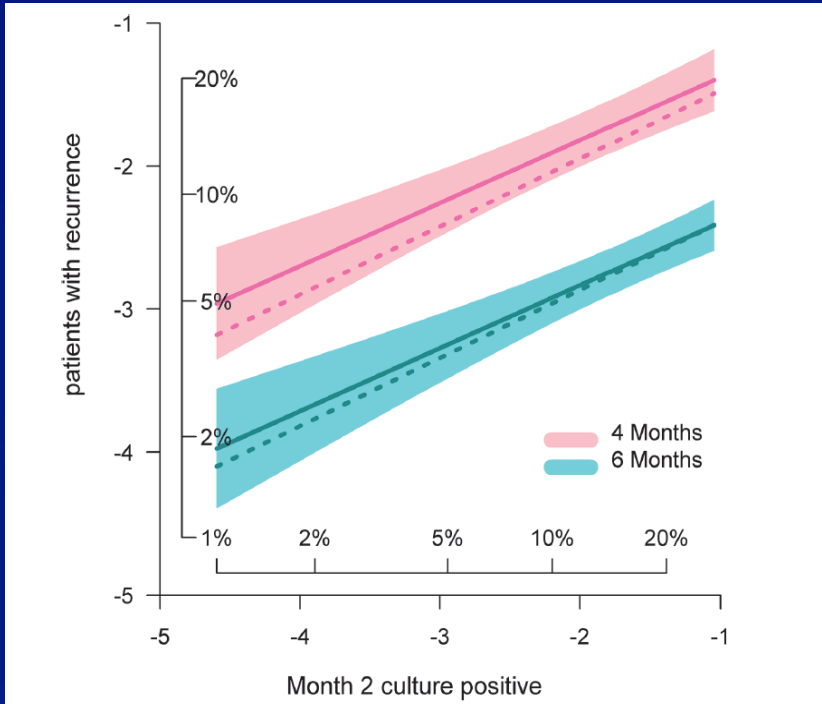
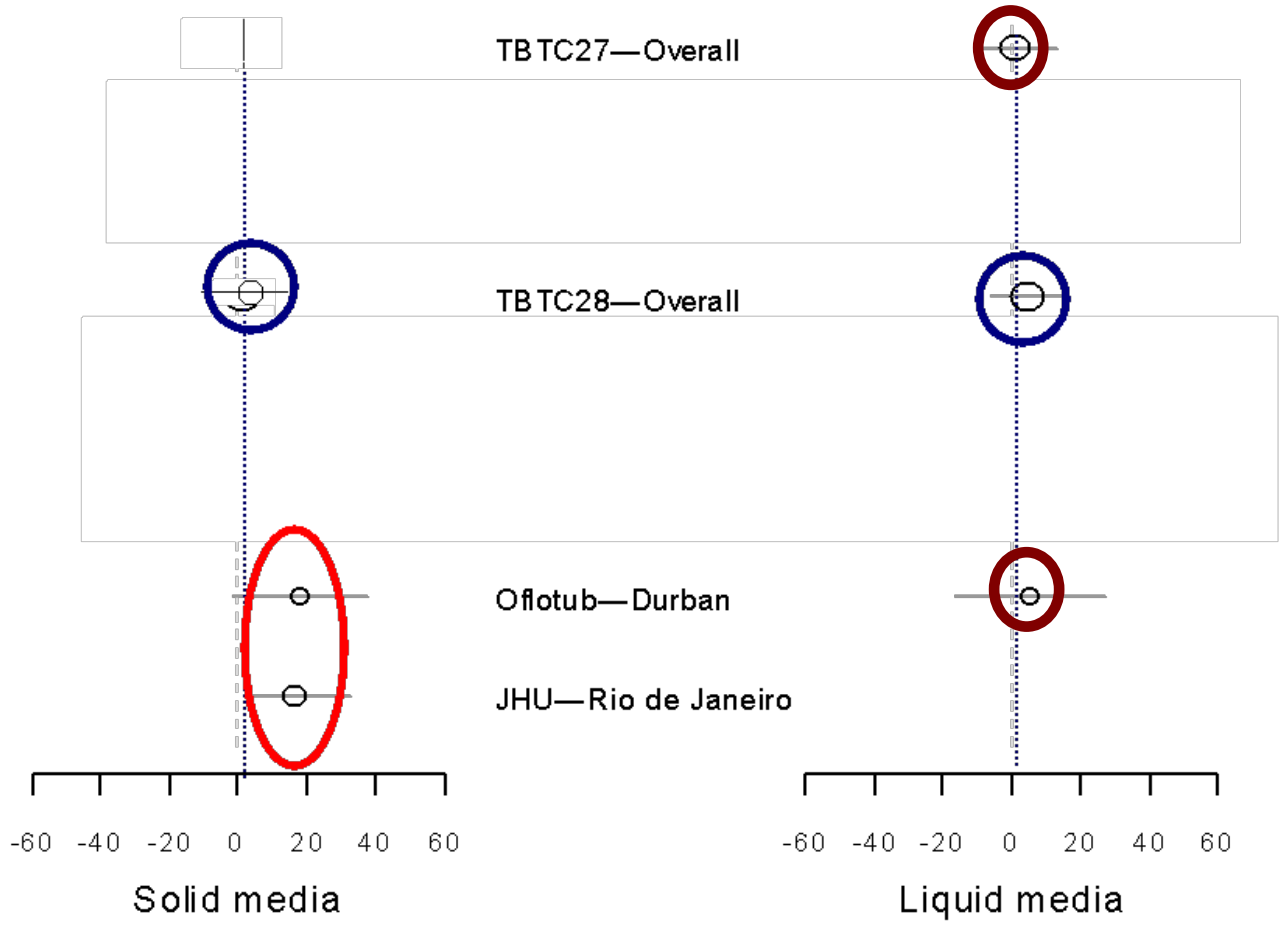


Fig 2. Predicted proportion of patients with recurrence based on the proportion positive after 2 months of treatment, for regimens of 4 and 6 months duration. Axes indicate logit-transformed proportions; inset scales indicate corresponding percentages. Solid and dotted lines indicate updated and original model predictions, respectively. Shading indicates 80% confidence intervals for the updated estimates.

Culture conversion at 2 months in 4 phase-2 trials: percentage difference between moxifloxacin and isoniazid



Pointwise 95% confidence intervals with continuity correction

OPEN ACCESS Freely available online PLOS | ONE

Randomized Clinical Trial of Thrice-Weekly 4-Month Moxifloxacin or Gatifloxacin Containing Regimens in the Treatment of New Sputum Positive Pulmonary Tuberculosis Patients

Mohideen S. Jawahar[1¤], Vaithilingam V. Banurekha[1], Chinnampedu N. Paramasivan[1], Fathima Rahman[1], Rajeswari Ramachandran[1], Perumal Venkatesan[1], Rani Balasubramanian[1], Nagamiah Selvakumar[1], Chinnaiyan Ponnuraja[1], Allaudeen S. Iliayas[2], Navaneethapandian P. Gangadevi[2], Balambal Raman[1], Dhanaraj Baskaran[3], Santhanakrishnan R. Kumar[2], Marimuthu M. Kumar[2], Victor Mohan[2], Sudha Ganapathy[1], Vanaja Kumar[1], Geetha Shanmugam[1], Niruparani Charles[1], Murugesan R. Sakthivel[2], Kannivelu Jagannath[3], Chockalingam Chandrasekar[4], Ramavaram T. Parthasarathy[3], Paranji R. Narayanan[1]

1 National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Chennai, India, 2 National Institute for Research in Tuberculosis (formerly Tuberculosis Research Centre), Madurai, India, 3 Institute of Thoracic Medicine, Chennai, India, 4 Government Rajaji Hospital, Madurai, India, 5 Government Tiruvalleeswarar Hospital, Chennai, India

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis

Corinne S. Merle, M.D., Katherine Fielding, Ph.D., Omou Bah Sow, M.D., Martin Gninafon, M.D., Mame B. Lo, M.D., Thuli Mthiyane, M.Sc., Joseph Odhiambo, M.D., Evans Amukoye, M.D., Boubacar Bah, M.D., Ferdinand Kassa, M.D., Alimatou N'Diaye, M.D., Roxana Rustomjee, M.D., Bouke C. de Jong, M.D., Ph.D., John Horton, M.D., Christian Perronne, M.D., Charalambos Sismanidis, Ph.D., Olivier Lapujade, B.Sc., Piero L. Olliaro, M.D., Ph.D., and Christian Lienhardt, M.D., Ph.D., for the OFLOTUB/Gatifloxacin for Tuberculosis Project*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

Stephen H. Gillespie, M.D., D.Sc., Angela M. Crook, Ph.D., Timothy D. McHugh, Ph.D., Carl M. Mendel, M.D., Sarah K. Meredith, M.B., B.S., Stephen R. Murray, M.D., Ph.D., Frances Pappas, M.A., Patrick P.J. Phillips, Ph.D., and Andrew J. Nunn, M.Sc., for the REMoxTB Consortium*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis

Amina Jindani, F.R.C.P., Thomas S. Harrison, F.R.C.P., Andrew J. Nunn, M.Sc., Patrick P.J. Phillips, Ph.D., Gavin J. Churchyard, Ph.D., Salome Charalambous, Ph.D., Mark Hatherill, M.D., Hennie Geldenhuys, M.B., Ch.B., Helen M. McIlleron, Ph.D., Simbarashe P. Zvada, M.Phil., Stanley Murgofa, M.P.H., Nasir A. Shah, M.B., B.S., Simukai Zizhou, M.B., Ch.B., Lloyd Magweta, M.B., Ch.B., James Shepherd, Ph.D., Sambayawo Nyirenda, M.D., Janneke H. van Dijk, Ph.D., Heather E. Clouting, M.Sc., David Coleman, M.Sc., Anna L.E. Bateson, Ph.D., Timothy D. McHugh, Ph.D., Philip D. Butcher, Ph.D., and Denny A. Mitchison, F.R.C.P., for the RIFAQUIN Trial Team*

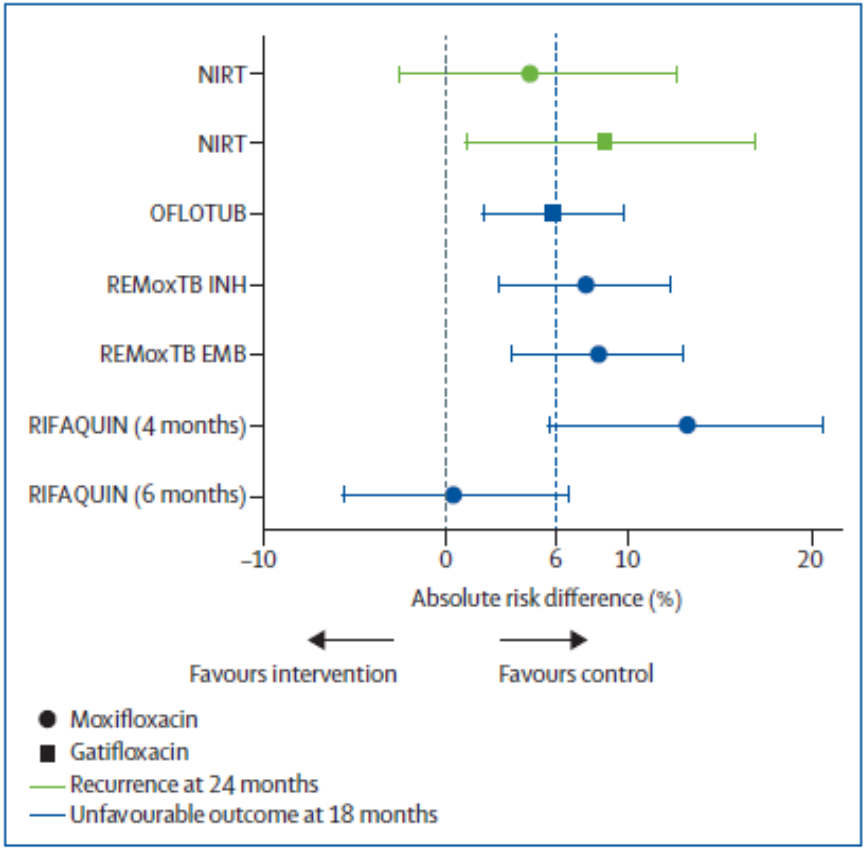
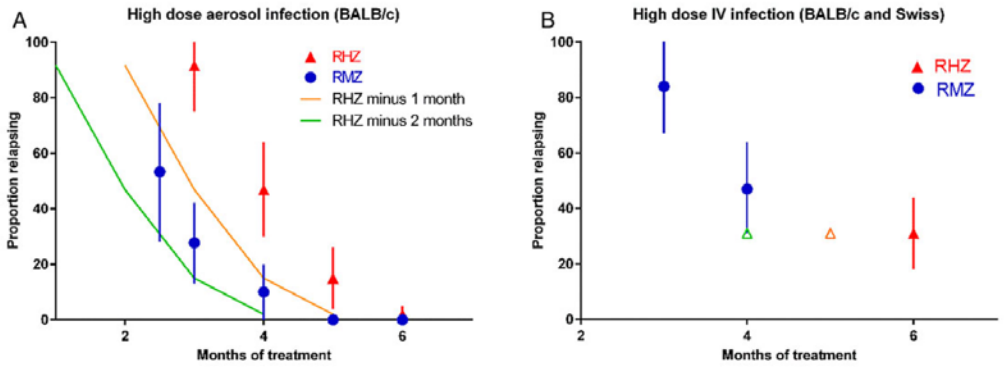
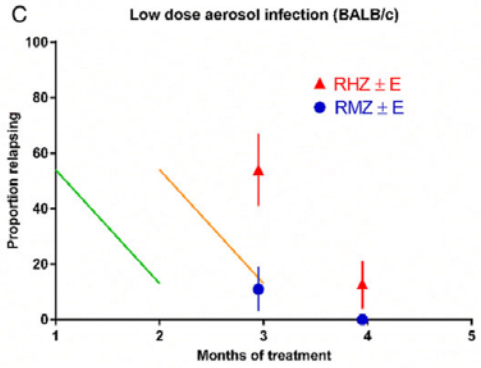


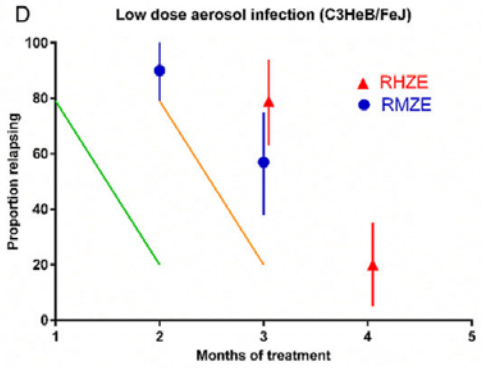
Figure: **Quinolone-containing regimens compared with standard treatment for tuberculosis**

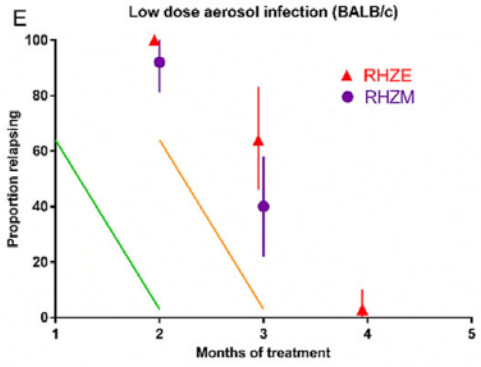
Unfavourable outcome at 18 months after randomisation follows trial-specific definitions that were broadly similar (including treatment failure and relapse).

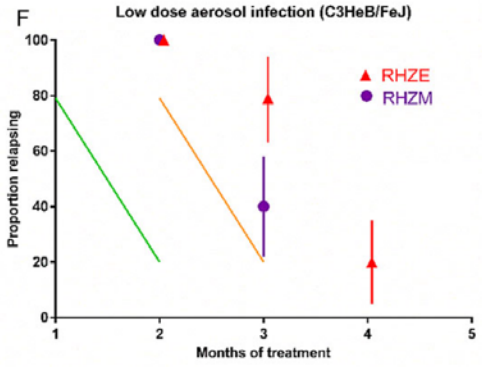
Nimmo et al, Lancet Infection, 2015





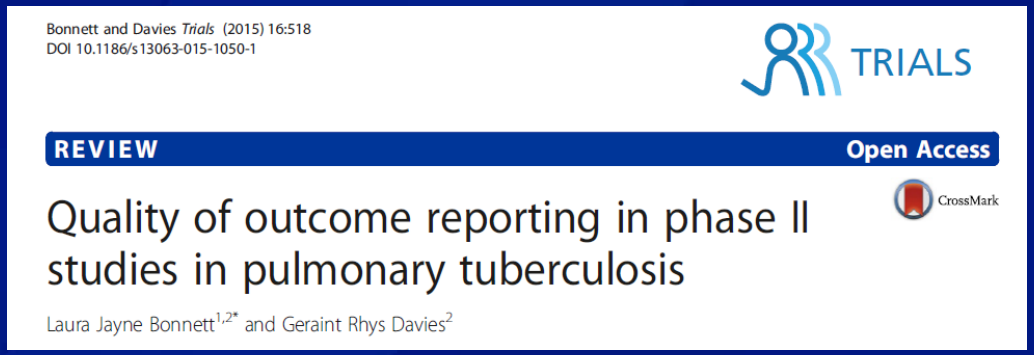






Lanoix et al, CID 2016

“We share the views that further development and validation of more pathologically similar, yet reproducible, animal models such as C3HeB/FeJ mice, rabbits, and marmosets is warranted, as each may develop cavitary disease. We also agree that more predictive biomarkers for phase 2 trials should be sought. However, the analyses of murine model data presented here and the predictions from the model of Wallis et al suggest that the principal failure in the development of these regimens was not misplaced confidence in murine models and trials based on sputum culture-based surrogate endpoints but, rather, an overly optimistic translation of the output from these studies into expectations of a 2-month treatment-shortening effect.”



Bonnett and Davies *Trials* (2015) 16:518
DOI 10.1186/s13063-015-1050-1

TRIALS

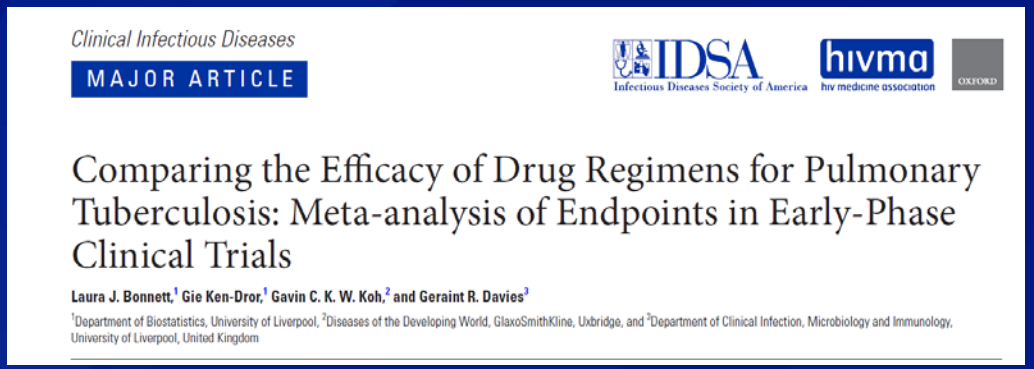
REVIEW Open Access

CrossMark

Quality of outcome reporting in phase II studies in pulmonary tuberculosis

Laura Jayne Bonnett[1,2*] and Geraint Rhys Davies[2]

2015



Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association OXFORD

Comparing the Efficacy of Drug Regimens for Pulmonary Tuberculosis: Meta-analysis of Endpoints in Early-Phase Clinical Trials

Laura J. Bonnett,[1] Gie Ken-Dror,[1] Gavin C. K. W. Koh,[2] and Geraint R. Davies[3]

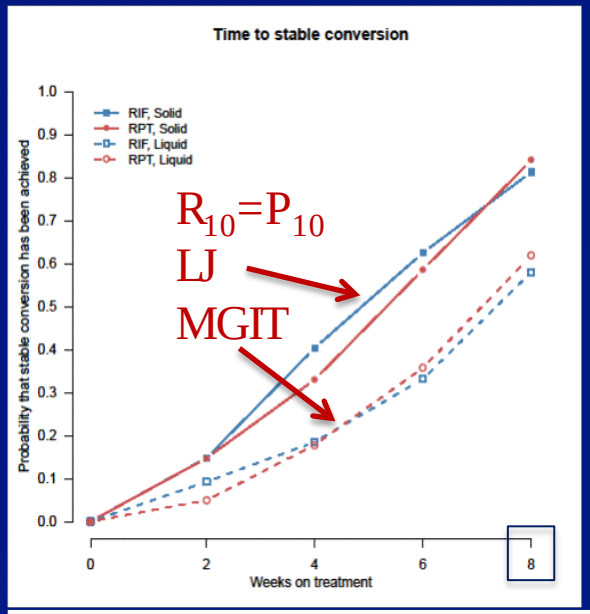
[1]Department of Biostatistics, University of Liverpool, [2]Diseases of the Developing World, GlaxoSmithKline, Uxbridge, and [3]Department of Clinical Infection, Microbiology and Immunology, University of Liverpool, United Kingdom

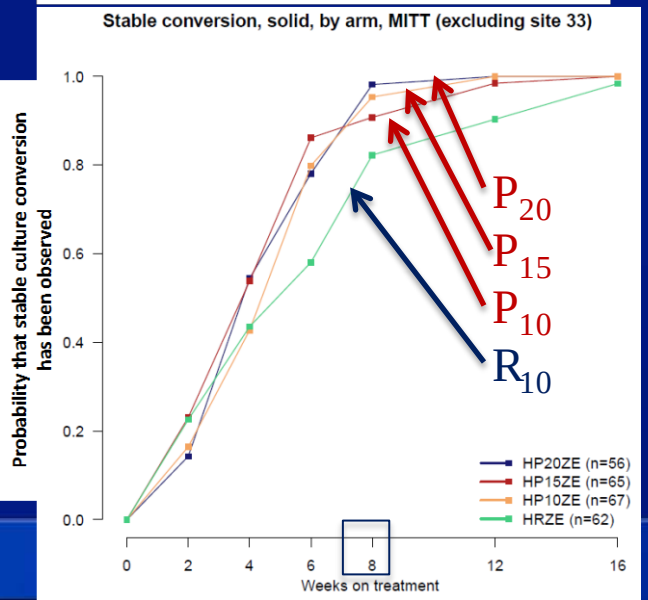
2017

"…we identified 133 trials reporting phase 2A and 2B outcomes comprising >37 000 patients and 67 drug combinations….The striking feature of the available dataset is the variability of pooled estimates of effect for all the endpoints examined…..Our review shows that the existing evidence base supporting phase 2 methodology in tuberculosis is highly incomplete. To truly understand and improve drug development in tuberculosis, it is desirable that a broader range of drugs and combinations be more consistently studied across a greater range of phase 2 endpoints than is currently available and that these regimens be rigorously compared in a cumulative meta-analytic framework."

Efficacy Summary: S29 and S29X

	MITT-LJ % cx neg @wk 8	MITT-MGIT % cx neg @wk 8
Study 29 (all fasting)		
RIF 10 mg/kg	79.2	62.6
RPT 10 mg/kg	82.8	66.7
--- Dose low, no food, no weekend doses ---		
Study 29X (RIF mostly fasting, RPT with hi-fat)		
RIF 10 mg/kg	81.3	56.3
RPT 10 mg/kg	92.5	74.6*
RPT 15 mg/kg	89.4	69.7
RPT 20 mg/kg	94.7*	82.5*





ORIGINAL ARTICLE

Daily Rifapentine for Treatment of Pulmonary Tuberculosis

A Randomized, Dose-Ranging Trial

Susan E. Dorman[1], Radojka M. Savic[2], Stefan Goldberg[3], Jason E. Stout[4], Neil Schluger[5], Grace Muzanyi[6], John L. Johnson[6,7], Payam Nahid[2], Emily J. Hecker[4], Charles M. Heilig[3], Lorna Bozeman[3], Pei-Jean I. Feng[3], Ruth N. Moro[3,8], William MacKenzie[3], Kelly E. Dooley[1], Eric L. Nuermberger[1], Andrew Vernon[3], Marc Weiner[9], and the Tuberculosis Trials Consortium

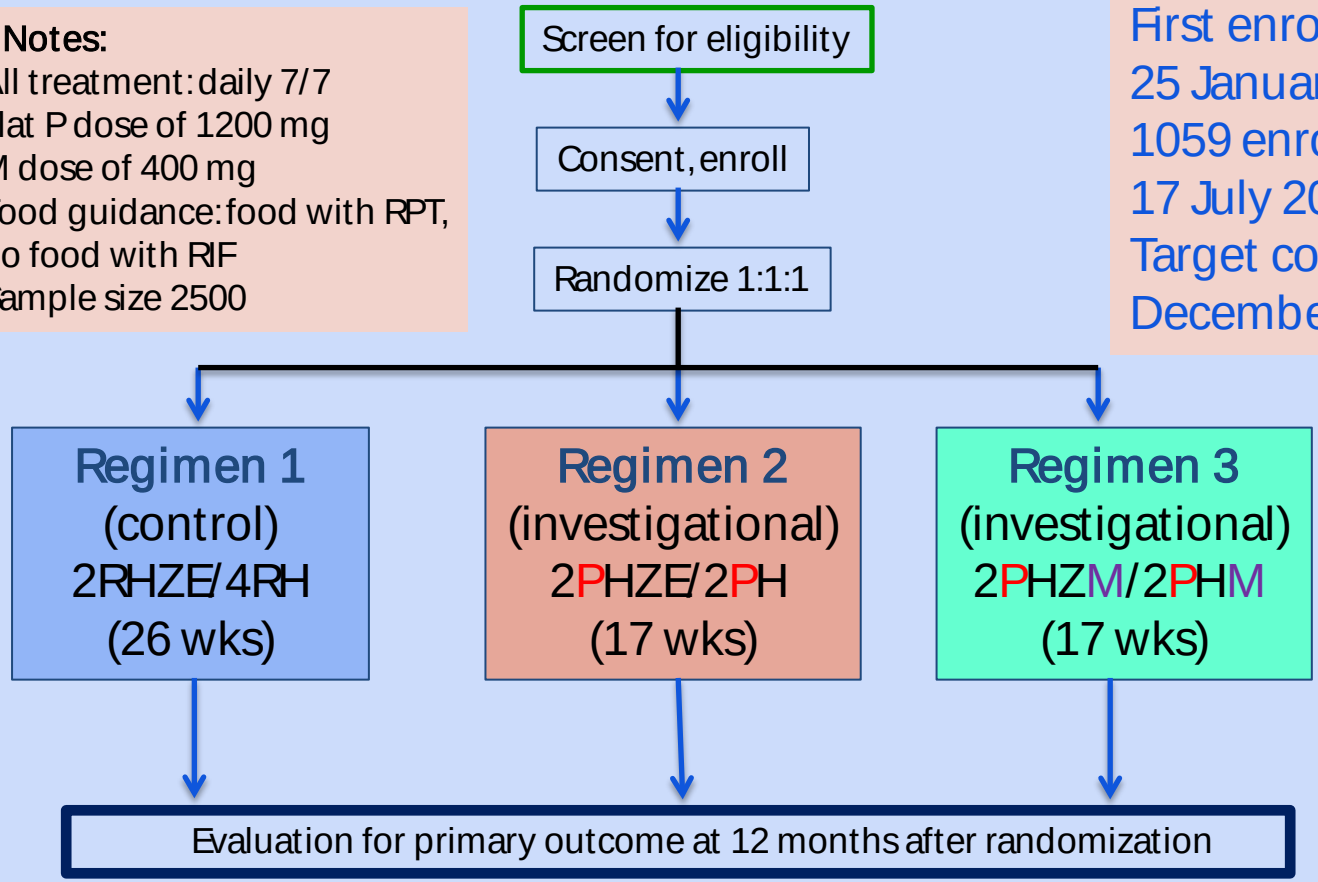
	Rifampin	Rifapentine AUC ≤ 323 μg · h/ml	Rifapentine AUC 324–513 μg · h/ml	Rifapentine AUC > 513 μg · h/ml
Solid culture medium				
% (n/n) with negative cultures	81.3 (52/64)	83.9 (52/62)	100.0 (63/63)	92.3 (60/65)
% difference vs. rifampin (95% CI)		2.6 (−12.2 to 17.4)	18.8 (7.6 to 29.9)	11.1 (−2.0 to 24.2)
P value		0.88	<0.001	0.11
Liquid culture medium				
% (n/n) with negative cultures	56.3 (36/64)	54.8 (34/62)	90.5 (57/63)	80.0 (52/65)
% difference vs. rifampin (95% CI)		−1.4 (−20.4 to 17.5)	34.2 (18.5 to 50.0)	23.8 (6.6 to 40.9)
P value		1.00	<0.001	0.007

Definition of abbreviations: AUC = areas under the concentration–time curve; CI = confidence interval.

TBTC Study 31 / ACTG A5349 Schema

Key Notes:

- All treatment: daily 7/7
- Flat P dose of 1200 mg
- M dose of 400 mg
- Food guidance: food with RPT, no food with RIF
- Sample size 2500



First enrollment
25 January 2016
1059 enrolled by
17 July 2017
Target completion
December 2018

Slide from Stefan Goldberg

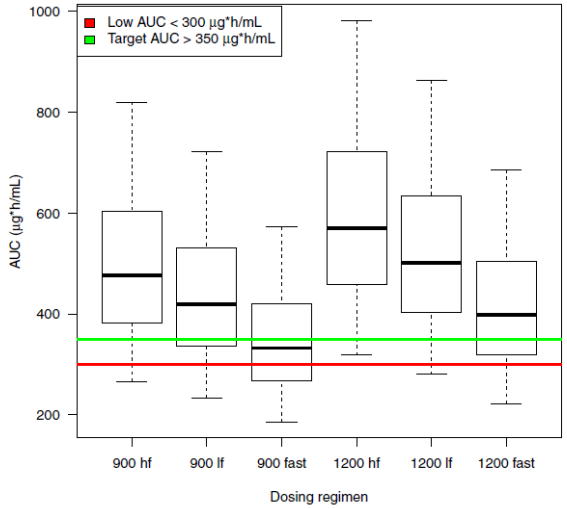


Figure 3 Relation between rifapentine area under the concentration–time curve (AUC) from 0 to 24 h ($AUC_{0\text{-}24}$) vs. dose (900 or 1,200 mg) and food type (high fat (hf), >27 g fat; lower fat (lf), 1 to 27 g fat; or fasting (fast)). Target rifapentine $AUC_{0\text{-}24}$ needed for 95% participants with no or small (<4 cm) lung cavities at baseline radiograph to achieve persistently negative cultures (AUC_{95}) in liquid media indicated by the green horizontal line. Insufficient exposure indicated by the red line. Model estimates of rifapentine AUC_{95} and **Figure 1** were used to formulate target cutoffs of rifapentine $AUC_{0\text{-}24}$ >350 µg × h/mL and low target rifapentine $AUC_{0\text{-}24}$ of <300 µg × h/mL using sputa cultures in liquid media.

ARTICLES

Defining the Optimal Dose of Rifapentine for Pulmonary Tuberculosis: Exposure–Response Relations From Two Phase II Clinical Trials

RM Savic[1], M Weiner[2,3], WR MacKenzie[4], M Engle[3], WC Whitworth[4], JL Johnson[5,6], P Nsubuga[6], P Nahid[7,8], NV Nguyen[8], CA Peloquin[9], KE Dooley[10], SE Dorman[10]
for the Tuberculosis Trials Consortium of the Centers for Disease Control and Prevention

Savic et al., Clin Pharm Therap, 2017

Table 4 Rifapentine and rifampin pharmacokinetic/pharmacodynamic outcomes in liquid media

Rifapentine pharmacokinetic/pharmacodynamic outcomes[a]				
Rifapentine $AUC_{0\text{-}24}$[a] (µg × h/mL)	Aggregate cavity size on chest radiograph (cm)	Study site in Africa	Percent participants with negative cultures in liquid media at completion of intensive-phase therapy, mean [95% CI]	Time (d) calculated for 50% participants to develop stable conversion to negative cultures in liquid media while receiving antituberculosis treatment [range: 5%, 95% participants]
> 350	< 4	Yes	67 [53, 83]	45 [14, 88]
	≥ 4	Yes	40 [20, 56]	66 [20, > 120][b]

Nix TB trial of TB Alliance

Pts with XDR, preXDR or failing/intolerant of MDR Rx

6 mo Regimen: Pretonamid 200mg qd
Bedaquiline 200 tiw (after load)
Linezolid 1200 qd

Conradie reported 2 mo conversion of 74% (CROI 2017)

Everitt reported that of 30 pts who had completed 6 months of therapy followed by 6 months of follow-up (as of May 11, 2017) , overall rate of relapse-free cure was 26/30, or 87% (TBTC May 2017)

TABLE 2 Lung CFU counts assessed during treatment and proportion of mice relapsing after treatment completion in experiment 1

Drug regimen	Mean (±SD) $\log_{10}$ CFU count at[a]:					Proportion (%) relapsing after treatment for:		
	D13	D0	M1	M2	M3	2 mo	3 mo	4 mo
Untreated	2.69 ± 0.13	6.17 ± 0.27	6.47 ± 0.06					
2RIF+INH+PZA/RIF+INH			3.47 ± 0.37	1.59 ± 0.25	0.50 ± 0.51		13/15 (87)	1/20 (5)
BDQ			3.24 ± 0.25					
PMD			4.57 ± 0.22					
LZD			4.97 ± 0.26					
SZD			3.85 ± 0.37					
BDQ+PMD			4.21 ± 0.40	1.62 ± 0.19	0.52 ± 0.36	15/15 (100)	10/15 (60)	2/20 (10)
BDQ+LZD			2.82 ± 0.15	1.91 ± 0.66				
BDQ+SZD			2.88 ± 0.07	0.65 ± 0.50				
PMD+LZD			3.23 ± 0.41	1.48 ± 0.12				
PMD+SZD			1.65 ± 0.33	0.23 ± 0.40				
BDQ+PMD+LZD			3.28 ± 0.65	0.34 ± 0.41	0.00 ± 0.00	12/15 (80)	0/14 (0)	0/20 (0)
BDQ+PMD+SZD			0.94 ± 0.14	0.00 ± 0.00		14/20 (70)	1/14 (7)	

[a] Time points are shown in days (e.g., D13, day 13; D0, day 0) or months (e.g., M1, 1 month) of treatment.

TABLE 3 Lung CFU counts assessed during treatment and proportion of mice relapsing after treatment completion in experiment 2

Regimen	Mean (±SD) $\log_{10}$ CFU count at[a]:				Proportion (%) relapsing after treatment for:	
	D13	D0	M1	M2	1.5 mo	2 mo
Untreated	4.42 ± 0.15	7.92 ± 0.26				
RIF+INH+PZA				2.06 ± 0.37		
BDQ+PZA+PMD_{50}			2.91 ± 0.33	0.95 ± 0.38		
BDQ+PZA+PMD_{100}			2.93 ± 0.31	0.06 ± 0.13	9/15 (60)	1/15 (7)
1BDQ+PZA+PMD_{100}+LZD/1BDQ+PZA+PMD_{100}			0.11 ± 0.24		0/15 (0)	0/15 (0)
BDQ+PZA+PMD_{100}+LZD					0/15 (0)	1/15 (7)

[a] Time points are shown in days (e.g., D13, day 13; D0, day 0) or months (e.g., M1, 1 month) of treatment.

Tasneen et al., Antimicr Ag Chemo, 2016

Efficacy of Bedaquiline, Pretomanid, Moxifloxacin & PZA (BPaMZ) Against DS- & MDR-TB

Rodney Dawson (1), Kendra Harris (2)*, Almari Conradie (3), Divan Burger (4), Stephen Murray (5), Carl Mendel (2), Mel Spigelman (2)

(1) University of Cape Town, Mowbray, South Africa, (2) Global Alliance for TB Drug Development, New York, NY, (3) The Global Alliance for TB Drug Development, Pretoria, South Africa, (4) QuintilesIMS, Bloemfontein, South Africa, (5) Mallinckrodt Pharmaceuticals, Bedminster, NJ

Table 4. Percentage of Patients Culture Negative at 2 Months
Kaplan-Meyer Analysis

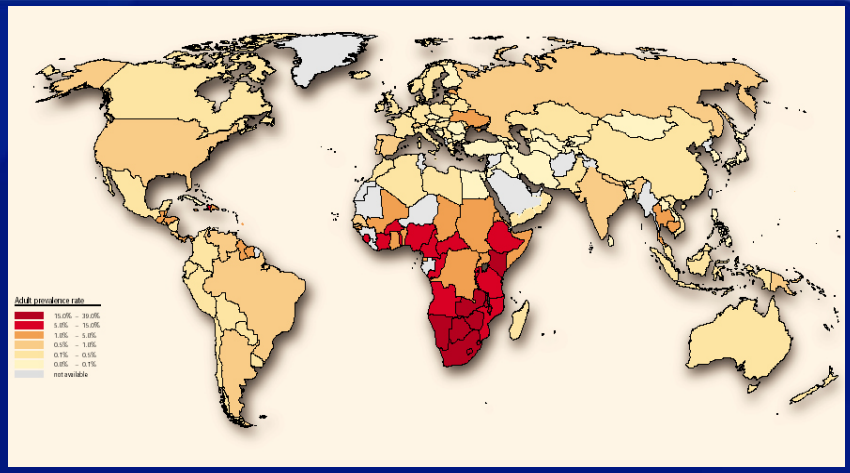
	Growth Medium	
	Liquid	Solid
	Overnight	Overnight
B(loading)PaZ	66%	89%
B(200mg)PaZ	75%*	84%
BPaMZ (MDR) Z-sensitive	96%*	100%*
BPaMZ (MDR) Z-resistant	78%*	95%*
HRZE control	51%	86%

*The difference compared to HRZE is statistically significant.

TB ALLIANCE

5. Other networks

ACTG
AIDS CLINICAL TRIALS GROUP



1. TB treatment shortening
2. MDR Treatment
3. Preventive therapy
4. TB/HIV Co-treatment
5. Transformative science: PK/PD, Biomarkers, lab monitoring & diagnostics, preclinical studies (animal models)

Thanks to Richard Chaisson for materials for this and next 3 slides

Completed or Active ACTG TB Trials

Type of Trial	ACTG ID	Topic of Trial
Strategy trials	5221 5274	When to start ART in TB pts (Stride) IPT vs presumptive TB Rx w/ART (Remember)
Diagnostic	5295 5302	Xpert performance Biobank with TBA and TBTC
PK	5221PK 5267 5279 PK 5306 5311 5343 5338	EFV/RIF DDI BDQ/EFV DDI EFV/daily HP DDI Pretonamid DDI with EFV and RIF HD RPT in healthy vol's BDQ/DEL PK and safety DMPA/RIF/EFV in women HIV-TB (Pride HT)
Phase 2a	5307 5312	EBA INH d0-14 EBA HD INH with inhA mutation
TB Rx	5349	4mo Rx HD RPT
Prevention	5279 5300	4wk daily HP in HIV+ in HBCs 6m DEL for MDR LTBI (Phoenix)

"Partnerships are essential for conducting TB clinical trials"

R Chaisson, ACTG

TBTC – Study 31

TBTC and TB Alliance – Biomarkers

IMPAACT – Phoenix

Pharma (Sanofi, Otsuka, Janssen) – multiple studies

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TB clinical trials landscape

Network/Group	Location	Funding	Trials
ACTG	Global	NIH	Multiple
TBTC	Global	CDC	"Programmatically relevant trials" Study 31, Study 35, ASTEROID
IUATLD/ UK MRC	Africa, Asia, Eastern Europe	USAID	STREAM 1 and 2
PanACEA	Africa	European Union	Hi-RIF
PIH-MSF	Global	UNITAID	End TB
TB Alliance	Global	Gates, others	NC-005, NC-005, NiX
Inter-TB	Africa	MRC, others	Rifashort
Multiple academic groups	Global	Various	Multiple

Conclusions

1. Need for more , and more consistent, work in pre-clinical and in phase 1/phase 2 evaluation of new agents and regimens

2. More strategically linked phase2b-phase2c-phase3 efforts, begun with the successful end in mind, and substantially simplifying the administrative environment of major development efforts

3. Continued and increased collaborations among the major trials networks and funders. A useful step toward this goal might be the creation of an annual or bi-annual international research conference on the effort to improve and strengthen treatment and prevention of tuberculosis.

4. Continued substantive efforts by regulatory authorities and international bodies to educate their interested communities, and to improve the development path. Workshops such as this are a promising step.

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