Tuberculosis Trials Consortium

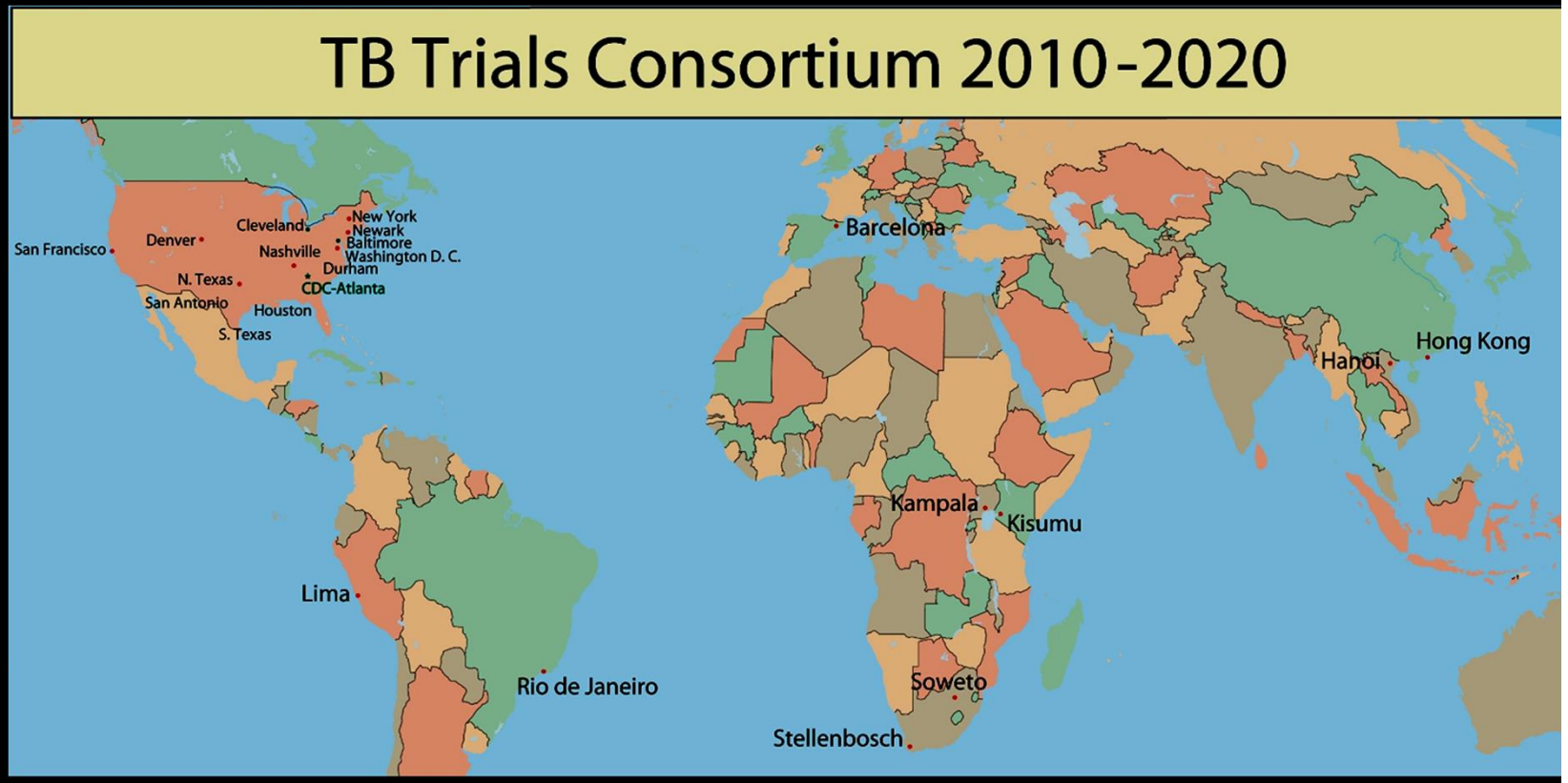
Present and Future Research

November 27, 2018

Key characteristics of the TB Trials Consortium

- Established informally in 1993-94; formally in 1997
  - Two 10-year contracts (2nd runs through September 2019)
    - Continuity; flexibility to adapt scientific direction
    - Collegiality: CDC, academic centers, public health develop agenda
    - U.S. sites, with international partners
      - Network of high capacity: data, laboratory
    - High quality, which has attracted excellent collaborators
      - Further increase in quality, but also ↑ capacity and ↓ TBTC burden
    - Development of new generation of investigators
- Programmatically relevant research
  - Studies conducted in public health clinics
    - Facilitates uptake of new findings and regimens
  - Results affect U.S. and global TB care, and guidelines

TBTC has created a network of high-capacity and high-quality clinical trials sites



TBTC has enrolled over 11,000 patients in Phase 2 and Phase 3 trials in latent and active tuberculosis

TBTC maintains strong links between academia, local TB control programs, and community

- TBTC depends on partnerships between leading academic medical centers and local TB Control Programs
  - Universities:
    - Johns Hopkins, Duke, Columbia, UCSF, University of Colorado, Vanderbilt, George Washington, University of North Texas
  - Health Departments:
    - NYC TB Control Program, Denver Public Health, Nashville Metro Public Health, Texas Department of Health, California Department of Health, North Carolina
  - International sites:
    - South Africa (Cape Town, Soweto), Kenya, Uganda, Hong Kong, Vietnam, Peru
  - Patients/community:
    - Community Research Advisory Group

- These partnerships enhance the impact of TBTC studies and help to broaden the generalizability of the results

Current TBTC Research Priorities

- Top tier
  - Shorten treatment duration for drug-susceptible TB
  - Shorten treatment duration for latent infection

  Rationale: shorter treatment and improved tolerability → higher completion rates → higher cure rates → lower disease burden

  Improved treatment of TB disease and LTBI: ↓ the pool of drug-resistant TB

- Include in the above studies:
  - HIV-infected persons
  - Children
  - Pharmacokinetic, biomarker, diagnostics sub-studies

- Perform as possible and at specific sites
  - MDR-TB

TB Trials Consortium

Overall approach

- Phase 2 TB treatment studies to inform phase 3 treatment shortening studies
  - Improvements in treatment of TB disease are important for both U.S. and global TB control
- Phase 3 studies of treatment of latent *M. tuberculosis* infection
  - Of greatest importance for TB elimination in the U.S., but now also of increasing importance globally
    - Directly addresses several components of DTBE mission
- Include important populations
  - Persons with HIV, children, pregnant women, MDR-TB
- Important to be engaged in all areas, but with a mix of primary and secondary focus so that there is always ongoing activity of the consortium

The Approach and Results of TBTC

Phase 2 and Phase 3 TB Treatment Studies

- Approach
  - Evaluated fluoroquinolone substitutions for EMB and INH in phase 2
    - Did not ↑ cx conversion
  - Evaluated daily rifapentine to improve sterilization
    - Required two phase 2 studies to identify the correct rifapentine dose
    - PK sub-studies critical
- Results
  - Did not pursue phase 3 TB treatment shortening trials with fluoroquinolones
  - Delayed the initiation of a phase 3 study, but now studying two regimens with higher likelihood of success in Rx shortening (Study 31 / ACTG 5349)
  - Influenced 2016 ATS/IDSA/CDC TB treatment guidelines

The Approach and Results of TBTC

Treatment of Latent TB Infection

- Approach
  - Studied 3HP in low TB incidence settings (Study 26)
  - Included sufficient children and HIV+ persons to evaluate safety and effectiveness in these populations
  - Evaluated 3HP self-administered (Study 33)
  - Will evaluate RPT PK in young children (Study 35)
  - Initiating study of even shorter duration
    - 6 weeks daily rifapentine
    - Study 37 (ASTEROID)
- Results
  - Changed CDC guidelines (2011, 2018), but also contributed to WHO issuing their first LTBI guidelines for low TB burden countries (2015, 2018)
  - Broad uptake of 3HP in the U.S.

The Approach and Results of TBTC

TB Diagnostics and Treatment of MDR-TB

- Approach
  - Collaborated with ACTG to evaluate GeneXpert in low TB incidence settings (Study 34)
  - Collaborated with NIH to determine the optimal levofloxacin dose in MDR-TB (OptiQ; Study 32)
- Results
  - Contributed to change in NTCA/APHL guidelines for discontinuation of respiratory isolation
  - Enrollment complete; analysis in early 2019

Study 31/ACTG 5349 Primary Objectives

- Evaluate efficacy of a high dose rifapentine-containing regimen to determine whether the single substitution of RPT for RIF makes it possible to reduce to 4 months (17 weeks) the duration of treatment
  - 2PHZE/2PH

- Evaluate efficacy of a 4 month (17 weeks) regimen that substitutes a) high dose RPT for RIF and b) MOX for EMB to determine whether reduction to 4 months (17 weeks) duration is possible *(optimized regimen using existing drugs)*
  - 2PHZM/2PHM

Study 31/ACTG 5349 Study Design

- International, multicenter
- 3 arms, randomized 1:1:1
- Open-label
- Non-inferiority design
- N = 2500 (enrollment completed October 2018)
- Several secondary objectives and sub-studies, including PK/PD and biomarker studies
- FDA registration-level quality controls
- DSMB review annually and as needed
- Registration of ClinicalTrials.gov: NCT02410772

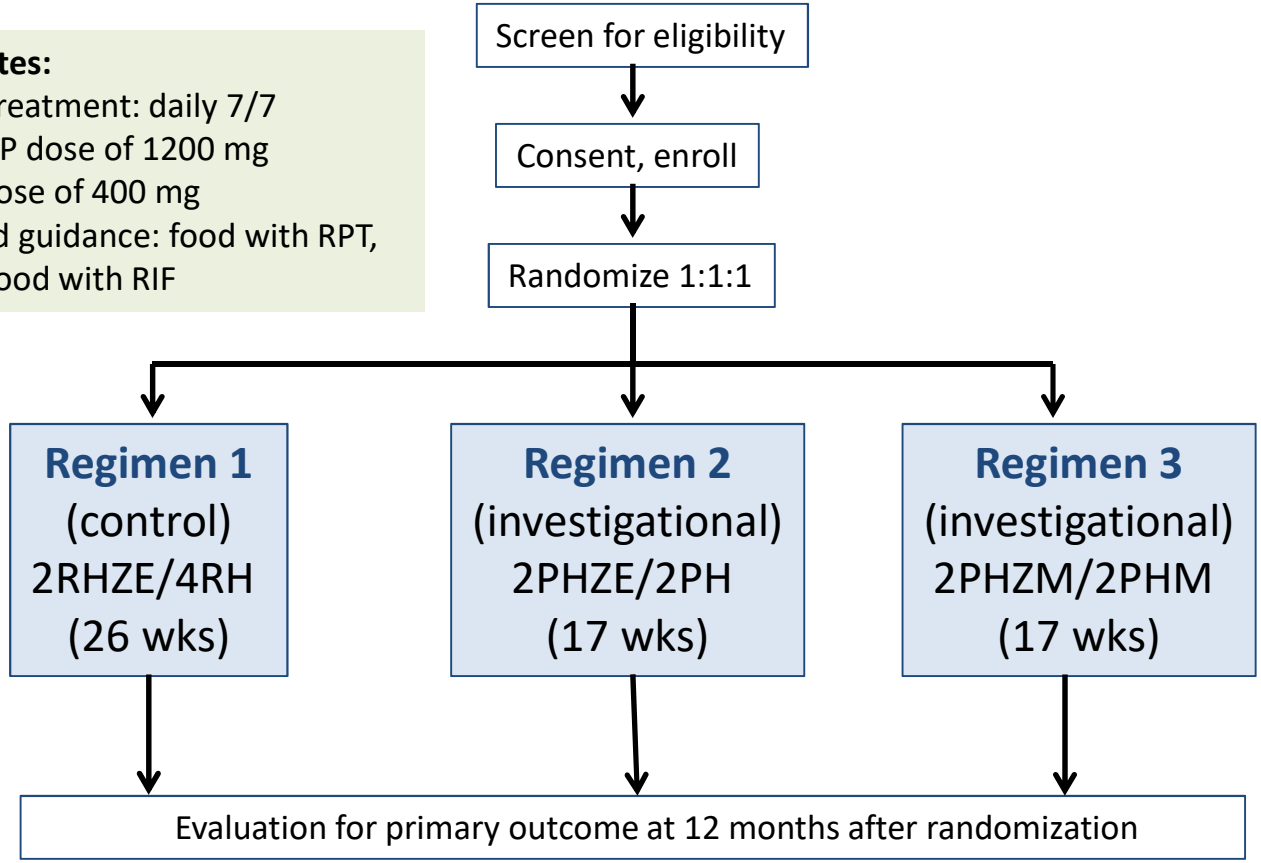
Study 31/ACTG 5349 Selected Eligibility Criteria

- Inclusion
  - Positive sputum smear for AFB or positive *Xpert MTB* with medium or high result
  - Age >= 12
  - If HIV (+), CD4 T cell count >= 100 cells/mm^3
    - Initially enrolled only persons stable on efavirenz-based ART, for drug interaction PK and viral load testing
- Exclusion
  - > 5 days TB treatment within previous 6 months
  - > 5 days treatment with anti-TB drugs within previous 30 days
  - TB of CNS, bones or joints, military, pericardial
  - Weight < 40 kg

Study 31/ACTG 5349 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



SECONDARY: Evaluate safety and tolerability of the regimens, extensive PK of ALL TB drugs and EFV, biobanking

ASTEROID

Study 37

- Study design
  - Randomized, controlled, open-label non-inferiority trial
- Regimens
  - Experimental: 6wP (daily). Rifapentine dose: 600 mg/day with food
  - Comparator: 12-16 week rifamycin-based treatment:
    - 3HP once-weekly, 3HR daily, 4R daily
- Inclusion criteria
  - ≥ 12 years old, TST/IGRA+, high risk for TB
- Exclusion criteria
  - Rifamycin intolerance, rifamycin resistant source case, AST/ALT >5x ULN
- Study population
  - Primarily HIV-seronegative, though HIV-positive persons eligible
  - Recruitment in low TB incidence countries
- Non-inferiority margin:
  - safety: 4%; effectiveness: 0.75%
- Sample size
  - 560 per arm (1,120 total) for safety and tolerability
  - 1,700 per arm (3,400 total) for effectiveness

Conclusions

- After 25 years, we have gained some important insights from our successes and unexpected findings
- We are enrolling into an important phase 3 study that could shorten TB treatment to 4 months
- We are launching an important phase 3 study that could shorten treatment of LTBI to 6 weeks
- We think this work will identify regimens that contribute to TB elimination in the U.S. and globally

TB Trials Consortium
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