Treating Patient, Not Disease: People-Centered Approach

7th TB Symposium – Ministry of Health of the Kyrgyz Republic and Médecins Sans Frontières

1-2 March, 2018, BISHKEK, KYRGYZSTAN

Experience/results of endTB clinical trial

Lorenzo Guglielmetti

endTB Co-Principal Investigator, MSF
Outline

• Overview
• Models of care
• Trial progress
• Challenges
Expand New Drugs for TB

Funding partner:

Unitaid

Three consortium partners:

MEDECINS SANS FRONTIERES

Partners In Health

Project duration: 4 years.
Project budget = $60.4 million
Principles for designing future regimens for multidrug-resistant tuberculosis

At least one new drug class
At least 3 and max 5 effective drugs
Effective against MDR and XDR strains
Short
Oral
Simple dosing schedule
Good side effect profile, limited monitoring
Minimal interaction with antiretrovirals

Bull WHO 2014;92:68-74
endTB trial summary

- Randomized, controlled, Bayesian response-adaptive, non-inferiority, Phase III
  - Identify ALL non-inferior regimens
- Five 39-week experimental regimens vs. conventional, standard-of-care control
- FQ-susceptible, pulmonary RIF-R TB
- Sample size: 750 randomized participants
endTB Trial Objectives

- Primary: Outcomes of (5) experimental regimens at **73 weeks** vs. control

- Secondary efficacy: Compare to control
  - Early treatment response (**8 weeks**)
  - Outcomes at **39 weeks**
  - Outcomes at **104 weeks**, including relapse

- Secondary safety: Compare to control
  - At **73 and 104 weeks**
endTB Trial Endpoints

- E1
- E2
- E3
- E4
- E5

0 Random
W8 culture conversion
W39 outcome
W 73 primary outcome
W104 outcome

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Study Population: Inclusion

- Pulmonary TB, RIF-resistant & FQ-susceptible, by validated rapid molecular test;
- ≥18 years of age (≥15 where accepted);
- Negative pregnancy test & willingness (♀ & ♂) to use appropriate contraception;
- Informed consent;
- Intent to remain accessible to study.
Study Population: Exclusion

- Allergy or hypersensitivity to study drugs
- Pregnant, breastfeeding
- Unable or unsafe to comply with study
- Exposure/proven or likely resistance to bedaquiline, delamanid, linezolid, clofazimine (last 5 years)
- Exposure to second-line drugs for ≥15 days in the current MDR/RR-TB treatment episode (v3.0)
- Hematology/chemistry/electrolyte abnormalities
- Cardiac risk factors
- Participating in other trial
- Must take disallowed medications
# Experimental 9-month Regimens

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Standard of care control, per WHO Guidelines, may include Dlm or Bdq.

Bdq=bedaquiline, Dlm=delamanid, Cfz=clofazamine, Lzd=linezolid, FQ=fluoroquinolone (Mfx=moxifloxacin, Lfx=levofloxacin), Z=pyrazinamide

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Models of care (1)

- Enrollment: centralized at TB Hospital
- Follow-up visits: TB Hospital/TB clinic
- Supervised DOT: TB Hospital/TB clinic
Models of care (2)

- **Enrollment**: TB Hospital/TB Clinic
- **Follow-up visits**: TB Hospital/TB Clinic/peripheral health facilities
- **DOT with treatment supporter**: home
endTB trial in KG (1)

Catchment area: Kara-Suu district + Osh city

Screening and FU: Osh TB Hospital
Preparation steps to date

- Bioethical Committee (MOH) approval (June 2017)
- Preparations at Osh TB Hospital for Trial Licence:
  - Medical Accreditation (August 2017)
  - Local IRB established + GCP training for staff
  - Renovated MDR-TB ward and ICU
  - Local Site SOPs developed
  - Clinical Trial Site License assessment (Feb 2018)
Next steps

- Clinical trial Site License
- DDP Regulatory approval
- CT trainings (first part done in Dec 17)
- Site Initiation Visit and enrolment start
Update: Feb 13, 2018
## endTB Timeline

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Challenges

- Secular changes in MDR-TB epidemiology
- Regulatory barriers
- Patient refusal
- DOT Decentralization
- Changing standard of care
- Variability across sites in implementation
Substudies

• PandrTB (Pharmacometrics to advance novel regimens for drug-resistant tuberculosis)

• PK/PD of Bdq, Dlm, Cfz, Lzd, Mfx, Lfx and Z
  • Time to culture positivity, MICs, drivers of efficacy, PK and toxicity, interactions (ie. ARVs)

• Funding: Wellcome Trust

• PI: Hellen McIlIeron, UCT, Cape Town
endTB-Q trial

- Rifampicin- and FQ-resistant pulmonary TB
- Randomized, controlled, open-label, non-inferiority, Phase III trial
- Multiple experimental arms (24-39 wks) vs. control
- Approx 500 randomized participants
- Primary and final endpoint: 73-week outcomes

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<th>Multiple experimental arms and a control arm</th>
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On behalf of endTB central Trial Investigators

Co-PI: Carole Mitnick

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Maryline Bonnet  Bouke de Jong
Elisabeth Baudin  Francis Varaine
Gabriella Ferlazzo

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Dr Sean Wasserman
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- Global TB CAB
- MSF MDR-TB Clinical Trial Scientific Advisory Committee
- Division of Global Health Equity, Brigham & Women’s Hospital
- Ministries of Health: Georgia, Kazakhstan, Kyrgyzstan, Lesotho, Peru, South Africa
Thank you...Questions?

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