Nix-TB trial

Francesca Conradie
University of Witwatersrand
• What is XDR TB?
• How big is the problem?
• What is prognosis?
• What are current treatment options?
• What is the Nix trial?
TB resistance

- **DS**
  - Rifampicin
  - Isoniazid

- **MDR**
  - Rifampicin
  - Isoniazid

- **Pre-XDR**
  - Rifampicin
  - Isoniazid
  - Fluoroquinolone
  - Amikacin or kanamycin or capreomycin

- **XDR**
  - Rifampicin
  - Isoniazid
  - Fluoroquinolone
  - Amikacin or kanamycin or capreomycin
TB resistance

**DS**
- Rifampicin
- Isoniazid

**MDR**
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- Isoniazid

**Pre-XDR**
- Rifampicin
- Isoniazid
- Fluoroquinolone
  - or
  - Amikacin or kanamycin or capreomycin

**XDR**
- Rifampicin
- Isoniazid
- Fluoroquinolone
  - or
  - Amikacin or kanamycin or capreomycin

Diagnosed by GXP
TB resistance

Diagnosed by LPA and Culture
TB resistance

Diagnosed by Culture

DS
- Rifampicin
- Isoniazid

MDR
- Rifampicin
- Isoniazid

Pre-XDR
- Rifampicin
- Isoniazid
- Fluoroquinolone
  - Amikacin or kanamycin or capreomycin

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How big is the problem?
Snap shot of South Africa

- Population: 50,586,757
  - Provinces – 9
  - Districts - 53
  - Sub districts - 253
  - Health facilities – 4790

- MDR-TB beds: Approx. 3,000

- DR-TB treatment sites: 578
TB Burden in South Africa

• TB patients initiated on treatment **decreasing**: 406,082 to 332,170 (2009 and 2013)

• Treatment success rate: **80,9 %** for 2012 DS cohort

• MDR-TB numbers initiated on treatment **doubled** between **2010 and 2013** (5,313 to 10,719)

• MDR-TB treatment success rate of **49 %** (2012 cohort > 8,000)

• XDR-TB treatment success rate is **20 %**
XDR-TB Treatment Outcomes (24 months)
Countries (in Red) that had Notified at least One Case XDR-TB, by end 2013

WHO. Drug-Resistant TB. Supplement Global TB Report 2014
Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis

Adapted from Brenner H (2002); The Lancet, 360: 1131-1135 by Edward Tufte (http://www.edwardtufte.com)

XDR-TB 23

 Courtesy: Jaramillo E, WHO
Why do people get XDR TB?

• Original cases were due to non-adherence
• Now at least 79% of cases are transmitted
Current treatment of XDR TB

• Based on Resistance tests and prior exposure to other TB drugs
• Duration is at least 24 months
Current treatment of XDR TB

- Commonly used drugs
  - Capreomycin- injectable agent, cross resistance is high to other injectable
  - PAS- poor side effect profile
  - PZA, terizidone, ethionamide etc. dependant of prior exposure them.
  - Newer drugs available in some countries
    - Bedaquiline
    - Linezolid
    - Delaminid
What would be the ideal regimen?

- Safe and effective
- Shorter and injection free
- Three new drugs to which there is no resistance
Nix-TB Rescue Study

A Phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus Pretomanid (PA-824) plus linezolid in subjects with pulmonary infection of either extensively drug-resistant tuberculosis (XDR-TB) or treatment intolerant / non-responsive multi-drug resistant tuberculosis (MDR-TB).
Nix-TB Rescue

- Patients with XDR TB or Who Have Failed MDR Treatment

**XDR TB**
- Pa-824 200 mg
- Bedaquiline 200 mg tiw after 2 week load
- Linezolid 600 mg bid

**6 months of treatment**
Additional 3 months of treatment if sputum positive at 4 months

**Serial early morning sputum samples in liquid culture throughout**

3 monthly follow up for relapse-free cure over 24 months

Sites: Durban, Sizwe, Brooklyn Chest, SA
Nix-TB Objective and Primary Endpoint

• Objective
  – To evaluate the efficacy, safety, tolerability and pharmacokinetics of bedaquiline plus PA-824 plus linezolid after 6 months of treatment (option for 9 months for subjects who remain culture positive at month 4) in Subjects with either pulmonary XDR tuberculosis, treatment intolerant or non-responsive multi-drug resistant tuberculosis (MDR-TB).

• Primary Endpoint
  – Incidence of bacteriologic failure or relapse or clinical failure through follow up until 24 months after the end of treatment.
Nix-TB
Safety and Tolerability Endpoints

• All cause mortality.

• Incidence of Treatment Emergent Adverse Events (TEAEs) will be presented by severity (DMID Toxicity Grade), drug relatedness and seriousness, leading to early withdrawal and leading to death.

• Quantitative and qualitative clinical laboratory result measurements

• Quantitative and qualitative measurement of ECG results

• Descriptive statistics of ophthalmology slit lamp examination data (age related eye disease study 2 [AREDS2] lens opacity classification and grading).

• Changes in ophthalmic exam for visual acuity and color vision

• Changes noted in peripheral neuropathy signs and symptoms
Analyses, DSMC Meetings

• Exploratory Analyses:
  – Evaluate whether any of the secondary endpoints predicts relapse free cure.
  – Sub-analysis of populations by HIV status and CD4 count.
  – Correlation of Time over mitochondrial protein synthesis inhibition (MPS50) with linezolid toxicity (The MPS50 will be an assumed value from the literature).

• DSMC Meetings & Futility Analyses:
  – Frequent DSMC meetings to review safety/efficacy and futility.
    • Safety/Efficacy
      DSMC Meetings will be held at least every 6 months
      Ad hoc meetings can/will be held if there are concerns with safety or efficacy between these meetings
    • Futility
      Interim analyses for futility will be performed for every 20 patients who reach the primary efficacy endpoint, treatment failure (that is, bacteriologic failure, or relapse, or clinical failure).