Priorities and Lessons Learned in the endTB Multi-Country Observational Study: Future Analysis Plans

Uzma Khan
15 Nov 2018
Lessons Learned
Lessons Learned 1
Barriers to Access: Drug Procurement

Drug importation
- Procure Bdq, Dlm, Lzd, Cfz
  - Support documentation and importation process
  - Establish communication b/w implementing projects and procurement agent

Issues faced
- Lengthy and different process across countries
Lessons Learned 1
Barriers to Access: Approvals from Ethical Review Boards

- Ethical approvals were required, not just for the observational study but also for introducing Bdq and Dlm in some countries for routine clinical care
- Central and site specific approval obtained
  - Time consuming process, caused additional delays in access
Lessons Learned 2
Capacity Building: Trainings
Lessons Learned 3
Strengthening Capacity: Resources – clinical guidance

The endTB Clinical Guide

- Guidance on regimen design, drug interactions, safety monitoring and management
- Used by clinicians and programs
- Dynamic document, incorporates learnings from the field, last version 4.0
- Available in different languages – English, Russian and Spanish
Lessons Learned 3
Strengthening Capacity: Resources - PV Unit

- Safety reporting
- Access to new information
- Access to resources
- Interactions between sites to improve knowledge and experience
- Advise on PV issues and dissemination of information
Lessons Learned 3
Strengthening Capacity:
Resources - endTB Medical Committee

- Includes internal and external experts on weekly roster
- Direct access to country teams to share cases and seek advise
- So far >550 cases reviewed from 20 countries
- 57% from non-endTB countries
Lessons Learned 3
Strengthening Capacity: Resources-endTB Website

A new partnership to improve TB treatments around the world

endTB aims to find shorter, less toxic and more effective treatments for ‘multidrug-resistant TB’ (MDR-TB) through:

- endTB clinical guide
- PV Forms
- E-learning modules
- Report - endTB interim analysis
Lessons Learned 3
Strengthening Capacity: Clinical Evaluation and Monitoring

- Brief Peripheral Neurophathy screen
- Visual acuity screen
- Color Blindness screen
- ECG
- Audiometry (hearscreen app)
- Lab capacity: routine SL DST not available in some countries. Introduced Second-line LPA, additional tests not routinely done
Lessons Learned 3
Strengthening Capacity: Development of the endTB EMR

- Developed customized EMR
- Standardized data collected at all sites
- Can be used for clinical monitoring
- Generate customized reports
- Global resource and “endTB legacy”
Lessons Learned 4
Data Management

Trainings
Importance of data collection and using it for programmatic decision making

On-Site Data Quality Checks
Improving data completeness, and communication between data and clinical teams

Central Data Quality Check
Queries sent back to sites, sites then make changes as needed

Funding
Huge amount of effort – even with single EMR takes a long time – cleaning, verifying, resolve outstanding queries, analysis. Time and labor intensive and costs!! Requires $$$
Lessons Learned 5
Informed Consent

- Time consuming process
  - Additional consent forms signed for treatment with Bdq or Dlm
- Risk of patient refusals
- Should be universal for all regimens, not specific to a drug
Lessons Learned 6
Patient-Centered Care

- Individualized regimen design
- Empowering clinicians & patients in clinical decision making
- Treating patients with co-existing conditions (HIV, hep C), children and pregnant women
- Experience in prolonged use of Bdq, Dlm and concomitant use
Lessons Learned 7
Diverse Implementation strategies

- Heterogenous care models
- Private sector engagement
- HIV or hep C co-infected populations
- Urban and rural; developing or integrating existing strategies to link patients to healthcare centers
Lessons Learned 8
Working in a Consortium
Lessons Learned 9 - endTB Interim Analysis

http://www.endtb.org/resources/endtb-interim-analysis-july2018

Delamanid analysis
- ≥ Grade 3 QTc interval prolongation infrequent:
- Culture conversion occurs in ~ 80%, including among XDR and patients with comorbidities
- Balance of efficacy and safety supports delamanid use

Injectable analysis
- Important toxicity common among patients receiving SL injectable
  - 20% of patients had hearing loss
  - 36% had injectable-related AE (hearing loss, acute renal failure, electrolyte imbalance)
- Balance of evidence does not support universal use of SL injectable
- Monitoring of injectable-related toxicity key
Lessons Learned - Summary

- PV as done for endTB observational study impractical for routine care
- Good clinical monitoring for toxicity essential for all drugs and regimens.
- Important to empower clinicians to make decisions with good supervision
- Some of the resources from endTB should have been routinely available, however that was not always the case (e.g. audiometry, second-line DST)
PossibleNs for reporting on endTB outcomes, by date and endpoint

Possible Reporting Date
- 7-Jul-18
- 31-Dec-19
- 31-Jul-21

# eligible for analysis
- 12 months follow up (safety)
- 6-month effectiveness
- 12-month effectiveness
- 24-month effectiveness
- 30-month effectiveness (incl 6 months post-treatment FU)
Priorities for Future Analysis - 1

- Culture Conversion at six months, reversion
- Safety analysis (AEs and SAEs)
- Safety & effectiveness of prolonged and concomitant use
- At least 50% of the endTB cohort on prolonged use
- Safety & effectiveness of companion drugs
  - Linezolid (by duration, baseline anemia)
  - Injectables (by SLI)
Priorities for Future Analysis - 2

- Special population subgroup analyses
  - Children
  - Pregnant women
  - Hep C, HIV co-infected patients
  - Less “chronic” MDR-TB patients
- Optimal monitoring schedule for toxicity
- endTB experience of setting up, implementing PV and lessons learnt
- Other Sub-studies
  - Amplification of resistance
  - Specific AEs related to drugs – e.g. linezolid