

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

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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

N11.



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

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- Developed customized EMR
- Standardized data collected at all sites
- Can be used for clinical monitoring
- Generate customized reports
- Global resource and "endTB legacy"

Rule Name	Treatment Reg No	Name	Treatment Facility	EMR ID	Notes	Endtb Exports		
Baseline Firstline DST missing					DST more than a m	Date	Job Status	Download
Baseline Firstline DST missing					No results by the e treatment.	05-Sep-2017 23:30	COMPLETED	*
Baseline Firstline DST missing					No results by the e treatment.	05-Sep-2017 16:20	COMPLETED	*
Baseline Firstline DST missing					No results by the e treatment.	04-Sep-2017 23:30	COMPLETED	*
Baseline Firstline DST missing					No results by the e treatment.	03-Sep-2017 23:30	COMPLETED	1
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Baseline Firstline DST missing					No results by the e treatment.	31-Aug-2017 23:30	COMPLETED	*
Baseline Firstline DST missing			tri,		No results by the e treatment.	30-Aug-2017 23:30	COMPLETED	4
Baseline Firstline DST missing					No results by the e treatment.	29-Aug-2017 23:30	COMPLETED	*
Baseline Firstline DST missing					No results by the e treatment.	28-Aug-2017 23:30	COMPLETED	*

Lessons Learned 4 Data Management



Trainings

Importance of data collection and using it for programmatic decision making



Central Data Quality Check

Queries sent back to sites, sites then make changes as needed

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



Funding

Huge amount of effort – even with single

EMR takes a long time – cleaning,

verifying, resolve outsanding 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 coexisting conditions (HIV, hep C), children and pregnant woment
- Experience in prolonged use of Bdq, Dlm and concomitant use

Lessons Learned 7 Diverse Implementation strategies

- Heterogenous care models
- Private sector engagement

\$17

- HIV or hep C coinfected 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

- \geq 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)

Possible Ns for reporting on endTB outcomes, by date and endpoint





Priorities for Future Analysis - 1



- Culture Conversion at six months, reversion
- Safety analysis (AEIs 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 AEIs related to drugs e.g. linezolid