The Union

Shortened MDR-TB Regimens: Union-Supported Research

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Outline

- MDR-TB burden and treatment limitations
- Early Union involvement in shortened MDR-TB regimens
- Bangladesh MDR-TB treatment pilot project
- STREAM clinical trial
- Observational treatment cohorts
- Conclusions

MDR-TB – burden and treatment limitations

- WHO estimates approximately 480,000 new MDR-TB cases globally in 2013
- An estimated 210,000 deaths due to MDR-TB in 2013
- Of reported MDR-TB patients treated - only 48% were successfully treated
- Currently recommended treatments are lengthy and often difficult to tolerate

Union involvement in shortened MDR-TB regimens

- Union believed/believes strongly that a more accessible and tolerable treatment for MDR-TB was/is urgently needed

- Experience from a Damien Foundation pilot programme utilizing a nine-month treatment regimen in Bangladesh demonstrated impressive results

‘Bangladesh’ Regimen

Daily treatment for 9 months

Drug	Months**
Kanamycin*	1–4
Isoniazid (H)	1–4
Prothionamide	1–4
Clofazimine	1–9
Gatifloxacin	1–9
Ethambutol	1–9
Pyrazinamide	1–9

* Kanamycin 3 times/week in month 4

** The intensive phase can be extended to 6 months

Sequential Cohort Appraoch

- Six consecutive regimens between 1997 and 2007
- Treatment outcomes and adverse drug reaction frequency directed regimen adjustments
- New regimen cohort was started when results of previous one seemed sufficiently clear

Regimen Highlights

- Removing INH from the regimen resulted in poor treatment outcomes (57% cure)

- Absence of both Prothionamide and Clofazimine in continuation phase resulted in high failure rate (13.3%) (Pto throughout regimen increased default rate)

- Clofazimine replacing Pto in continuation demonstrated best results

Results from Bangladesh Project

Published cohort (206 pts)	
Cure	82.5%
Completion	5.3%
Default	5.8%
Death	5.3%
Failure	0.5%
Relapse	0.5%

Overall success rate:

87.9%

Am J Respir Crit Care Med 2010

Updated total (515 pts)
82.1%
2.3%
7.8%
5.6%
1.4%
0.8%

Overall success rate:

84.5%

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Union involvement in shortened MDR-TB regimens

- Union requested an international review of the pilot programme in an effort to see the shortened regimen endorsed globally

- World Health Organization/Green Light Committee-led review of Damien Foundation Project in 2007 concluded:

  - Additional data from larger studies required...this should preferably be done in randomized-controlled clinical trials conducted under Good Clinical Practice (GCP) conditions

  - Consider using a 12 or 15-month instead of 9-month treatment regimen....with a careful (multicenter) cohort study of this approach

Union involvement in shortened MDR-TB regimens

•The Union began to search for the necessary resources for further research of the Bangladesh regimen

• In early 2008 a USAID RFA for a new research cooperative agreement highlighted the opportunity for clinical trials on priority MDR-TB topics

• The Union developed a clinical trial protocol as part of a larger TB research proposal (TREAT TB) and was awarded a five-year cooperative agreement

A Parallel Approach

- *Additional cohorts*
  - Cameroon
  - Benin
  - Niger
  - Other countries
- *Randomised trial*
  - STREAM, a non-inferiority design RCT

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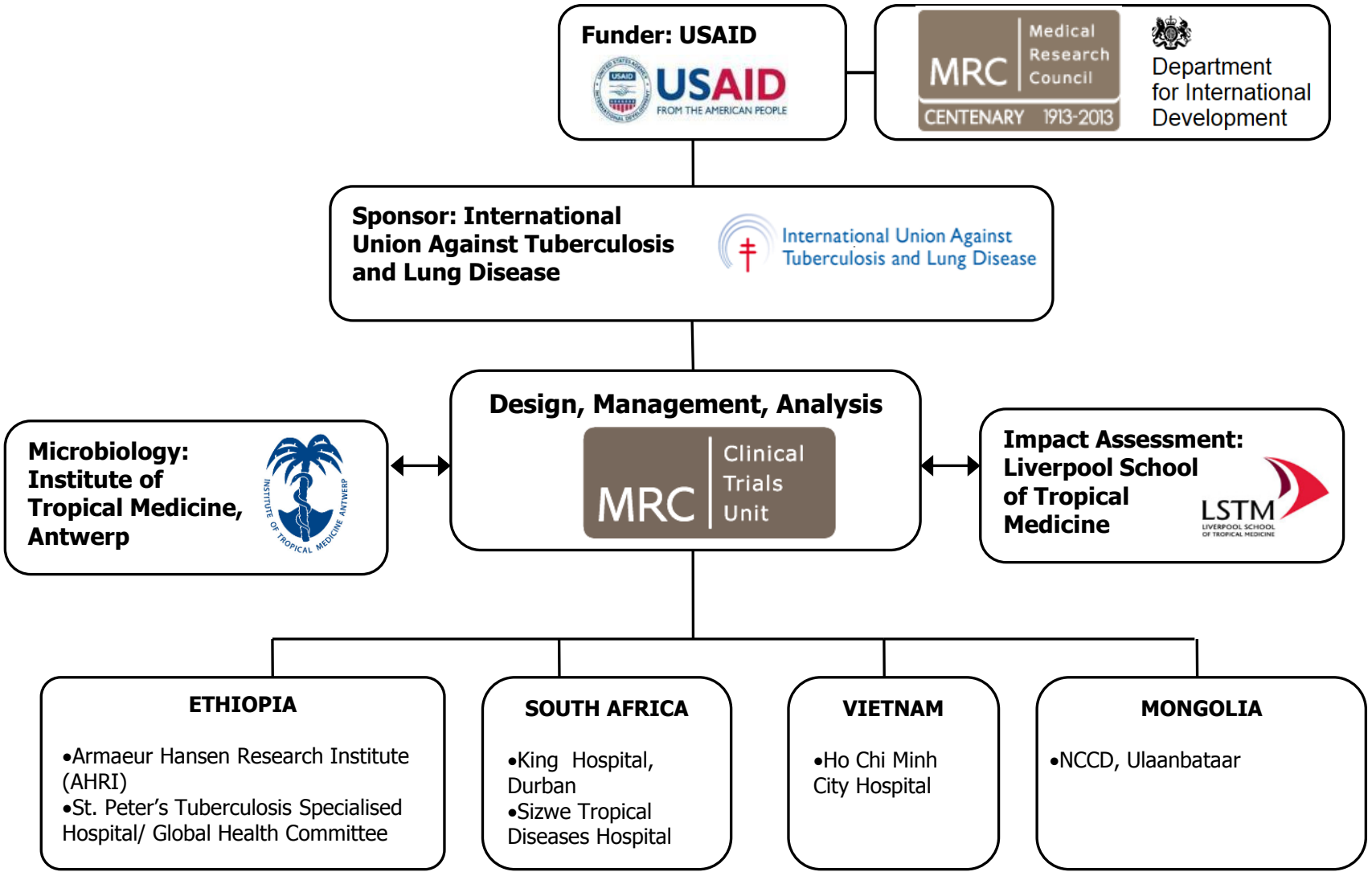
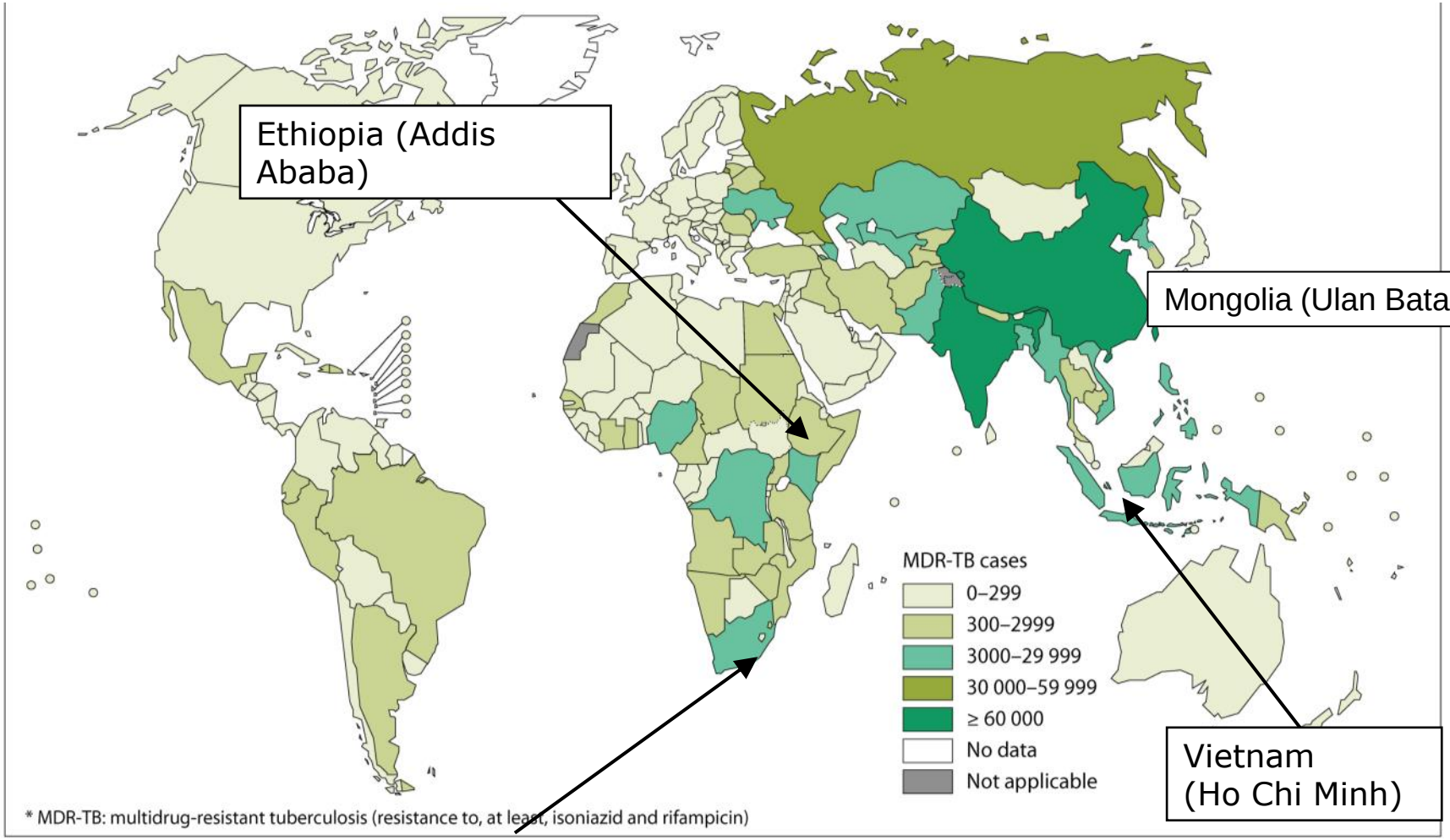
STREAM Trial Design

- STREAM is a randomised controlled trial of non-inferiority design
- The control regimen is the locally used WHO recommended regimen in the participating countries
- The study regimen is very similar to the regimen in Bangladesh with the exception that high dose moxifloxacin replaces high dose gatifloxacin

STREAM Study Partners



STREAM Trial Sites



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Source: *Global Tuberculosis Report 2012*. WHO, 2012.

World Health Organization

Primary Objectives

1. To compare the proportion of patients with a favourable outcome in the study regimen and a standardised control regimen.

2. To compare the proportion of patients who experience grade 3 or greater adverse events at any time during follow-up on the study regimen as compared to the control regimen.

STREAM Trial Regimen

Daily treatment for 9 months

Drug	Months**
Kanamycin*	1-4
Isoniazid (H)	1-4
Prothionamide	1-4
Clofazimine	1-9
Moxifloxacin	1-9
Ethambutol	1-9
Pyrazinamide	1-9

* Kanamycin 3 times/week in month 4

** The intensive phase can be extended to 6 months

Selected Reasons for Ineligibility

1. Extra-pulmonary TB only (i.e. no pulmonary tuberculosis)
2. Resistance to second-line injectables by line probe assay
3. Resistance to fluoroquinolone by line probe assay
4. Critically ill, and unlikely to survive more than 4 months
5. Known to be pregnant or breast-feeding
6. Pre-existent QT prolongation (QTc >500ms) on ECG prior to randomisation

STREAM timelines

	Actual	Planned
First patient randomised:	27th July 2012	
Enrolled	389	400
Completion of recruitment:		Q2 2015
Final patient follow-up visit:		Q3 2017
Results expected:		Q4 2017

STREAM Stage 2

- Early in 2013 in recognition of the progress made to date in STREAM and noting the provisional licensing of the first new drug for TB for almost 50 years we were asked to consider:
  - is it possible to include additional regimens to the current STREAM trial?
  - if so, what would be the appropriate regimens to evaluate?

Additional regimens proposed for Stage 2

- After extensive discussions between the study team, the local investigators and other experts it was agreed that the primary interest to patients and programmes would be:
  - a fully oral 9-month regimen
  - a 6-month simplified regimen
- Both of these regimens would include bedaquiline as part of a broader agreement for support with Janssen Pharmaceuticals

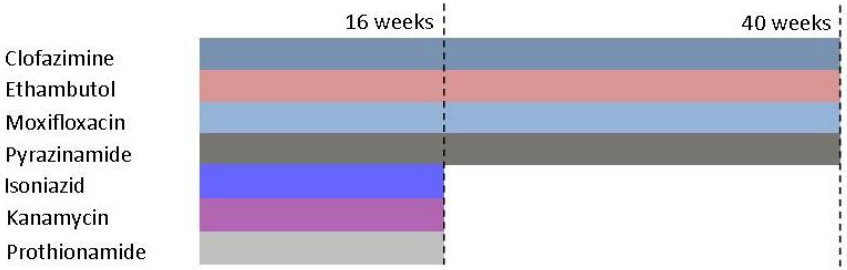
STREAM Treatment Regimens

Regimen A

Locally used WHO-approved MDR-TB regimen

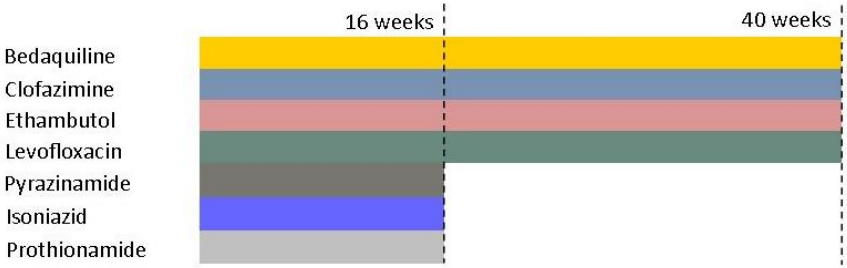
Regimen B

(Stage 1 study regimen)



Regimen C

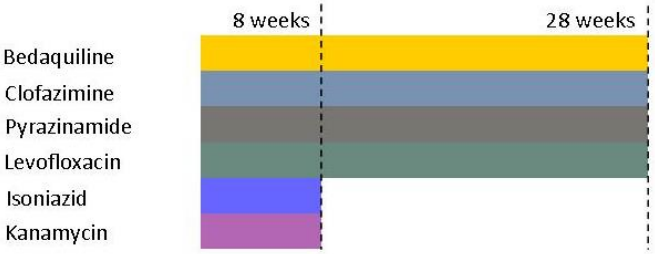
(modified Stage 1 study regimen, all oral)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Kanamycin dropped**

Regimen D

(modified Stage 1 study regimen, shortened)



- **Bedaquiline added**
- **Moxifloxacin replaced by levofloxacin**
- **Prothionamide dropped**
- **Ethambutol dropped**

Regimen C

- In Regimen C, the fully oral regimen, kanamycin is replaced by bedaquiline and moxifloxacin by levofloxacin

Product	Weeks	Weight group		
		Less than 33 kg	33 kg to 50 kg	More than 50 kg
Bedaquiline	1 – 40	400 mg once daily for first 14 days/200 mg thrice weekly thereafter		
Levofloxacin	1 – 40	750 mg	750mg	1000 mg
Clofazimine	1 – 40	50 mg	100 mg	100 mg
Ethambutol	1 – 40	800 mg	800 mg	1200 mg
Pyrazinamide	1 – 40	1000 mg	1500 mg	2000 mg
Isoniazid	1 – 16	300 mg	400 mg	600 mg
Prothionamide	1 – 16	250 mg	500 mg	750 mg

The intensive phase can be extended by 4 or 8 weeks if smear conversion has not occurred by 16 or 20 weeks respectively

Regimen D

- In Regimen D prothionamide is replaced by bedaquiline, moxifloxacin is replaced by levofloxacin, ethambutol is removed, the dose of isoniazid is increased and the total duration is reduced from 40 to 28 weeks

Product	Weeks	Weight group				
		Less than 33 kg	33 kg to less than 40 kg	40 kg to less than 50 kg	50 kg to less than 60 kg	More than 60 kg
Bedaquiline	1 – 28	400 mg once daily for first 14 days/200 mg thrice weekly thereafter				
Levofloxacin	1 – 28	750 mg	750 mg		1000 mg	
Clofazimine	1 – 28	50 mg	100 mg		100 mg	
Pyrazinamide	1 - 28	1000 mg	1500 mg		2000 mg	
Isoniazid	1 – 8	400 mg	500 mg	600 mg	800 mg	900 mg
Kanamycin	1 – 8	15 mg per kilogram body weight (maximum 1g)				

The intensive phase can be extended by 4 or 8 weeks if smear results is 2+ or more at 8 or 12 weeks respectively

Primary objectives in Stage 2

- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, the fully oral regimen, is not inferior to that on Regimen B at 76 weeks (18 months)

- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen D, the 6-month regimen, is not inferior to that on Regimen B at 76 weeks (18 months)

Parallel primary objective in Stage 2

- To assess whether the proportion of patients with a favourable efficacy outcome on Regimen C, the fully oral regimen, is superior to that at on Regimen B at 76 weeks (18 months)

Health Economics Evaluation

- In Stage 2 (as in Stage 1) comprehensive health economics evaluation to be undertaken assessing both patient and health system cost components with respect to all four treatment regimens

Community Engagement

- STREAM Stage 1 had varying levels of community engagement
- STREAM Stage 2 protocol reviewed by Global TB CAB
- STREAM Stage 2 to include strengthened community engagement with external training and support
- Appointment of community representative from a site Community Advisory Board as voting member of TSC

Stage 2 timeframe

- We plan to complete enrolment to Stage 2 in 3 years (1155 patients)
- If enrolment begins in Q2 of 2015
- Last patient enrolled Q2 of 2018 (approx time of Stage 1 results)
- Primary endpoint results of Stage 2 Q2 of 2020
- Last patient completes long term follow-up Q4 of 2020

A Parallel Approach

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  - Cameroon
  - Benin
  - Niger
  - Other countries
- *Randomised trial*
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Initial African Treatment Cohort

- Observational cohort study of 173 patients in Benin and Cameroon

- Modified Bangladesh regimen
    - 12 months treatment
    - normal dose gatifloxacin
    - prothionamide throughout treatment

- 91% treatment success (90% cured)

Niger Treatment Cohort

- Observational cohort study of 65 patients
- Modified Bangladesh regimen
    - 12 months treatment
    - normal dose gatifloxacin
    - prothionamide limited to intensive phase
- 89.2% cured

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Current West African Cohort Study

- Observational cohort study of 1000 patients on a modified Bangladesh regimen
- Utilizing normal dose moxifloxacin in place of gatifloxacin
- Prothionamide during intensive phase only
- As of end of 2014 – 870 patients recruited in nine countries in West Africa

Other Treatment Cohorts

- An increasing number of countries/projects utilizing shortened treatment regimens under observational research conditions will likely be initiated in the near future

- ? Kazakhstan
- ? Laos
- ? The Philippines

Outstanding issues in treatment shortening research

- Observational cohort research
- Comparison requirements
- Regimen composition
- Site availability and capacity

Conclusions

- The Union supports further evaluation of the shortened regimens to find the optimal regimen for patients and programmes
- As new medicines become available their potential impact on treatment shortening must be evaluated in programme settings
- Capacity of programmes to evaluate regimens in both observational and RCT studies must be strengthened

Acknowledgements

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