Tuberculosis in 2017: Searching for new solutions in the face of new challenges

6th TB Symposium – Ministry of Health of the Republic of Belarus, Republican Scientific and Practical Center for Pulmonology and Tuberculosis, and Médecins Sans Frontières

1-2 March , 2017, MINSK , BELARUS

Short MDR-TB Regimen, Uzbekistan

Zinaida Tigay

Republican TB Hospital 2, Nukus, Uzbekistan

MEDECINS SANS FRONTIERES

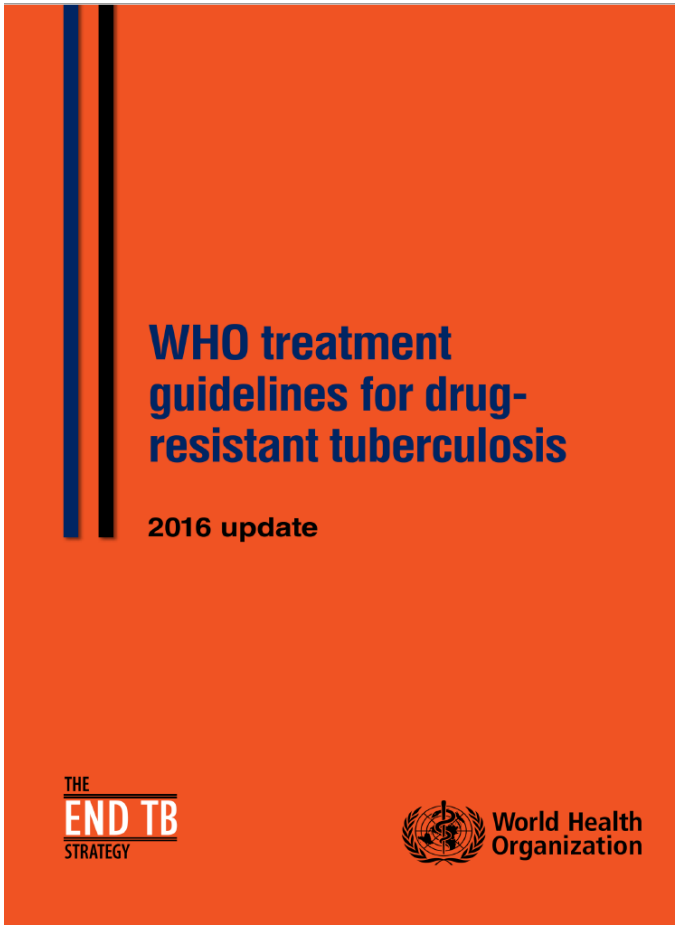
Short MDR-TB Regimen, Uzbekistan

P du Cros[1], A Khamraev[2], D Lister[3], A Ronnachit[3], C Berry[1], J Greig[1], N Parpieva[4], M Tillyashaykhov[4], G Cooke[5], S Dietrich[6], T Pylypenko[1], Z Tigay[2], J Achar[1]

[1] Manson Unit, Médecins Sans Frontières, London, UK
[2] Ministry of Health, Nukus, Uzbekistan
[3] Médecins Sans Frontières, Nukus, Uzbekistan
[4] Ministry of Health, Tashkent, Uzbekistan
[5] Imperial College, London, UK
[6] Operations Department, Médecins Sans Frontières, Berlin, Germany

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Problem Statement



- WHO recommends the shorter MDR-TB treatment regimen (SCR) under specific conditions

- But is this feasible in Europe?

Overview

- Study Design
- Overall Cohort Results
- Comparison SCR vs standard of care
  - Sputum Culture conversion at 2 months
  - Outcomes 20+ months
- Implications

MEDECINS SANS FRONTIERES
ВРАЧИ БЕЗ ГРАНИЦ

Background

- Karakalpakstan Population 1.7 million
- TB prevalence: 100.3/100, 000
- MDR: New = 23 % Retreatment cases = 62%
- MDR-TB success rate = 57%
- Amongst MDR-TB patients
  - Ethambutol resistance = 77.1%
  - Pyrazinamide resistance = 73.6%

Short Course Study

Ўзбекистон Республикаси
Соғлиқни сақлаш вазирлиги

MEDECINS SANS FRONTIERES

Effectiveness of a simplified short regimen for

Multidrug Resistant Tuberculosis treatment in Karakalpakstan, Uzbekistan

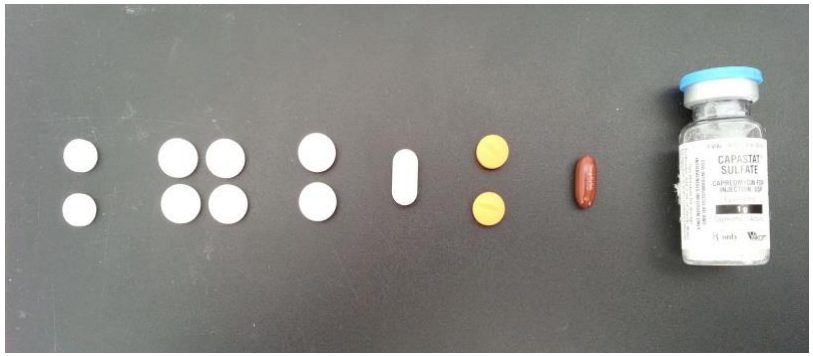
Joint MSF - Operational Centre Amsterdam / MOH Uzbekistan Research Protocol

Research Protocol - amendment
April 2014

Philipp du Cros[1]
Khamraev Atadjan (deputy of Chairman of Supreme Council of Karakalpakstan)[2]
Tillashaikhov Mirzagalib (MoH Uzbekistan, Director of specialized medical center of TB and pulmonology)[2]
Parpieva Nargiza (MoH Uzbekistan, chief TB specialist)[2]
Tezay Zmaida (Chief of TB2)[2]
Sholtaeva Marjan (Chief TB doctor of Kegeily rayon)[2]
Abdrasuliev Tleubergen (Chief TB doctor of Shumanay rayon)[2]
Marttje Betlam (Doctor Kegeily Rayon)[1]
Emily Wise (Doctor Shumanay)[1]
Teshome Ashagre (Medical Coordinator)[1]
Johanna Kuhlin[1]
Andrii Slyzkyi(laboratory manager)[1]
Alla Taye Epidemiologist Uzbekistan[1]
Sebastian Dietrich[1]
Bern-Thomas Nyangwa[1]
Jane Greig[1]
Pamela Hepple[1]
Graham Cooke[3]
Krzysztof Herboczek[1]
Muhammad Asif[1]
Jay Achar[1]
Catherine Berry[1]

[1] Médecins Sans Frontières, Operational Center Amsterdam
[2] Ministry of Health Uzbekistan
[3] Imperial College London

- Single-arm prospective observational
- Standardised assessment
  - ECG, Audiometry, Visual assessment
  - GeneXpert, Hain First & Second line, smear, culture
- Ethics approval from National and MSF ERBs



Intensive Phase

4-6 Cm/Km – Mfx – Pto – Cfz – Z – H_{HD} – E

Continuation Phase

5 Mfx – Pto – Cfz – Z – E

Moxifloxacin dose = 400 mg

Eligibility

Inclusion Criteria

- RR TB patients (GeneXpert, Hain MTBDR and/or DST)
- If <14yo, confirmed close contact with RDR TB case
- Informed consent

Exclusion Criteria

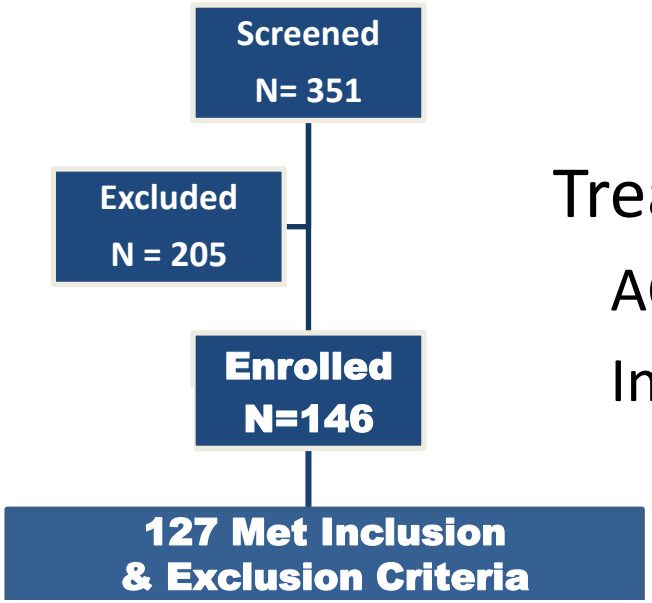
- Taken Second line drugs > 1 month
- Critically ill
- Meningeal/Osteoarticular disease
- Resistance to Ofx or dual-injectables (Km/Cm) or XDR TB
- CrCl <30ml/min
- QTc >500ms
- Pregnancy

Treatment model

- Ambulatory care from diagnosis
- Social, psychological and adherence support
- Early identification and management of side-effects
- Direct observed therapy 7 days per week
- Additional ECG monitoring (baseline, 2w, 4w) for SCR
- Follow-up at 2 weeks, then monthly & 6 & 12 months post-treatment

Snapshot

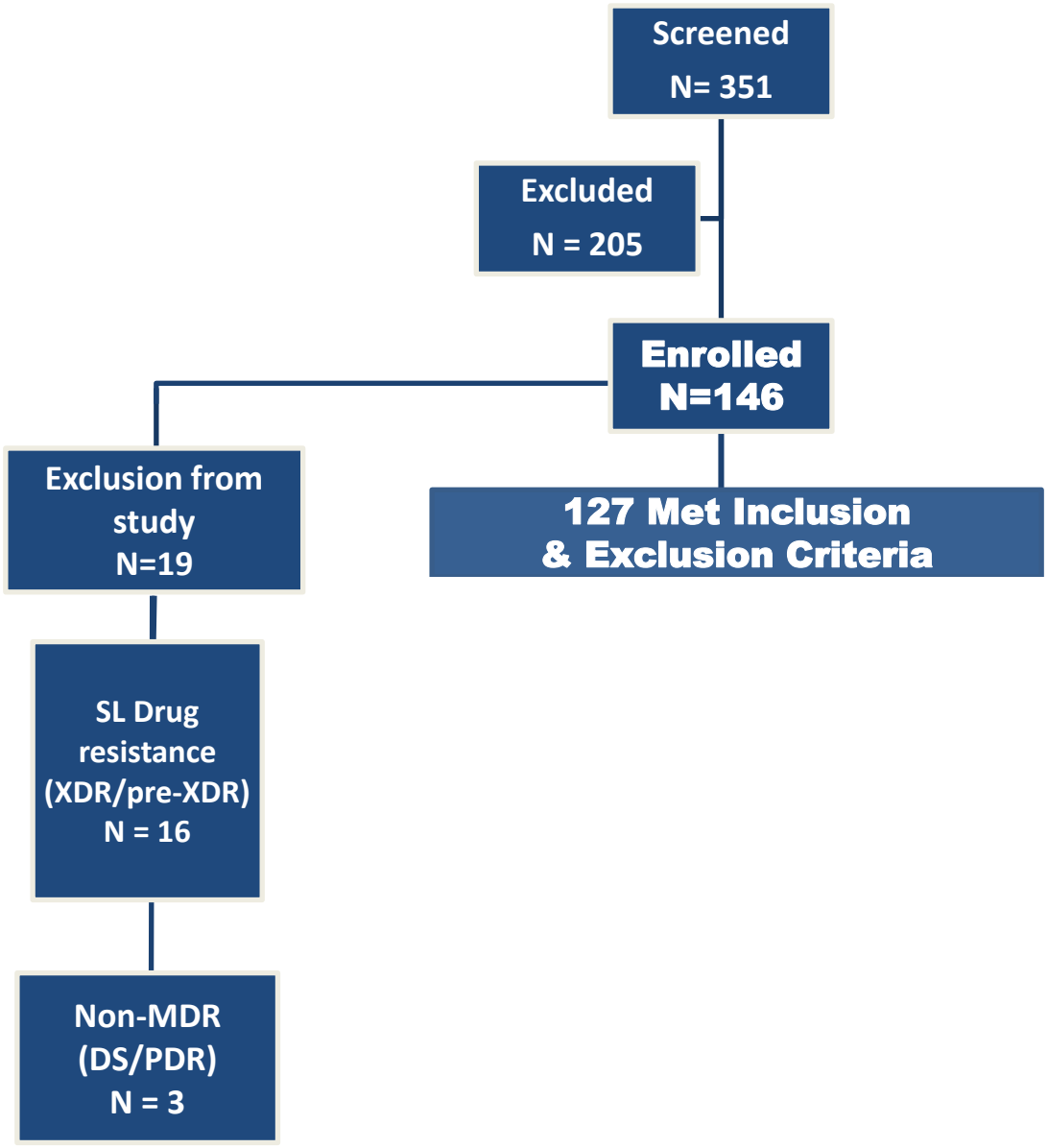
- Recruited September 2013 - May 2015 in 3 Rayons
- 127 patients met inclusion and exclusion criteria
- Additional 19 patients commenced SCR but met exclusion criteria → withdrawn
- Last patients completed treatment Feb 2016
- Final follow up visits and cultures still in progress

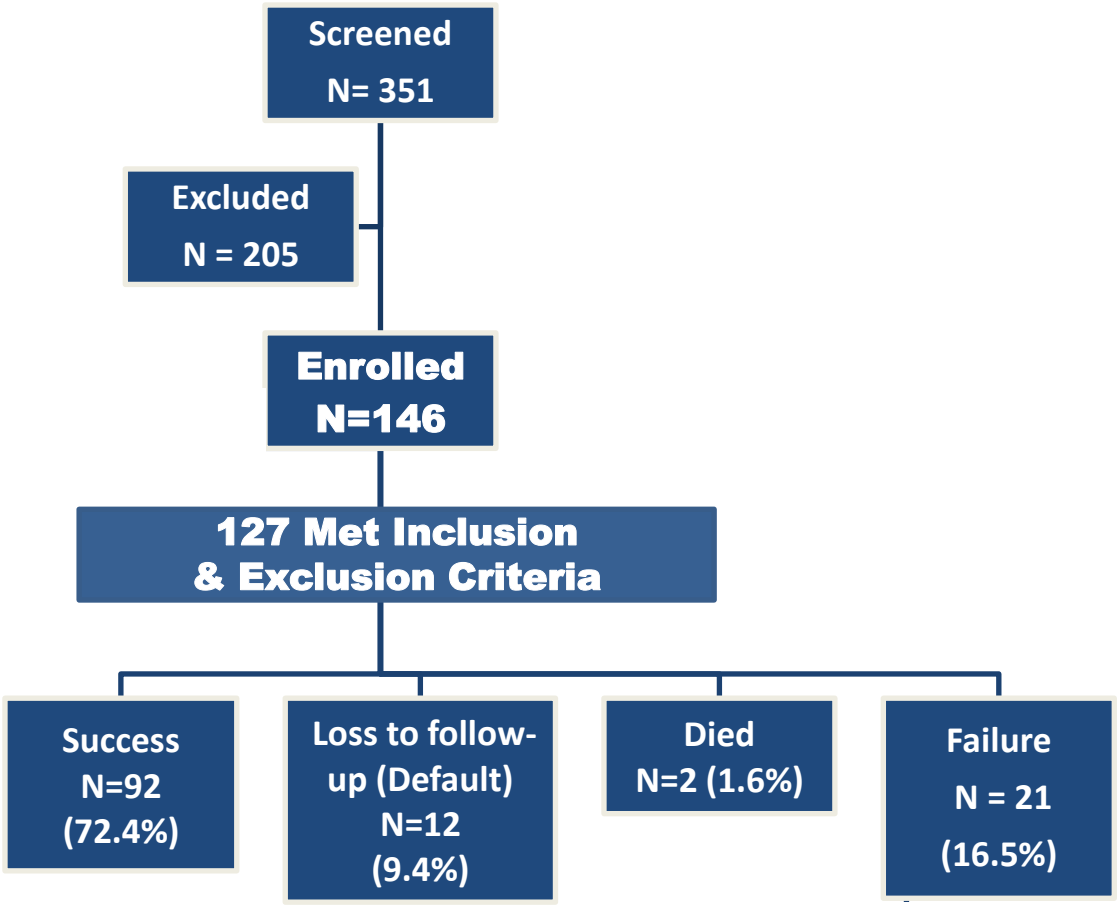


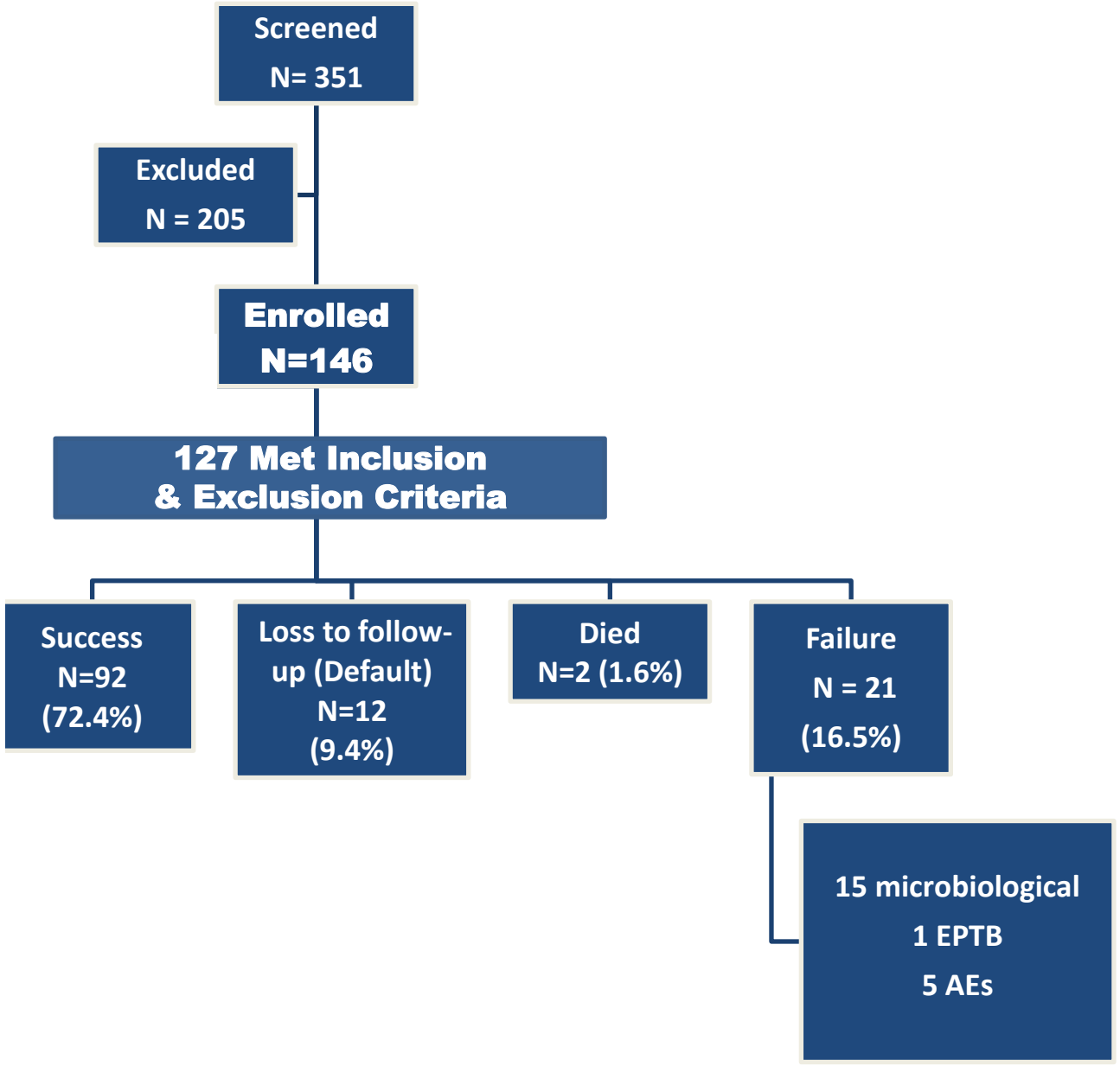
Treatment model:

ACD1	85%
Inpatient	15%

Main Reasons Exclusion	%
History of 2nd Line drug use > 1 month	25%
Additional resistance (Ofx, dual-injectables)	19%
Lost to follow up	11%
Lack of consent	17%


Screened
N= 351
Excluded
N = 205
Enrolled
N=146
Exclusion from study
N=19
127 Met Inclusion & Exclusion Criteria
SL Drug resistance (XDR/pre-XDR)
N = 16
Non-MDR (DS/PDR)
N = 3


Screened
N= 351
Excluded
N = 205
Enrolled
N=146
127 Met Inclusion
& Exclusion Criteria
Success
N=92
(72.4%)
Loss to follow-up (Default)
N=12
(9.4%)
Died
N=2 (1.6%)
Failure
N = 21
(16.5%)


Screened
N= 351
Excluded
N = 205
Enrolled
N=146
127 Met Inclusion
& Exclusion Criteria
Success
N=92
(72.4%)
Loss to follow-up (Default)
N=12
(9.4%)
Died
N=2 (1.6%)
Failure
N = 21
(16.5%)
15 microbiological
1 EPTB
5 AEs

Adverse Events

- Any adverse event 78% pts
- 1 grade 4 adverse event
- >75% adverse events grade 1 and 2
- Major adverse events: gastrointestinal, headache, arthralgia, anorexia, elevated creatinine, tinnitus/hearing loss
- Serious adverse events:
  - 15 SAEs;
  - 2 deaths

Interim follow-up outcomes

Follow up point	No. of patients	Completed Clinical Ax	Sputum not collected	Relapse	Confirmed Relapse Free
12 months	90	82	6	1*	66 culture neg (cultures results still awaited)

- Patient was out of country at 12 months – on return at 17 months had positive sputum culture – currently being considered as relapse.

Comparison of SCR versus Standard of Care in Uzbekistan

- Comparison of SCR with the Standard of Care
- Analysis 1 – 2 month culture conversion comparison
- Analysis 2 – SCR with 1 year follow-up and Standard of Care after 20+ months treatment
- Exclusions: 2nd line drug exposure, Km/Cm or ofloxacin resistance, EPTB

Analysis 1:
2-month culture conversion

- Short course regimen associated with higher proportion of 2-month culture conversion
  - SCR: adjusted odds ratio of 2.28 (95% CI 1.24-4.18; p=0.08)
  - Adjusted for age, gender, baseline smear
  - Baseline DST to pyrazinamide, ethambutol and kanamycin had not significant effect

Preliminary analysis 2: End of treatment outcomes

- SCR 1 year post treatment follow up (21-23 months) versus standard of care (20-24 months)

- No statistical evidence of difference between short course regimen and standard of care at 20+ months
  - aOR 1.19 (95% CI 0.71 – 2.00; p=0.498)

  - Adjusting for age, gender, baseline kanamycin resistance

  - Further analyses still in progress

In summary…

- The 2 analyses show faster culture conversion, and similar final treatment outcomes
  - For appropriately selected patients
  - Region with high rates of second-line drug resistance

Implications for scale up of the regimen

Patient selection in contexts with high second line drug resistance

- Not suitable for all patients
  - 35-50% patients eligible in this context
- Importance of adherence support for commencing ambulatory treatment from day 1

Patient selection in contexts with high second line drug resistance

- What to do with Z or Km resistance?
  - Preliminary analysis suggests could still use, but may be prudent to await more data on Km resistance
  - An option – wait for full DST results and then switch patients to SCR

Management of patients failing the regimen

- If failing regimen
  - 4-6 Cm/Km – Mfx – Pto – Cfz – Z – H_{HD} – E
- Likely effective drugs
  - (Injectable), Cs, Lzd, Bdq, Dld, Imp/Clv, PAS

Conclusions

- Good end-of-treatment and interim follow-up outcomes in selected group of patients

- Adverse events and LTFU in this study highlight importance of adherence support management

Conclusions

- SCR achieves faster sputum culture conversion
- SCR has low relapse rate
- Roll out SCR in high SLD resistance context requires molecular test lab capacity and roll out of Group C and D drugs

Acknowledgements

Patients, doctors and nurses in Karakalpakstan
MSF field teams

National TB institute, Uzbekistan

Prof Nargiza Parpieva

Dr Mirzagalib Tillashaikov

Ministry of Health, Karakalpakstan

Dr Atadjan Khamraev

Dr Zinaida Tigay

MoH staff in TB#2 hospital, TB#1 hospital, Kegeily Rayon, Nukus city Rayon and Shumanay rayon

MSF

Dr Amrita Ronachit

Dr Philipp Du Cros

Dr Jane Greig

Dr Jay Achar

Dr David Lister

Dr Catherine Berry

Tanya Pylypenko

Dr Tleubergen

Data Management Team

MSF Team Uzbekistan