Global Consultation on Best Practices in MDR-TB Care

Operational Research on All-Oral Shortened Regimens

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IRD
Interactive Research & Development

MEDECINS SANS FRONTIERES

Partners In Health

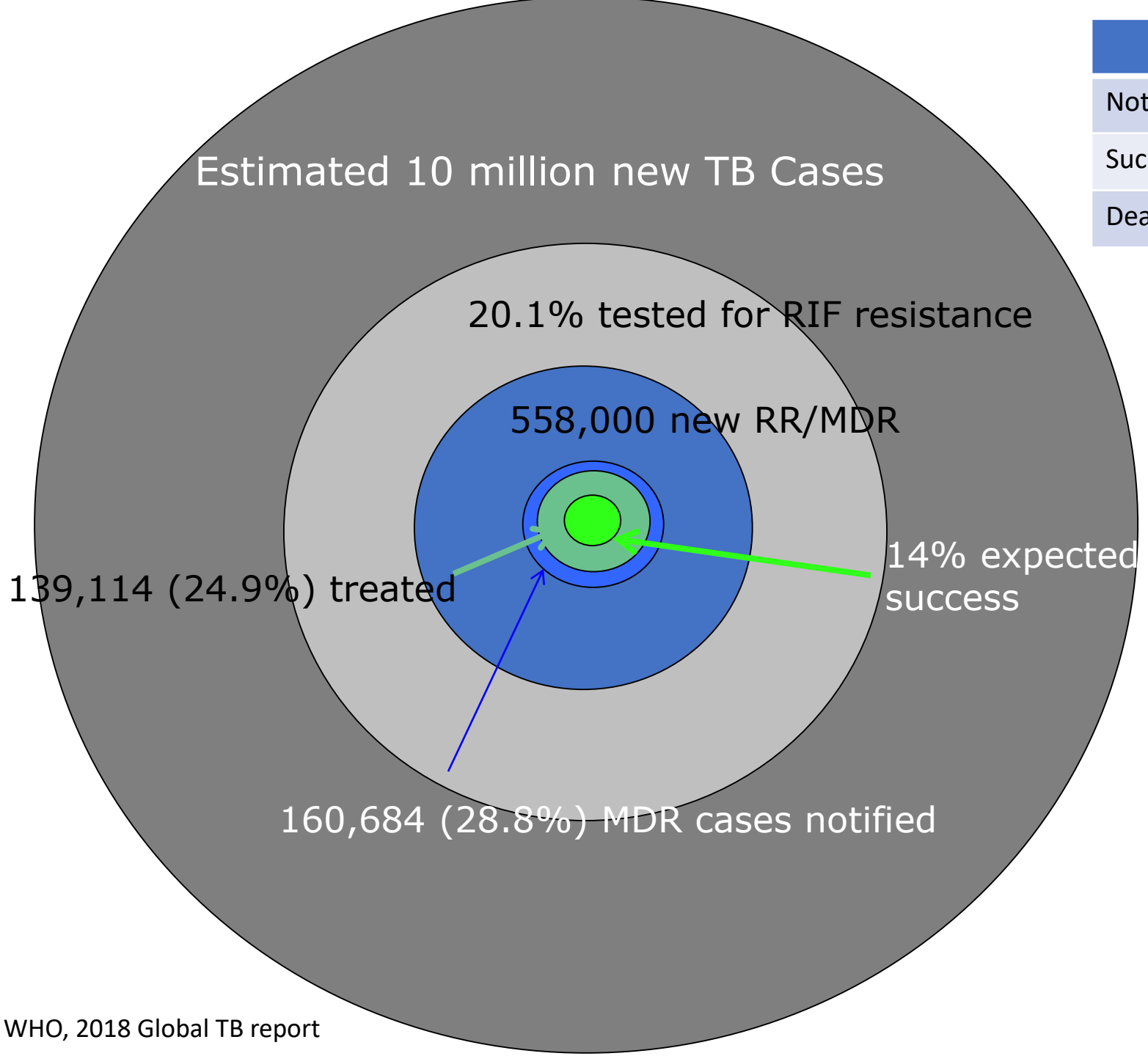
Sentinel Project
on pediatric drug-resistant tuberculosis

Gratitude

- Harvard Center for GHD-Dubai
  - Salmaan Keshavjee, Jennifer Puccetti, Dara Kelleher,
- PIH/HMS: Sue Kulkarni, Megan Striplin, Sarah McAnaw

OR for all shortened regimens

- Why
- History of shortening TB treatment with addition of RIF/PZA
- Open questions
- Regimens being studied in trials
- What OR can offer for all-oral shortened (AOS) regimens
- Importance of data collected and special methods for drawing inference
- Preview of next 2 days



	TB	RR/MDR
Notified cases	6.7 million	160,684
Success	82%	55%
Death	16%	40%

WHO, 2018 Global TB report

Only standard of care in RR-TB through 2016

Photo: Daily MDR-TB regimen in Mozambique. Why we're investing w/ @PIH, IRD & @MSF for better treatment! pic.twitter.com/j7zovDfIQ3 (UNITAID Twitter feed May 7, 2014)

Typical Daily Pill Burden for MDR-TB/HIV Co-infected Patient >60 kg

Morning dose	Evening dose
Pyrazinamide: 4 tablets Kanamycin: 1 g IM Levofloxacin: 2 tablets Ethionamide: 1 tablet Cycloserine: 1 capsule PAS: 1 sachet	Ethionamide: 2 tablets Cycloserine: 2 capsules PAS: 1 sachet Pyridoxine: 4 tablets
AZT/3TC combination: 1 tablet Cotrimoxazole: 1 tablet	AZT/3TC combination: 1 tablet EFV (600 mg): 1 tablet

Priority questions addressed by 2018 WHO Guideline Revision (relevant to AOS regimens)

"The composition of longer MDR-TB regimens: optimal combination of medicines and approach towards regimen design for patients with MDR/RR-TB and extensively drug-resistant (XDR)-TB"

"The duration of longer MDR-TB regimens: identifying the best range for the total length of treatment, duration of the intensive phase and time after culture conversion"

"Use of the shorter MDR-TB regimen: the role of the standardized 9-12-month regimen recommended by WHO since 2016"

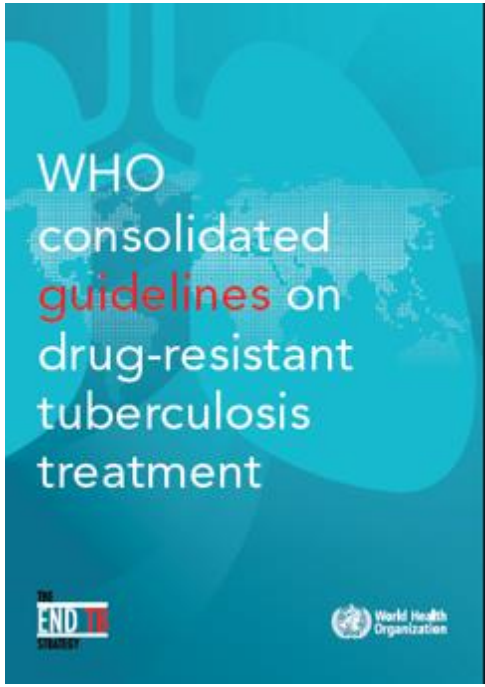
2019 WHO Recommendations: Sections 2 & 3

Groups & Steps	Medicine	Abbreviation
Group A **Include all 3 medications**	levofloxacin or moxifloxacin	Lfx, Mfx
	bedaquiline	Bdq
	linezolid	Lzd
Group B Add one or both medicines	clofazimine	Cfz
	cycloserine or terizidone	Cs, Trd
Group C Add to complete the regimen and when medicines from Groups A & B cannot be used	ethambutol	E
	delamanid	Dlm
	pyrazinamide	Z
	imipenem-cilastitin or meropenem	Imp-Cln, Mpm
	amikacin (or streptomycin)	Am (S)
	ethionamide or prothionamide	Eto, Pto

- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included … If only one or two Group A agents are used, both Group B agents are to be included.
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it).
- In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months is suggested:
  - Intensive phase of 6–7 months;
  - 15–17 months after culture conversion;

(for most, may be modified based on response)

2019 WHO Recommendations Section 4:



Shortened regimen: In MDR/RR-TB patients who have not been previously treated for more than 1 month with second-line medicines used in the shorter MDR-TB regimen or in whom resistance to fluoroquinolones and second-line injectable agents has been excluded, a shorter MDR-TB regimen of 9–12 months may be used instead of the longer regimens

4–6Km–Mfx–Cfz–Eto–Z–E–H_{HD}/5Mfx–Cfz–Z–E

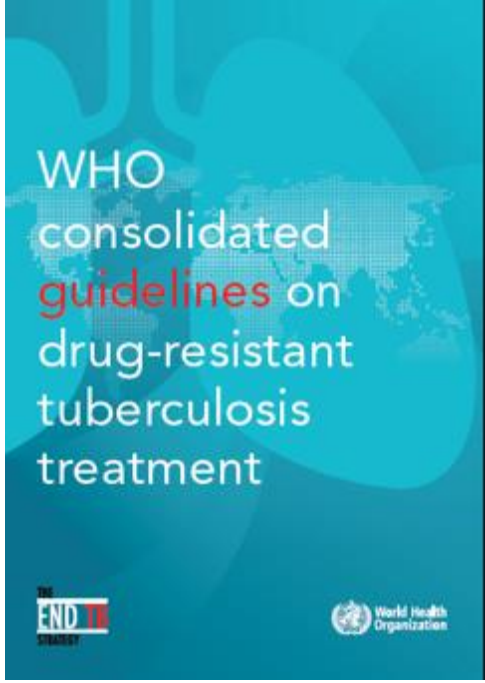
Is any of the following present?

- Preference by the clinician and patient for a longer MDR-TB regimen
- Confirmed resistance to or suspected ineffectiveness of a medicine in the shorter MDR-TB regimen (except isoniazid resistance)*
- Exposure to one or more second-line medicines in the shorter MDR-TB regimen for >1 month (unless susceptibility to these second-line medicines is confirmed)
- Intolerance to medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug–drug interactions)
- Pregnancy
- Disseminated, meningeal or CNS TB
- Any extrapulmonary disease in PLHIV
- One or more medicines in the shorter MDR-TB regimen not available

FAILING SHORTER REGIMEN or NON-RESPONSE, DRUG INTOLERANCE, EMERGENCE OF ANY OTHER EXCLUSION CRITERION

YES → **Individualized, longer MDR-TB regimens**

NO → **Standardized, shorter MDR-TB regimen may be offered** (conditional recommendation)



Criteria to decide when the shorter regimen may be offered

If the shorter regimen is used, the GDG recommended:

1) Shared decision-making, clinician-patient
2) DST for FQ & 2nd-line injectables, other components
3) KM be replaced by AMK
4) Other exclusion criteria

Caveats, all sections

Recommendations are conditional, with (very) low confidence in estimates of effect.

Certainty of evidence	Definition
High	Further research is very unlikely to change our confidence in the estimate.
Moderate	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Limited data on important subgroups: with comorbidities (HIV, DM, Hep C, addiction), pregnant women, children, homeless, particularly marginalized groups.

Caveats: Section 2, Composition of long regimen

Groups & Steps	Medicine	Abbreviation
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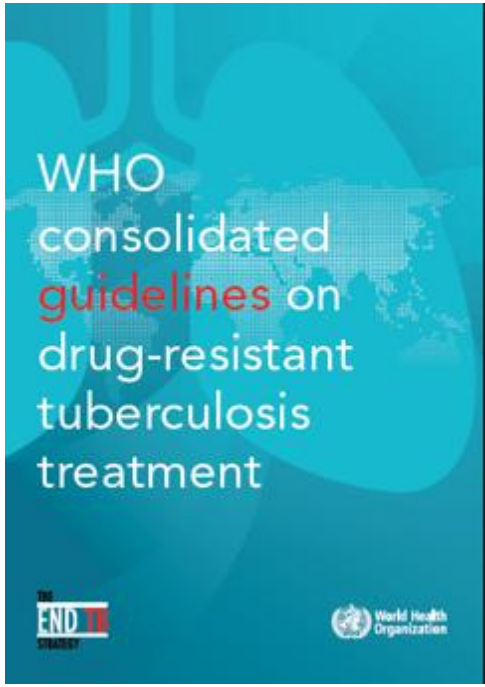
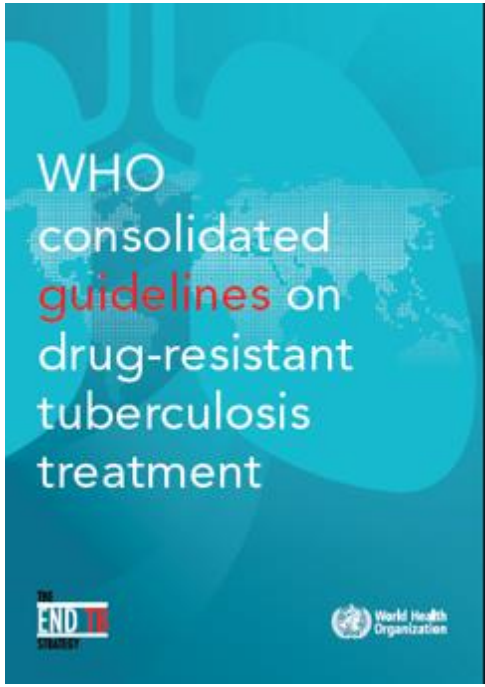


- Regimens comprised according to these recommendations have NOT been studied
- Data not available on regimen changes

Caveats: Section 3, Duration of long regimen

- Durations recommended are based on those that have been used and may reflect patient condition, but info not available:
- Potential biases:
  - Shorter in those LTFU, died, with limited disease
  - Longer in those with extensive disease, many changes, good outcomes
- Duration analysis was independent of regimen
  - Accounted for a few drug groups but not full regimen



Caveats: Section 4 (2)

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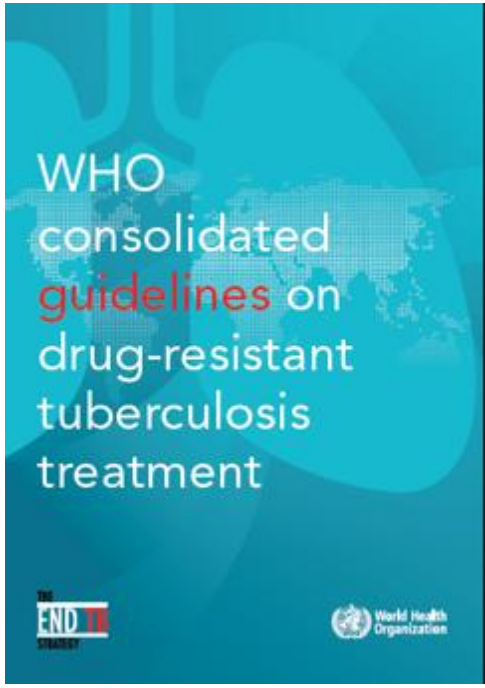
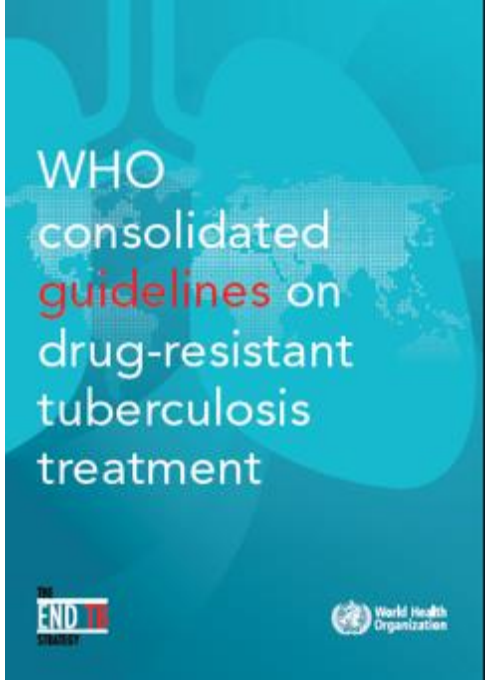
"If the shorter regimen is to be used, the GDG recommends that: kanamycin be replaced by amikacin…"



"No data from variants of the shorter regimen, in which the injectable agent was replaced by bedaquiline, were reported to WHO while the 2018 guideline update was in progress. Regimens that vary substantially from the recommended composition and duration (e.g., a standardized 9-12-month shorter MDR-TB regimen in which the injectable is replaced by bedaquiline) can be explored under operational research conditions..."

Open questions: WHO guidelines



- Regimens that vary substantially from the recommended composition and duration (e.g. standardized 9-12-month shorter MDR-TB regimen in which the injectable is replaced by bedaquiline) can be explored under operational research conditions;
- The effectiveness/safety of variants of the shorter MDR-TB treatment regimen in which the injectable agent is replaced by an oral agent (e.g. bedaquiline) and the total duration reduced to 6 months or less;
- Comparison of the effectiveness of these variants of the shorter regimen would be helpful in:

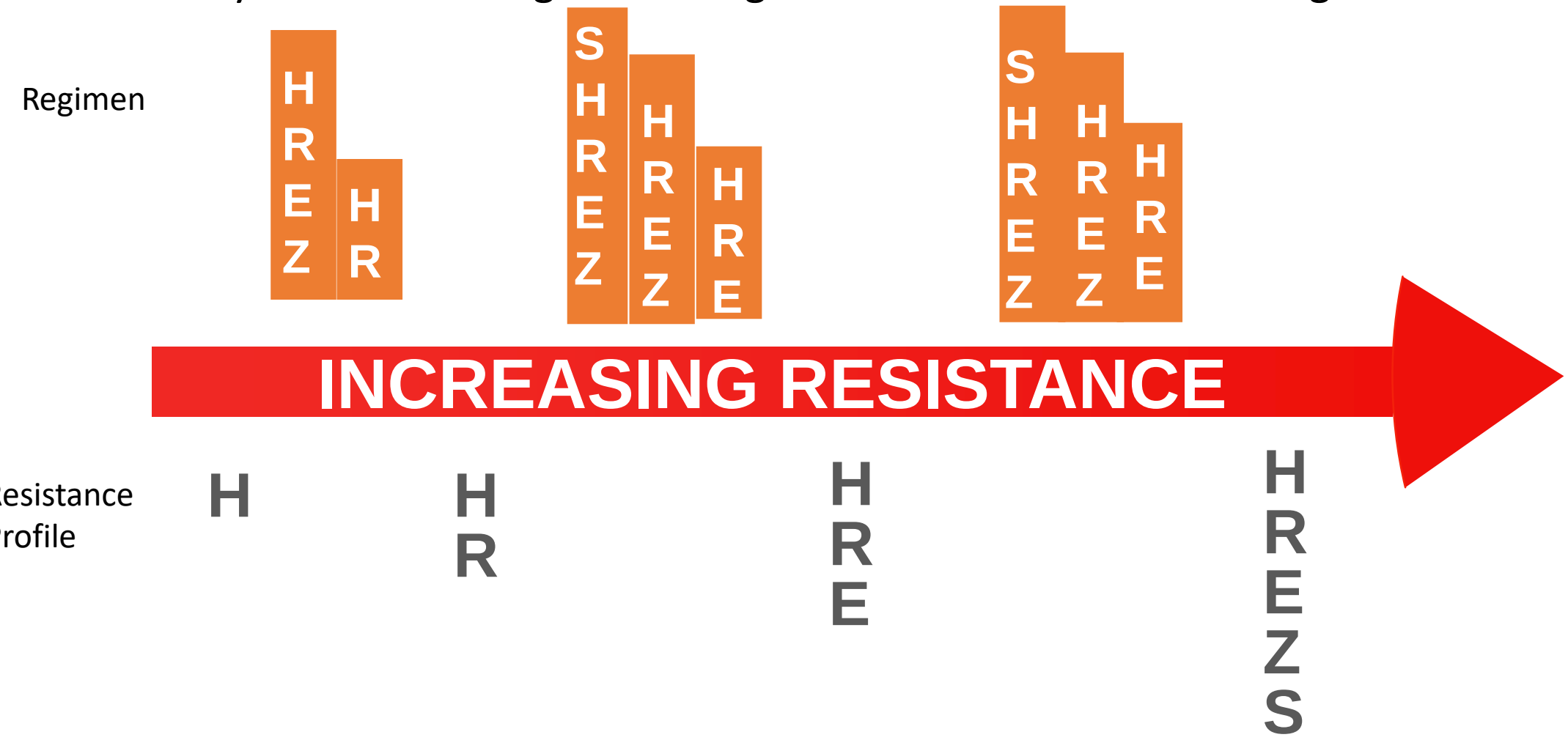
1) patient subgroups that have often been systematically excluded from studies or country programme cohorts, such as children, patients with additional resistance, those with extrapulmonary TB, pregnant/breastfeeding women;

2) settings where background resistance to drugs other than fluoroquinolones and second-line injectable agents is high (e.g. pyrazinamide or high-level isoniazid resistance).

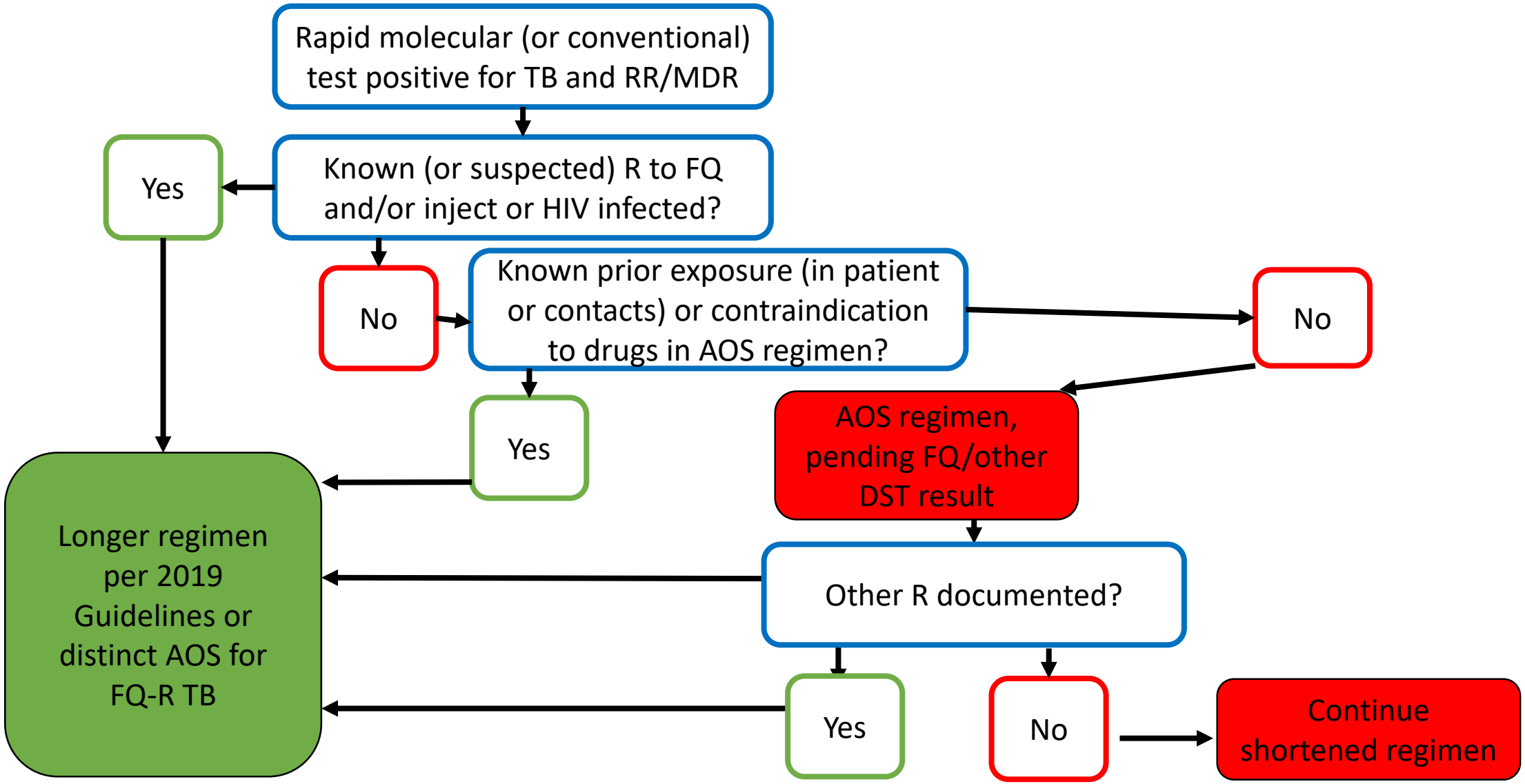
Open questions on AOS regimens, Guidelines and Beyond

- What is place of AOS regimen in TB strategy?

History of universal regimen & slight variation should caution against similar approach



Consider possible flow for continuous process of evaluating who gets shortened regimen to avoid repeating mistakes



Open questions on AOS regimens, Guidelines and Beyond

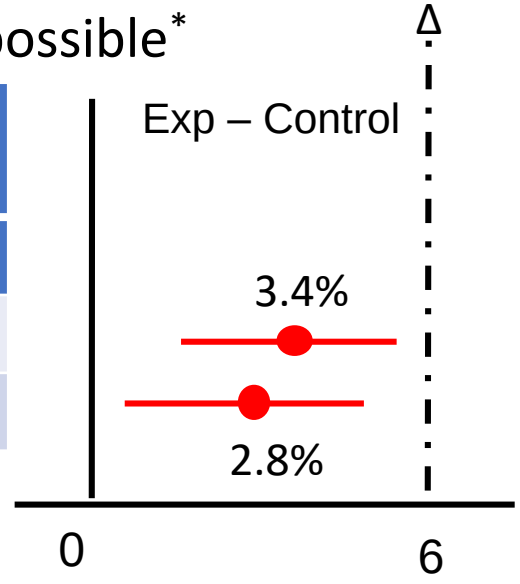
- What is place of AOS regimen in TB strategy?
  - History of “universal” treatment for TB cautions against
  - e.g., different regimens for resistance/prior exposure (XDR, pre-XDR), other characteristics (comorbidities)

- Should combination/duration of all-oral, shortened regimens be different for different populations
  - By risk factors: Imperial et al

Consider longer AOS regimen for patients with risk factors

- Could assign treatment duration according to patient characteristics, similar to STREAM, Nix/ZeNix (e.g., 9 months, extend to 11; 6 months, extend to 9)
- Supported by a 2018 meta-analysis on Phase III trials to shorten DS-TB treatment: in subgroups with limited disease, treatment shortening is possible*

Pts from 3 Phase III treatment shortening trials	N	% with unfavorable outcomes	
Subgroups eligible for shortened treatment		Exp	Control
Sm <2+ or no cavity	1591	19.9	16.5
Sm 2+ & no cavity OR Sm <2+	1156	19.1	16.3



- Caution: deviating from 7/7 day treatment administration had >2 fold risk for poor outcomes; HR for 5/7 days: 28.9 (95% CI: 10.5-80) of increased risk of poor outcomes

* Imperial et al, Nature Med 2018.

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- What is place of AOS regimen in TB strategy?
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  - e.g., different regimens for Resistance/prior exposure (XDR, pre-XDR), other characteristics (comorbidities)
- Should duration (combination) of AOS regimens be different for different populations
  - By risk factors: Imperial et al
- How to include pregnant women, children, & other special populations in study of AOS regimens?

Children & pregnant women with RR-TB: Inclusion in Operational Research on All-Oral Regimens

- Injectable therapy has more serious and long-term consequences in children, contraindicated in pregnancy
- Shorter duration of therapy already recommended for children with non-severe disease
- Bedaquiline recommended in children as young as age 6 years; better evidence for safety in pregnancy than most drugs used
- Delamanid recommended in children as young as 3 years; likely similar toxicity risk to most drugs used in pregnancy
- Ongoing dosing and safety studies likely to lead to universal recommendations for these drugs in children the next 12 months
- Evidence on safety of all 2nd-line drugs in pregnant women lagging but essential

Nachman et al., Lancet, 2015; McKenna et al, CID, 2016

Children & Pregnant Women with RR-TB: Inclusion in Operational Research on All-Oral Regimens

- Children are vulnerable: systematic exclusion violates their human rights.
- OR may be only way to obtain information in children & pregnant women.
- “Protecting” children (pregnant women), by excluding from research leads to lower standards of care, uncertainty & delays in implementation.
- Pediatric formulations of second-line drugs available
- Excellent technical support and guidance available *pro bono* via Sentinel Project
- Data can be added to registries of children & pregnant women

Management of Multidrug-Resistant Tuberculosis in Children:
A FIELD GUIDE

Nachman et al., Lancet, 2015; McKenna et al, CID, 2016

Inclusion of Other Special Populations in Operational Research on All-Oral Regimens

- Populations: extra-pulmonary TB, prisoners, migrants, substance use, etc.
- OR often the only way to obtain information on these populations.
- Social reasons for exclusion are unethical and may lead to falsely elevated rates of treatment success

Open questions on AOS regimens, Guidelines and Beyond

- What is place of AOS regimen in TB strategy?
  - History of “universal” treatment for TB cautions against
  - e.g., different regimens for Resistance/prior exposure (XDR, pre-XDR), other characteristics (comorbidities)
- Should duration (combination) of AOS regimens be different for different populations
  - By risk factors: Imperial et al
- How to include pregnant women, children, & other special populations in study of AOS regimens?
- What are optimal (for effectiveness and safety) combinations?
  - Optimized use of individual drugs

To assess optimal composition, randomization is ideal

Or:

- Need heterogeneity
- Need to document conditions at time of/reasons for different choices, and for any changes
- Then, can use inverse probability weighting (IPW) and marginal structural models to estimate the effect of the regimen differences

Example: Effect of HAART for HIV in observational study

Analysis approach	HR	95% CI
Conventional, Adjusted*	0.81	0.61, 1.07
IPW*	0.54	0.38,0.78

*Accounted for same covariates: age, gender, race, calender year at entry, baseline CD4 and RNA, time-varying CD4 and RNA, symptoms, ART, PCP prophylaxis and days since prior visit.

Cole et al., AJE, 2003

Open questions on AOS regimens, Guidelines and Beyond

- What is place of AOS regimen in TB strategy?
  - History of “universal” treatment for TB cautions against
  - e.g., different regimens for Resistance/prior exposure (XDR, pre-XDR), other characteristics (comorbidities)
- Should duration (combination) of all-oral, shortened regimens be different for different populations
  - By risk factors: Imperial et al
- How to include pregnant women, children, & other special populations in study of AOS regimens?
- What are optimal (for effectiveness and safety) combinations?
  - Optimized use of individual drugs
- What is optimal (for effectiveness and safety) duration?
  - Optimized duration of individual drugs

To assess optimal duration, randomization is ideal

Or:

- Need heterogeneity
- Only people still alive long enough to receive longer treatment can receive it
- Need to document conditions at time of/reasons for choice of duration, and reasons for change
- Then, can emulate trial analysis through three step procedure (cloning, censoring, and weighting) to estimate the effect of treatment duration

Example: Effect of aspirin on 2-year mortality

Analysis approach	Risk of death, 2 yrs aspirin vs. none
standard	1.0
Cloned & censored	1.07
IP weighted	1

Hernan BMJ 2018;360:k182

Reminder of how we got to SSCC for DS-TB

Monotherapy-1948	
Regimen	**Resistance**
18S	76%

2-drug therapy 1952-62	
Regimen	**% Failure**
6HR	0.5
6HS	2.0
6HE	4,0
6HPas	12.0
12STh	16.0

SCC: 1962-1970s	
Regimen	**% Relapse @ 24 months**
6SHR	3
6SHZ	8
6SHT	22
6SH	29
2SHRZ/5SHZ$_2$	2.3
3SHRZ/2SHZ$_2$	4
3SHRZ	20

Addition PZA 1960-70s		
Regimen	**Culture positive @ 2 mos**	**% Relapse @ 24 months**
6SH vs 6HSZ	51 vs. 24	29 vs 11
2SHR/4Th vs 2SHRZ/4Th	25 vs. 13	13 vs 6
2SHRE/4SHE2 vs. SHRZ//4SHZ2	16 vs 6	23 vs 7
6SHR vs. 2SHRZ/4STh	30 vs 18	NA
2EHR/7HR vs. 2EHRZ/4HR vs. 2SHRZ/4HR	36 vs 23 vs 23	NA

Mitchison, AJRCCM, 2005

Regimens being studied in trials-timeline for results

Trial Name	Regimens tested	Study Population	Results expected	Registry URL
Nix ZeNix	6/9Pa-Bdq-Lzd (dose-ranging)	XDR, difficult-to-treat RR-TB	2019: >80% success 2021	NCT02333799 NCT03086486
endTB	9Bdq-Lzd-Mfx-Z 9Bdq-Cfz-Lzd-Lfx-Z 9Bdq-Dlm-Lzd-Lfx-Z 9Dlm-Cfz-Lzd-Lfx-Z 9Dlm-Cfz-Mfx-Z	FQ-S RR-TB	2022	NCT02754765
endTB-Q	6/9Bdq-Dlm-Cfz-Lzd	FQ-R RR-TB	2022	NCT03896685
STREAM 1	4-6Km-H_{HD}-Pto/9-11Mfx (Lfx)-Cfz-Z-E 16wH-Pto/ 40wBdq-Cfz-E-Lfx-Z 8Km-H_{HD}/Bdq-Cfz-Lfx-Z	FQ-, SLI-S RR-TB	Nunn et al., 2019 2022	NCT02409290
MDR-END	9-12 Dlm-Lzd-Lfx-Z	FQ-S RR-TB	2021	NCT02619994
TB-PRACTECAL	6 Bdq-Pa-Mfx-Lzd 6 Bdq-Pa-Cfz 6 Bdq-Pa-Lzd	RR-TB	2021/2023	NCT02589782
SimpliciTB	Pa-Bdq-Mfx-Z	FQ-S RR-TB	2022	NCT03338621
BEAT-TB	6Bdq-Lzd-Del-Lfx-Cfz	RR-TB	>2021	

What OR on AOS regimens can offer

- Injectable-free care, possibility to free up health systems to treat more patients
- Earlier, complementary answers
- Larger safety database: systematic reporting of select events
- Broader population (HIV, any CD4; addiction; very sick; in need of surgery; pregnant; pediatric)
- More options: combinations, durations
- Capacity building, improved data quality
- Alternative to centralized review of patients; increased autonomy for clinicians
- Possibly better adherence, outcomes, cost-effectiveness; reduced toxicity, cost

<u>Implementers should have modest expectations for comparative analysis</u>

Operational Research Conditions

- **A study protocol**. Multiple templates will be discussed, provided
- **Consent**. Best practice for medical care; all MDR patients should be consented with honest, balanced discussion of risks and benefits of longer, or AOS regimens. Additional consent required for use of data for research
- **Patient education materials**
- **A list of all variables to be collected.** Needs to be pre-specified, standardized; samples will be provided, discussed
- **Standardized data collection instruments.** Versions (adapted) from endTB observational study are made available to capture full list
- **A clinical treatment guide on AOS regimens**. Adapted from endTB clinical guide, can be easily modified for the specific needs of a country. Part of meeting materials
- **A system to monitor and manage adverse events and report serious ones**. Adapted from endTB observational study, proposed reporting standards and tools

What we'll do days 2 & 3

- How to, hands on, time to work on your own protocols and plans for your country, discuss with colleagues
- Discuss regimen options, how to choose
- How to include special groups
- Draft protocols, objectives & corresponding endpoints
- Consider data-collection instruments and system
- Demystify safety reporting with alternative that allows consistent reporting of select events
- Other supports available

Key messages

- Great opportunity, many questions
- Opportunity to advance evidence on important, neglected populations
- Can systematically explore options that may have advantages to patients and health systems
- Packages available for adaptation
- Complementary to trials
- Comparisons difficult in OR, but not impossible with appropriate methods