Unitaid
SAVE LIVES FASTER

ascent
Adherence Support Coalition to End TB

TAG
Treatment Action Group

An Update on Drug-Resistant TB in Children, Adolescents, Pregnant Women/People and other Special Populations

December 12, 2024

Unitaid
SAVE LIVES FASTER

ascent
Adherence Support Coalition to End TB

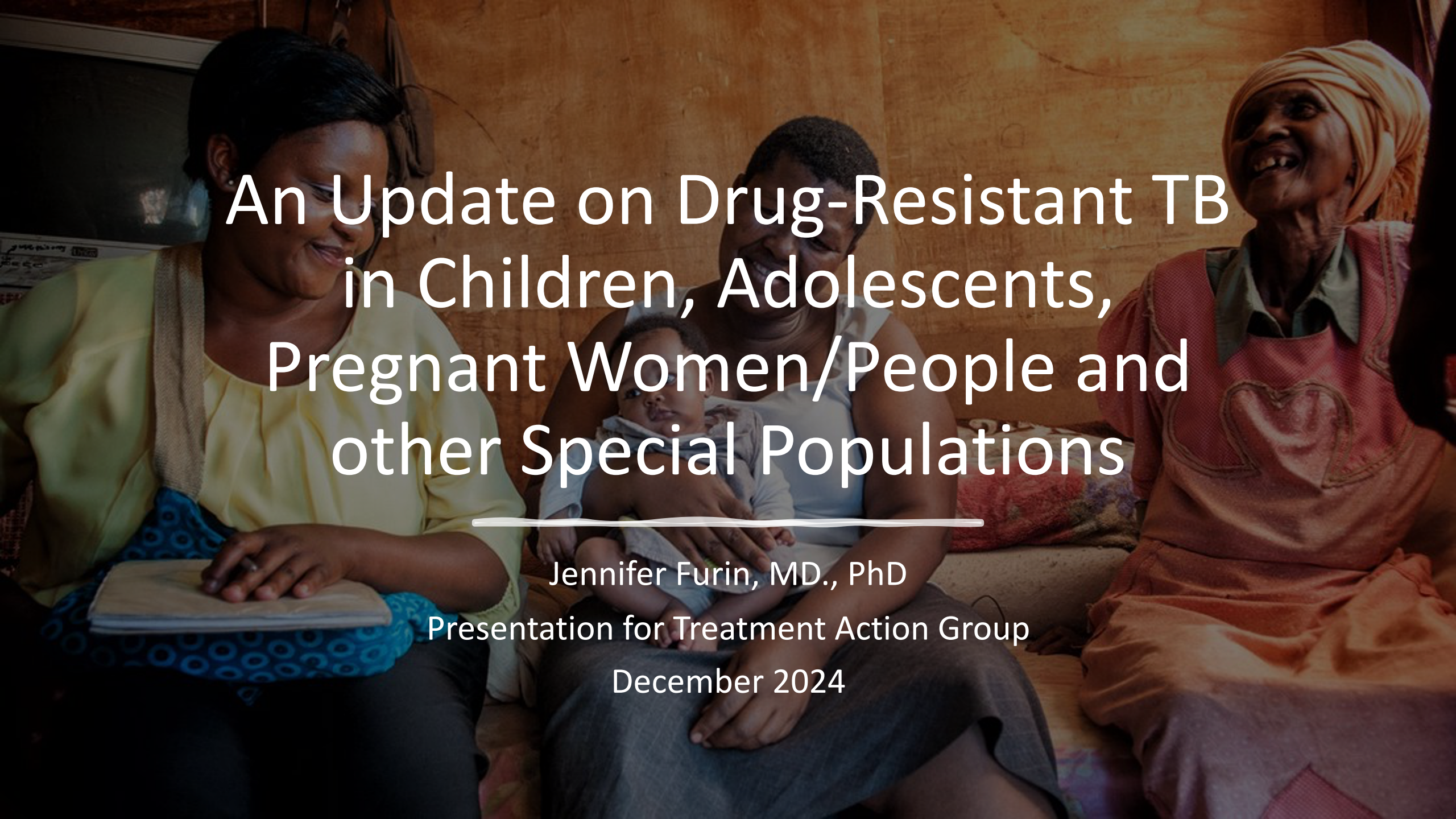
TAG
Treatment Action Group

Agenda

1. Welcome – 10 mins

2. An Update on Drug-Resistant TB in Children, Adolescents, Pregnant Women/People and other Special Populations (Dr Jennifer Furin, Harvard Medical School & Sentinel Project on Pediatric Drug-Resistant TB) – 45 mins

3. Q&A – 35 mins



An Update on Drug-Resistant TB in Children, Adolescents, Pregnant Women/People and other Special Populations

Jennifer Furin, MD., PhD

Presentation for Treatment Action Group

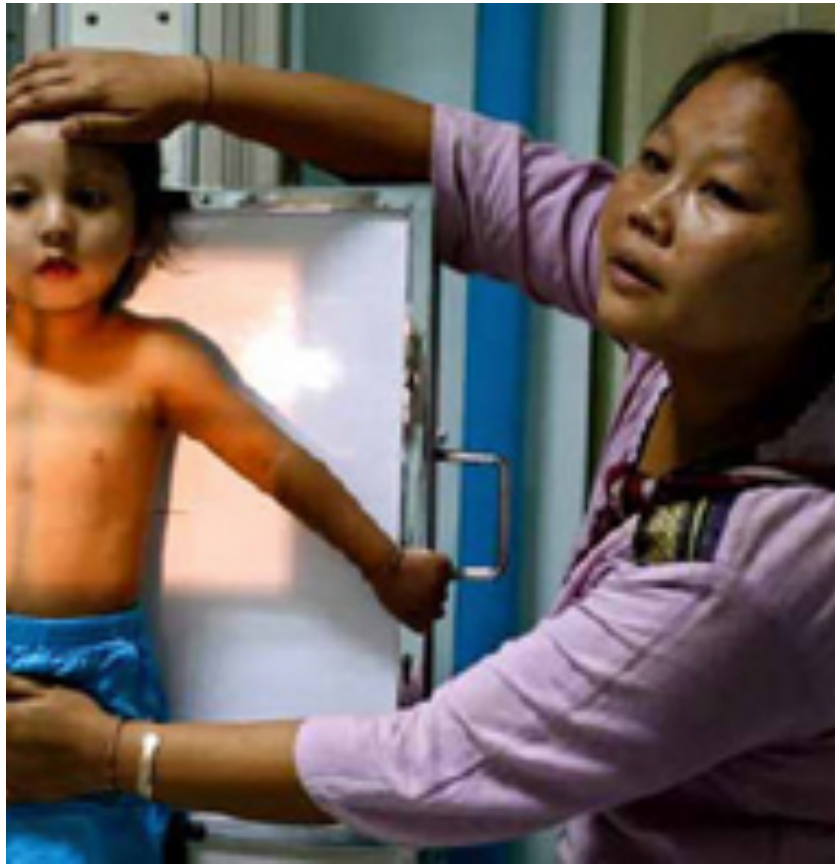
December 2024

Objectives

- To review updates on the diagnosis, treatment, and prevention of DR-TB in children and adolescents;
- To present updates in the treatment and prevention of DR-TB in pregnant women/people;
- To discuss updates in DR-TB prevention and treatment for other special populations, including people who are incarcerated, people on the move, and people with co-morbid conditions such as HIV and hepatitis C

Diagnosis of DR-TB in children/adolescents

- Based on history, clinical, radiographic findings as well as, in some patients, bacteriology;
- Stool Xpert testing—a negative test does not rule out TB;
- Xpert MTB Host Response cartridge (with DR-TB contact);
- Adolescents have adult-type disease but may need more support to access care;
- If programs are only treating children with bacteriologic confirmation, they are UNDERTREATING.



Treatment of DR-TB in children/adolescents

- endTB regimens 1-3 all use drugs that have been given to children safely;
- BEAT Tuberculosis regimens use drugs that have been given safely to children;
- Children still being overlooked in trials;
- Adolescents may need tailored support during therapy;
- SHINE study for DS-TB suggests children with non-severe disease could be treated with shorter regimens—this could be applied to DR-TB (?).

endTB regimens

- Randomized controlled trial using adaptive/Bayseian methods to compare 5 all-oral, shorter regimens with locally accepted SOC;
- Found 3 of the regimens to be non-inferior.

Study treatment regimens

Trial Regimens	Bedaquiline	Delamanid	Clofazimine	Linezolid	Quinolone	Pyrazinamide	Non-inferiority established
endTB 1 - BLMZ	Bdq			Lzd	Mfx	Z	Yes
endTB 2 - BLLCZ	Bdq		Cfz	Lzd	Lfx	Z	Yes*
endTB 3 - BDLLZ	Bdq	Dlm		Lzd	Lfx	Z	Yes
endTB 4 - DLLCZ		Dlm	Cfz	Lzd	Lfx	Z	No
endTB 5 - DMCZ		Dlm	Cfz		Mfx	Z	Inconclusive**
Control Arm	Standard of care, composed according to WHO Guidelines						

endTB 1 to 5 = 9 months - Control Arm = 18-24 months.
Mfx = moxifloxacin; Lfx = levofloxacin.
*superiority was also established; **non-inferiority was established in mITT (modified intent to treat) population but not in PP (per protocol) population.

BEAT Tuberculosis regimens

- 6-month regimen od BDQ-DLM-LZD-LFX-CFZ tests in South Africa;
- Once results of FLQ susceptibility available, either LFX or CFZ is dropped;
- Shown to be non-inferior to the 9-month, 7-drug regimen, although sample size was small.

SHINE trial for DS-TB

- Randomized, controlled trial of a shorter regimen (4 months) using usual first-line drugs for children with non-severe forms of TB;
- 4 month regimen was non-inferior to the 6 month standard of care;
- Challenges in how to operationalize definition of non-severe disease in real-world practice.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

ABSTRACT

BACKGROUND

Two thirds of children with tuberculosis have nonsevere disease, which may be treatable with a shorter regimen than the current 6-month regimen.

METHODS

We conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 months (16 weeks) or 6 months (24 weeks) of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the World Health Organization. The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment.

RESULTS

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Turkova can be contacted at a.turkova@ucl.ac.uk or at the Medical Research Council Clinical Trials Unit, University College London, 90 High Holborn, London WC1V 6LJ, United Kingdom.

*The members of the SHINE Trial Team are listed in the Supplementary Appendix, available at NEJM.org.

Drs. Gibb and Crook contributed equally to this article.

This article was updated on March 18, 2022, at NEJM.org.

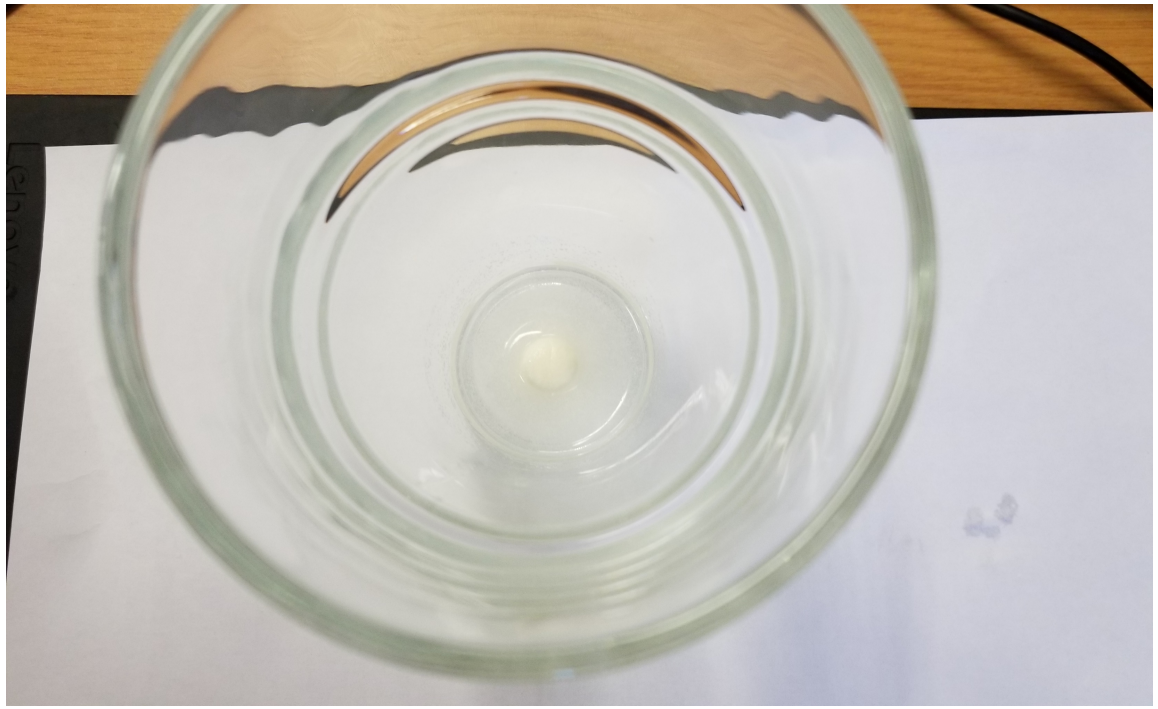
This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Final Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is

What about pretomanid/BPaLM for children/adolescents

- Semen studies in adult males suggest no reproductive toxicity in adult males with TB;
- Stringent regulatory review on reproductive safety of pretomanid still pending;
- Unclear how best to dose pretomanid in children, but studies for this are ongoing;
- Adolescents can likely receive pretomanid

Other issues in DR-TB treatment in children/adolescents

- Linezolid is the most toxic drug for children;
- It can be hard to monitor for symptoms and signs of toxicity in young children;
- Linezolid also requires routine blood draws in children;
- Could linezolid-free regimens be prioritized for children meeting the definition of non-severe disease from the SHINE trial (i.e. endTB regimen 5 of DLM-CFZ-MFX-PZA for 9 months?);
- Children/adolescents with meningitis, OA forms of TB need at least 12 months of therapy;
- Child-friendly formulations available from GDF for all second-line drugs (except pretomanid).



DR-TB prevention in children/adolescents

- TB CHAMP, V-QUIN and WHO recommendations all support 6 months levofloxacin for household contacts of all ages;
- Focus on “under-5s” ignores the rising in prevalence of TB starting at age of 10 years;
- Nutritional supplementation as per the RATIONS trial;
- Counseling and support for families;
- Improved access to CXR would be helpful in DR-TB post-exposure management;
- DR-TB post-exposure package of care tools available through Sentinel Project.

Treatment for DR-TB in pregnant women/people

- Excluded from most trials, but people who became pregnant were allowed to stay on study;
- Good outcomes seen in studies on all-oral shorter regimens, including endTB, BEAT Tuberculosis, and TB PRACTECAL;
- Multiple options exist and no reason to exclude pregnant people/women from all-oral shorter regimens;
- Breastfeeding should still be encouraged, although studies ongoing about passage of newer agents in the breastmilk (i.e. bedaquiline).

Prevention of DR-TB in pregnant women/people

- Pregnancy is a time of increased risk for development of TB disease;
- Levofloxacin should be given to pregnant people/women exposed to DR-TB in the household, as the benefits likely outweigh the risks;
- Nutritional support should be given to all pregnant people/women exposed to DR-TB in the household;
- The benefits of levofloxacin during pregnancy and breastfeeding likely outweigh the risks in pregnant or breastfeeding women/people exposed to DR-TB in the household.

DR-TB treatment and prevention in incarcerated individuals

- Active case finding key;
- All-oral shorter regimens should be prioritized;
- DR-TB preventive therapy should be prioritized;
- Should not be excluded from advances in DR-TB care and prevention.

DR-TB treatment and prevention in people in the move

- High risk for developing TB and having lack of access to care;
- Should receive priority for all-oral, shorter regimens that are easy to take in case they need to move;
- Should be offered nutritional support and levofloxacin treatment of infection after exposure.

DR-TB treatment and prevention in people living with HIV

- Studies have included a small proportion of people with HIV, but no differences seen in efficacy;
- Watch for drug-drug interactions (largely with efavirenz and bedaquline) as well as overlapping toxicities (linezolid, AZT) with ART.

DR-TB treatment and prevention in people with hepatitis C

- WHO recommends co-treatment instead of a sequential approach;
- Co-treatment results in lower rates of hepatotoxicity;
- Unclear if there is a similar benefit with hepatitis B;
- Possible increased risk for liver toxicity with pretomanid and pyrazinamide-containing regimens.

World Health Organization

Co-administration of treatment for drug-resistant tuberculosis and hepatitis C

Rapid Communication

March 2024

Summary

- All populations can and should benefit from all-oral shorter regimens;
- Multiple options now exist for all-oral shorter regimens for all populations;
- Advocacy needed to ensure people have access to these as part of the right to health and the right to benefit from science.

Thank you!

jenniferfurin@gmail.com