Medications used in the Treatment of Rifampicin/Multidrug-Resistant Tuberculosis: Side Effects, Drug interactions, and Optimal Monitoring Strategies

February 6, 2025

Agenda

1. Welcome – 10 mins
2. Introductory remarks – 10 mins
3. Medications used in the Treatment of Rifampicin/Multidrug-Resistant Tuberculosis: Side Effects, Drug Interactions, and Optimal Monitoring Strategies (Dr Jennifer Furin, Harvard Medical School & Sentinel Project on Pediatric Drug-Resistant TB) – 40 mins
4. Q&A – 30 mins

Medications used in the Treatment of Rifampicin/Multidrug-Resistant Tuberculosis: Side Effects, Drug Interactions, and Optimal Monitoring Strategies

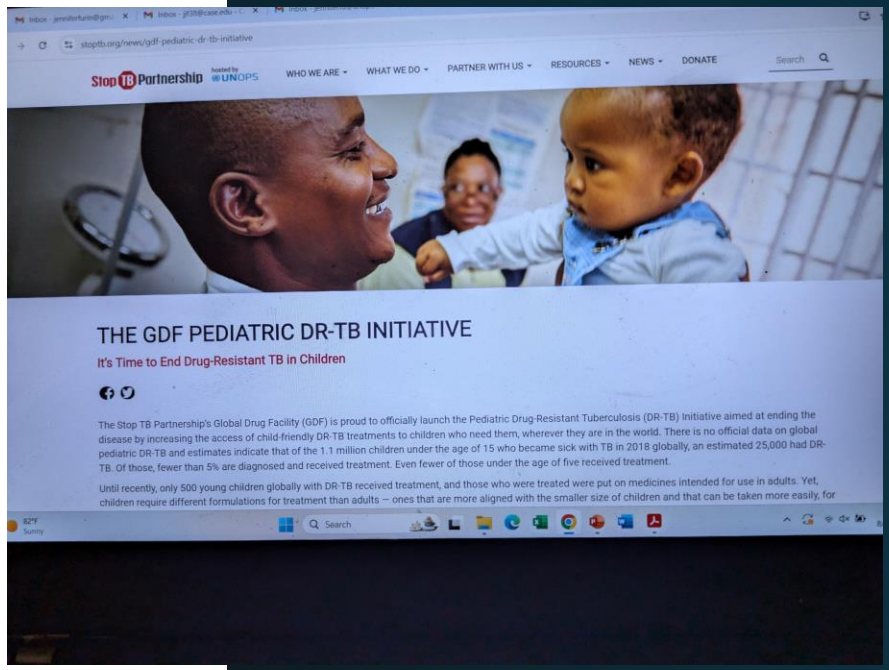
Jennifer Furin, MD., PhD

Presentation for Treatment Action Group

October 2024

Competing interests

- An organization I work with (Sentinel Project on Pediatric Drug-Resistant Tuberculosis) has received grant funding from the Stop TB Partnership's Global Drug Facility.



Objectives

- To review the drugs currently being used in regimens to treat drug-resistant tuberculosis, with a focus on side effects and drug-drug interactions;
- To discuss optimal monitoring strategies for people taking these medications as part of their therapy.

Treatment of RR/MDR-TB: Principles of Drug Therapy

- Medications always used in combination;
- Newer regimens are more tolerable, with fewer side effects compared to older regimens, but they still have multiple toxicities;
- Informed partnership between providers and people on therapy can improve process and outcomes of treatment.

Improving Approaches to Toxicity: Active Therapeutic Partnerships

- Older approach: “Don’t tell people about side effects because then they will never agree to treatment”;
- Wisdom of a person on treatment: “These are our bodies: do they think we are not going to notice?”
- Data from studies show that better communication and information between providers and people receiving care improves outcomes.

Submit a Manuscript: https://www.f6publishing.com
World J Clin Cases 2024 July 16; 12(20): 4191-4198
DOI: 10.12998/wjcc.v12.i20.4191
ISSN 2307-8960 (online)
ORIGINAL ARTICLE
Clinical Trials Study

Clinical effects of detailed nursing management interventions on medication adherence and disease perception in patients with drug-resistant tuberculosis

Yan-Li Chen, Ya-Qin Xie, Ming-Yue Wei, Dong-Mei Xu

Specialty type: Medicine, research and experimental

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Andreas K, United States

Received: April 10, 2024
Revised: May 16, 2024
Accepted: May 29, 2024
Published online: July 16, 2024
Processing time: 81 Days and 18.1 Hours

Yan-Li Chen, Ya-Qin Xie, Dong-Mei Xu, Nursing Department, The First People's Hospital of Tianmen in Hubei Province, Tianmen 431700, Hubei Province, China

Ming-Yue Wei, Infectious Disease Department, The First People's Hospital of Tianmen in Hubei Province, Tianmen 431700, Hubei Province, China

Corresponding author: Dong-Mei Xu, MM, Nurse, Nursing Department, The First People's Hospital of Tianmen in Hubei Province, No. 1 East Renmin Avenue, Tianmen 431700, Hubei Province, China. 18972189235@163.com

Abstract

BACKGROUND
Tuberculosis (TB) is a chronic respiratory infectious disease that considerably jeopardizes human health, and there is no effective vaccine suitable for its prevention in the entire population.

AIM
To investigate the promotion of medication adherence and disease cognition in patients with drug-resistant (DR-)TB using detailed nursing management.

METHODS
In total, 114 patients with DR-TB who were diagnosed and treated at our hospital between January 2019 and January 2023 were included in this study. Patients in the control group (n = 57) were managed with conventional nursing care, while those in the observation group (n = 57) were managed with detailed nursing care. Medication adherence, disease awareness scores, medication safety, and nursing satisfaction were compared between the two groups after the intervention.

RESULTS
The post-intervention medication compliance rate was 91.23% in the observation group and 75.44% in the control group, with the former being 15.79% higher than the latter (P < 0.05). There was no statistically significant difference in the disease awareness scores between the two groups before the intervention; the disease awareness scores of the observation group were significantly higher than those of the control group after the intervention (P < 0.05). The incidence of gastrointestinal reactions, joint swelling and pain, hearing loss, electrolyte disorders, and

Bedaquiline

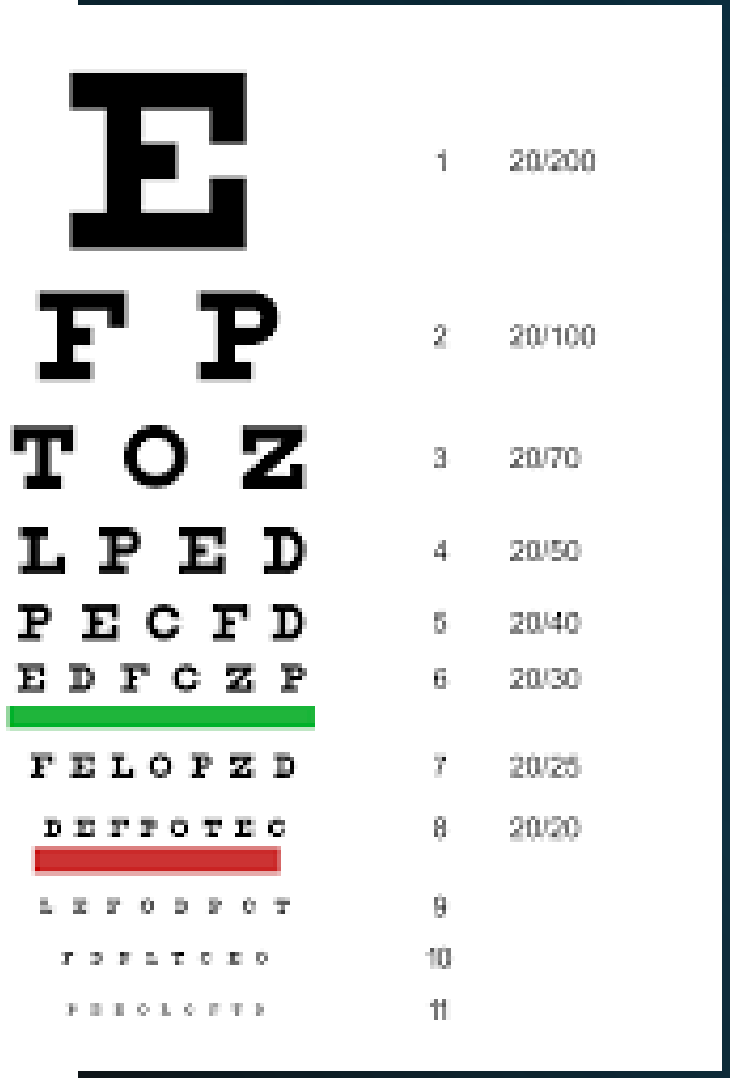
- Unusual pharmacokinetics, including need for loading dose and long terminal elimination half-life;
- QTcF prolongation is main concern (although not nearly as problematic as originally thought);
- Drug-drug interactions with rifampicin and efavirenz (reduce the concentrations of BDQ);
- Concentrated in the adipose tissue (including breast milk);
- QTcF prolongation is usually asymptomatic but could be associated with dizziness, fainting, chest pain.
- Baseline ECG then monitoring at month 1 and month 3 (?): more frequently in people who have cardiac issues, are other QTcF prolonging medications, etc.
- Most QTcF prolonging events occur by week 12 and there is no increased risk of QTcF prolongation when BDQ given beyond 6 months.

Linezolid

- Most toxic drug being used routinely for RR/MDR-TB today;
- Early toxicities: bone marrow suppression (anemia, thrombocytopenia, leukopenia) and lactic acidosis;
- Later toxicities: optic neuritis and peripheral neuropathy;
- Marrow suppression may manifest as fatigue, dizziness, easy bruising;
- Optic neuritis may present as blurry vision, problems with red-green color differentiation;
- Neuropathy may present as burning, numbness, tingling in hands/feet;
- Toxicities usually related to the trough (lowest) concentrations.

Linezolid (continued)

- Overlapping toxicities with AZT, INH, alcohol;
- Higher rates of toxicity with HIV and with DM;
- May have overlapping toxicity with mental health medications (i.e. antidepressants);
- Monitoring needs to include baseline and monthly CBC, formal testing of visual acuity (and red/green color vision) and peripheral neuropathy testing (symptoms and brief peripheral neuropathy screen);
- Management includes holding the drug, lower dose reintroduction, planned dose reduction.



Levofloxacin

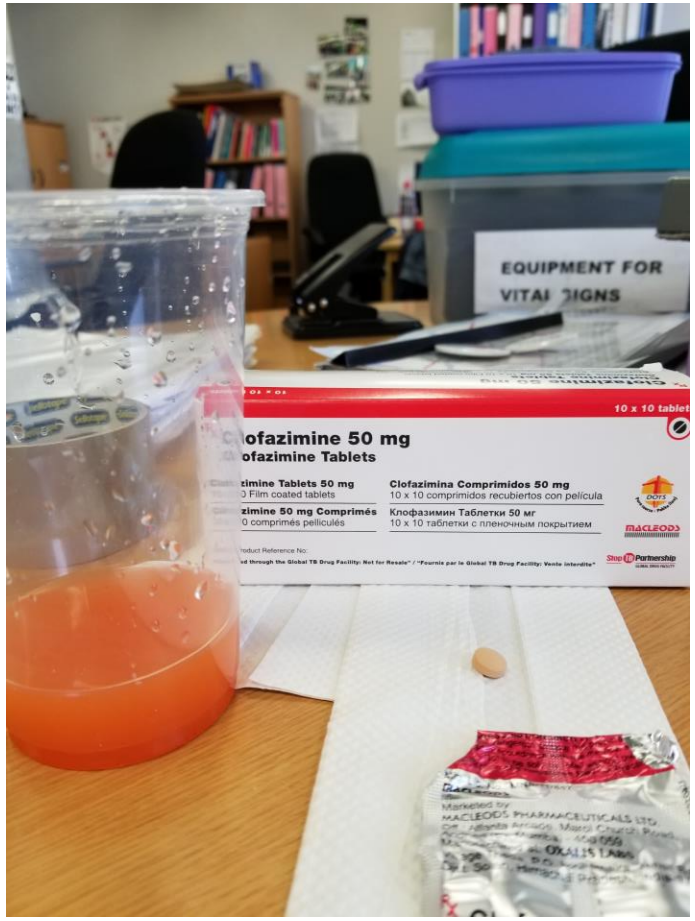
- Relatively well tolerated;
- Side effects include myalgia (muscle pain), arthralgia (joint pain), confusion, Achilles' tendon rupture (very rare), and QTcF prolongation;
- Symptom screening and symptom-directed management usually enough.

Moxifloxacin

- Relatively well tolerated;
- QTcF prolongation more common than with levofloxacin;
- Can also cause myalgia, arthralgia, confusion, Achilles' tendon rupture;
- Symptom screening and symptom-directed management usually enough.

Clofazimine

- Concentrated in the adipose tissue (including breast milk);
- Skin hyperpigmentation: may lead to inadvertent disclosure, stigma—counseling support needed;
- QTcF prolongation (especially when used in combination with other QTcF prolonging agents—often asymptomatic but can present as dizziness, fainting, chest pain;
- Nausea, vomiting, abdominal pain;
- Need ECG monitoring, symptomatic management, ongoing counseling support.



Are we worrying too much about QTcF prolongation?

- Change in the electrical system of the heart;
- Formal QTcF studies are required for new drugs to be registered in the U.S (and other countries);
- Heavy emphasis on this when BDQ first came on the market;
- Data suggest clinically significant QTcF prolongation is rare;
- Data from TB-PRACTECAL showed only 1 instance for QTcF prolongation > 500msec among 328 participants.
- May be able to reduce routine monitoring for most patients.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Check for updates

| Antimicrobial Chemotherapy | Full-Length Text

How much should we still worry about QTc prolongation in rifampicin-resistant tuberculosis? ECG findings from TB-PRACTECAL clinical trial

Ilaria Motta,[1] Martina Cusinato,[2] Andrew J. Ludman,[3] Nathalie Lachenal,[4] Matthew Dodd,[5] Moe Soe,[6] Tleubergen Abdrasuliev,[7] Ruzilya Usmanova,[8] Ilhomjon Butabekov,[8] Tigay Zinaida Nikolaevna,[9] Irina Liverko,[8] Nargiza Parpieva,[8] Ronelle Moodliar,[10] Varvara Solodovnikova,[11] Emil Kazounis,[1] Bern-Thomas Nyang'wa,[1] Katherine L. Fielding,[2] Catherine Berry[1]

AUTHOR AFFILIATIONS See affiliation list on p. 9.

ABSTRACT Regimens for the treatment of rifampicin-resistant tuberculosis currently rely on the use of QT-prolonging agents. Using data from the randomized controlled trial, TB-PRACTECAL, we investigated differences in QTcF among participants in the three interventional arms: BPaL (bedaquiline, pretomanid, and linezolid), BPaLC (BPaL with clofazimine), and BPaLM (BPaL with moxifloxacin). Additionally, we assessed whether age, body mass index, and country were causally associated with QTcF prolongation. The trial included participants from South Africa, Uzbekistan, and Belarus. A *post hoc* analysis of electrocardiogram data was undertaken. Random effects regression was used to model QTcF longitudinally over 24 weeks and causal frameworks guided the analysis of non-randomized independent variables. 328 participants were included in BPaL-based arms. The longitudinal analysis of investigational arms showed an initial QTcF steep increase in the first week. QTcF trajectories between weeks 2 and 24 differed slightly by regimen, with highest mean peak for BPaLC (QTcF 446.5 ms). Overall, there were 397 QTcF >450 ms (of 3,744) and only one QTcF >500 ms. The odds of QTcF >450 ms among participants in any investigational arm, was 8.33 times higher in Uzbekistan compared to Belarus (95% confidence interval: 3.25–21.33). No effect on QTcF prolongation was found for baseline age or body mass index (BMI). Clinically significant QTc prolongation was rare in this cohort of closely monitored participants. Across BPaL-based regimens, BPaLC showed a slightly longer and sustained effect on QTcF prolongation, but the differences (both in magnitude of change and trajectory over time) were clinically unimportant. The disparity in the risk of QTc prolongation across countries would be an important factor to further investigate when evaluating monitoring strategies.

CLINICAL TRIALS This study is registered with ClinicalTrials.gov as NCT02589782.

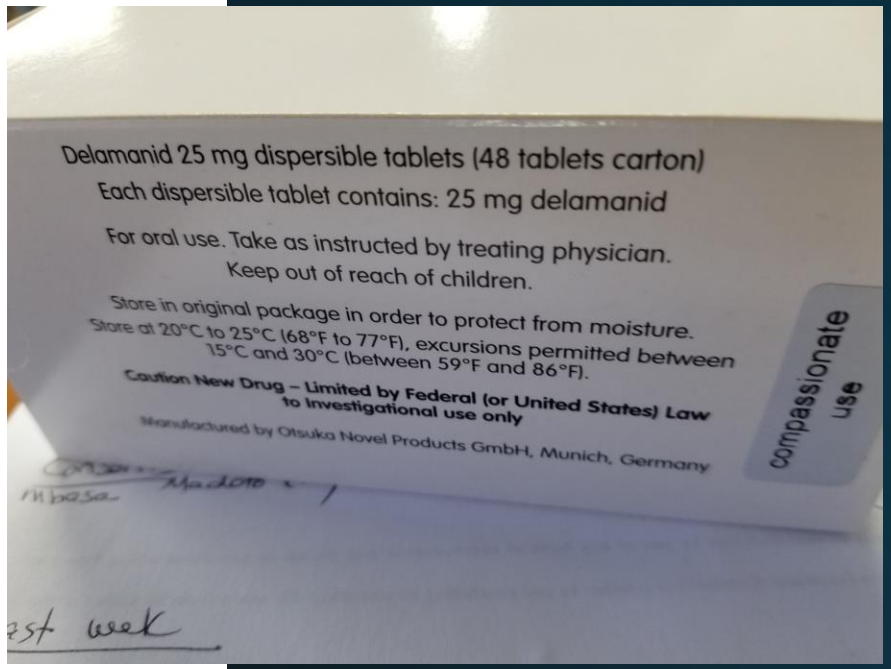
Editor Sean Wasserman, St. George's, University of London, London, United Kingdom

Cycloserine/Terizidone

- Primary side effects include central nervous system effects, such as depression, anxiety, psychosis, hallucinations, suicidal thoughts;
- May be exacerbated by substance use and alcohol use;
- May have overlapping toxicity with delamanid, isoniazid, efavirenz;
- Need to screen for depression, anxiety using standard tools at each visit;
- Counseling and ongoing psychosocial support key for people on this medication;
- Vitamin B supplementation can be considered, but not likely to be helpful beyond standard doses.

Delamanid

- Relative well-tolerated;
- Mild QTcF prolongation;
- Central nervous system effects, including hallucinations, psychosis, depression;
- Overlapping toxicity with terizidone, alcohol, other substances;
- Need to screen for depression, anxiety using standard tools at each visit;
- Counseling and ongoing psychosocial support key for people on this medication.

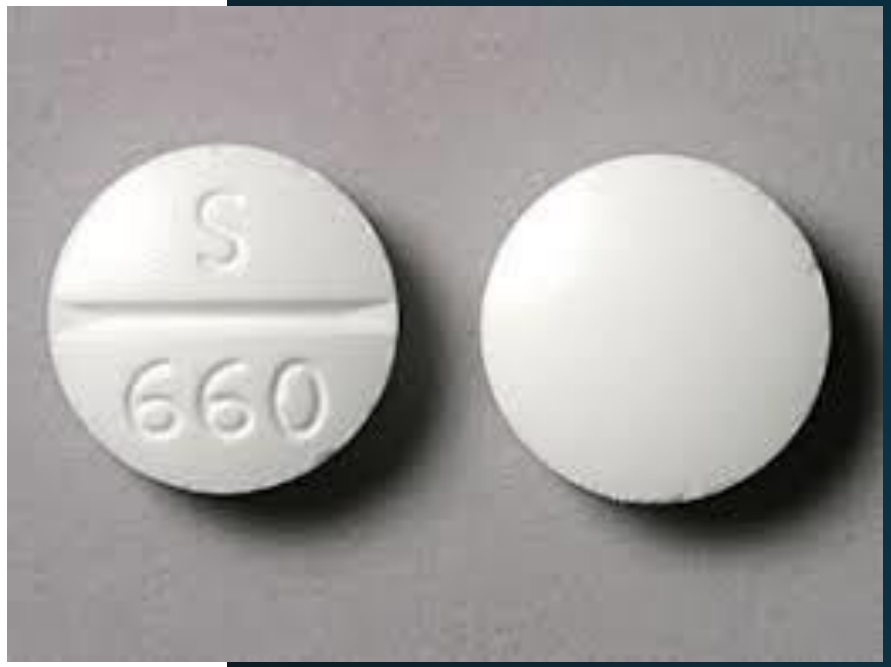


Pretomanid

- Not much known about this drug since has only used in combination with other medications;
- Studies in DS-TB suggest high rates of hepatotoxicity (may be a result of using in combination with PZA);
- May present with abdominal pain, nausea, vomiting, change in skin/eye color, change in color of the stool;
- Appears to be well-tolerated in cohorts of patients with RR/MDR-TB as part of a combination regimen;
- Associated with cataracts in animal studies but unclear if this is a problem in humans
- Testicular toxicity in animal studies not likely to be a problem in humans based on semen studies: waiting for formal opinion of FDA;
- Consider routine monitoring of liver function (especially in high risk groups such as people with liver disease or alcohol use) or baseline assessment and symptom directed monitoring afterward.

Pyrazinamide

- Sometimes used in the treatment of RR/MDR-TB (i.e. endTB regimens, MDR-END);
- May have some synergy with BDQ;
- DST for PZA is challenging;
- Primary side effects are liver toxicity (dose-dependent), arthralgia (joint pain), arthritis;
- Overlapping toxicity with alcohol;
- May present as nausea, vomiting, abdominal pain, change in color of skin/eyes/stool;
- Consider routine monitoring of liver function (especially in high- risk groups such as people with liver disease or alcohol use) or baseline assessment and symptom directed monitoring afterward;
- No need to check uric acid and can use symptom-directed therapy for joint issues (be careful with paracetamol).



Ethambutol

- Rarely used in RR/MDR-TB;
- Generally well-tolerated but can cause optic neuropathy;
- Can be asymptomatic or lead to blurry vision or changes in red/green color vision;
- Overlapping toxicity when given with linezolid;
- Visual acuity monitoring monthly

Carbapenems

- Must be given intravenously and in combination with clavulanic acid or they do not kill TB;
- Side effects include rash, seizures, vomiting, diarrhea;
- Most challenges are with long-term IV therapy, including line infections and blood clots;
- Would be safer if could be given orally (? Tebipenem with clavulanic acid)

Amikacin

- Highly toxic drug that should only be given with documented susceptibility and if there are no other oral options;
- Side effects include renal failure, hearing loss, ringing in ears, balance loss;
- Overlapping toxicity with tenofovir;
- People on amikacin need to have baseline and monthly audiometry and baseline and monthly creatinine—the drug should not be given if these tests cannot be done (except in very rare situations);
- Toxicity may be lower with three times a week dosing or if given with the anti-oxidant medication N-acetylcysteine;
- Can mix with lidocaine to lessen the pain of the injection.

Ethionamide

- Older medication that should only be used in “rescue” regimens;
- Main side effects are nausea and vomiting, which can be quite severe (and impact ability to continue taking treatment);
- Can also cause bitter taste in mouth and hypothyroidism;
- Hypothyroidism can present as fatigue, dry skin, hair loss;
- Overlapping toxicity with PAS;
- Should have thyroid function testing done baseline and every three months after that while on ethionamide;
- Will need antiemetics and counseling support.

PAS

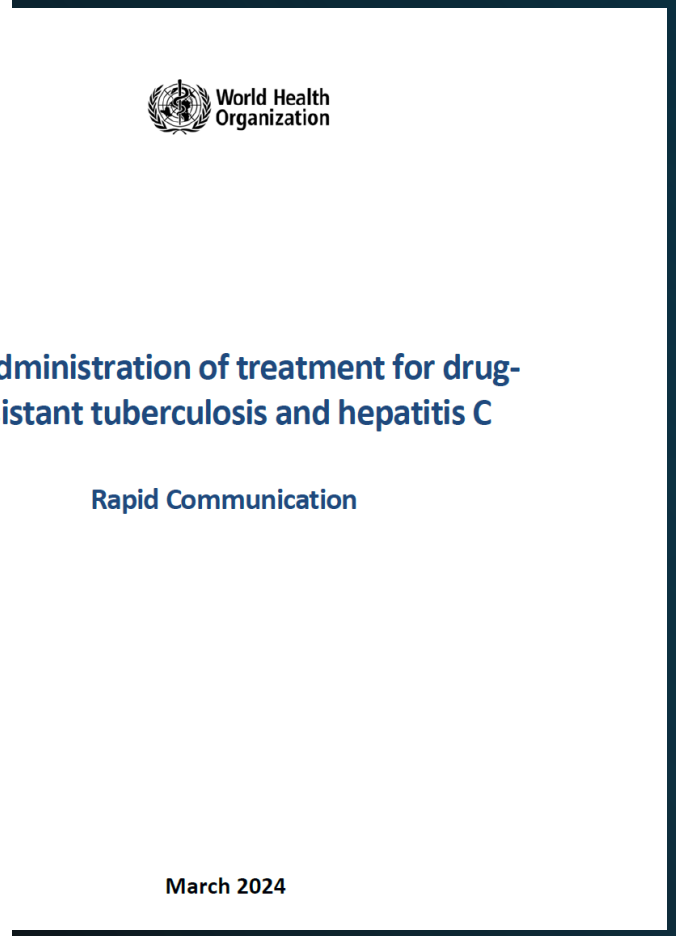
- Older medication that should only be used in “rescue” regimens;
- Usually comes as a “granule” formulation that often has to be given with acidic foods (i.e. yogurt);
- Main side effects are nausea vomiting, and diarrhea
- Can also cause bitter taste in mouth and hypothyroidism;
- Hypothyroidism can present as fatigue, drug skin, hair loss;
- Overlapping toxicity with ethionamide;
- Should have thyroid function testing done baseline and every three months after that while on PAS;
- Will need antiemetics and counseling support.

Co-morbidities: HIV

- People with HIV may have challenges with absorption of TB medications;
- Drug-drug interactions between bedaquiline and efavirenz as well as between bedaquiline and protease inhibitors (although less than with efavirenz);
- Multiple ARVs have overlapping toxicities with second-line TB medications (i.e. AZT and LZD; tenofovir and amikacin; cycloserine and efavirenz)

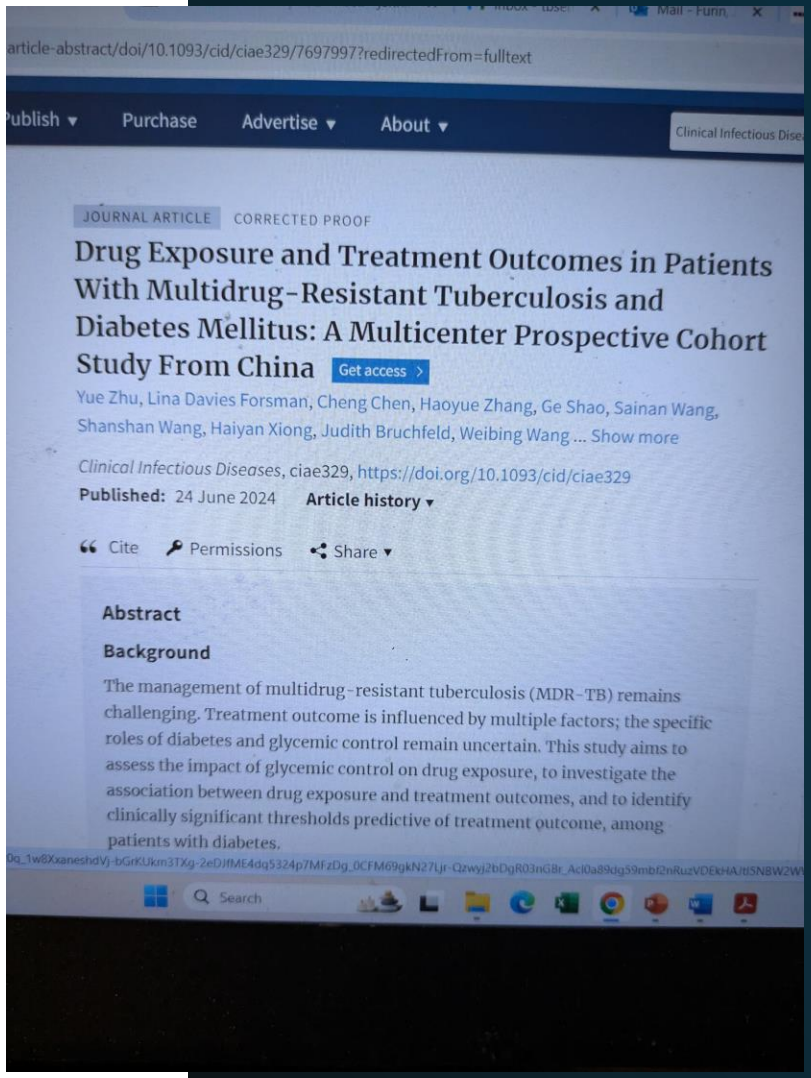
Co-morbidities: Hepatitis C

- Used to recommend a staged treatment approach (treated RR/MDR-TB first and then hepatitis C);
- This staged approach showed increased rates of morbidity and mortality;
- Now recommend co-treatment for hepatitis C and RR/MDR-TB as there are no notable drug-drug interactions and there is more toxicity if the hepatitis C is not treated.



Co-morbidities: Diabetes Mellitus

- Common co-morbidity;
- Although there are not drug-drug interactions or overlapping toxicities with the medications, there are important interactions;
- Poorly controlled DM can lead to lower drug levels and higher rates of poor outcomes;
- DM causes vision impairment and peripheral neuropathy, which can be seen with some TB drugs, including LZD, EMB, and INH;
- Close monitoring needed for glycemic control and more intense monitoring for vision changes and peripheral neuropathy.



Co-morbidities: mental health

- Multiple TB drugs can cause depression, psychosis, etc., including LFX, MFX, DLM, CS;
- TB itself can lead to mental health stresses;
- LZD can have overlapping toxicities with antidepressants;
- Generally safe with other mental health medications, methadone;
- Screening for mental health issues key at every visit.

Family planning and TB treatment

- Few interactions with family planning medications and second-line TB drugs;
- If possible, pregnancy should be deferred until treatment completion;
- Family planning services should be offered as routine part of DR-TB treatment.

Monitoring and Management Tools

- Routine labs/testing
- Symptom directed testing;
- Recording of AEs in patient records;
- Reporting of AEs;
- Management of AEs: this is an essential part of treatment and should be free of charge

Table	Common Terminology Criteria for Adverse Events Grade and Clinical Severity[1]
Grade	Clinical severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

ADL indicates activities of daily living.

Grading of adverse events

- Use of standard values/scales to determine severity;
- Often based on a scale of 1-4, with 1 being “mild” and 4 being severe;
- Try to add a more “objective” value to the types of side effects seen-but can still be very subjective;
- Try to determine if the side effect interferes with daily activities/functioning.

When should a drug be discontinued?

- Balance between how much the drug is needed to treat the TB versus how troubling the side effect is;
- Try other management strategies first (i.e. lowering dose, other medications);
- If side effect is permanent or severe, then discontinuation may be needed, with substitution with another agent.

Summary

- Adverse events and overlapping toxicities are common in RR/MDR-TB treatment and partnership approach needed for optimal management;
- Adverse events may be more common in populations at high risk for RR/MDR-TB, especially people living with HIV and DM;
- Adverse event detection, monitoring, and management essential parts of treatment for RR/MDR-TB.

Thank you!

jenniferfurin@gmail.com