Conflicts

I have no conflicts of interest to disclose

18-year-old woman with pulmonary and nodal TB

- Diagnosed with cervical nodal and pulmonary drug-susceptible TB.
- Started 4HPZM due to her strong wish to have the shortest treatment possible
- Recurrent nausea and vomiting during the first week of treatment
- In clinic for evaluation
- Past medical history – from Vietnam, no other medications for chronic illnesses, HIV neg.
- BP – 114/74, P – 117, weight decreased 1 kg
- Abdominal exam – normal
- ALT - normal

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Frequency of "gastrointestinal disorders" in a large, multicenter clinical trial

Regimen	% with nausea/vomiting (grade 3-4)
4HPZM – active TB	0.2% (2/825)

Dorman S, et al. N Engl J Med 2021;384:1705-18
*(**Supplementary Appendix, page 38**)*

"Most TB patients complete their treatment without any significant adverse drug effect. However, a few patients do experience adverse events."

WHO TB treatment guidelines, 2010

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Frequency of nausea/vomiting in two clinical cohorts treated with 4HPZM

Study	AE reported	Grade 1-2	Grade 3-4	HPZM discontinued
San Francisco	Nausea and/or vomiting	9/22 (41%)	0	**7 (32%)**
New York City *	Nausea	9/30 (47%)	0	**7 (23%)**
	Vomiting	5/30 (26%)	0	

* Patients started on HPZM were younger and less often had other chronic illnesses and medications than patients treated with standard therapy

Overall outcomes of HPZM treatment:

- San Francisco: 11/22 (**50%**), New York City: 15/36 (**42%**) stopped due to AEs

- *Louie J, et al. Open Forum Inf Dis 2024 Mar 26;11(4):ofae178*
- *Galvis M, et al. Int J Tuberc Lung Dis 2025; 29: 318-24*

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Representativeness of participants in 40 clinical trials for RIF-susceptible TB

Characteristic	Inclusion criterion	Reported enrollment	Pooled proportion	Prevalence in global TB
≥ 65 years	**23 (58%)**	**6 (15%)**	**Insufficient data**	**13%**
Diabetes	15 (38%)	9 (23%)	9%	15%
HIV	17 (43%)	17 (43%)	26%	12%
Alcohol use disorder	**2 (5%)**	**2 (5%)**	**Insufficient data**	**30%**
Chronic Hep B	4 (10%)	3 (8%)	Insufficient data	6%

- Subgroups known to be at increased risk of side effects were often excluded from trials
- When allowed to enroll, participation of some subgroups was often not reported
- When reported, participation of persons in key subgroups (other than HIV) was lower than the global TB pandemic

Burman W, et al. Lancet Inf Dis 2025; 25: e86-98

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Problems of side effect measurement and analysis in clinical trials

- Clinical trials always underestimate side effects
  - Biases inherent in the clinical trials process
  - Study populations that are not representative
  - Failure to include patient-reported outcomes
- Problems with side effect analysis and interpretation
  - Premature conclusions of safety and tolerability from underpowered studies ("toxicity minimization language")
  - Analytic techniques that don't capture important aspects of the patient experience
    - Failure to analyze grade 1-2 side effects
    - No assessment of duration or recurrence of side effects

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The systematic neglect of side effects in the treatment of drug-susceptible TB

- Assumption that RIPE is safe and well-tolerated
- Lack of data on side effects: frequency, severity, and timing
- Lack of awareness of the impacts of side effects on treatment outcomes
- Lack of evidence-based recommendations:
  - Preventing and treating side effects
  - Safety monitoring
- Clinical trials that ignore tolerability and downplay toxicity

Result: frequent side effects, little guidance on how to manage them, lack of new regimens that are safer and better tolerated

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Key messages

- Side effects (adverse events) are common
  - Standard therapy (HRZE) is neither safe nor well-tolerated
  - Therefore, a new regimen that has safety and tolerability similar to HRZE is not safe and well-tolerated
- Side effects are a leading cause of poor TB treatment outcomes
  - We won't improve TB treatment outcomes until we have regimens that are safer and better-tolerated
- Need more data on how to prevent and treat side effects
  - Make better use of data that is available
  - Use data from other fields of medicine

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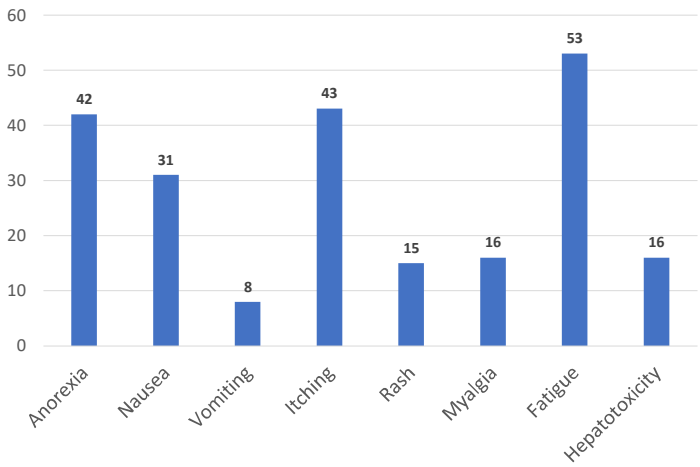
Side effects are common: Prospective study of adults being treated for drug-susc. TB, South Korea (n = 410)



Mean age – 52
Diabetes – 12%

68% had side effect ≥ grade 2

10% changed therapy due to adverse events

Mean treatment duration: 216 days

Treatment success: 96%

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Choi H, et al. Pharmacoepidemiol Saf 2022; 31: 1153-63

RIPE is not well-tolerated: treatment interruption/change; clinical cohort in South Korea

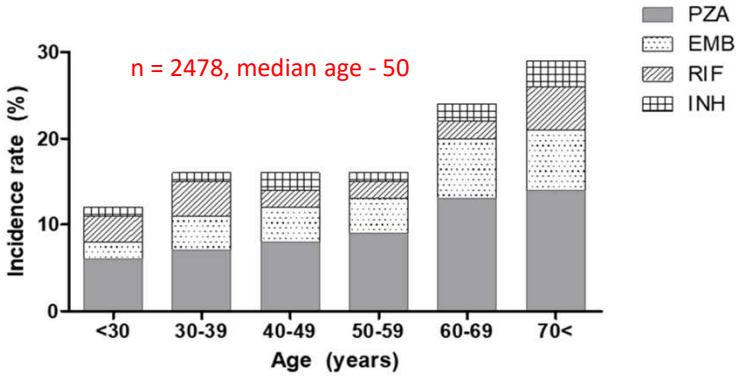

Fig 3. Incidence of serious adverse events due to pyrazinamide according to age group.

- Patients with treatment failure were not included in the analysis

Kwon BS, et al. 2020; PLoS ONE 15(7): e0236109.

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Standard TB treatment is not safe: meta-analysis of hepatotoxicity in India (43 studies, n = 12,041)

- Drug-induced liver injury – 12.6%
- Acute liver failure ~ 0.9%, (72% fatality rate) [8 studies])

Kumar R, et al. Indian J Gastroenterol 2025;44(1):35-46

- FDA - "Finding one Hy's Law case in the clinical trial database [of 1-2,000 patients] is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population."

https://www.fda.gov/media/116737/download

TB treatment has a risk of severe liver injury > 10 x that of drugs removed from the U.S. market for hepatotoxicity

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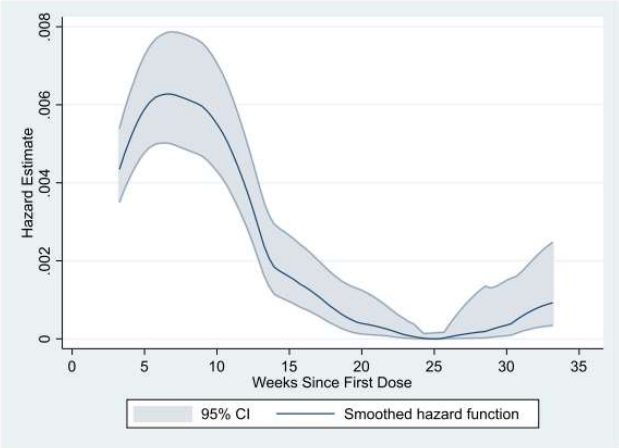
Most side effects occur early: time to Grade 3+ adverse events, control arm of the ReMox trial



~75% of grade 3+ adverse events were within the first 8 weeks

Similar data for grade 2 AEs (*Choi H, et al. Pharmacoepidemiol Saf 2022; 31: 1153-63*)

Tweed CD, et al. BMC Infectious Diseases 2018; 18: 317

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Side effects are increasingly common: meta-analysis of the trend in incidence of hepatoxicity from TB treatment, 1999-2020

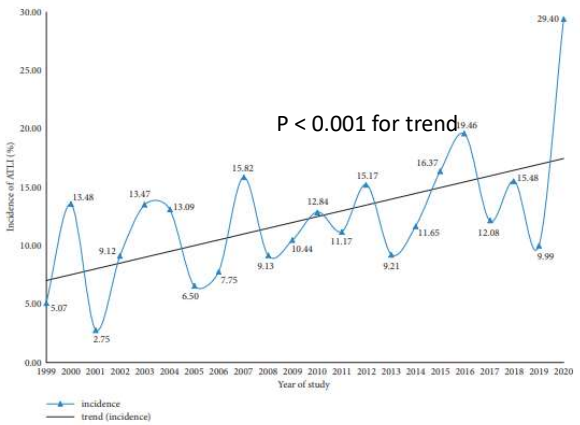

FIGURE 4: Temporal trend of the pooled incidence of ATLI worldwide (ATLI, antituberculosis drug-induced liver injury).

Recent clinical cohorts: ~ **15%** of patients developed hepatotoxicity

Possible reasons

- Increasing age of TB patients
- Increasing frequency of metabolic syndrome (fatty liver)
- Increasing alcohol use

Wang N, et al. J Trop Med 2022: doi: 10.1155/2022/8266878

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Summary – frequency and risk factors for adverse events effects during TB treatment

- Common adverse events: nausea/vomiting, anorexia, hepatoxicity, rash/itching, fatigue, arthralgia
- Risk factors for adverse events are common (U.S., 2024):
  - Age ≥ 65 – 26%
  - Diabetes – 23%
  - Alcohol use disorder – 8%; other drug use – 9%
  - HIV – 5%; chronic viral hepatitis – 3%
  - Non-HIV immunosuppression – 8%
- Timing – most occur (75%+) within the first 2 months
- Side effects are becoming more common

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AEs are expensive for patients and programs, 432 patients with HIV/TB in Thailand (adjusted U.S. dollars)

Severity of adverse event	Direct medical costs, mean (SD)	Direct non-medical costs, mean (SD)	Indirect costs, mean (SD)	Total
Mild	16 (45)	69 (74)	106 (250)	**$191**
Moderate	355 (855)	179 (293)	226 (334)	**$759**
Severe	1392 (3385)	684 (195)	1,396 (1,820)	**$5,555**

- Direct medical – "costs related to public health facilities and out-of-pocket payments by patients"
- Direct non-medical – "transportation, meal, accommodation, and caregiver time loss"
- Indirect – "patient time lost due to morbidity or mortality"

Adjusted for purchasing parity

Rochanathimoke O, et al. ClinicoEconomics and Outcomes Research 2022:14 587–599

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Adverse drug reactions are a common cause of missed doses

174 adult patients on RIPE in Latvia (treated from 2015-2022)

- 13.5% of all doses were missed
- 54 patients (31%) missed doses due to ADRs
  - 21% of all missed doses were due to ADRs
- Hepatotoxicity caused long gaps in treatment (median 15 days)

Dixon E, et al. Br J Clin Pharmacol 2025;91:3461-70

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Adverse events: the most common cause of treatment interruption (Malaysia, 2024)

16% of patients (475/2953) interrupted TB treatment

Reason	N	%
Adverse drug reaction	**253**	**53%**
Reason not stated	**149**	**31%**
Logistics (e.g., transportation)	47	10%
Personal issues (e.g., finance)	34	7%
Traveling	26	6%
Other	69	15%

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Oh AL, et al. Top Med Int Health 2024; 24: 434-45

Treatment interruptions increased treatment changes, prolongation and loss to follow-up (Malaysia, 2024)

Consequence	No interruption or interruptions < 2 weeks (n = 2478)	Interruption > 2 weeks (n = 475)
Change in meds	**5%**	**48%**
Treatment duration, median (days)	**194 days**	**247 days**
Loss to follow-up	**0**	**13.5%** (64)

Oh AL, et al. Top Med Int Health 2024; 24: 434-45

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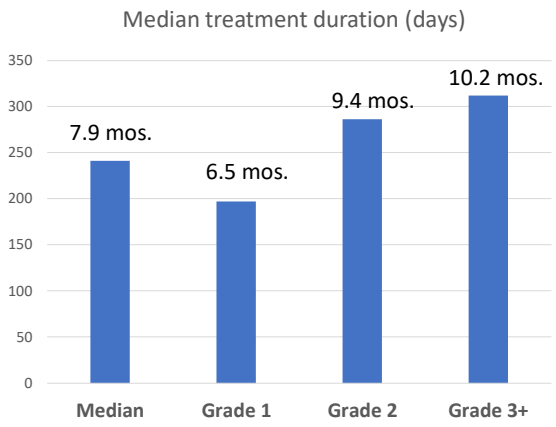
Outcomes of "short-course" TB treatment in a contemporary U.S. cohort – San Francisco (2016-20)

373 patients – median age of 62

- 35% had Grade 2+ adverse event, interrupted therapy
- More common in those 65+ (45%)
- Drug implicated: PZA > RIF > INH



Louie J, et al. Clin Infect Dis 2023; 76: 1121-4

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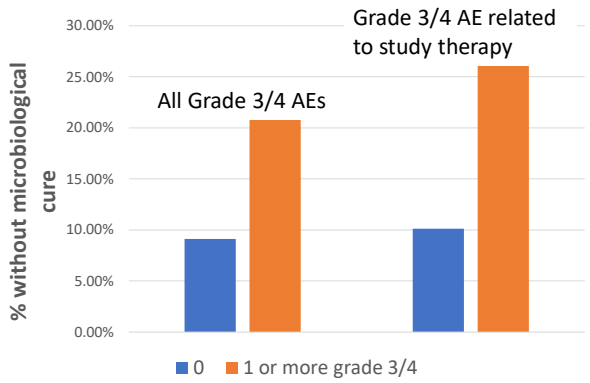
Side effects cause poor TB treatment outcomes: control arm of the ReMox clinical trial



- **Adj OR 3.1 [**1.6–6.1], p < 0.001) for failure/relapse
- Adverse events associated with **36% of all primary endpoints** in HRZE arm of the trial
- Similar results in multiple cohort studies

Tweed et al. BMC Infectious Diseases (2018) 18:317

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Adverse event analysis: comparison by grade of AE among patients on RIPE vs. triple-dose rifampin (with INH, PZA, linezolid)

	Standard (RIPE), n = 91		Triple dose RIF, n = 88	
Adverse event	Any grade	Grade 3-4	Any grade	Grade 3-4
Hepatic disorder		5%		7%
Dizziness		0		1%
Headache		0		0
Abdominal pain		0		0
Nausea		0		0

Paton NI, et al. Lancet Infect Dis 2025; 25: 1084–96; ***Supplementary Tables S6, S15, pages 39, 53***

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Adverse event	Any grade	Grade 3-4	Any grade	Grade 3-4
Hepatic disorder	12%	5%		7%
Dizziness	3%	0		1%
Headache	2%	0		0
Abdominal pain	**12%**	0		0
Nausea	**14%**	0		0
Vomiting	**16%**	1%		0

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Paton NI, et al. Lancet Infect Dis 2025; 25: 1084–96; ***Supplementary Tables S6, S15, pages 39, 53***

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Hepatic disorder	12%	5%	31%	7%
Dizziness	3%	0	14%	1%
Headache	2%	0	16%	0
Abdominal pain	**12%**	0	**28%**	0
Nausea	**14%**	0	**33%**	0
Vomiting	**16%**	1%	**45%**	0
Did not complete on time	**3%**		**25%**	

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Paton NI, et al. Lancet Infect Dis 2025; 25: 1084–96; ***Supplementary Tables S6, S15, pages 39, 53***

How many of us would put up with grade 2 nausea/vomiting (CTCAE table)?

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	Loss of appetite, no alteration in eating	Oral intake decreased without weight loss	**Inadequate oral intake; tube feeding, TPN, or hospitalization needed**	
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	**Tube feeding, TPN, or hospitalization indicated**	Life-threatening consequences

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

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Summary – impacts of adverse events during TB treatment

- ↓ quality of life for patients
- ↑ costs for patients and programs (e.g., clinic visits, lab tests)
- ↑ missed doses
- ↑ interruptions/changes in treatment, prolonged treatment
- ↑ in not completing treatment
- ↑ failure, recurrence, death during treatment
- It's not just grade 3/4 adverse events; grade 1-2 increase poor treatment outcomes

Side effects are a major barrier to TB cure – we won't improve outcomes without improving the safety and tolerability of treatment

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18-year-old woman with pulmonary and nodal TB

- Diagnosed with cervical nodal and pulmonary drug-susceptible TB.
- Started 4HPZM due to her strong wish to have the shortest treatment possible
- Recurrent nausea and vomiting during the first week of treatment
- In clinic for evaluation
- Past medical history – from Vietnam, no other medications for chronic illnesses, HIV neg.
- BP – 114/74, P – 117, weight decreased 1 kg
- Abdominal exam – normal
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Recommendations for management of nausea in international and prominent national guidelines

Guidelines	Recommendations for managing treatment-related nausea/vomiting
US (IDSA/ CDC/ATS)	"The optimum approach to management of…nausea with tuberculosis drugs is not clear…may take the medications at bedtime…can be treated with antacids [preferred to taking with food]…Some experts report success with proton pump inhibitors for reducing gastrointestinal upset". (2016)
WHO	None
EU	None
MSF	**Detailed recommendations, including drug, dose, dosing in children**

No recommendations for managing nausea in current guidelines from UK, Canada, and Australia

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Burman W, et al. eClinicalMedicine 2025;82: 103148

Ease of use of guidelines containing recommendations for AE management

	High-burden country (N = 23)	International (n = 4)	Non-governmental (n= 8)
At least 1 table/figure for AEs	52%	50%	100%
Number of tables/figures, mean (range)	2.7 (1-9)	1 (1)	3.0 (1-8)
Clear path to AE recs.	61%	75%	100%
Specific medications	96%	0	75%
Specific doses	70%	0	25%
Key drug interactions noted	9%	0	13%

- *78% for pyridoxine (Vit B6); only 17% had doses for nausea treatment*
- *No guidelines noted interactions between RIF and common meds for GI symptoms (ondansetron, metoclopramide, omeprazole)*

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Burman W, et al. eClinicalMedicine 2025;82: 103148

Summary of published articles on management of nausea/vomiting – the most common side effect of TB treatment

- Prevention of nausea
  - Non-pharmacologic interventions (e.g., dosing with meals) – **no publications**
  - Clinical trial of an "extract of a stingless Indonesian bee" – 13 patients per arm, trend toward decreased nausea in the two groups receiving the extract
  - Clinical trial of a ginger extract (500 mg) – 30 patients per arm, nausea in 70% compared to 90% with placebo
  - Clinical trial of probiotic, *Lactobacillus casei* (2 doses) – 142 patents/arm, decrease in overall GI side effects but not nausea/vomiting
- Treatment of nausea
  - Non-pharmacologic interventions (e.g., dosing with meals) – **no publications**
  - Medications – **no publications**

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Burman W, et al. PLoS One. 2025 Dec 26;20(12):e0339354. doi: 10.1371/journal.pone.0339354

Use existing data: TB treatment regimen changes to consider in the patient with nausea/vomiting

- Discontinuation of PZA
- Temporary discontinuation, followed by challenge using graded dose escalation
- Twice-daily dosing
  - Small study (61/arm), trend toward ↓adverse events
- Split dosing – 2 meds (RE) on one day, followed by the other 2 meds (IP) on alternate days
  - GI AEs: Split - **3%** (28/822) vs. daily - **7%** (29/418), p = 0.01
  - Favorable outcome at 5 years: Split – 91%, 93% vs. daily – 90%

Chuchottaworn C, et al. J Med Assoc Thai 2012; 95 (Suppl. 8): S1-S5
Santha T et al. Trop Med Int Health. 2004;9(5):551–8

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Use data from other fields of medicine: management of nausea/vomiting

- PubMed search (2/26) – treatment of nausea/vomiting
  - Randomized trials – 16,649
  - Meta-analyses – 3,390
- Major fields: cancer chemotherapy, radiation therapy, post-operative management, acute N/V
- Lessons across these fields
  - Prevention is more effective than treatment of nausea/vomiting
  - Preventing nausea improves treatment outcomes (cancer chemotherapy)
  - At least 5 drug classes are effective anti-emetics
  - Adding a new drug class more effective than higher doses of initial drug class

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Recommendations for treatment of nausea/vomiting from other fields of medicine

	Initial drug of choice	Dose of oral ondansetron
Acute nausea/vomiting (ED)	No clear winner for efficacy, ondansetron often used	4-8 mg (thrice-daily)
Cancer chemo (oral therapy)	Ondansetron *	8 mg (daily or BID) or 24 mg single dose
Radiation therapy	Ondansetron	8 mg (daily or BID)
Post-operative nausea/vomiting	No clear winner for efficacy, ondansetron often used	8-16 mg (single dose)

* Or other member of this drug class (5HT3 receptor blockers); ondansetron is cheapest

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Summary of anti-emetic drug classes, for patients being treated for TB

Drug class (example)	Efficacy	Toler-ability	Comments on side effects	RIF effects	Cost
5 HT-3 inhibitors (odansetron)	+++	+++	**Headache, constipation, QT (high-dose IV)**	**65% ↓**	**$**
Dopamine antagonists					
Metoclopramide	++	++	Sedation, movement disorder, weight gain	50% ↓	$
Prochlorperazine	++	++	Sedation, movement disorder, weight gain	No effect	$
Olanzapine	+++	++	Sedation, movement disorder, weight gain, QT	50% ↓	$
Antihistamines (hydroxyzine)	+	+++	Sedation	No effect	$
NK-1 inhibitors (aprepitant)	++++	++++	Few side effects	> 80% ↓	$$$$
Corticosteroids	+++	++	Insomnia, many with chronic use	50% ↓	$

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Where do we go from here to improve safety and tolerability of TB treatment?

- Push for treatment guidelines that provide recommendations for preventing and treating side effects
  - Use available evidence from TB
  - Use evidence from other fields of medicine
  - Provide expert opinion for common side effects for which there are data gaps
- Observational cohort studies – prospective, retrospective
  - Frequency, severity, timing, impact on treatment outcomes
  - Management of side effects
- Clinical trials
  - Enroll participants that are representative of our patients
  - Identify safer, better-tolerated treatment regimens
  - Evaluate ways to prevent and treat side effects

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Taking Side Effects Seriously | Nausea & Vomiting

A Curry International Tuberculosis Center National Webinar

Monday, March 30, 2026

12:00 – 1:30 pm Pacific Time

The first session of the *Taking side effects seriously - an interactive and* evidence-*based webinar series* will cover the risks, impacts, and management of TB treatment-associated nausea and vomiting.

Speakers: Bill Burman, MD & Janice Louie, MD, MPH
Moderated by: Lisa Chen, MD

UCSF University of California San Francisco

CURRY INTERNATIONAL TUBERCULOSIS CENTER

http://tiny.ucsf.edu/OGa1fM

https://tiny.ucsf.edu/OGa1fM

Register Here!