Center for Tuberculosis

Management of Adverse TB Drug Reactions

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Learning Objectives

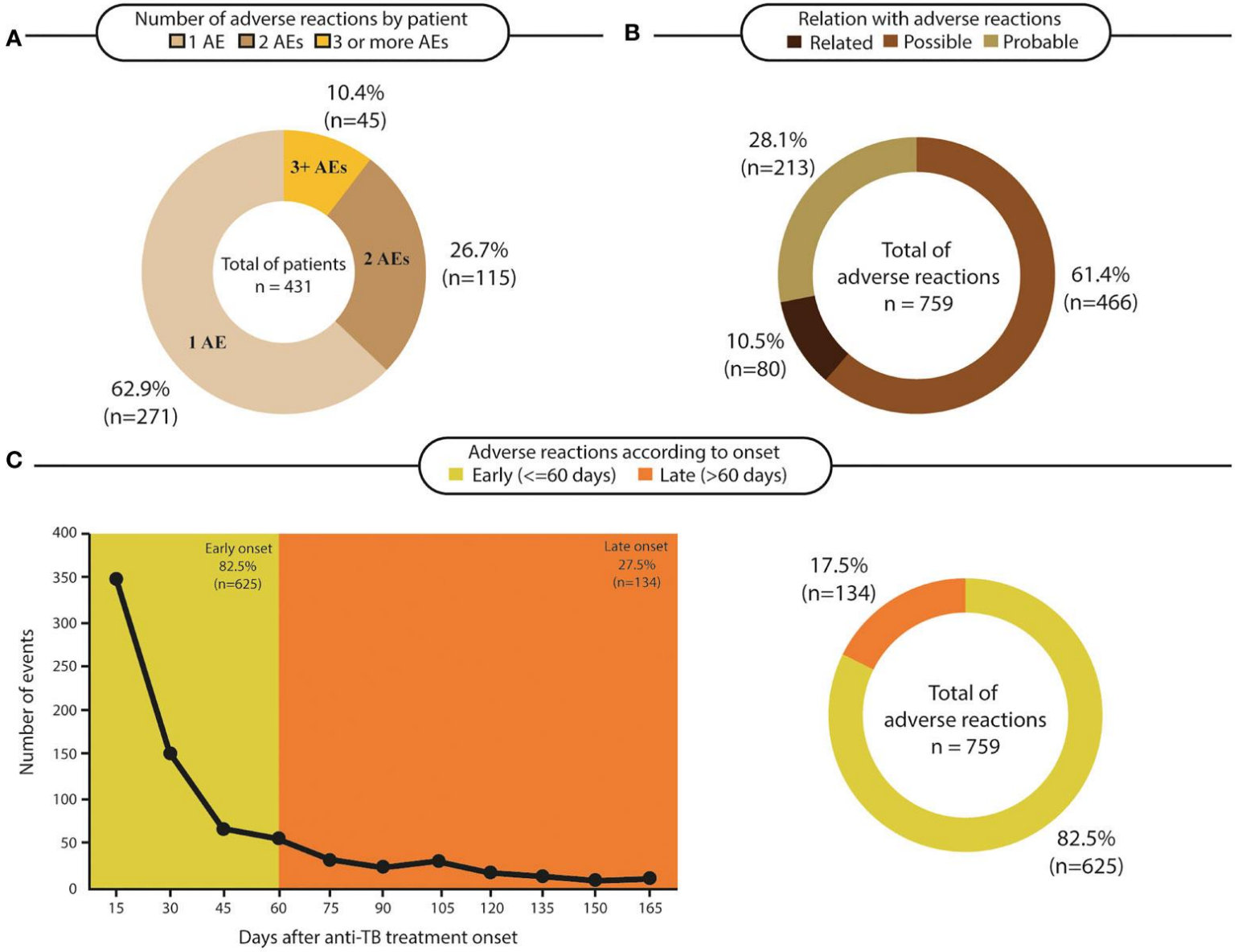
Describe the burden of adverse drug reactions during TB treatment

Apply a general approach to managing Adverse TB drug reactions

The Magnitude of the problem

Drug-Susceptible Tuberculosis

First-line drugs
INH/RIF/EMB/PZA X 2 months
INH/RIF X 4 months



Adverse Drug Reactions Related to Treatment of Drug-Susceptible Tuberculosis in Brazil: A Prospective Cohort Study

https://www.frontiersin.org/articles/10.3389/fitd.2021.748310
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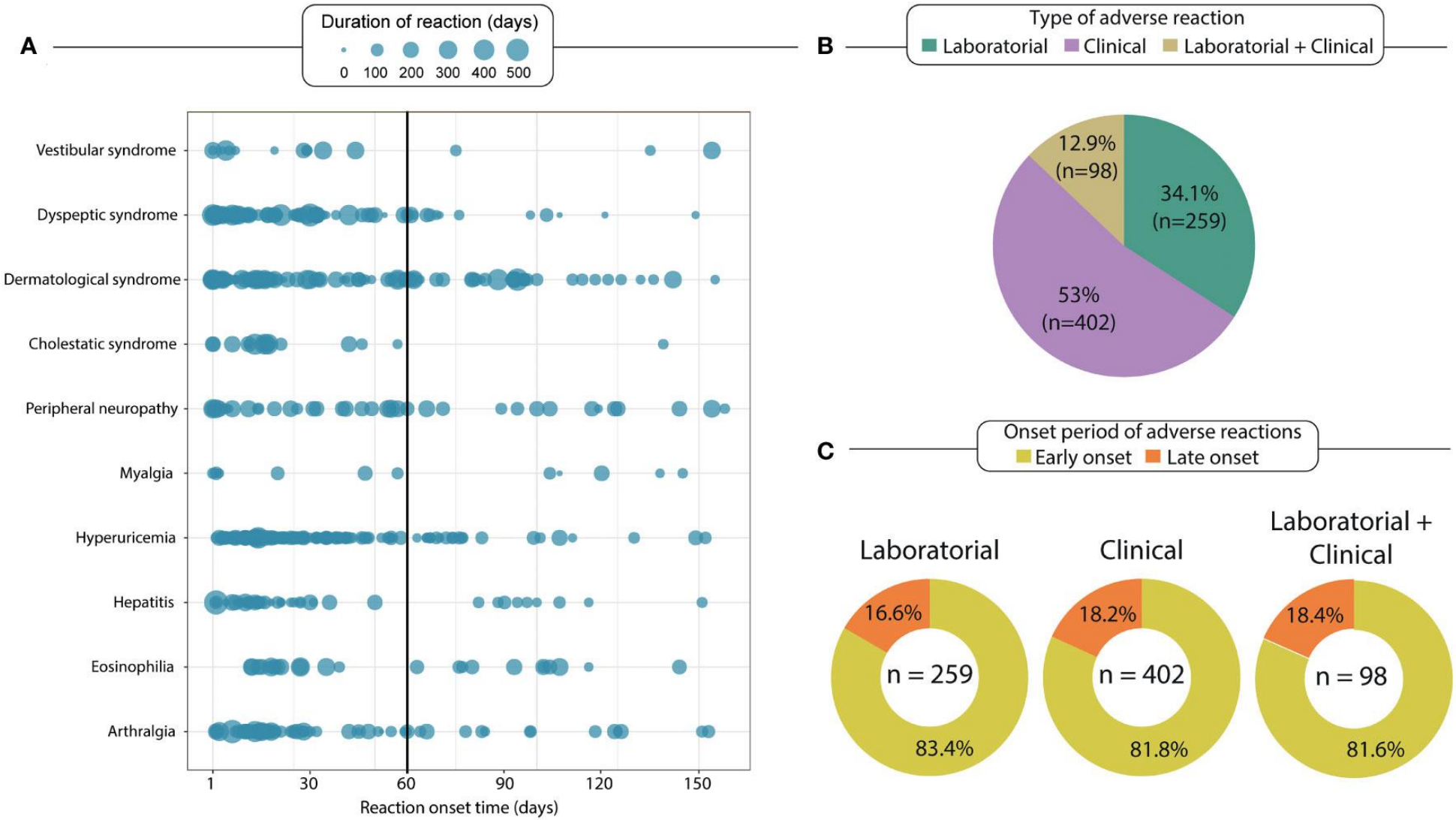

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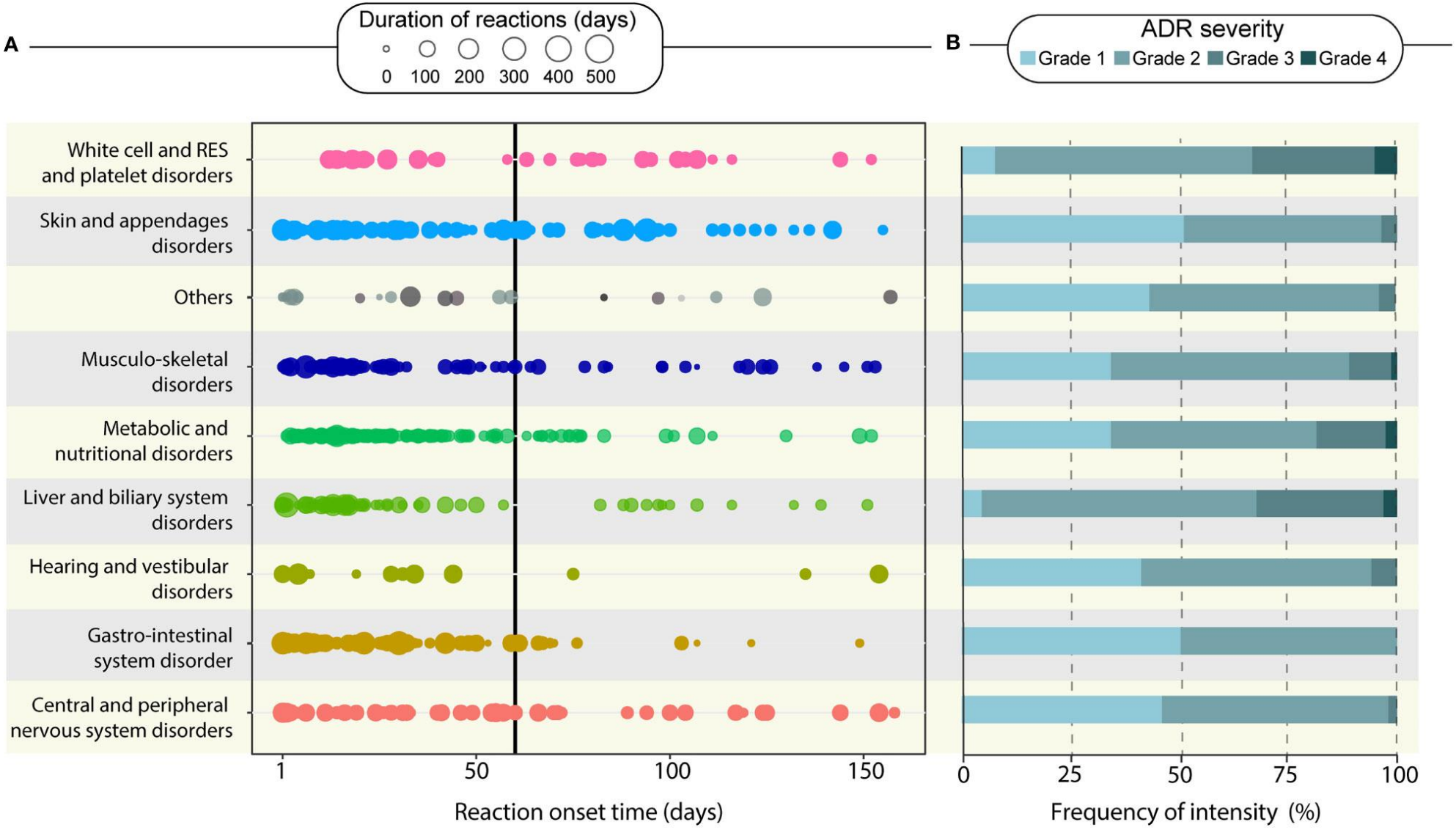

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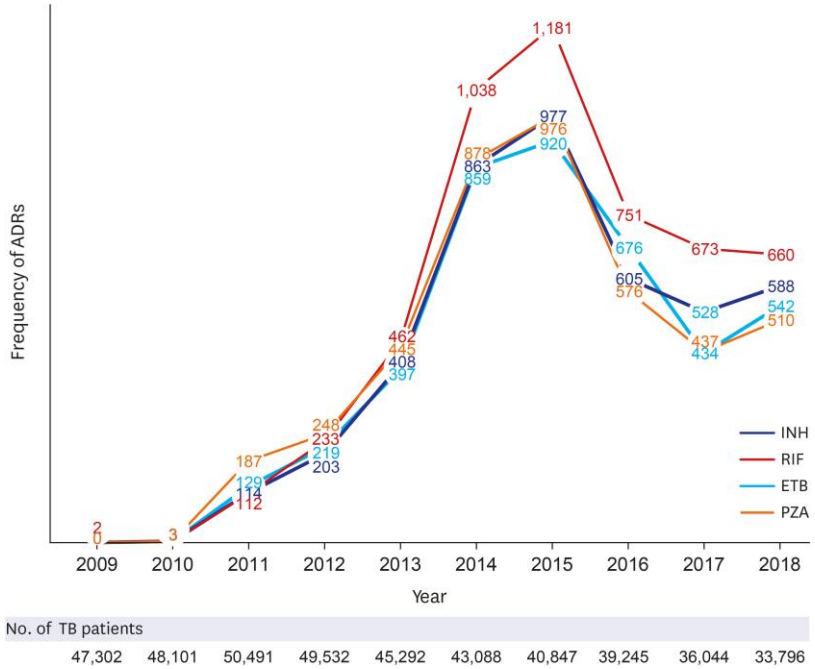
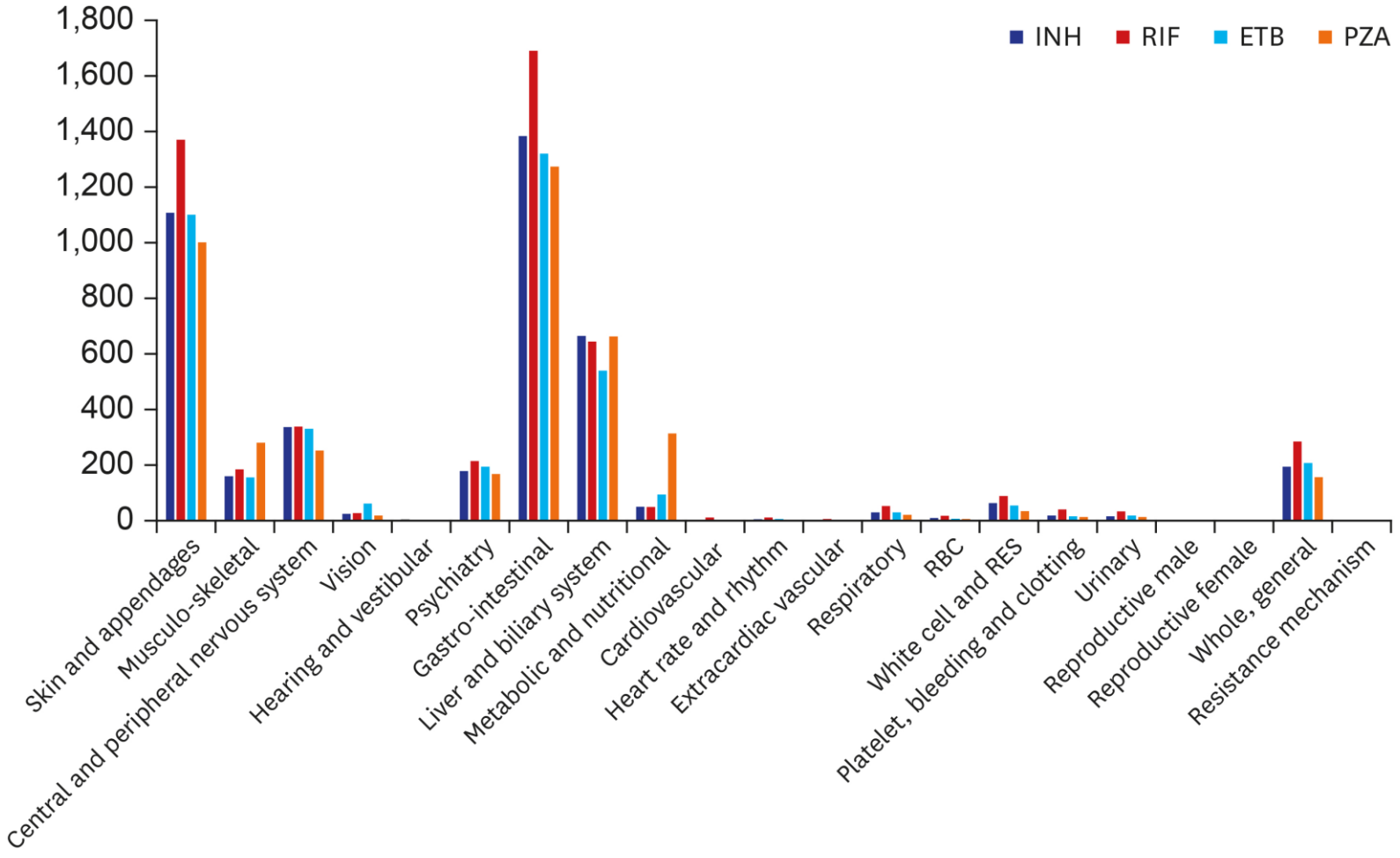
ADRs to first-line anti-TB drugs from 2009 to 2018.





J Korean Med Sci 2022 Apr;37(16):e128. https://doi.org/10.3346/jkms.2022.37.e128

Classification of Drugs for Treatment of Drug-Resistant TB

Group A	Group B	Group C
levofloxacin or moxifloxacin	clofazimine	Ethambutol
bedaquiline	cycloserine or terizidone	delamanid
linezolid		pyrazinamide
		imipenem-cilastatin or meropenem
		amikacin (or streptomycin)
		ethionamide or Prothionamide
		p-aminosalicylic

Number of Drugs for Intensive and Continuation Phase

2019 ATS/CDC/ERS/IDSA Treatment of DR-TB guidelines recommend:

(Conditional recommendations, very low certainty of evidence)

- **At least 5 drugs should be used in the intensive phase and 4 drugs in the continuation phase of treatment of MDR-TB.**
- Drugs of poor or doubtful efficacy should not be added to a regimen purely to ensure that the recommended number of drugs is obtained.

Duration for Intensive and Continuation Phase

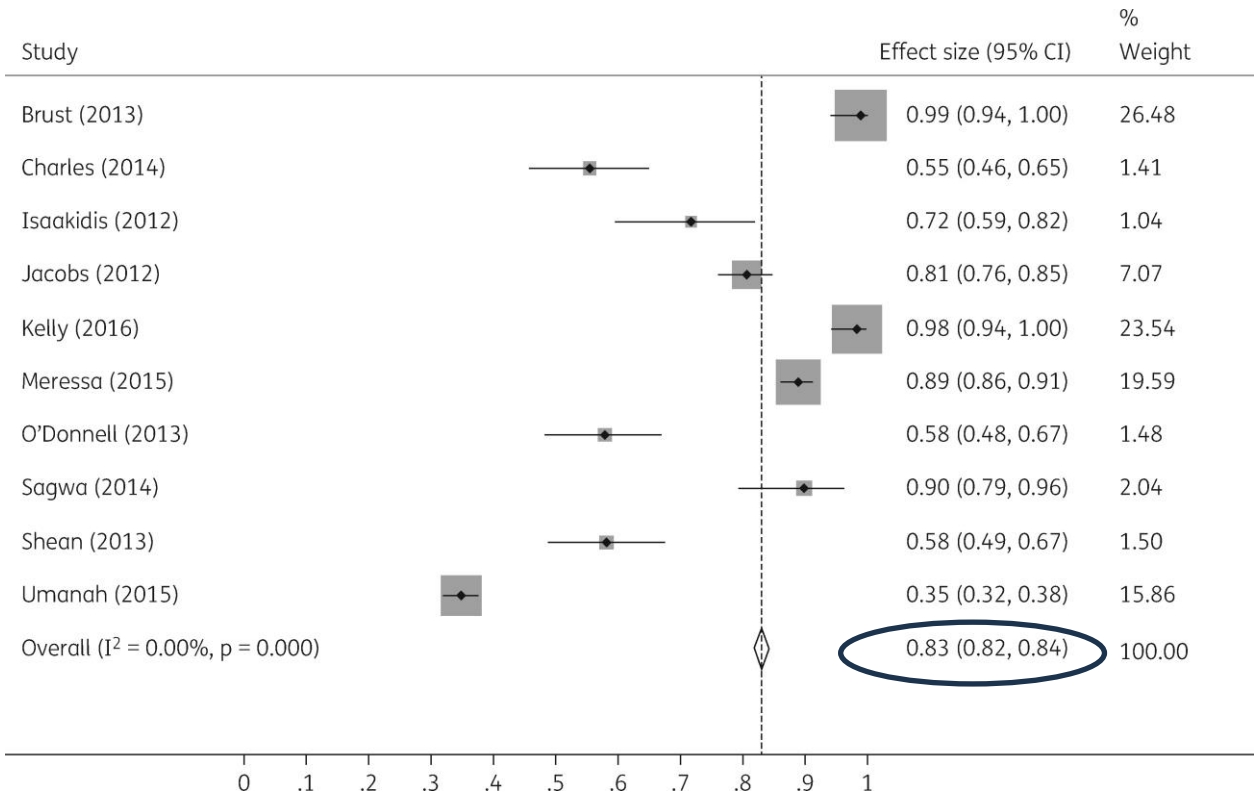
When using an individualized, longer treatment strategy:

2019 ATS/CDC/ERS/IDSA Treatment of DR-TB guidelines recommend:

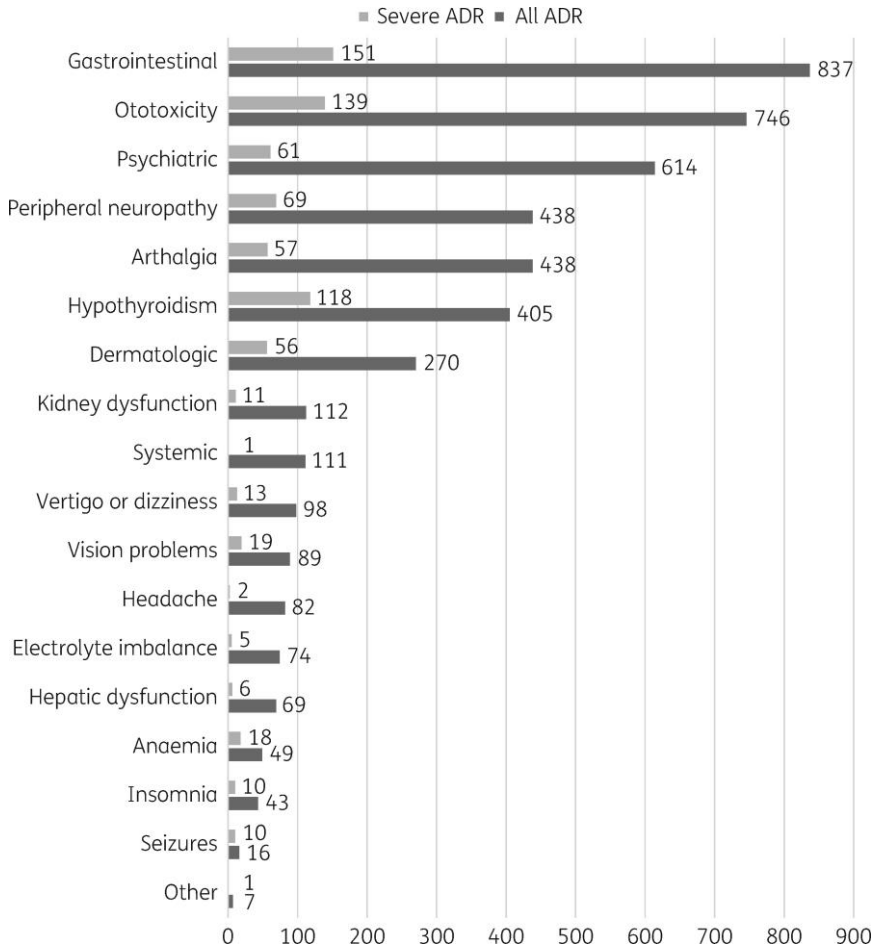
(Conditional recommendations, very low certainty of evidence)

- **Intensive phase duration:** 5-7 months beyond culture conversion in patients with MDR-TB
- **Total treatment duration:** at least 15-21 months after culture conversion in patients with MDR-TB
- In patients with **pre-XDR or XDR-TB**, a total treatment duration of between 15-24 months is suggested

Proportion of patients experiencing one or more ADR during treatment of drug-resistant TB.



Frequency of all ADR and severe ADR reported by type. 4498 events across 4274 patients from 18 studies



J Antimicrob Chemother, Volume 72, Issue 7, July 2017, Pages 1871–1879, https://doi.org/10.1093/jac/dkx107

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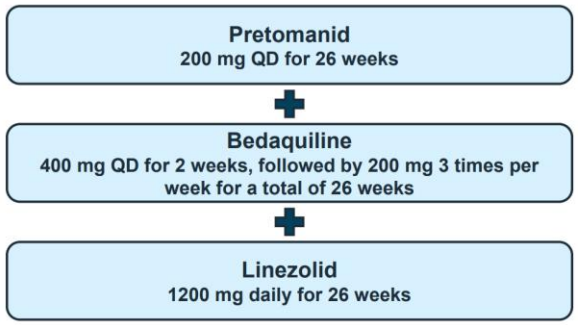
BPaL/M

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

Nix-TB: Adverse Events



Adverse Events	BPaL Regimen N=109 n (%)
Any AE	109 (100)
SAE	19 (17)
AEs by severity	
Grade 1	8 (7)
Grade 2	43 (39)
Grade 3	41 (38)
Grade 4	17 (16)

Adverse Events	BPaL Regimen N=109 n (%)
Peripheral sensory neuropathy	75 (69)
Anemia	40 (37)
Nausea	40 (37)
Vomiting	37 (34)
Headache	28 (26)
Dermatitis acneiform	26 (24)
Dyspepsia	26 (24)
Decreased appetite	24 (22)
Pleuritic pain	20 (18)
Upper respiratory tract infection	20 (18)
Gamma-glutamyltransferase increased	18 (17)
Rash	17 (16)

DRUG THERAPY

TUBERCULOSIS

Very Common

A general approach to managing drug adverse reactions during the treatment of tuberculosis

Adverse Reactions to Anti-TB Drugs

Drug	Adverse Reaction	Signs and Symptoms
EMB	Eye damage	• Blurred or changed vision • Changed color vision
INH	Nervous system damage	• Dizziness • Tingling or numbness around the mouth
	Peripheral neuropathy	• Tingling sensation in hands and feet
PZA	Stomach upset	• Stomach upset • Vomiting • Lack of appetite
	Gout	• Abnormal uric acid level[b] • Joint aches
RIF	Bleeding problems	• Easy bruising • Slow blood clotting
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses
	Drug interactions	• Interferes with certain medications (e.g., birth control pills, birth control implants, certain ART medications, or methadone treatment)
	Sensitivity to the sun	• Frequent sunburn

Drug	Adverse Reaction	Signs and Symptoms
Any drug	Allergic	• Skin rash
INH PZA RIF	Hepatic toxicity	• Abdominal pain • Abnormal liver function test results •Fever for ≥3 days • Flu-like symptoms • Lack of appetite • Nausea • Vomiting • Yellowish skin or eyes

Case

A 24year old female with systemic lupus erythematosus (SLE)

On high dose prednisolone and chloroquine phosphate

Presented with dry cough, fever, and weight loss for two months.

CXR – right upper lobe consolidation

GeneXpert +, no rifampin resistance

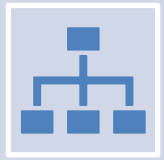
Baseline liver enzymes, renal function test, serum electrolytes were within normal range.

No other co-morbidities

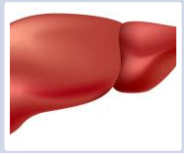
Started with Rifampin, isoniazid, ethambutol, and pyrazinamide

Case: History of Present Illness

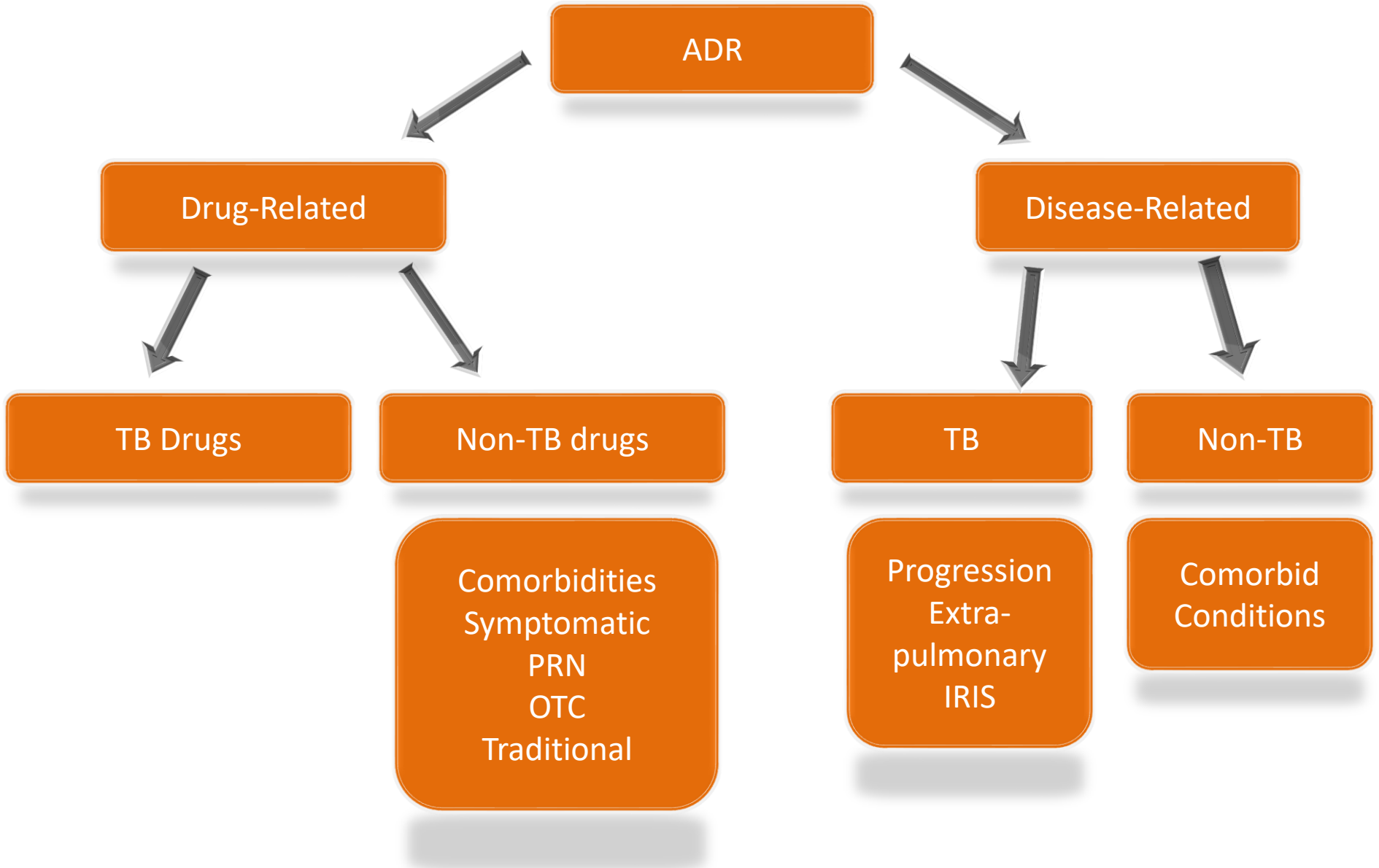
Complaints of nausea, vomiting and right upper quadrant pain of a week duration.



WBC: 6.8, Hgb 11.9, PLT 120,000.



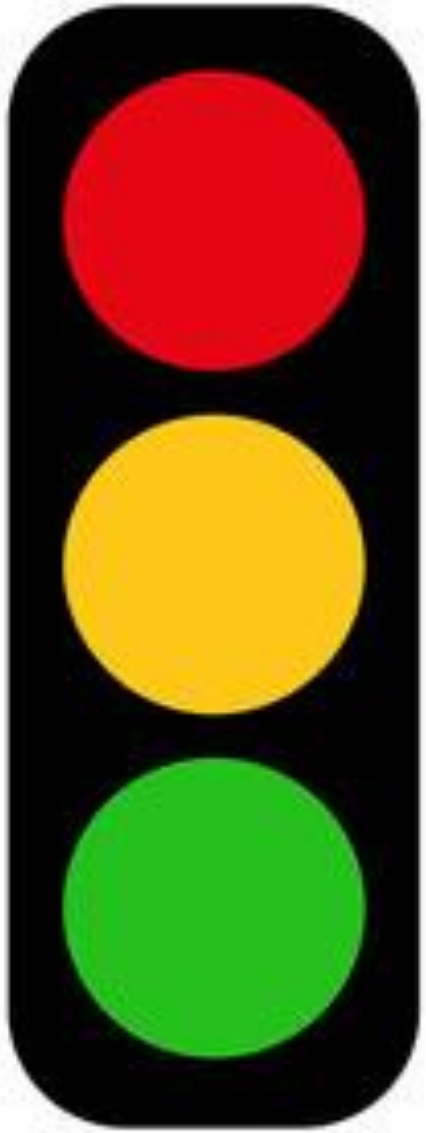
Liver enzymes: ALT - 589, AST-431, Bilirubin (total 6 and direct 2.2).


ADR
Drug-Related
Disease-Related
TB Drugs
Non-TB drugs
TB
Non-TB
Comorbidities
Symptomatic
PRN
OTC
Traditional
Progression
Extra-
pulmonary
IRIS
Comorbid
Conditions

Evaluation

Severity	• Urgent Evaluation vs Monitor
Cause	• Medication vs Other
Response	• Next Steps

Stopping Rules



NAUSEA AND VOMITING GRADING SCALE NCI CTCAE (Version 4.03)					
	GRADE 1 (Mild)	GRADE 2 (Moderate)	GRADE 3 (Severe)	GRADE 4 (Life Threatening)	GRADE 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feedings, TPN or hospitalization may be indicated	–	–
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hours	3-5 episodes (separated by 5 minutes) in 24 hrs	≥ 6 episodes separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death

Managing ADR

- Depends on severity
- Simple measures and reassurance may suffice
- Life-threatening will require discontinuation of entire regimen
- Monitor AE until resolution

Nausea/Vomiting: Self-care

- Eat small, bland meals served cool. i.e. rice, crackers, toast.
- Sip water and other fluids
- Maintain oral hygiene
- Restrict fluids with meals
- Avoid alcohol and tobacco
- Avoid lying down after eating-sit upright 30-60 minutes
- May need anti-emetics and/or anti-nausea medication

Hepatotoxicity: Potential Causes

	ALT	ALP/Bili	Comments	Onset
Viral Hepatitis	X	-	Acute vs Chronic	
Biliary Tract Disease	-	X		
Alcohol	X	-	AST:ALT >2	
Other drugs (APAP, statins, herbal supplements)	X	-	Variable	
Rifampin	X	X	Mixed	1-6 weeks
Isoniazid	X	-	Hepatocellular	2-26 weeks
Pyrazinamide	X	-	Hepatocellular	4-8 weeks

Clin Infect Dis. 2016; 63(7): e147–e195.
Am J Respir Crit Care Med2006; 174:935–52.
LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/

LFT Monitoring AND CUT-OFFS FOR STOPPING DRUGS

Authority	Monitoring in presence of risk factors (especially liver diseases)	Cut-off levels for DILI and stopping drugs
ATS	Yes	ALT >200 IU/l or, ALT 120 IU/l with symptoms
BTS	Yes	ALT or AST >200 IU/l, rise in bilirubin
ERS, WHO, IUATLD	-	AST > 200 IU/l
HKTBS	Yes	ALT >200 IU/l , bilirubin > 40µmol/l

LFT, liver function test; ALT, alanine transaminase; ALP, alkaline phosphatase; ATS, American Thoracic Society; BTS, British Thoracic Society; ERS; European Respiratory Society; WHO, World Health Organisation; IUATLD, International Union Against Tuberculosis and Lung Disease; HKTBS, Hong Kong Tuberculosis Service

Resumption of treatment

- ADR needs to be resolved
- The ultimate aim of drug reintroduction is to establish an effective regimen in a safe and speedy fashion.
- Sequential reintroduction may help identify the cause
- Different algorithms exist
- Symptomatic pre/peri treatment may be necessary

GUIDELINES ON THE MNAGEMENT OF TB-ASSOCIATED DILI

Authority	Stopping TB drugs if clinical or symptomatic hepatitis	When to restart TB drugs	What TB drugs to start	Recommended LFT monitoring on rechallenge	What if DILI recurs
ATS	Yes	ALT < 80	R +/- E full dose After 3-7 days H (full dose) Z only if mild DILI	Check ALT 3-7 days after H rechallenge	Stop last drug added
BTS	Yes	ALT within normal limits	S + E (if unwell or sputum smear positive within two weeks of commencing treatment) H (dose titration, every 2-3 days) R (dose titration, every 2-3 days) Z (dose titration, every 2-3 days)	Daily monitoring of LFT	Stop offending drug, alternative regimen advised by fully trained physician
ERS, WHO, IUATLD	Yes	LFT within normal limits	Start all drugs at full dosage	LFT monitoring (no recommendation on frequency)	Stop all drugs, start S + E and start other drugs one at a time
HKTBS	Yes	-	-	-	-

WHICH RECHALLENGE PROGRAM IS BEST

175 HIV-negative patients randomized to receive one of three rechallenge regimens

Study arm	Regimen
Arm I	H, R, and Z at maximum dosages from day 1
Arm II	R at maximum dosage from day 1, H at maximum dosage from day 8, and Z at maximum dosage from day 15
Arm III	H at dosage of 100 mg/day from day 1, maximum dosage from day 4; R at dosage of 150 mg/day from day 8, maximum dosage from day 11; and Z at dosage of 500 mg/day from day 15, maximum dosage from day 18

NOTE. Maximum dosage was determined according to body weight, as follows: H, 5 mg/kg; R, 10 mg/kg; and Z, 25 mg/kg. H, isoniazid; R, rifampicin; Z, pyrazinamide.

No significant difference in recurrence rate (p=0.69)

Sharma SK et al. Clin Infect Dis 2010;50(6).

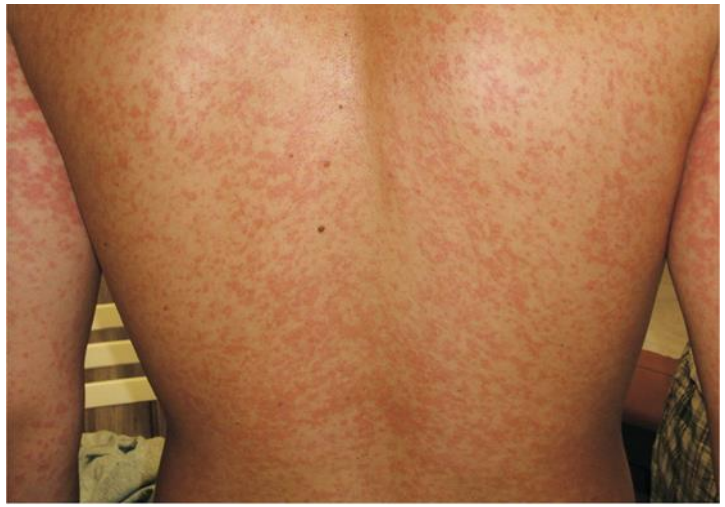
Case 2: Rash

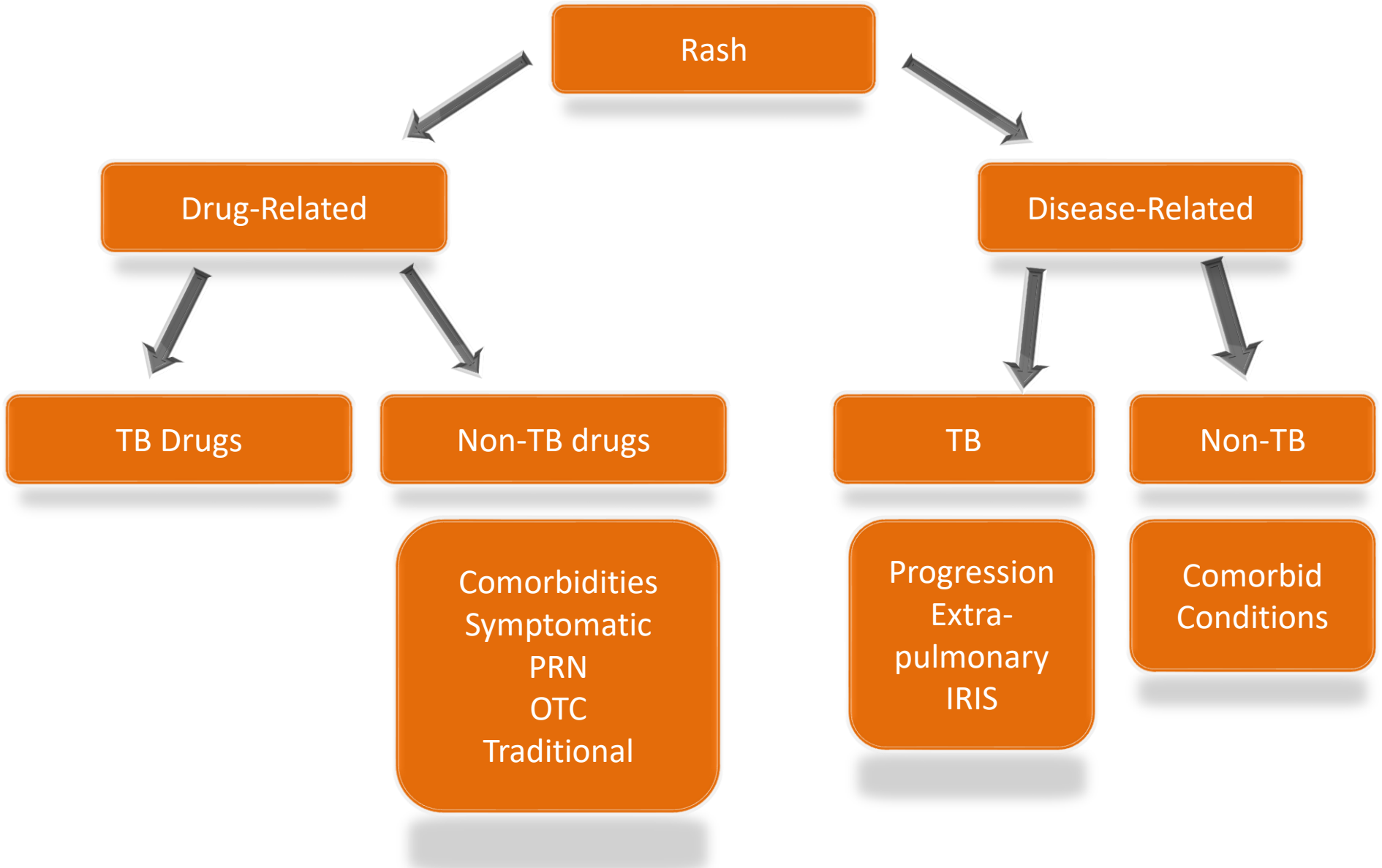
Case 2: Background

- A-30-year-old male diagnosed with HIV 6 years ago
  - On dolutegravir/tenofovir/lamivudine since diagnosis, same dose
- Three weeks ago, diagnosed with pulmonary tuberculosis after he presented with cough, night sweats and chest pain.
  - CXR – right upper lobe consolidation
  - Sputum smear negative
  - Started on rifampin, isoniazid, pyrazinamide, ethambutol, and pyridoxine

Case 2: History of Present Illness

- Developed a progressive, pruritic rash spreading from his trunk and covering most of his body, but sparing his face, palms and soles.
- Physical exam
  - No fever, Vitals stable
  - No oral lesions
  - Maculopapular rash trunk and extremities

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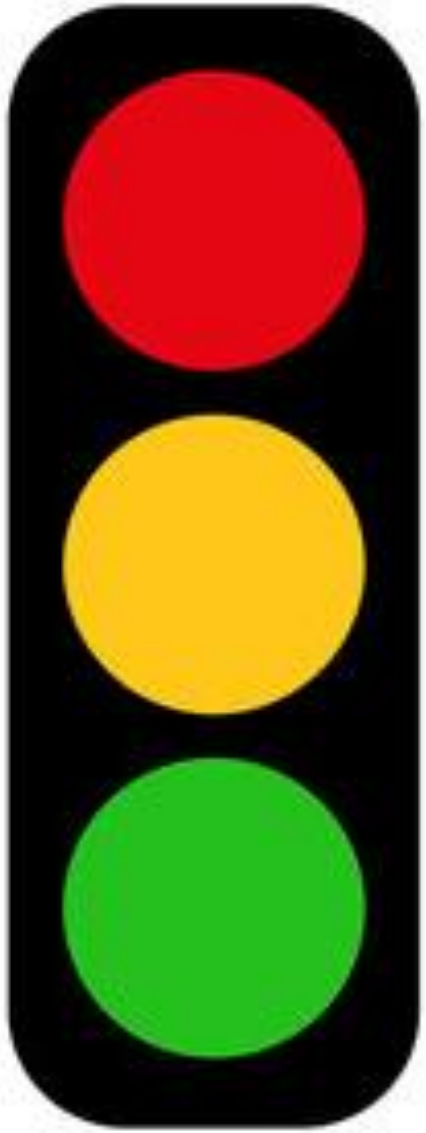
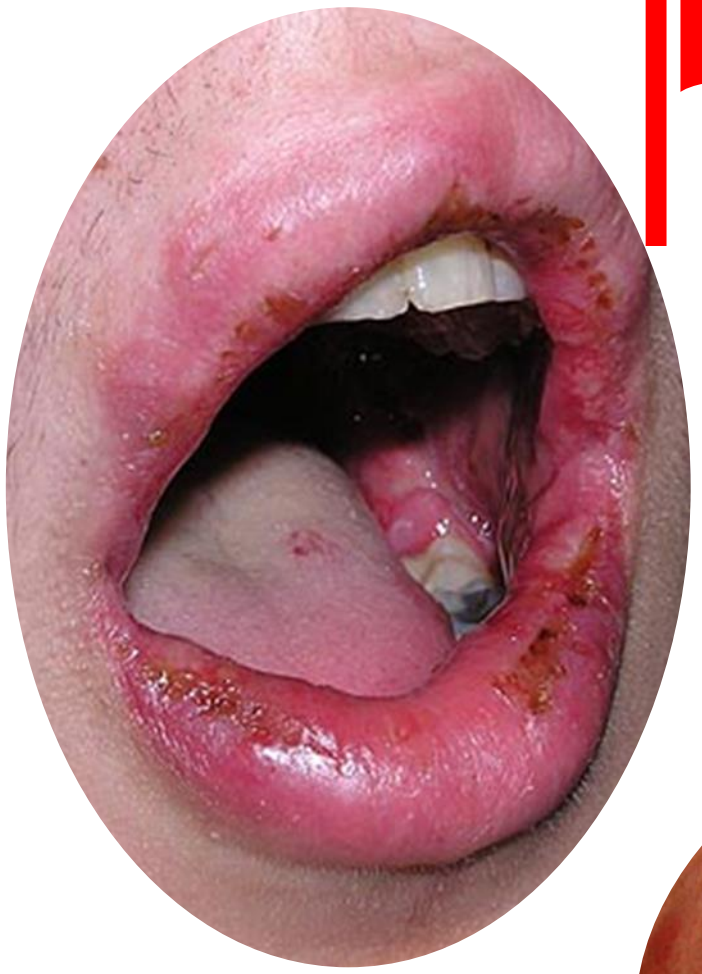
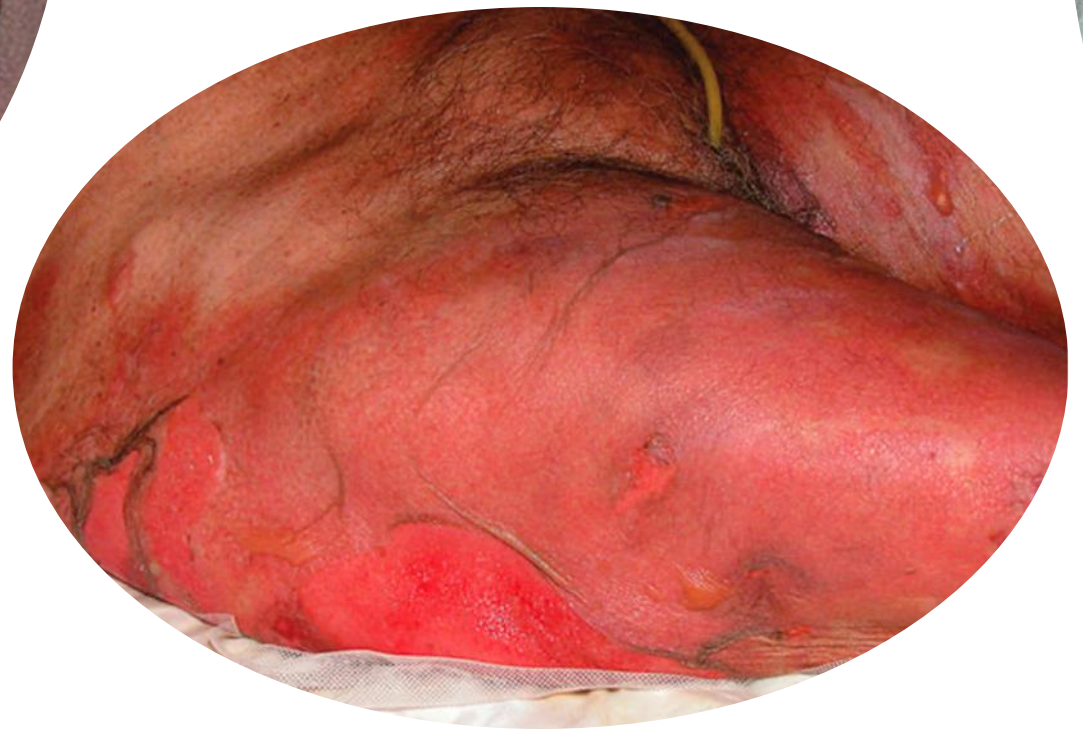
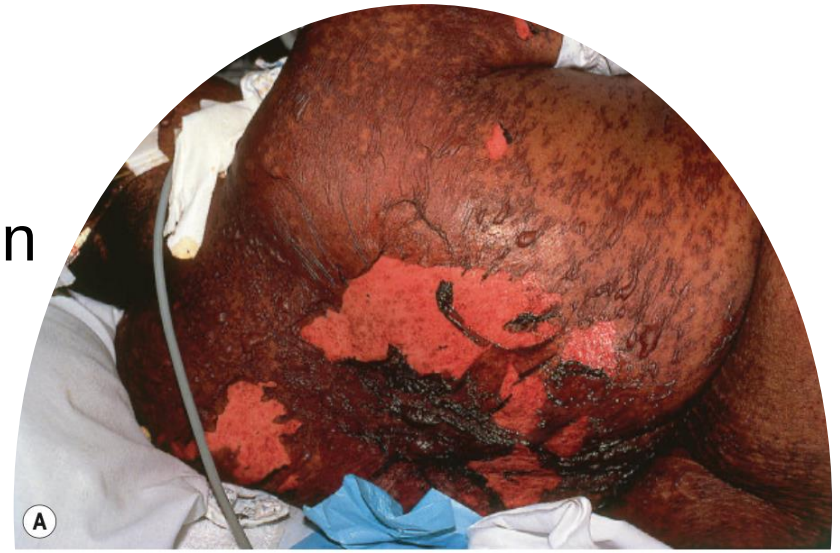
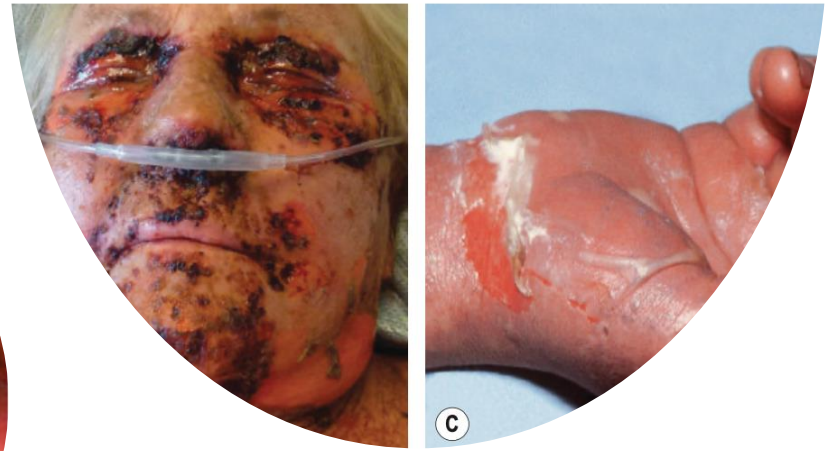




- Fever
- Mucosal involvement
- Painful rather than pruritic skin
- Epidermal detachment or blistering
- Organ involvement







Rash: General Principles of Management

Discontinuation of the offending agent, if possible.

Treatment of is generally supportive: self management, symptomatic treatment

Life-threatening reactions will require discontinuation of entire regimen

Prompt treatment with antihistamines, systemic corticosteroids, fluid replacement, pain control

Rash: Self-Management

- **Avoid rubbing and scratching.**
- **Avoid irritants.** Choose mild, unscented, laundry detergent. Wear cotton clothing.
- **Apply cool, wet compresses.**
- **Warm bath.**
- **Moisturize your skin.**
- **Nonprescription anti-inflammation and anti-itch products.**

Resumption of treatment

- ADR needs to be resolved
- The ultimate aim of drug reintroduction is to establish an effective regimen in a safe and speedy fashion.
- Sequential reintroduction may help identify the cause
- Different algorithms exist
- Symptomatic pre/peri treatment may be necessary

Resumption of Treatment: Considerations

- Ideally, in a controlled environment
- In which sequence should the drugs be introduced?
  - With the most likely culprit?
  - With the least likely culprit?
- Should we use incremental or full doses of each drug during reintroduction?

Drug	Trial dose	Trial dose 2	Trial dose 3
H	50 mg	Full dose	Full dose
R	75 mg	300 mg	Full dose
Z	250 mg	1000 mg	Full dose
E	100 mg	500 mg	Full dose

MSF TB guidelines
https://medicalguidelines.msf.org/en/viewport/TUB/english/introduction-20320166.html

A lead-in period of a long-acting, non-sedating antihistamine (cetirizine 10mg given daily)

25 diphenhydramine given 30-45min prior to administering the drug.

Summary

- Adverse Events during the Treatment of TB are very common
- Even mild and common events can affect treatment outcomes
- Some adverse events can be life-threatening
- Some adverse events cause permanent disability
- Timely recognition and management of adverse events important for adherence and completion of treatment
- Critical drugs may be discarded if not properly addressed
- A multi-disciplinary, thoughtful, and coordinated approach essential for success

Thank you