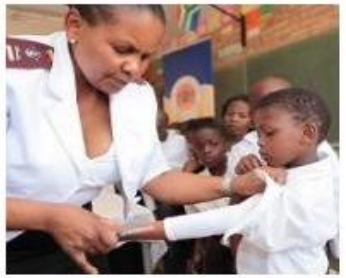
Drug-Induced Liver Injury in AHD



Facilitator Slide Pack

Updates on the 2026 National Consolidated Guidelines for the Prevention and Management of HIV

Session 2 · Drug-Induced Liver Injury · Tuesday 25 August 2026 · 13h00–15h00 SAST

Consolidated Guidelines pp. 108–110 (Tables 35 & 36) · SAHCS DILI Guideline 2024

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DILI — Recognition, Classification, Management & Re-challenge

If you see a patient on TB treatment with rising liver enzymes, what is your first question?

Talking point 1 — When to suspect AT-DILI and the three diagnostic criteria

Suspect AT-DILI: patient on TB treatment + (1) hepatitis symptoms (jaundice, nausea, vomiting, fatigue, RUQ pain, pale stools) OR (2) new rash (systemic hypersensitivity) → Do LFTs and INR IMMEDIATELY

DILI criteria — met if ANY ONE is present:

1	ALT > 120 IU/L (or > 3× ULN) WITH symptoms or jaundice OR total bilirubin > 40 µmol/L
2	ALT > 200 IU/L (or > 5× ULN) regardless of symptoms
3	Known liver disease OR baseline ALT > 120 IU/L — AND ALT now > 2× baseline

If criteria NOT met — two separate branches: (a) Total bilirubin > 2× ULN with ALT < 3× ULN → continue TB treatment, repeat LFTs in 1 week; if bilirubin > 5× ULN (>100 µmol/L) discuss with an expert. (b) Isolated GGT/ALP elevation → continue TB treatment, investigate TB-IRIS or biliary obstruction, do HBsAg, consider abdominal ultrasound, repeat LFTs in 1 week. (c) ALT < 3× ULN with no symptoms → continue TB treatment, repeat LFTs in 1 week.

Definitive AT-DILI = no other diagnosis found AND ALT decreases after TB treatment interruption. All initial diagnoses are PRESUMPTIVE.

Talking point 1b — Abnormal LFTs that are NOT AT-DILI

Not every enzyme rise on TB treatment is DILI. Anti-tuberculous drugs also cause HEPATIC ADAPTATION — a transient, asymptomatic, low-grade transaminase rise that settles while the drug is continued and needs no intervention. Stopping TB treatment for adaptation deprives the patient of effective therapy.

Three patterns that do NOT meet AT-DILI criteria:

1. **Hepatic adaptation** — rifampicin causes mild, transient, asymptomatic transaminase elevation in up to 20% of patients in the first 2 weeks. Isoniazid, pyrazinamide and the fluoroquinolones do the same. Continue treatment and monitor.

2. **Isolated hyperbilirubinaemia** — total bilirubin >40 µmol/L (>2× ULN) with all other LFTs normal. Usually benign and temporary: rifampicin interferes with bilirubin transport. Continue TB treatment, repeat LFTs weekly; if bilirubin rises above 100 µmol/L (>5× ULN) discuss with an expert. If it persists beyond a few weeks, consider cholestatic hepatitis.

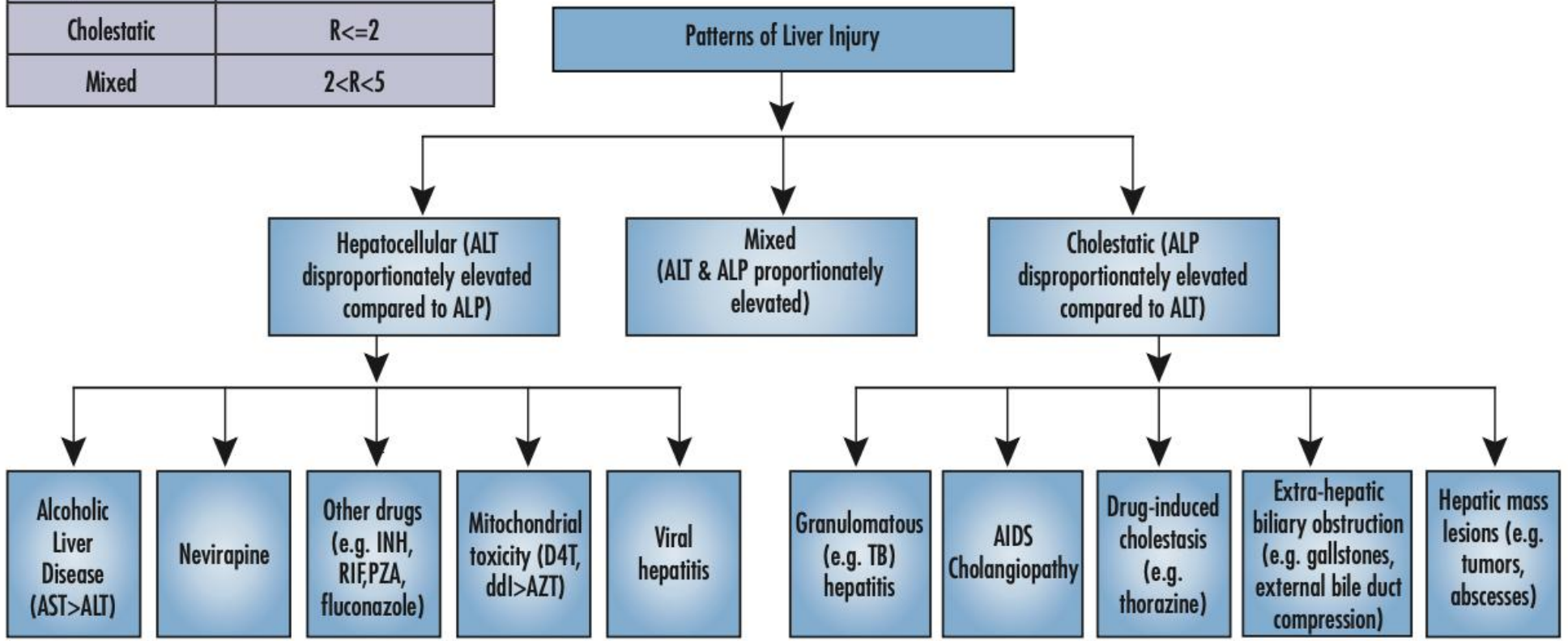
3. **Cholestatic pattern** — raised ALP and/or GGT, often with raised bilirubin, but ALT <120 IU/L (<3× ULN). The differential is broad: TB-IRIS and biliary obstruction are more likely than TB drugs, and co-trimoxazole and fluconazole also cause cholestasis. Continue TB treatment, do an abdominal ultrasound, discuss if no cause is found.

Levofloxacin — used in the DILI background regimen — itself causes a transient transaminase rise in 1–3% of patients; moxifloxacin more often than levofloxacin.

Baseline LFTs are not routine. Do them where risk factors are present: HIV, hepatitis B or C, chronic liver disease, high alcohol intake, malnutrition, low BMI, older age, female sex. In children, low albumin is a specific risk factor.

Talking point 1C — Pattern of Hepatic Enzyme Elevation

Pattern	(ALT/ULN)/(ALP/UL N)=R
Hepatocellular	R>=5
Cholestatic	R<=2
Mixed	2<R<5



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Antiretroviral Therapy in South Africa: A Pocket Guide on Prevention and Management of Side Effects and Drug Interactions. Second Edition, 2009 Published by the National Department of Health, South Africa.

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Talking point 2 — AT-DILI vs TB-IRIS: the critical distinction

The management is OPPOSITE: AT-DILI → STOP TB drugs. TB-IRIS → CONTINUE TB treatment. Confusing the two can be fatal in either direction. CAUTION: rifampicin itself can cause a cholestatic or mixed picture, and co-trimoxazole and fluconazole also cause cholestasis — an ALP/GGT-dominant pattern raises the probability of IRIS, it does not prove it.

Feature	AT-DILI	TB-IRIS
Hepatomegaly	Absent	Present
Jaundice	Common	Uncommon
Dominant LFT elevation	ALT / AST ↑↑	ALP / GGT ↑↑
Other IRIS features	Absent	Present — lymphadenopathy, worsening OI
Context	TB drugs toxic to hepatocytes	Immune system reacting to TB antigens after ART
Correct management	**STOP TB treatment**	**CONTINUE TB treatment and ART**

Talking point 3 — DILI classification and 7-step immediate management

DILI severity classification:

Mild	**No symptoms + INR < 1.5**
Moderate	**Symptoms present + INR < 1.5**
Severe	**INR > 1.5 — regardless of symptoms**

7-step immediate management:

1	Admit. Mild DILI may be outpatient ONLY if results are back within 24 h and follow-up is reliable (SAHCS)
2	Review ALL medications
3	Stop TB treatment. Intensive phase background: Hb ≥8 → **EMB+LFX+LZD**; Hb <8 → CFZ or TRD instead of LZD
4	Consider stopping ART: <6m → interrupt. DTG >6m → continue. LPV/r or EFV → switch to DTG. DRV/r or ATV/r → stop ART; use RIFABUTIN on re-challenge
5	Stop other hepatotoxins incl. co-trimoxazole. Fluconazole for CM: stop ONLY if CD4 >200 AND on maintenance. Counsel on OTC/herbal medicines
6	Review the TB diagnosis. If not microbiologically confirmed and now unlikely → stop TB treatment, do NOT re-challenge
7	Investigate other causes: children → Hep A. Adults → Hep A, B and E

Talking point 3b — Supportive care: what to do, and what NOT to do

Once TB drugs are stopped, most of the work is monitoring and exclusion — not treatment. Search actively for alternative causes and exacerbating factors, including viral hepatitis and a full medication history covering over-the-counter, herbal and traditional medicines.

Three things that are often missed:

1	Pregnancy test every woman of childbearing potential. Liver disease in pregnancy can be more severe, and a positive test means escalation to a higher level of care. This is a strong SAHCS recommendation and it is routinely skipped.
2	Do NOT routinely give vitamin K, lactulose, antibiotics, glucose monitoring or specific nutritional support in mild or moderate AT-DILI. Abdominal ultrasound is usually unhelpful except where the pattern is cholestatic.
3	N-acetylcysteine: a South African randomised trial found no difference in time to ALT <100 IU/L or in mortality, but a shorter median time to discharge (9 vs 18 days). NOT recommended in mild or moderate DILI; may be used in severe DILI on specialist advice only.

In severe DILI (INR >1.5): stop ALL drugs, assess for encephalopathy, and check INR AND serum glucose — hypoglycaemia in acute liver failure is treatable and easily missed. Same-day specialist contact or transfer.

Monitor ALT 2–3 times per week. A downward trend within a few days of stopping supports the diagnosis; if ALT does not fall in that time frame, reconsider the diagnosis and seek specialist advice.

Talking point 4 — TB drug re-challenge schedule and key timeframes

Pre-condition: ALT < 100 IU/L AND total bilirubin on a DOWNWARD trend (even if not yet normal). Median time to reach <100 IU/L: 8 days (IQR 5–13). Monitor ALT 2–3 times per week during recovery and re-challenge, then WEEKLY FOR 4 WEEKS after re-challenge is complete.

Day	Action	Check
Day 1	Start INH 300 mg/day (stop LZD, CFZ or TRD) → Patient on: INH + EMB + LFX	
Day 3	Check ALT — if raised: STOP INH	⚠ ALT
Day 4	Add Rifampicin 600 mg/day → Patient on: RIF + INH + EMB + LFX	
Day 7	Check ALT — if raised: STOP Rifampicin	⚠ ALT
Day 8	Decide on PZA (TBM or failed INH/RIF) • Stop LFX • Final regimen: RIF/INH/EMB ± PZA	
Day 10	Check ALT	✓ ALT

After 2 weeks stable: re-challenge ART. If ALT unchanged, re-challenge cotrimoxazole. Re-challenge order: (1) TB treatment → (2) ART → (3) Prophylaxis. Avoid EFV and LPV/r if possible.

If reintroduction fails at any step: omit that drug, wait for effects to subside, continue to the next. Hepatotoxicity usually recurs within 5–7 days of reintroduction. 20–90% of patients can have regimen 1 successfully reintroduced — but re-challenge PZA only for TBM or when INH/RIF cannot be reintroduced, as recurrence is strongly associated with PZA (SAHCS). SEVERE DILI: specialist only.

Talking point 5 — Alternative TB regimens and dosages (Tables 35 & 36)

Table 35 — If a drug is permanently not tolerated:

PZA not tolerated	RIF + INH + EMB × 2 months, then RIF + INH × 7 months (9 months total) TBM: RIF + INH + EMB + LFX × 12 months
INH not tolerated	RIF + EMB + PZA + LFX × 6–9 months (same for TBM)
Rifampicin not tolerated	Treat as RR-TB — manage per RR-TB Clinical Reference Guide TBM: RR-TB CNS regimen per Reference Guide

Rifampicin intolerance = manage as RR-TB. These patients require specialist management and the RR-TB regimen.

Table 36 — Alternative drug dosages:

Drug	Weight	Dose	Weight	Dose
EMB	< 45 kg	800 mg	> 45 kg	1200 mg
LFX	< 45 kg	750 mg	> 45 kg	1000 mg
LZD	> 30 kg	600 mg	Hb ≥8 only	(myelosuppressive)
CFZ	All weights	100 mg	Use if Hb <8	(instead of LZD)
TRD	> 35 kg	750 mg	If Hb <8	(instead of LZD)

Key facts: Hepatotoxicity usually recurs within 5–7 days of reintroduction. Median 8 days (IQR 5–13) for ALT to fall <100 IU/L. Start date of TB treatment = start date of the final tolerated regimen. Severe DILI — specialist only.

Part 2: Case Study Reviews

5 Clinical Vignettes

Case 1: Does this patient have AT-DILI?

DILI criteria | Difficulty: Foundational

Clinical vignette

Thokozile is a 34-year-old woman on rifampicin-based TB treatment for 3 weeks. Fatigue, mild nausea and right upper abdominal fullness. No jaundice. ALT 4× ULN. INR 1.2. No known baseline liver disease. Clinician says: 'ALT is not 5× ULN and there is no jaundice — she does not meet DILI criteria. Repeat LFTs next week.'

Discussion questions (5–7 minutes group work):

1. Is the clinician’s interpretation of the DILI criteria correct? Which criterion applies?
2. How should Thokozile be classified and what immediate management is required?
3. Is hospital admission necessary?

Case 1 — Model answer (facilitator only)

FACILITATOR USE ONLY — reveal only after plenary discussion

Model answers

1	No, the clinician is wrong. Criterion 1 applies: ALT >120 IU/L (>3× ULN) WITH symptoms. Thokozile has fatigue, nausea and right upper quadrant discomfort at ALT 4× ULN. Neither jaundice nor ALT >5× ULN is required once the patient is symptomatic. Repeating LFTs in a week risks progression to INR >1.5 or acute liver failure.
2	This is presumptive AT-DILI, classified as MODERATE: symptoms present with INR <1.5. Immediate management: stop TB treatment (she is at 3 weeks, so intensive phase — give a background regimen of EMB + LFX + LZD if Hb ≥8, or CFZ or TRD instead of LZD if Hb <8); review all medication including co-trimoxazole; review the TB diagnosis; test for hepatitis A, B and E; and do a pregnancy test.
3	The Consolidated Guidelines say admit. SAHCS allows mild disease to be managed as an outpatient if results are available within 24 hours and follow-up is reliable — but Thokozile is moderate, not mild, so she is admitted under either document. The diagnosis stays presumptive until ALT falls after interruption.

Most commonly missed criterion in practice. Participants default to hunting for jaundice or ALT >5× ULN and miss the symptomatic patient at 3–5× ULN.

Counter-check: had she been asymptomatic at ALT 4× ULN, criteria would NOT be met — continue TB treatment and repeat LFTs in one week (see Talking point 1b).

Case 2: DILI or TB-IRIS?

DILI vs IRIS | Difficulty: Intermediate

Clinical vignette

Sibusiso (CD4 55 cells/mm³) started ART 3 weeks after initiating TB treatment. Six weeks in, he presents with worsening fever, rapidly enlarging cervical lymph nodes, and rising liver enzymes: ALT 2.5× ULN, ALP 4× ULN, GGT 5× ULN. Mild hepatomegaly. No jaundice. Total bilirubin 1.5× ULN. The nurse asks whether TB treatment should be stopped.

Discussion questions (5–7 minutes group work):

1. Do the LFT results meet AT-DILI criteria? What does the enzyme pattern suggest?
2. What is the more likely diagnosis, and what features support this?
3. What is the danger of stopping TB treatment in this patient?

Case 2 — Model answer (facilitator only)

FACILITATOR USE ONLY — reveal only after plenary discussion

Model answers

1 No. ALT is 2.5× ULN — below the 3× threshold — and there is no jaundice, so no DILI criterion is met. The pattern is ALP/GGT-dominant with only modest transaminase rise: a cholestatic rather than hepatocellular picture.

2 Paradoxical TB-IRIS is the more likely diagnosis. Supporting features: CD4 55, ART started only 3 weeks after TB treatment, presentation at 6 weeks, rapidly enlarging cervical nodes, fever, hepatomegaly, and ALP/GGT predominance. Continue TB treatment AND ART; consider prednisone 1.5 mg/kg/day weaned over 4 weeks for severe paradoxical TB-IRIS.

3 Stopping TB treatment would remove effective therapy from a patient with a CD4 of 55 and active TB, while doing nothing for the immune-mediated process actually driving his deterioration. Meanwhile: continue TB treatment, do HBsAg, consider abdominal ultrasound, and repeat LFTs in one week.

CAUTION for the debrief: the ALP/GGT rule raises the probability of IRIS but does not prove it. Rifampicin itself can be cholestatic or mixed, and co-trimoxazole and fluconazole cause cholestasis — exclude biliary obstruction.

IRIS is a diagnosis of exclusion. Make sure the underlying OI is correctly diagnosed and adequately treated, and exclude drug resistance, before settling on it.

Case 3: The ART decision in confirmed AT-DILI

ART management in DILI | Difficulty: Intermediate

Clinical vignette

Nomvula (41 years) has confirmed AT-DILI (ALT 7× ULN, jaundiced, INR 1.3). On TB treatment for 5 weeks and on LPV/r-based ART for 4 months. She is admitted and TB treatment is stopped. The clinician needs to make an ART decision.

Discussion questions (5–7 minutes group work):

1. Given 4 months of ART, what does the guideline recommend about ART interruption?
2. What additional ART-specific problem applies to LPV/r in this context?
3. What instructions apply to fluconazole if Nomvula was on fluconazole for CM maintenance?

Case 3 — Model answer (facilitator only)

FACILITATOR USE ONLY — reveal only after plenary discussion

Model answers

1 She has been on ART for 4 months — under 6 months — so the guideline says CONSIDER INTERRUPTION of ART. The short interruption risk is outweighed by the liver injury risk. Note the two documents differ: SAHCS would switch a PI-based regimen to an integrase inhibitor rather than interrupt, so state which you are following.

2 LPV/r is itself hepatotoxic, and with rifampicin it must be double-dosed to 800/200 mg 12-hourly — a regimen carrying a recognised additional risk of hepatotoxicity. The guideline instruction is to switch LPV/r (or EFV) to DTG. Contrast with DRV/r or ATV/r, which cannot be given with rifampicin at all: stop ART, and use RIFABUTIN instead of rifampicin on re-challenge.

3 Fluconazole may be stopped ONLY if BOTH conditions hold: CD4 >200 AND she is on maintenance (secondary prophylaxis). If she is in the intensive or consolidation phase, or CD4 <200, discuss with an expert. Premature cessation risks CM relapse. Prophylactic co-trimoxazole should also be stopped — it causes DILI with a mixed picture.

Common error: stopping fluconazole on CD4 alone. Both criteria are required. The same slide-5 step also asks you to counsel on over-the-counter, herbal and traditional medicines.

Re-challenge order after 2 weeks stable on the new TB regimen: TB treatment first, then ART, then prophylaxis. Avoid EFV and LPV/r on re-challenge if at all possible.

Case 4: Re-challenge sequence and timing

Re-challenge schedule | Difficulty: Intermediate

Clinical vignette

Lungani (46 years) had all TB treatment stopped 10 days ago. His ALT has fallen from 8× ULN to 80 IU/L (<100 IU/L) and bilirubin is on a clear downward trend. He is clinically improving. The clinician is ready to re-challenge TB treatment.

Discussion questions (5–7 minutes group work):

1. Has the pre-condition for re-challenge been met?
2. Walk through the day-by-day re-challenge sequence with ALT monitoring timepoints.
3. On Day 3, ALT rises significantly after INH introduction. What should the clinician do?

Case 4 — Model answer (facilitator only)

FACILITATOR USE ONLY — reveal only after plenary discussion

Model answers

1 Yes. Both pre-conditions are met: ALT is below 100 IU/L and total bilirubin is on a clear downward trend — bilirubin need not be normal, as it lags behind ALT and is an unreliable marker of hepatocellular recovery. His 10 days sits within the expected median of 8 days (IQR 5–13).

2 Day 1: INH 300 mg daily, stop LZD (or CFZ/TRD) — he is now on INH + EMB + LFX. Day 3: check ALT. Day 4: add rifampicin 600 mg daily — now RIF + INH + EMB + LFX. Day 7: check ALT. Day 8: decide on PZA (only for TBM, or if INH or RIF could not be reintroduced) and stop LFX. Day 10: check ALT. Then check ALT WEEKLY FOR 4 WEEKS.

3 Stop INH — it is the implicated drug. Omit it, allow the ALT to settle, then continue to the next drug in the sequence. His regimen becomes rifampicin + EMB + PZA + LFX for 6–9 months (Table 35). Document clearly which drug caused the injury: it matters for any future TB episode.

The Day 3, 7 and 10 checks are diagnostic checkpoints, not just safety checks — sequential introduction is what makes drug-specific attribution possible. Hepatotoxicity usually recurs within 5–7 days.

The start date of TB treatment is the start date of the FINAL tolerated regimen — not the original start date. This changes his completion date and is frequently recorded incorrectly.

Case 5: The patient with severe DILI

Severe DILI / specialist referral Difficulty: Advanced

Clinical vignette

Busisiwe (29 years) is admitted with jaundice, confusion and coagulopathy (INR 2.8). She is on TB treatment (week 3) and TLD (2 months). ALT 12× ULN. The admitting doctor stops all TB drugs, orders viral hepatitis serology and plans to restart TB medications in about a week. He asks the nurse to monitor and says he will review in 3 days.

Discussion questions (5–7 minutes group work):

1. Classify this DILI. What do INR 2.8 and confusion indicate clinically?
2. What critical management error has the doctor made?
3. What is the guideline recommendation for managing severe DILI and re-challenge?

Case 5 — Model answer (facilitator only)

FACILITATOR USE ONLY — reveal only after plenary discussion

Model answers

1

SEVERE AT-DILI: INR >1.5 regardless of symptoms. INR 2.8 with confusion indicates impaired hepatic synthetic function with encephalopathy — acute liver failure. This is a medical emergency with high mortality, not a ward problem to review in three days.

2

The errors are the delay and the plan to re-challenge without help. Severe DILI requires same-day specialist contact or transfer, and ALL drugs stopped — not TB drugs alone. She is on TLD for 2 months (under 6 months), so ART interruption should be considered. Serum glucose has not been checked: hypoglycaemia in acute liver failure is treatable and easily missed. A pregnancy test is also indicated.

3

Severe DILI, including re-challenge of ALL drugs, must be managed by a specialist. The day-by-day re-challenge schedule taught in this session must NOT be attempted without expert supervision, and certainly not "in about a week" on a ward round. Monitor ALT 2–3 times per week and expect a downward trend within a few days of stopping.

If ALT does not begin to fall within a few days of stopping all drugs, reconsider the diagnosis — something else may be driving the liver injury.

N-acetylcysteine is not recommended in mild or moderate DILI, but may be prescribed on specialist advice in severe AT-DILI. Do not start it independently.

Key messages

- ALT > 120 IU/L (>3× ULN) WITH symptoms = DILI criteria met. Jaundice or ALT >5× ULN are NOT required in a symptomatic patient
- AT-DILI (STOP TB drugs) vs TB-IRIS (CONTINUE TB drugs): ALT/AST dominant = DILI; ALP/GGT dominant + hepatomegaly + IRIS features = IRIS — but rifampicin, co-trimoxazole and fluconazole also cause cholestasis
- Fluconazole for CM: stop ONLY if CD4 >200 AND on maintenance phase. One criterion alone is NOT sufficient. Stop prophylactic co-trimoxazole too
- Re-challenge: INH Day 1 → rifampicin Day 4 → PZA Day 8 (TBM or INH/RIF failure only). ALT on Days 3, 7, 10, then weekly for 4 weeks
- Severe DILI (INR >1.5): URGENT specialist referral, stop all drugs, check glucose. Re-challenge in severe DILI is specialist-managed