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Key principles in the management of patients with suspected drug-induced liver injury (DILI) while on TB treatment (with or without ART)

The management of such patients is complex and usually needs to be individualised. Some of the key principles and issues in management are summarised below:

- Mild transient and asymptomatic "transaminitis" (ALT < 200) is common with the introduction of many drugs. This is known as hepatic "adaptation" and is not a reason for interrupting drugs, but patients should be monitored closely as this may evolve to significant DILI.
- Significant ALT (or bilirubin) elevations with symptoms of hepatitis (nausea, vomiting, abdominal pain, systemic symptoms) due to TB drugs or ART represent a serious clinical problem.
- The combination of significant transaminitis plus jaundice is a marker of severe DILI (mortality around 10%).
- If a patient on TB treatment and/or ART complains of hepatitis symptoms, then examine for jaundice and send blood to laboratory for urgent ALT test and follow-up of result.
- Most idiosyncratic DILI events occur within 3 months of starting the drug.
- Always consider whether the LFT derangement is due to other causes (e.g. viral hepatitis, TB or TB-IRIS involving the liver). ART can induce exacerbation of chronic viral hepatitis B and C (IRIS).
- The following TB medication is potentially hepatotoxic: Pyrazinamide (PZA), Rifampicin, isoniazid (INH).
- Nevirapine is the most hepatotoxic of the ART drugs, but Efavirenz and PI's (especially double dose Lopinavir/ritonavir) are also potentially hepatotoxic.
- Many other drugs used in HIV treatment can cause DILI (e.g. Co-trimoxazole, Fluconazole).
- The SA HIV Clinicians Society definition of TB drug DILI is (any one of the following 3 criteria define DILI):

1. ALT level > 120 AND symptomatic (nausea, vomiting, abdominal pain, jaundice)
2. ALT level > 200 even if asymptomatic
3. Total bilirubin concentration > 40

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- If patients on TB treatment fulfill the ALT definitions (1 or 2) management involves:

    - Stop potentially hepatotoxic drugs. This includes INH, rifampicin, PZA, co-trimoxazole and ART. The two NRTI drugs in the ART regimen should be continued for 5-7 days after stopping the NNRTI in a regimen to cover the NNRTI "tail"
    - While patient is off standard TB treatment use 3 alternate TB drugs and continue these as a backbone during rechallenge (3 drugs = ethambutol, moxifloxacin, kanamycin/amikacin)
    - Rechallenge when ALT <100 and jaundice resolved
    - In HIV-TB patients priority is to do TB drug rechallenge then ART
    - Rechallenge Rifampicin then INH with frequent ALT monitoring
    - PZA is generally not rechallenged, but this may be considered in patients with resistance to other drugs or TB meningitis/miliary TB, particularly if DILI occurred early during intensive phase
    - Monitor ALT weekly for 4 weeks after successful rechallenge (also monitor clinically for recurrent symptoms and jaundice)
    - Modify regimen depending on which drugs are not re-introduced successfully (see table below)
    - Restart ART drugs all at once. For ART regimen do NOT rechallenge Nevirapine, but Efavirenz rechallenge can be considered unless DILI was severe

- Consult the SA HIV Clinicians Society Consensus Statement (see below) for management of bilirubin elevations when ALT < 120 (this may be due to rifampicin, co-trimoxazole or TB/TB-IRIS of the liver, and less commonly due to the other drugs).
- In patients hospitalized with DILI check the INR. A raised INR is a marker of significant liver damage.
- Rechallenge is **NOT** recommended for those who have had fulminant hepatitis (defined as hepatic encephalopathy with coagulopathy). Once LFT resolves, treat with MDR regimen avoiding PZA (substitute it with ethambutol).

TB treatment regimens suggested for patients with drug susceptible TB when a first-line drug is omitted:

Drug omitted	Intensive phase	Continuation phase
Rifampicin	INH, Moxifloxacin, Ethambutol, kanamycin/amikacin x 2 months*	INH, Moxifloxacin, Ethambutol x 16 months
INH	Rifampicin, Moxifloxacin, Ethambutol x 2 months*	Rifampicin, Moxifloxacin, Ethambutol x 10 months
PZA	Rifampicin, INH, Ethambutol x 9 months	

*May consider PZA rechallenge and use during intensive phase particularly if DILI occurred early during intensive phase, and there is TB meningitis/miliary TB.

Clinicians are referred to the following sources for more detailed recommendations:

1. Southern African HIV Clinicians Society Consensus Statement: The management of **drug**-induced **liver** injury in **HIV** positive patients treated for TB http://www.sajhivmed.org.za/index.php/sajhivmed/article/view/976/857
2. AfA Clinical Guidelines 9th edition. Pages 90-92.

The perinatally infected adolescent

Large numbers of HIV-infected children are approaching adolescence and represent a diverse population. Although the majority presented in infancy or early childhood, there is a growing recognition of later presentation either due to late postnatal acquisition through breast feeding or slower progression of perinatal infection. There is an unmet need to test older children and adolescents from homes where HIV is present. These adolescents often have severe morbidity. The majority of adolescents with HIV began ART in early childhood.

These adolescents have unique challenges; there is a complex interplay between the normal pubescence, chronic illness, societal issues of HIV and a health service that does not recognize the unique needs of adolescents. The table below summarizes some of the developmental characteristics of normal adolescents (Source: Dr. Helena Rabie).

	EARLY (10–15 years)	MIDDLE (14–17 years)	LATE (16–19 years)
Family	Begins transition from dependence to independence	Conflicts with authority	Adult-adult relationships
Peers	Very important for development. Intense friendships with same sex. Contact with opposite sex in groups	Strong peer friendships affirm self-image. Peers define right and wrong	Decisions/values more influenced by individual friendships. Individual choice rather than what others think.
Sexuality	Focus on self-exploration And evaluation	Romantic fantasy. Tests how can attract others. Sexual drives emerging	Stable relationships. Mutual and balanced sexual relations. Able to manage close and long-term sexual relationships. Plans for the future.
Growth	Secondary sexual characteristics. Rapid growth	Advanced secondary sexual characteristics. Growth slows down; reaches ± 95% of adult size	Mature
Cognition	Thinks in concrete terms. Does not understand how actions affect future.	Thinking more abstract, but reverts to concrete thinking if under stress. More understanding of long term consequences of own actions.	Abstract thinking established. Plans for the future. Understands how decisions influence the future.
Psychosocial	Worries about rapid physical growth and body image. Frequent mood changes	Established body image. Fantasizes. Impossible dreams. Feels very powerful. Experimentation.	Plans long term goals. Established sense of identity

A special supplement on the perinatally infected adolescent appeared in the Journal of the International AIDS Society, July 2013. (http://www.jiasociety.org/index.php/jias/article/view/18778) The theme was the "challenge of success". Many adolescents have underlying cognitive, emotional, metabolic, respiratory and cardiovascular issues, some of which can be sub-clinical. Psychiatric illness also causes morbidity. In addition many adolescents are treatment-experienced, therefore with limited therapeutic options. Adherence to ART can be especially challenging. Adolescents initiating ART are more likely to fail than those initiating as children or adults. Clinicians treating these adolescents should remain supportive and simplify regimens to be compatible with the adolescent's life style. All adolescents should be aware of their status before becoming sexually active and need help and space to deal with these issues. Birth control should be addressed proactively.

Rifabutin in HIV medicine

Rifabutin is a rifamycin antibiotic, like rifampicin. In HIV medicine its main use is to replace rifampicin when treating tuberculosis in patients on protease inhibitor-based ART who cannot tolerate adjusted doses of lopinavir-ritonavir. Rifabutin also has activity against *Mycobacterium avium-intracellulare* complex (MAC) and is sometimes used in conjunction with clarithromycin and ethambutol to treat disseminated MAC infections.

Rifabutin is metabolised by the cytochrome (CYP) P450 enzyme CYP3A4. Dose adjustments of rifabutin need to be made when it is co-administered with drugs that inhibit or induce CYP3A4. The usual dose is 300 mg daily. When co-administered with efavirenz, which induces CYP3A4, the dose should be increased to 450 mg daily. When co-administered with protease inhibitors, which inhibit CYP3A4, the dose should be decreased to 150 mg on alternate days. Rifabutin is a weak inducer of drug metabolising enzymes and transporters, and dose adjustments of co-administered antiretroviral drugs is not necessary.

Rifabutin can cause drug-induced liver injury or hypersensitivity skin rashes, like rifampicin. Cross-reactions between rifabutin and rifampicin have been described with rashes, and are likely to occur with hepatitis. In addition, rifabutin has two common dose-related toxicities: uveitis and neutropenia. Regular monitoring of full blood counts is recommended during rifabutin therapy. Immediate discontinuation of rifabutin is advised as soon as uveitis develops as permanent loss of vision may occur.

Telephonic and Online Registration

Please note that in order to comply with the proposed Protection of Personal Information Act, AfA will need to amend the current process with regard to telephonic and internet patient registration (excluding Swaziland and Botswana). The patient will be required to sign a consent form which will need to be sent to AfA in order to complete the application process, before any medication and tests can be approved. A copy of the patient consent form is attached to this email for your information.

Should one discontinue co-trimoxazole prophylaxis in children established on ART?

There are few data to guide paediatric practice. In a sub-study of the ARROW (AntiRetroviral Research fOr Watoto) trial conducted in Zimbabwe and Uganda, 758 children with a median of 2.1 years on ART (IQR: 1.8-2.2) were randomized to stop (382) or continue (376) daily co-trimoxazole. Eligibility included being over three years of age, on ART > 96 weeks, currently on daily co-trimoxazole, using an insecticide-treated bed net if in a malaria-endemic area and no previous *Pneumocystis jirovecii* pneumonia (PCP).

At randomization, the median age was seven (IQR: 4-11) years and the CD4 was 33 (IQR: 26-29)%. The two groups were similar in age, sex, CD4 percentage and cell count, and years on ART.

There was a 60% increase in hospitalization or death, hazard ratio: HR - 1.57, 95% CI: 1.09-2.26, p=0.007 in children who stopped co-trimoxazole. The benefits of continuing co-trimoxazole were greatest for CD4 percentage ≥30%.
In those stopping co-trimoxazole, increased hospitalization for malaria (49 versus 20) and non-malarial infections (53 versus 25; mainly pneumonia, sepsis and meningitis) was noted.

Stopping co-trimoxazole had a two-fold increased risk for malaria, HR: 2.10, 95% CI: 1.43-3.09, p<0.0001, with higher parasite density. Although risks for grade 3 and 4 adverse events (AEs) combined were similar (HR: 1.17, 95% CI: 0.82-1.68, p=0.39), grade 4 AEs were significantly higher (HR: 2.03, 95% CI: 0.98-4.18, p=0.05) when co-trimoxazole was stopped, with 12 cases of anaemia in those who stopped and two in those who continued. The WHO will revise their recommendations based on this trial.

Note: The WHO will revise their recommendations based on this trial. It is possible that the disease profile in South Africa is different to Uganda and Zimbabwe, not only for malaria. Although much of the benefit of continued co-trimoxazole was related to malaria, its use was associated with significantly less hospitalization for non-malaria infections as well.

Reference:

1. Bwakura-Dangarembizi M et al. *Randomized comparison of stopping vs. continuing co-trimoxazole prophylaxis among 758 HIV+ children on long-term ART: The Anti-Retroviral Research for Watoto trial.* 20th Conference on Retroviruses and Opportunistic Infections, Atlanta, abstract 86, 2013.