CASE SERIES

Clinical challenge: Deteriorating liver function in TB and HIV co-treatment

F Venter,[1] FCP (SA); **N Masingi**,[2] MB BCh; **S Stacey**,[2] MB BCh, FCP (SA), Cert ID (SA); **S Fidler**,[3] BSc, MBBS, FRCP, PhD

[1] *Wits Reproductive Health & HIV Institute, University of the Witwatersrand, Johannesburg, South Africa*
[2] *Charlotte Maxeke Academic Hospital, Department of Medicine, University of the Witwatersrand, Johannesburg, South Africa*
[3] *Faculty of Medicine, Imperial College, London, United Kingdom*

Editor's note: In this section of the *Journal*, we present complex, real-world HIV medicine cases to two experienced clinicians working in very different environments, and ask them to describe the approach that they would take if they saw the case in their local hospital setting. In our first edition, a patient with deteriorating liver function is presented by Prof. Francois Venter and Dr Ntsakisi Masingi, and then discussed by Dr Sarah Stacey in Johannesburg and Dr Sarah Fidler in London.

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Case

Prof. F Venter and Dr N Masingi

A 30-year old male taxi driver (CD4$^+$ count 5 cells/µl) presented with a vague history of weight loss and night sweats. He had received tuberculosis (TB) treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) for one month. He was initiated on antiretroviral therapy (ART) including tenofovir, lamivudine and efavirenz.

The clinician involved was concerned about the low CD4$^+$ cell count, and brought the patient back for follow-up after 4 weeks. At that time, the patient said he felt much better. Objectively, the patient had gained 4 kg and was slightly jaundiced. He had no hepatomegaly and there were no other clinical findings. The clinician phoned the patient after receiving his 4-week blood test results, and asked him to return for follow-up. His blood test results before and after ART initiation are summarised in Table 1. Five weeks after ART initiation, the clinical examination results were unchanged. The patient refused inpatient care, as he had to drive his taxi.

With this background, we put the following questions to our clinical experts in Johannesburg and London:

- How would you practically manage this patient at your institution, with available resources?
- What would be your top differential diagnoses?
- What would make you change your management plan, if anything, as you implement it?
- Is there anything that may emerge over time that would worry you?

Response

Dr S Stacey (Johannesburg)

I would consider, as possible causes of this common problem:

- A drug reaction to:
  - TB therapy
  - ART
  - prophylactic co-trimoxazole
- TB-IRIS reaction
- Ingestion of other hepatotoxic substances including traditional medicines
- Acute viral infections.

I would prefer to investigate and manage the patient as an inpatient in the infectious diseases ward, especially because of the long waiting list for outpatient investigations, but would not insist on admission if the patient adamantly refused.

I would stop the TB therapy and co-trimoxazole and repeat the liver function tests (LFTs) after 5 - 7 days. Co-trimoxazole can cause a cholestatic picture alone or a hepatocellular and cholestatic pattern together. Due to the very rapid rise in liver enzymes, I would also stop ART. Although I think the prescribed antiretrovirals (ARVs) are the less likely suspects and he is asymptomatic, he is also jaundiced and his enzymes are more than five times the baseline value. Efavirenz has been associated with liver failure and liver fatalities.

Other blood tests would include repeat viral hepatitis serology for types A, B and C to exclude recently acquired acute hepatitis, a cytomegalovirus (CMV) polymerase chain recation (PCR) test, full blood count and differential and inflammatory markers.

I would question the patient about the use of over-the-counter and traditional medicines and alcohol, and advise him to discontinue their use.

In the meantime, I would use a liver-sparing regimen for TB therapy, consisting of an aminoglycoside, moxifloxacin and ethambutol. I have chosen these drugs because although none of them are as effective as rifampicin or isoniazid (INH), I would like to

Table 1. Patient blood test results before and after ART initiation

	Time relevant to ART initiation		
Result	**1 week before**	**4 weeks after**	**5 weeks after**
Hb (g/dl) (normal 12 - 15)	9	8.5	8
Platelets (normal 140 - 400)	500	480	450
Bilirubin	Normal	10 x normal	10 x normal
AST	2 x normal	8 x normal	10 x normal
ALT	3 x normal	8 x normal	10 x normal
GGT	2 x normal	10 x normal	10 x normal
ALP	2 x normal	10 x normal	10 x normal
INR			Normal (1.1)
Creatinine clearance	Normal	Normal	Normal
Urine dipstix	Normal	Bilirubin, protein	Bilirubin, protein
Hepatitis B/C screening serology	Negative		
Viral load (copies/ml)	1 000 000	2 000	
$CD4^+$ cell count (cells/µl)	5	50	

ART = antiretroviral therapy; Hb = haemoglobin; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; INR = international normalised ratio.

ensure that I am still providing a combination that is effective in the continuation phase. I would substitute dapsone for co-trimoxazole, because dapsone is not associated with liver injury.

If the patient's liver enzymes showed signs of improvement on this regimen, I would wait until they approached normal and then reintroduce the TB drugs one at a time (although we are usually anxious to restart full TB therapy as soon as possible because we believe that liver-sparing treatment is less effective than standard therapy). We still do not restart pyrazinamide in these patients, but I would attempt to reintroduce both INH and rifampicin, although we have noticed that some patients tolerate reintroduction of full TB therapy with the fixed-dose combination (FDC). It is also much more practical to prescribe the FDC, as single drugs are only available at tertiary sites and, even there, are not stocked consistently. If the patient tolerated TB therapy, I would attempt to reintroduce ART using the same regimen.

I would request an ultrasound of the liver as well, but booked on an outpatient basis, this investigation may be several weeks away at our hospital. Hypodense lesions in the liver, associated with lymphadenopathy, and splenic lesions could suggest TB-immune reconstitution inflammatory syndrome (TB-IRIS), although the initial diagnosis of TB was sufficiently vague to make other (unmasked) infections of the liver worth considering, such as fungal infections, non-tuberculous mycobacterial infections and viral infections like CMV. Depending on the results of the ultrasound, I would proceed to recommend a liver biopsy and/or magnetic resonance cholangiopancreatography (MRCP) if the patient's liver functions did not improve off medication.

Response

Dr S Fidler (London)

First, I would take a full history – plus a sexual history – to exclude other sexually transmitted infections (STIs) that could affect liver function (e.g. hepatitis B and C virus, which could be acute infections even though he was initially antibody-negative), and ask about travel to consider other acquired co-infections, other family or close contacts who were unwell, other medications, over-the-counter medications, recreational drugs and especially alcohol. I would ask about malaena, gastrointestinal symptoms, nausea, vomiting and fevers.

Blood tests to add: repeat hepatitis A, B and C; CMV PCR; Epstein-Barr virus (EBV); toxoplasmosis; STI screen; syphilis; drug levels (efavirenz, rifampicin); and bacterial and mycobacterial blood cultures.

My differential diagnosis would include: a drug reaction to either co-trimaoxazole, any TB drug or ART – most likely efavirenz or tenofovir, alcohol or other medication not disclosed.

Other causes, if all of the above were excluded, could include lymphoma (a very low $CD4^+$ cell count suggests long-standing untreated HIV).

I would admit the patient to hospital for investigation and observation, exclude other causes, and treat as diagnosed. If he declined admission and his liver dysfunction continued, I would advise him to stop driving his taxi – especially if alcohol abuse was suspected, or LFT results were increasingly abnormal. If he continued to decline admission, I would repeat his LFTs and clotting three times a week. I would arrange an urgent liver ultrasound scan, and potentially magnetic resonance imaging (MRI), depending on the outcome of the ultrasound. I would do a regular review of the patient in the outpatient clinic to ensure that there was no clinical evidence of hepatic failure

or encephalopathy. If there was any evidence of liver failure, I would admit the patient.

As the patient's LFTs were increasingly abnormal, I would stop all drugs. The goal is to reintroduce drugs, preferably individually, prioritising TB treatment first, but preventing other opportunistic infections in view of the patient's severe immunosuppression. I would anticipate that once all drugs were stopped, the LFT results would return to within normal limits.

I would then review the patient's treatment options for both TB and HIV. This would include the use of GeneXpert for determining TB drug sensitivities and HIV genotyping, including integrase and tropism (this should be available from the baseline sample taken on all new HIV-positive individuals) prior to restarting therapy. The first priority would be TB treatment: based on the test results, I would restart an effective regimen for TB, introducing single agents with close monitoring of LFTs and clotting (three times weekly). Once the patient was established on TB treatment, I would re-start his ART regimen: I would check the viral genotype to confirm whether or not there was any drug resistance and determine the potential for other ART options. Ideally, tenofovir/emtricitabine/efavirenz would be the preferred option in view of TB drug interactions and available safety data, but I would monitor LFTs and therapeutic drug levels. If efavirenz was the potential cause of abnormal LFTs, I would consider triple nucleosides while the patient was receiving TB drugs or potentially, but cautiously, raltegravir with tenofovir/emtricitabine, although there are fewer data on interactions, so the patient would require close monitoring of viral load (VL). I would avoid PIs altogether due to drug interactions. If, despite starting ART, there was clinical or ultrasound evidence suggestive of TB-IRIS, I would consider adding steroids to treat the suspected IRIS, while continuing TB treatment and ARVs unchanged.

Final outcome

Prof. F Venter and Dr N Masingi

We elected to continue the ARVs and TB continuation phase treatment, phoning the patient daily to make sure he was alright. We were a little suspicious about the use of traditional medicines (he seemed unsure when we asked him), so we asked a counsellor to speak to him, who agreed that he may be using something. We then gave him general counselling about unknown drug interactions, and showed him his LFT results and how they were deteriorating. We were worried about the patient driving a taxi (on efavirenz, potentially encephalopathic), but he had no objective signs of liver failure, his international normalised ratio (INR) remained normal, suggesting his liver synthetic function was still alright – and he was not prepared to stop driving. An ultrasound three weeks later showed liver and splenic micro-abscesses, so the patient could also have had a TB-IRIS reaction. He is fine now, with a $CD4^+$ count >300 cells/µl, an undetectable VL 8 months later, he is still driving his taxi, but we never proved TB.

These cases are hard, but access to additional and repeated laboratory investigations and rapid radiology can help. The differential diagnosis of drug toxicity, TB-IRIS, toxin or new opportunistic illness all look alike, and if the patient's LFTs had continued to decline, we would have stopped all treatment and slowly re-introduced his TB medication, then ART, once his LFTs had settled.