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Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

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MBChB; DipHIVMan(SA)
Student Number: schcha019

Mini-dissertation presented for the degree of

Masters Degree in Public Health (Clinical Research)

in the School of Public Health and Family Medicine

August 2012

Supervisor:
Graeme Meintjes
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6. Data capture forms:
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3. Table: Other Causes of Liver Dysfunction
Professor Blockman  
UNIVERSITY OF CAPE TOWN  
Faculty of Health Sciences  
Research Ethics Committee  
E52- 23 Old Main Building  
Groote Schuur Hospital  
Observatory, 7925

Dear Professor Blockman

We wish to request permission from the Research Ethics Committee to perform a retrospective observational study of all patients who presented with hepatitis at GF Jooste hospital during 2009. This study will aim to describe the numbers of patients seen with hepatitis, the spectrum of causes of hepatitis, outcome, and the current burden on the health care system.

We will review case notes and laboratory records of all patients who were seen at GF Jooste during 2009 with an ALT of more than 200 and or total billirubin of more than 50. We will ascribe the most likely cause for hepatitis in each case, look at the relation of hepatitis to TB medication and ART, the duration of hospital stay and outcome.

The focus will be to find out how many HIV and TB co infected patients present with drug induced hepatitis due to TB medication and ART. Our current clinical impression is that this is a frequent treatment complication in our setting and is associated with long hospital stays and lengthy drug rechallenges. However, this has not been formally described in our setting. With this study we will build a data base from which we can plan a future prospective study to look more in depth at causes of drug induced hepatitis, management thereof and the role of liver biopsy in this setting.

This study is strictly a retrospective data analysis and will be conducted according to GCP/ICH guidelines.

Yours sincerely
Graeme Meintjes
MBChB MRCP(UK) FCP(SA) DipHIVMan(SA)
Infectious Diseases Physician
(Supervisor)

Dr Charlotte Schutz
MBChB, DipHIVman(SA)
Infectious Diseases Principal Medical Officer GF Jooste Hospital
(Lead Investigator)

Other co-investigators:
Professor Robert Wilkinson
Dr Chris Kenyon
Dr Suzaan Marais
Dr Zahira Ismail
18 December 2009

REC REF: 522/2009

Dr G Meintjes
Dept of Medicine
Division of Infectious Diseases & HIV Medicine

Dear Dr Meintjes

PROTOCOL TITLE: A RETROSPECTIVE OBSERVATIONAL STUDY OF ALL PATIENTS WHO PRESENTED WITH HEPATITIS AT GF JOoste HOSPITAL DURING 2009.

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has formally approved the above mentioned study.

Approval is granted for one year until 24 December 2010.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Yours sincerely

[Signature]

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Medical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Nywabi
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
FHS017: Annual Progress Report
Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

Principal Investigator to complete the following:

1. Protocol information

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<tr>
<th>Date</th>
<th>17 July 2012</th>
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<tbody>
<tr>
<td>HREC REF Number</td>
<td>522/2009</td>
</tr>
<tr>
<td>Protocol title</td>
<td>Burden of Tuberculosis and Antiretroviral Drug-Induced Liver Injury at a Secondary Hospital in South Africa</td>
</tr>
<tr>
<td>Protocol number (if applicable)</td>
<td></td>
</tr>
<tr>
<td>Principal Investigator</td>
<td>Charlotte Schutz (Supervisor: Graeme Meintjes)</td>
</tr>
<tr>
<td>Department / Office Internal Mail Address</td>
<td>CIDRI Office, IIDMM, UCT Medical School</td>
</tr>
</tbody>
</table>

1.1 Does this protocol receive US Federal funding? □ Yes √ No

2. Protocol status (tick ✓)

- Research-related activities are ongoing
- Data collection is complete, data analysis only

3. Protocol summary

| Total number of records or specimens collected, reviewed or stored since the original approval | 318 records reviewed |
| Total number of records or specimens collected, reviewed or stored since last progress report | 318 records reviewed |

Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report. □ No ✓ Yes

4. Signature

Signature of PI

Signature of Supervisor (if PI is a student)
FHS017: Annual Progress Report

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

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<td>Expiry date:</td>
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<td>Chairperson of the HREC signature</td>
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Principal Investigator to complete the following:

1. Protocol information

| Date | 17 July 2012 |
| HREC REF Number | 522/2009 |
| Protocol title | Burden of Tuberculosis and Antiretroviral Drug-Induced Liver Injury at a Secondary Hospital in South Africa |
| Protocol number (if applicable) | |
| Principal Investigator | Charlotte Schutz (Supervisor: Graeme Meintjes) |
| Department / Office Internal Mail Address | CIDRI Office, IIDMM, UCT Medical School |
| 1.1 Does this protocol receive US Federal funding? | ☐ Yes ☑ No |

2. Protocol status (tick ✓)

| ☐ Research-related activities are ongoing |
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| Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report. | ✓ Yes ☐ No |

4. Signature

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PART A: Protocol

Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

Aims:

1. To determine the proportion of patients who present with TB treatment and or ART-associated drug-induced liver injury (DILI) amongst all patients presenting with significant liver injury to GF Jooste Hospital during the study period.
2. To describe baseline clinical characteristics and management of TB treatment and or ART-associated DILI patients.
3. To describe the in-patient and 3-month mortality of TB treatment and or ART-associated DILI patients.

Background and Rationale:

GF Jooste Hospital is a public sector referral hospital and serves a densely populated area with a high burden of HIV and tuberculosis (TB). ART rollout in the Western Cape started in 2001/2002 at two pilot clinics and is now well established (1). Many patients are on concomitant TB treatment and ART. At ART clinics in the referral area 25-40% of patients are on TB treatment when they start ART (2, 3).

At GF Jooste hospital many HIV positive patients are seen who are on TB treatment and or ART, and present with symptomatic liver dysfunction. Patients are on multiple hepatotoxic drugs, may have multiple opportunistic infections, systemic sepsis and hepatic TB immune reconstitution disease also plays a role. Anecdotally, these patients are complex to manage, require frequent specialist input, spend a long time in hospital and have high mortality. Management guidelines are based on expert opinion and is not evidence based. In practice management relies heavily on the attending clinicians’ experience and clinical judgment and management often differ widely between clinicians. Mortality could be due to progression of TB and or HIV because of interruption of effective therapy, other opportunistic infections or hospital acquired infections. Few early liver biopsies are done and it is not known if early liver biopsies would aid by guiding management of these patients. Prospective studies are urgently needed to guide management in these patients.

The burden of TB treatment and or ART-associated drug induced liver injury in this setting has not been described to our knowledge, neither has management, outcome or mortality. This study was performed to aid planning of prospective studies in this field.

Study Site:

GF Jooste Hospital is a public sector referral hospital, which serves a largely socio-economically disadvantaged population of 1.2 million people. In Khayelitsha, which is the largest of the areas referring to GF Jooste Hospital, the TB notification rate is 1 600/100 000 and the antenatal HIV seroprevalence is
Patients from surrounding ART and TB clinics who present with symptomatic liver dysfunction are referred to GF Jooste Hospital where liver function tests are performed. Based on the results of the liver function tests and clinical condition, patients are either admitted, or managed as outpatients. GF Jooste Hospital has an Infectious Diseases Referral Unit at which some patients with liver dysfunction could be managed as outpatients.

**Design:**

Retrospective observational study.

**Methods:**

Results of all liver function tests (LFT) performed at the GF Jooste Hospital National Health Laboratory Service laboratory from 1 January to 30 June 2009 were reviewed. Records for all patients who met criteria for significant liver dysfunction (see case definition below) were reviewed and data was extracted with a data extraction sheet developed for the study (see appendix A & B).

The following information was added to the protocol after protocol approval in response to a request from an external reviewer: The liver function tests were retrieved with a search function from the NHLS database. This produced a list of all liver function tests performed at GF Jooste hospital for a specific time period. The researcher sorted through this list manually to identify all values that met study criteria and to eliminate duplicates. Permission was obtained from the local NHLS laboratory manager.

**Inclusion Criteria:**

1. Presence of significant liver dysfunction on GF Jooste laboratory records (refer to case definition below).

**Case definitions:**

**Significant liver dysfunction**

Liver dysfunction was defined as significant hepatocellular or cholestatic liver injury. Significant was defined as resulting in Grade 3 or 4 elevation of alanine amino transferase (ALT) and or total billirubin (TBR). The values are ALT≥200 U/l (>5 times the upper limit of normal and indicative of hepatocellular injury), and TBR≥44 μmol/l (>2.5 times the upper limit of normal and indicative of cholestatic injury) (5). The Division of AIDS table for grading he severity of Adult and Pediatric Adverse Events was used to determine these cut-off points, see appendix C & D. Patients who fulfilled one or both criteria were included. The rationale for the case definition was that drug-induced liver injury may present with either hepatocellular or cholestatic liver function test results and at GF Jooste Hospital it is clinical practice to generally not request full liver function
tests on patients to save laboratory costs. In practice an ALT is done to screen for hepatocellular injury and total billirubin to screen for cholestatic injury.

**TB treatment or ART-associated liver dysfunction**
Patient was managed as TB treatment and or ART-associated drug induced liver injury (DILI) by the admitting team, evident by changing or stopping TB treatment and or ART during the hospital stay.

**Other causes of liver dysfunction**
A cause other than TB treatment and or ART-associated DILI is identified as the primary cause of liver injury and the admitting team’s treatment and management is aimed at this cause. Thus, patients receiving TB treatment and or ART who are admitted with another probable cause of liver injury and whose TB treatment and or ART is continued unaltered, are included in this category.

**Sepsis**
Sepsis was documented when the clinical presentation was compatible with sepsis and the admitting team managed infection as the primary cause of illness.

**Hepatic Encephalopathy**
The admitting team documented hepatic encephalopathy or signs and symptoms compatible with encephalopathy.

**Determination of Outcome:**

Clinical management and outcome data were ascertained by review of patient records. In-hospital and 3-month (within 90 days of presentation) mortality were recorded for TB treatment and or ART-associated DILI patients, including the cause of death where possible. Only in-hospital mortality was recorded for patients with liver injury due to other causes. Three-month retention in care was also recorded for the TB treatment and or ART associated DILI group. In the case of TB treatment and or ART-associated DILI, the Clinicom and eKapa electronic databases were consulted to ascertain follow-up and mortality documented elsewhere in the Western Cape. Loss to follow-up was defined as inability to trace any patient data after discharge but within 3 months of presentation.

**Statistical Analysis:**

Frequency statistics and survival analysis will be performed with STATA 11.1 software (2009).

**Appendices: (Following the protocol):**

- Data capture sheet for: GFJ Hepatitis Study: Initial Episode of Hepatitis/Cholestasis
- Data capture sheet for: GFJ Hepatitis Study: Subsequent Episode of Hepatitis/Cholestasis
• Division of AIDS Table for Grading the severity of Adult and Pediatric Adverse Events. Publish Date: December, 2004
• Laboratory Normal Value Ranges used at GF Jooste Hospital.

References

GFJ Hepatitis Study Initial Episode

1. Name______________________________________________
   GFJ Folder number____________________________________
   DOB__________________
   Date of presentation with hepatitis ____________
   Was patient admitted? Yes/No
   Date of discharge/death/transfer/abscondment ____________

2. HIV status at presentation? Positive/Negative/Not tested
   Most recent CD4 count _________Date of CD4 ______________

3. On ART at presentation? Yes/No/Unknown
   Date started ______________
   Regimen at presentation:
   AZT/3TC
   AZT/DDI
   D4T/3TC
   TDF/3TC
   NVP
   EFV
   Lop/Rit
   Other
   Unknown
   If other, name medication __________________________________

4. On TB treatment at presentation? Yes/No/Unknown
   Date started ______________
   Regimen at presentation:
   Rif/INH/EMB/PZA
   Rif/INH/EMB/PZA + STREP
   Rif/INH
   Rif/INH/EMB
   MDR
   Other
   Unknown
   If other TB medication, name medication ______________________

5. Cotrimoxazole Yes/No/Unknown
   Primary prophylaxis? Yes/No
   Secondary prophylaxis? Yes/No
   Treatment? Yes/No

---

Complete
Incomplete
GSH/Carnation/KDH folder needed
Busy with 3 month f/up

Name________________________________________________
GFJ Folder number____________________________________
DOB_____________
Patient Sticker

TB or ART DILI
Other
6. List all additional medication on presentation ____________________
________________________________________________________
________________________________________________________

7. Documented herbal medication/traditional medicine/OTC medication?
Yes/No/Unknown
List___________________________________________________
________________________________________________________

8. If TB treatment or ART NOT the cause of hepatitis, what is the most likely primary cause of hepatitis?

<table>
<thead>
<tr>
<th>Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
</tr>
<tr>
<td>Paracetomol</td>
</tr>
<tr>
<td>Alcohol</td>
</tr>
<tr>
<td>TB IRIS</td>
</tr>
<tr>
<td>Viral hepatitis (A,B,C)</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
</tr>
<tr>
<td>Other medication</td>
</tr>
<tr>
<td>Other cause</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

Name other cause __________________________________________
Name other medication _______________________________________
Details __________________________________________________
________________________________________________________
________________________________________________________

Possible contributing factors to hepatitis (differential diagnosis)
- ____________________
- ____________________
- ____________________

Outcome
- Died during initial admission
- Discharged
- Referred to another hospital
- Absconded

Date of last record of patient ________________
Cause of death ___________________________

9. LFT values:

<table>
<thead>
<tr>
<th></th>
<th>Presentation</th>
<th>Peak (this episode)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ALP  
TBR  
INR  

- Hepatic encephalopathy at presentation?  Yes/No  
- If INR >1.4, is there any reason for abnormal INR apart from liver dysfunction? (eg CCF/Warfarin/DIC)  Yes/No  
  Reason______________________________________

10. Hepatitis studies  
- Hep B sAg  
- Hep B eAg  
- Hep C Ab  

<table>
<thead>
<tr>
<th></th>
<th>Pos</th>
<th>Neg</th>
<th>N/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hep B sAg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep B eAg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hep C Ab</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

11. Outcome  
- Died acutely (during initial admission)  
- Died during follow up (3m)  
- Discharged and known to be alive and in care (3m)  
- Discharged, seen as outpatient, LTFU (3m)  
- Discharged with no information after discharge  
- Absconded  
  - Cause of death______________________________  
  - Date of last record of patient_________________

12. Management  
**TB treatment:**  
- Was treatment stopped completely?  Yes/No  
- Date stopped__________________________  
- Changed to liver safer medication?  Yes/No  
- Date started__________________________  
- Name liver safer medication_____________________

<table>
<thead>
<tr>
<th>Taking at presentation?</th>
<th>Stopped?</th>
<th>Rechallenged or started?</th>
<th>Tolerated?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rif</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>INH</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>EMB</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>PZA</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Strep</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>MDR</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bactrim</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

TB drug rechallenge not done?  Yes/No  
Reason________________________________________
ART:

<table>
<thead>
<tr>
<th>Unchanged?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Completely stopped?</td>
<td></td>
</tr>
<tr>
<td>NVP changed to EFV?</td>
<td></td>
</tr>
<tr>
<td>NVP interrupted and EFV restarted later?</td>
<td></td>
</tr>
<tr>
<td>EFV changed to Lop/Rit?</td>
<td></td>
</tr>
<tr>
<td>EFV interrupted and restarted on EFV later?</td>
<td></td>
</tr>
<tr>
<td>EFV interrupted and started on Lop/Rit later?</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Details of other</td>
<td></td>
</tr>
</tbody>
</table>

13. Time taken to get back onto optimal therapy

- TB treatment (Rif based) Date ________
- ART (Tripple therapy/PI based) Date ________
- If NOT back on optimal therapy, list regimen and reason
  - TB treatment____________________________________
  - ART_________________________________________

  - Loss to follow up during rechallenge? Yes/No

14. Additional relevant investigations Yes/No

<table>
<thead>
<tr>
<th>Liverbiopsy</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCP</td>
<td>Conclusion</td>
</tr>
<tr>
<td>USS abdomen</td>
<td>Conclusion</td>
</tr>
<tr>
<td>CT abdomen</td>
<td>Conclusion</td>
</tr>
</tbody>
</table>

15. Outpatient follow up related to hepatitis (within 3 months after initial presentation) Yes/No

Number of visits ______

16. Possible contributing factors to hepatitis? (differential diagnosis eg TB IRIS, heavy ETOH, chronic Hep B etc)

- ____________________________
- ____________________________
- ____________________________
- ____________________________

17. Did patient have a subsequent episode of abnormal LFT’s investigated at hospital? Yes/ No

If yes, complete subsequent episodes form
GF Jooste Hepatitis Study

Subsequent Episodes of hepatitis

1. Name________________________________________________
   GFJ Folder number________________________________________
   DOB__________________________  Patient Sticker

   Date of presentation with hepatitis ____________
   Was patient admitted?  Yes/No
   Date of discharge/death _____________

2. Likely primary cause of hepatitis
   • ______________________________
   Contributing factors/differential diagnosis
     • ______________________________
     • ______________________________

3. Drug interruptions/changes?
   • TB Treatment  Yes/No
     Details ______________________________________________________
     ______________________________
   • ART  Yes/No
     Details ______________________________________________________
     ______________________________
   • Other  Yes/No
     Details ______________________________________________________
     ______________________________

4. Additional investigations done?  Yes/No
   Investigation  Conclusion
   USS abdomen
   CT abdomen
   Liver biopsy
   ERCP
   Other
5. Followed up as outpatient? Yes/No  
   Number of visits (3 months after this episode) ____________

6. Outcome

<table>
<thead>
<tr>
<th>Died during initial admission</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharged</td>
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<tr>
<td>Referred to another hospital</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Absconded</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

   • Date of last record of patient ______________
   • Cause of death ___________________________

7. Other relevant information?

________________________________________________________________
________________________________________________________________
________________________________________________________________
### DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

**PUBLISH DATE: DECEMBER, 2004**

#### Quick Reference

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAMES AE grading table) is a descriptive terminology which can be utilized for Adult Event (AE) reporting. A grading severity scale is provided for each AE term.

#### General Instructions

**Estimating Severity Grade**

If the need arises to grade a clinical AE that is not identified in the DAMES AE grading table, use the category "Estimating Severity Grade" listed at the top of Page 5. For AEs that are not listed in the table, use the two levels, Mild and Moderate, to approximate the severity. Use the grading scale below for mild or moderate severity if specific severity applies within the protocol or as an appendix to the protocol. (Please see "Terminology" for the Excellent Adverse Event Reporting: Section of DAMES AE Protocol ".) This is particularly important for laboratory values because the "Estimating Severity Grade" category only applies to clinical symptoms.

**Grading Adult and Pediatric AEs**

The DAMES grading table includes parameters for grading both Adult and Pediatric AEs. When a single set of parameters is not appropriate for grading specific types of AEs for both Adult and Pediatric populations, separate sets of parameters for Adult and/or Pediatric populations (with specified respective age ranges) are given in the table. If there is no instruction in the table between Adult and Pediatric populations, the severity level of the parameter listed is to be used for grading the severity of both Adult and Pediatric events of the same type.

**Determining Severity Grade**

If the severity of an AE could fall under either one of two grades (e.g., the severity of an AE could be either Grade 2 or Grade 3), select the higher of the two grades for the AE.

#### Definitions

**Basic Self-Care Functions**
- **Adult**: Activities such as bathing, dressing, toileting, transfers/movement, conformance, and feeding.
- **Children**: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implements).

**Vital Signs**

- **Adult**: Medical interventions such as using medications, dressing, toilet, transfers/movement, conformance, and feeding.
- **Children**: Medical interventions such as use of pharmacologic or biological agents for treatment of an AE.

**Operative Intervention**

- **Adult**: Surgical or other invasive mechanical procedures.
- **Children**: Upper limit of normal

**Usual Social & Functional Activities**

- **Adult**: Adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, pursuing a hobby, etc.
- **Children**: Activities that are age and culturally appropriate (e.g., social interactions, play activities, learning tasks, etc.)

---

### Contents

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<th>Page</th>
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<td>Urology</td>
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</tr>
<tr>
<td>Respiratory</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular/Mucosal</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular</td>
<td>14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### CLINICAL

#### Parameter

**Grade 1 (Mild)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
</table>
| **Systemic**

**Acute systemic edema reaction**
Localized skin blanching with no medical intervention indicated.

| **Fatigue**

**Systemic fatigue**
Systemic fatigue greater than minimal interference with usual social and functional activities.

| **Tender (injection site)**

| **Pain (injection site)**

**DO NOT use for pain due to injection**
DO NOT use for pain due to injection (see Injection Site Reactions, injection site reactions, injection site reactions, injection site reactions).

| **Adult - 15 years**

**Erythema OR Induration**
Moderate redness (0.2 cm diameter)

| **Pediatric - 15 years**

**Erythema OR Induration**
Early erythema (0.2 cm diameter)

| **Basic Self-Care Functions**

- Adult: Activities such as bathing, dressing, toileting, transfers/movement, conformance, and feeding.
- Children: Activities that are age and culturally appropriate (e.g., feeding self with culturally appropriate eating implements).

**Usual Social & Functional Activities**

- Adult: Usual social and functional activities, such as going to work, shopping, cooking, etc.
- Children: Usual social and functional activities, such as going to work, shopping, cooking, etc.

---

**University of Cape Town**

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**Revision 1.0**

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**Page 3 of 20**

**Revision 1.0**

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**Page 4 of 20**

**Revision 1.0**
### CLINICAL

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus associated with resection</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Generalized itching, including pruritus localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

### SKIN - DERMATOLOGICAL

#### Algdsthesia

Dermatological symptoms attributable to the study agent. Nonpainful, nonitchy rash localized to the intraabdominal area. Complete lack of loss of appetite.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>No pruritus</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

#### Cough or respiratory distress

Dyspnea, cough, or other respiratory symptoms localized to the intraabdominal area. Complete lack of loss of appetite.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>No pruritus</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

### CARDIOVASCULAR

#### Cardiac arrhythmia (general)

Asymptomatic and non-irritative finding. Complete lack of loss of appetite.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>No pruritus</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

### GASTROINTESTINAL

#### Anorexia

Mild or moderate loss of appetite.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>No pruritus</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>

### OTHER

#### Acute renal failure

Loss of appetite associated with renal failure.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>No pruritus</td>
<td>Pruritus localized to the intraabdominal area, worsened by coughing or straining or with local skin treatment</td>
<td>Severe itching localized to the intraabdominal area, sleep disturbance, or functional activities</td>
<td>NA</td>
</tr>
</tbody>
</table>
## Clinical Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancrætic</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Unconsciousness, vomiting, or diarrhea</td>
<td>Unconsciousness, vomiting, or diarrhea</td>
<td>Unconsciousness, vomiting, or diarrhea</td>
<td>Unconsciousness, vomiting, or diarrhea</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

### Neurologic Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td>Memory</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td>Mood</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td>Cognitive behavior</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
</tbody>
</table>

### Respiratory Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchoconstriction</td>
<td>Erythema or fine labile rales</td>
<td>Dry cough</td>
<td>Persistent cough</td>
<td>Life-threatening respiratory failure (ARDS)</td>
</tr>
<tr>
<td>Difficulties breathing</td>
<td>Respiratory</td>
<td>Respiratory</td>
<td>Life-threatening respiratory failure (ARDS)</td>
<td>Respiratory failure (ARDS)</td>
</tr>
</tbody>
</table>

### Musculoskeletal Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td></td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
<tr>
<td></td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
</tbody>
</table>

### Bacterial Infections

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
</tbody>
</table>

### Viral Infections

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Subclinical AIO without hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Symptomatic AIO with hospitalization (diabetes, emesis, very rare events, requiring intervention)</td>
<td>Life-threatening AIO (diabetes, emesis, very rare events, requiring intervention)</td>
</tr>
</tbody>
</table>

### Other Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grade 1 (Mild)</th>
<th>Grade 2 (Moderate)</th>
<th>Grade 3 (Severe)</th>
<th>Grade 4 (Potentially Life-Threatening)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- **Adverse Events:** Events that are observed during the course of treatment for HIV/AIDS, including those that may be due to the underlying disease and those that may be due to the treatment of the disease.
- **Mild:** Symptoms or signs that are not compromising the patient's health and may be easily managed.
- **Moderate:** Symptoms or signs that are compromising the patient's health and may require medical attention.
- **Severe:** Symptoms or signs that are life-threatening and require immediate medical attention.
- **Potentially Life-Threatening:** Symptoms or signs that are life-threatening and require immediate medical attention.

**Basis:** The classification of adverse events is based on the severity of the event and its impact on the patient's health. The grading system is used to assess the severity of the adverse event and determine the appropriate level of care and monitoring.
DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

CLINICAL

PARAMETER | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 Potentially Life-Threatening
---|---|---|---|---
Malaise/fever | Mild | Moderate | Severe | Potentially Life-Threatening
Chills | NA | NA | NA | NA
Cough | NA | NA | NA | NA
Difficulty in breathing | NA | NA | NA | NA
Obstructive sleep apnea | NA | NA | NA | NA
Severe dermatologic reactions | Asymptomatic | Unresponsive | Life-threatening | Asymptomatic
Chest wall/subcutaneous | Symptomatic | Life-threatening | Life-threatening | Symptomatic
Abnormal LFTs | NA | NA | NA | NA

GASTROINTESTINAL

PARAMETER | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 Potentially Life-Threatening
---|---|---|---|---
Gastroesophageal reflux | MILD | MODERATE | SEVERE | POTENTIALLY LIFE-THREATENING
Carcinoid syndrome | Asymptomatic | Symptomatic | Life-threatening | Asymptomatic
Carcinoid crisis | Asymptomatic | Symptomatic | Life-threatening | Asymptomatic
Intestinal bleeding (IDB) | Life-threatening | Life-threatening | Life-threatening | Life-threatening
Urgent lower abdominal pain (dysfunction) | NA | NA | NA | NA

DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS
PUBLISH DATE: DECEMBER, 2004

LABORATORY

PARAMETER | GRADE 1 | GRADE 2 | GRADE 3 | GRADE 4 Potentially Life-Threatening
---|---|---|---|---
Hematology | Standard International Units are listed in brackets

CD4+ count | Adult and Pediatric | Adult and Pediatric | Adult and Pediatric | Adult and Pediatric
---|---|---|---|---
CD4+ count | 300-400/mm^3 | >400/mm^3 | >500/mm^3 | >600/mm^3
Absolute lymphocyte count (ALC) | 1.0 x 10^9/L | 1.0 x 10^9/L | 1.0 x 10^9/L | 1.0 x 10^9/L

Basic Social & Functional Activities - Adult: Activities that are age and culturally appropriate (e.g., social interaction, play activities, leisure tasks, etc.)

**Values are for both adults and children.

**Use age- and sex-appropriate indices (e.g., height-for-age, including protein intake).

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# DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

**Publication Date:** December, 2004

## LABORATORY

### DIVISION OF AIDS TABLE FOR GRADING THE SEVERITY OF ADULT AND PEDIATRIC ADVERSE EVENTS

**Publication Date:** December, 2004

### PARAMETER |
**GRADE 1 MILD** |
**GRADE 2 MODERATE** |
**GRADE 3 SEVERE** |
**GRADE 4 POTENTIALLY LIFE-THREATENING** |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumentin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Glucose</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Potassium, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Protein, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urea, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

### GRADE 2 MODERATE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Potassium, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Protein, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urea, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

### GRADE 3 SEVERE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Potassium, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Protein, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urea, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

### GRADE 4 POTENTIALLY LIFE-THREATENING

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Glucose, serum</td>
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<td>Low</td>
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<td>Low</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Lactate Dehydrogenase</td>
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<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Potassium, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Protein, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Urea, serum</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
</tbody>
</table>

### Notes

1. Use age and sex appropriate values (e.g., birthdate, including gestational age).
2. Values may be life limiting.
3. Use age and sex appropriate values (e.g., birthdate, including gestational age).
4. Values may be high risk.

---

**URINALYSIS**

**Standard International Units are listed in italics.**

**Publication Date:** December, 2004

### PARAMETER |
**GRADE 1 MILD** |
**GRADE 2 MODERATE** |
**GRADE 3 SEVERE** |
**GRADE 4 POTENTIALLY LIFE-THREATENING** |

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (monocyte)</td>
<td>5.0 - 15.0 mg/dL</td>
<td>5.0 - 15.0 mg/dL</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Creatinine (monocyte)</td>
<td>1.0 - 2.0 mg/dL</td>
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### Notes

1. Use age and sex appropriate values (e.g., birthdate, including gestational age).
2. Values may be high risk.
3. Use age and sex appropriate values (e.g., birthdate, including gestational age).
4. Values may be life limiting.
### Jooste Hospital: Results

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Part B: Structured literature review

Objectives

The objective of this literature review is to summarize key concepts related to tuberculosis (TB) treatment and or antiretroviral therapy (ART)-associated drug-induced liver injury (DILI) from currently published literature with the focus on HIV as a risk factor for TB DILI and concomitant ART and TB treatment as a risk factor for DILI. This review serves as an introduction to the research study that follows. The study was conducted at GF Jooste Hospital and assessed the burden of TB treatment and or ART-associated DILI at a referral hospital in South Africa.

Search Methods & Selection Criteria:
A Pubmed search was performed with key words and combinations of HIV, tuberculosis, hepatotoxicity and drug induced liver injury. All studies that reported hepatotoxicity and included 1) adult HIV positive patients on antiretroviral therapy and or; 2) adult patients on TB treatment and or; 3) adult patients on concomitant TB treatment and antiretroviral therapy, were reviewed. Studies including paediatric patients, studies concerning TB preventative therapy and studies in TB patients which did not include any HIV-infected patients were not assessed for this review. References of relevant studies were also examined and used to find additional articles for this review. The methods used in this review did not meet the criteria for a systematic review.
Background:

**Burden of tuberculosis and HIV:**

An estimated 34 million people are HIV-infected globally (1). There were an estimated 8.8 million incident TB cases worldwide in 2010, of which an estimated 1.3 million cases occurred in people who were HIV-infected (2). In South Africa TB case notifications reached almost 400 000 per annum in 2010, with 61% of incident TB cases being HIV co-infected (2). In the Western Cape province TB prevalence at ART initiation is very high. Two large public sector antiretroviral (ART) clinics in Cape Town reported concomitant TB treatment in 25% and 40% of patients respectively, at time of ART initiation (3, 4). Forty-two percent of HIV-positive incident TB cases in South Africa received both ART and TB treatment in 2009, compared with 18% in 2008 (5).

**The importance of drug induced liver injury (DILI):**

Multi-drug treatment for active TB has several well-known side effects. One of the most common and serious is hepatotoxicity (6). All classes of ART are potentially hepatotoxic (7). These overlapping toxicity profiles in often overlapping, multi-drug treatment regimens, cause complex clinical scenarios in patients who present with liver injury. Commonly used prophylactic medication like cotrimoxazole, fluconazole and other conditions like tuberculosis-associated immune reconstitution inflammatory syndrome (TB IRIS) and systemic sepsis may also contribute to liver dysfunction (8-10).

**Clinical presentation and diagnosis of DILI:**

Clinical presentation of DILI is non-specific and initially indistinguishable from liver injury due to other causes, like viral hepatitis (11, 12). DILI should always be considered in patients with liver dysfunction (13), especially in patients with
HIV infection and/or tuberculosis. There is no diagnostic test to distinguish DILI from other causes of liver dysfunction. Careful history taking (with focus on timing of initiation of all treatment regimens, including herbal medication and timing of symptom onset in relation to medication), physical examination and focused clinical investigations should rule out other causes of liver injury before making the diagnosis of DILI (13, 14).

**Mechanisms of DILI:**

Mechanisms of DILI are complex and poorly understood. It is likely that each drug has a unique mechanism of causing toxicity, which determines clinical presentation. Several drug targets have been identified and the pattern of cell injury depends on which target is affected by a specific drug. Each target triggers a different mechanism and thus a different pattern of hepatocyte injury. Manifestations of DILI in individuals are further influenced by demographic factors, genetic susceptibility and environmental factors (11, 13, 15, 16). First-line treatment for active TB in South Africa, includes rifampicin, isoniazid, ethambutol and pyrazinamide (17). Rifampicin, isoniazid and pyrazinamide are known hepatotoxic drugs. Isoniazid is thought to cause DILI through its toxic metabolites, acetylhydrazine or hydrazine (18). It is not well understood how rifampicin and pyrazinamide cause DILI (12). Antiretroviral treatment in South Africa includes nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI). NNRTI drugs (efavirenz and nevirapine) most commonly cause an allergic hepatitis, which is associated with rash and systemic symptoms (19). NRTI drugs (stavudine, didanosine, zidovudine and tenofovir), may cause mitochondrial toxicity with prolonged exposure, which results in a fatty liver
(20). This usually results in moderate elevations of liver enzymes. Importantly it has also been shown that ART naïve HIV-infected patients have underlying mitochondrial damage on liver biopsy (21): this may predispose to NRTI damage. It is unknown how PI’s cause DILI and occurrence of DILI varies with specific PI used (7). Depending on the mechanism of DILI, there may be mainly hepatocellular injury, cholestatic injury or a mixed pattern. This manifests as either a rise in transaminases (alanine transaminase [ALT] and aspartate aminotransferase [AST]) in the case of hepatocellular injury, a rise in cholestatic enzymes (gamma glutamyl-transpeptidase [GGT], alkaline phosphatase [ALP] and or/total bilirubin [TBR]) in the case of cholestatic injury or rise in both (mixed picture).

Management of DILI:

If liver injury is severe, treatment needs to be interrupted. Failure to interrupt the offending drug may result in death (22). Treatment interruption for TB and or HIV carries the risk of disease progression and death (6) and drug resistance. Once liver enzymes have normalized, relevant treatment needs to be re-introduced, usually in a step-wise manner. Details of management and drug re-challenge will not be discussed in this literature review.
Occurrence of TB treatment associated DILI (TB DILI) and HIV as a risk factor for TB DILI:

a) Observational studies that included HIV-infected and HIV-uninfected patients (but HIV testing was not routinely done) and reported tuberculosis treatment-associated drug-induced liver injury (TB DILI): (summarized in table 1)

Schaberg et al retrospectively reviewed a cohort of 519 hospitalized TB patients in Germany. 200 patients were tested for HIV and 9 were HIV positive. Patient records were reviewed for adverse events severe enough to interrupt TB treatment and 55 (11%) cases of hepatotoxicity meeting this criterion occurred. HIV infection was not found to be a risk factor for development of severe adverse events, but the number of HIV-infected patients in this cohort was small (23).

A study by Yee et al in Canada reported on all serious side effects of first line tuberculosis treatment, which resulted in the treatment being stopped or adjusted, and amongst these was hepatotoxicity. HIV infection had an adjusted hazard ratio (aHR) of 3.8 (95% confidence interval [CI] 1.05-13.4) for the development of serious adverse events on TB treatment. The hazard ratio of HIV infection for the development of DILI, specifically, was not reported (24).

A study in Malaysia by Marzuki et al, report a 9.7% prevalence of TB DILI in a retrospective cohort of 473 TB patients. They selected all 46 cases of TB DILI and then randomly selected 138 controls in a nested case control study. They reported HIV infection as a significant independent risk factor for developing TB DILI with an odds ratio of 3.54 (95% CI = 1.25-10.05). There were 9 (20%) HIV-infected persons amongst the DILI cases and 8 (6%) amongst the controls (25).
De Castro et al reported 30 cases of DILI in a prospective cohort of 154 TB patients in Brazil. 19 cases of DILI occurred amongst 60 HIV-infected persons and 11 amongst 94 HIV uninfected persons. In this study HIV infection was an independent risk factor for the development of TB DILI with a risk ratio of 2.72 (95% CI=1.39-5.28) (26).

In an Iranian study by Baghaei et al, a TB DILI incidence of 13% was reported in a prospective cohort study of 761 patients. The definition used for diagnosis of DILI was not clear. Few patients were tested for HIV infection. Amongst those who were tested, DILI occurred in 7/43 (16%) HIV positive patients and in 54/196 (28%) HIV negative patients. HIV was not reported as a risk factor for TB DILI in this study (27).

Tostmann et al enrolled 112 TB patients prospectively in Tanzania and found no cases of DILI. There was a low HIV co-infection rate with 11 patients HIV co-infected, and none were taking ART at the start of the study. 6 participants started efavirenz based ART during the course of the study. Patients were only followed during the two-month intensive phase of TB treatment (28).

In a prospective study reported by Lorent et al in Rwanda there were 24 (9.5%) episodes of DILI amongst 253 tuberculosis cases. Twenty-two (8.7%) of these episodes occurred amongst HIV-infected patients. Two thirds of the cohort (167) people were HIV-infected. A third of HIV-infected patients were on ART at time of initiation of TB treatment, a third started ART during intensive phase of TB treatment and virtually all patients were on cotrimoxazole prophylaxis. HIV infection was an independent predictor for serious adverse events during first line tuberculosis treatment; in this cohort 64 (23%) patients developed serious adverse events and 58 of these patients were HIV-infected. The adjusted hazard
ratio for HIV as a predictor of serious adverse events was 2.43 (95% CI = 1.35-8.67; p-value = 0.009) (29).

b) Studies that directly compared TB DILI in HIV-infected and HIV uninfected patients (HIV testing routinely done): (summarized in table 2)

Perriens et al enrolled 523 TB patients prospectively in Zaire. 335 patients were HIV co-infected and this was prior to availability of ART. They do not mention the definition of hepatitis, but state that no hepatitis was seen in the cohort, although increased levels of ALT, AST and bilirubin was sometimes seen. These liver enzyme elevations were not significantly associated with HIV infection (30).

In a prospective cohort study conducted in Haiti in 1990, Chaisson et al enrolled 427 TB patients of which 177 were HIV-infected. They found similar rates of DILI in both groups: 12% in the HIV-infected TB patients and 9% (not statistically significant) in the uninfected group. This was prior to availability of ART (31).

A retrospective study by Breen et al in the United Kingdom compared the occurrence of grade 3 and 4 adverse events (AE) during TB therapy between 156 HIV-TB co-infected patients and 156 HIV negative TB patients treated at the same facilities. They found an increased number of grade 3 and 4 adverse events amongst TB-HIV co-infected patients, 40% vs. 26% (p=0.008). However, there were 20 cases of DILI in each group and no excess treatment interruptions in the HIV-infected group. Seventeen co-infected patients had treatment interrupted due to DILI vs. 20 in the HIV negative group. Twenty-nine HIV-infected patients were on ART at initiation of TB treatment and a further 82 started ART within a median of two months of starting TB treatment. Of note, when stratified by
ethnic group, the black African population showed a difference between the groups, with more grade 3 and 4 AE’s and more TB treatment interruptions in those HIV-infected, 43% vs. 21%, and 13% vs. 6%, respectively. The numbers of DILI cases in the black African group was not reported (32).

A prospective study in Ethiopia by Yimer at al enrolled 197 consecutive TB patients. All patients were tested for HIV and 103 (52.3%) were HIV positive. 34 cases of DILI occurred and 26 were in HIV-infected persons. HIV was an independent risk factor for developing TB DILI in multivariate analysis with an adjusted odds ratio of 3.6 (95% CI=1.5-8.5; p=0.002). There was no mention of antiretroviral therapy in this paper despite 80% of patients having a CD4 cell count of less than 200 cells/mm³ (33).

A Brazilian case-control study by Coca et al analysed a cohort of 30 HIV positive TB patients and compared the occurrence of DILI with a control group of 132 HIV negative TB patients. They assessed the presence of DILI by using three different definitions of hepatotoxicity. The definitions were: a) ALT > three times the lower limit of normal (LLN), b) ALT > three times the upper limit of normal (ULN) and c) ALT >3 times ULN plus total bilirubin >2 ULN. The first definition is not clinically relevant. Hepatotoxicity, using definition b) occurred in 6 (20%) HIV-infected and 12 (9.1%) uninfected persons and using definition c) in 6 (20%) HIV-infected and 11 (8.3%) uninfected persons. There was no mention of antiretroviral therapy or CD4 counts in this paper. HIV was not a risk factor for developing hepatotoxicity in this study (34).
Identifying risk factors for DILI in HIV-TB co-infected patients:

Studies that included only HIV-TB co-infected patients: (summarized in table 3)

Dean et al retrospectively reviewed 188 HIV-TB co-infected patients treated at HIV clinics in London from 1996-1999. 15% of patients were on ART at start of TB treatment and 45% started ART during TB therapy at a median of 2 months. Details of therapy were only available for 99 patients and of these 11 experienced DILI. In multivariate analysis female gender (OR 2.03; 95% CI=1.09-3.77) and concomitant TB and HIV treatment (OR 1.88; 95%=1.03-3.42) were independently associated with the development of adverse events (35).

Tostmann et al reports on hepatotoxicity in a randomized controlled trial initially reported by Boeree et al (36). The trial investigated cotrimoxazole prophylaxis at different doses in newly diagnosed smear positive TB patients. All patients were HIV-infected, but none were taking ART. They report 3 cases of grade 3 DILI and none with grade 4 DILI. 25% of patients either died or were lost to follow up during the trial and those who were lost to follow up were more likely to have had a high ALT at inclusion. It is likely that the rate of DILI in this trial was underestimated and DILI could have been due to TB medication or cotrimoxazole prophylaxis (37).

Pukenyte et al performed a retrospective observational study in France to determine the incidence and risk factors for severe liver toxicity in HIV-TB co-infected patients. One hundred and forty four patients who were treated for TB at 6 different hospitals over a 12-year period were included. The majority of patients were not on ART. Of 25 patients who were on ART 3 developed DILI. Concomitant treatment with ART was not associated with increased risk of DILI.
In multivariate analysis, independent risk factors for liver toxicity were abnormal ALT at baseline with adjusted hazard ratio (aHR) = 3.86 (95% CI=1.15–12.88; p=0.028), increased baseline billirubin levels with aHR = 4.34 (95% CI=1.13–16.7; p=0.033), and the concomitant use of fluconazole with TB treatment, aHR = 4.90 (95% CI=1.52–15.86; p=0.008) (38).

Moses et al performed a retrospective observational study in Malawi, which included all new adult TB patients (n=156) registered in a rural hospital from June – December 2007. Patients were HIV-infected; ART-naive and received nevirapine based ART during TB treatment. Malawi used a fixed dose combination of stavudine, lamivudine and nevirapine as first line ART. Two patients developed grade 2 hepatotoxicity and 1 developed grade 3 toxicity, which was an incidence rate for grade 2-4 hepatotoxicity of 4.2 per 10 years of follow up, 95% CI=1.4-13.1 (39).

Mankhatitham et al analyzed the hepatotoxicity data of the N2R trial conducted by Manosuthi et al (40). The N2R trial was a randomized controlled trial in Thailand which enrolled 142 HIV-infected TB patients receiving rifampicin based TB treatment during 2006 & 2007. Patients were randomized to start either nevirapine or efavirenz based ART. These patients had a high rate of chronic viral hepatitis. Five percent had chronic hepatitis B and 25% had chronic hepatitis C infection at baseline. There were 9 episodes of grade 3 or 4 transaminitis or hyperbilirubinaemia. Chronic hepatitis C at baseline was the only independent predictor of hepatotoxicity in this study with an adjusted odds ratio = 3.03 (95% CI=1.26-7.29) (41).

Yimer et al studied a prospective cohort of Ethiopian patients enrolled from 2004-2007. All patients were started on rifampicin based TB treatment and then
started on efavirenz based ART within 8 weeks of starting TB treatment. Out of 373 patients 20 developed severely elevated (more than 5 times the ULN) transaminases (likely TB DILI) prior to starting ART and were excluded from the analysis. The reason for this was that the investigators wanted to assess risk factors for developing DILI on concomitant TB treatment and ART. There were 106 cases of DILI on concomitant TB treatment and ART, of which 65 were severe DILI with transaminases more than 5 times the ULN. They identified female sex, low BMI, high efavirenz levels, high pre-treatment ALT/AST, low hemoglobin (Hb) and low albumin to be associated with development of DILI. It is not clear whether this was on univariate or multivariate analysis. They also performed a case control study analysing genetic variants with respect to drug metabolising status and found slow acetylation status, CYP2B6*6/*6 and ABCB13435TT genotypes to be predictors of DILI in this population. It is not clear how the patients were selected from the cohort for this case control study (42).
Concomitant TB treatment as a risk factor for DILI in patients on ART:
Comparing DILI in patients on ART alone vs. patients on ART and TB
treatment: (summarized in table 4)

Hoffman et al retrospectively reviewed a cohort of 868 HIV-infected patients in South Africa in an occupational setting (mainly men), who accessed ART through a workplace programme. Twenty five percent of patients were on concomitant TB treatment and 17% of a randomly selected sub-group were hepatitis B co-infected. They found concomitant TB treatment and chronic hepatitis B infection to be independent predictors of grade 3 or 4 DILI with an adjusted hazard ratio of 8.5 (95% CI=2.7–27; p=<0.001) and 3.0 (95% CI=1.3–7.0; p=0.016) respectively (43).

Shipton et al performed a retrospective observational study in Botswana, analysing all patients in HIV care at a hospital in Gaborone from 2001 to 2004. They included all patients who were initially TB treatment and ART naïve and then started TB treatment during the study period and received concomitant ART. The control group with similar distribution of HIV viral load values were patients who received only ART treatment. TB treatment was initiated at a median of 81 days prior to ART. There were more episodes of hepatotoxicity in the group with concomitant TB treatment and ART as opposed to the ART-only group; 9% vs. 3% with p=0.05. Of note, there was no difference in rate of hepatotoxicity between patients taking efavirenz or nevirapine-based ART in either group (44).

Chu et al analyzed data from three large primary care ART clinics in the Western Cape province of South Africa to determine the occurrence of early hepatotoxicity on ART amongst 1809 ART naïve patients initiating nevirapine
based ART. Early hepatotoxicity was defined as ALT grade 0-2 at baseline, which increased to grade 3 or 4 within 102 days of starting ART. Early hepatotoxicity occurred with an incidence rate of 3.6-7.6 per 100 person years at the 102-day time point, depending on how regularly LFT’s were measured. Concurrent TB treatment was not a risk factor for development of DILI in this study. The number of patients on concurrent TB treatment is not mentioned in the study, but 4 of the 26 cases of DILI occurred in patients on TB treatment (45).

Kalyesubula et al enrolled 240 ART-naive patients prospectively in Uganda and monitored liver function after starting ART. Two hundred and thirty eight patients (99.2%) were receiving cotrimoxazole prophylaxis and 13 (5%) received concomitant TB treatment. Patients on concomitant ART and TB treatment were more likely to develop DILI with an odds ratio of 16.0 (95% CI; 2.4-104.2, P<0.01) (46).

Mugusi et al performed a prospective study in Tanzania and classified 473 ART-naive HIV-infected patients with CD4 count < 200 cells/µL into 2 clinical categories, HIV only (n=253) and HIV-TB co-infected (n=220). There were 37 episodes of DILI of which 22 (10% incidence) occurred in the HIV-TB co-infected group and 15 (5.9% incidence) in the HIV-only group. This suggests more DILI in HIV-TB co-infected patients although this difference was not statistically significant (p-value = 0.07). Predictors of DILI in this cohort were chronic hepatitis C infection, higher WHO stage at presentation, history of weight loss and CYP2B6*6 genotype (47).
Discussion:

The incidence of TB DILI in HIV-infected and uninfected patients is not frequently reported and varies (range 0-19.5%), depending on the definition for DILI. Studies reporting the occurrence of TB DILI, which includes both HIV-infected and HIV uninfected participants, report conflicting data regarding HIV as a risk factor for TB DILI. Some studies report HIV infection as an independent risk factor for TB DILI and thus higher rates of TB DILI in HIV positive patients (with estimates of roughly two-fold increase among HIV-infected), while other studies report similar rates of TB DILI in the HIV-infected and uninfected TB patients. No obvious reason was found for this discrepancy in the literature reviewed. Genetic factors and other differences between the populations studied could be responsible for this discrepancy.

In studies including only HIV-TB co-infected patients several risk factors have been identified to be independently associated with development of DILI across different studies: female sex, concomitant TB treatment and ART, elevation of baseline ALT and AST, fluconazole use, higher plasma efavirenz level, higher efv/8-hydroxyefavirenz ratio, lower baseline hemoglobin, lower serum albumin, NAT2 slow-acetylator genotype and ABCB1 3435TT genotype. However, only a few studies have reported pharmacogenetic profiling of patients who develop DILI.

Several studies which compared patients on ART alone to patients on ART and TB treatment, report conflicting data regarding the risk of concomitant TB treatment and ART for the development of DILI. All the studies assessed for this aspect of the literature review were from the African continent and again there was no obvious explanation found for the discrepancies reported. It may be due
to genetic and other differences between populations studied, or differences in the case definitions used for DILI.

**Conclusion:**

Drug induced liver injury is a poorly understood clinical entity and the cause of a substantial burden of disease. Mechanisms by which most drugs cause liver injury are unknown. Some risk factors for development of drug induced liver injury have been described. However, more studies are needed to better define mechanisms and risk factors for DILI. The role of HIV infection in development of TB DILI and the role of concomitant TB treatment and ART in the development of DILI need to be clarified.

**References:**


Table 1: Observational studies that included HIV-infected and HIV-uninfected patients (but HIV testing was not routinely done) and reported tuberculosis treatment-associated drug-induced liver injury (TB DILI):

<table>
<thead>
<tr>
<th>Reference Country</th>
<th>n</th>
<th>DILI among HIV positive</th>
<th>DILI among HIV negative</th>
<th>DILI Total</th>
<th>ART</th>
<th>HIV a significant risk factor for DILI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(23) Germany</td>
<td>519</td>
<td>NR/9</td>
<td>NR/191</td>
<td>55 (11%)</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>(24) Canada</td>
<td>430</td>
<td>NR/18</td>
<td>NR/149</td>
<td>12 (2.8%)</td>
<td>NR</td>
<td>1\textsuperscript{No}</td>
</tr>
<tr>
<td>(25) Malaysia</td>
<td>473</td>
<td>9/46 HIV-infected among DILI patients</td>
<td>8/138 HIV-infected among controls</td>
<td>46 (9.7%)</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>(26) Brazil</td>
<td>154</td>
<td>19/60</td>
<td>11/94</td>
<td>30 (19.5%)</td>
<td>29 on ART\textsuperscript{3}</td>
<td>Yes</td>
</tr>
<tr>
<td>(27) Iran</td>
<td>761</td>
<td>7/43</td>
<td>54/196</td>
<td>99 (13%)</td>
<td>NR</td>
<td>No</td>
</tr>
<tr>
<td>(28) Tanzania</td>
<td>112</td>
<td>0/11</td>
<td>0/90</td>
<td>0</td>
<td>6 started ART during study</td>
<td>No</td>
</tr>
<tr>
<td>(29) Rwanda</td>
<td>253</td>
<td>22/167</td>
<td>2/86</td>
<td>24 (9.5%)</td>
<td>65 on ART; 55 started ART during study</td>
<td>Yes\textsuperscript{4}</td>
</tr>
</tbody>
</table>

Legend for table 1:
n=number of patients in study.
DILI: Drug induced liver injury
DILI Total: Drug induced liver injury cases in total.
NR= not reported.
\textsuperscript{1}Not statistically significant with adjusted hazard ratio [aHR]=4.3 (95\% confidence interval [CI] 0.5 – 38). HIV was shown to be a risk factor for development of grade 3 or 4 adverse events with aHR =3.8 (95\% CI 1.05-13.4)
\textsuperscript{2}All cases of DILI were selected from the cohort and then controls were randomly selected for a case control study. Nine out of 46 patients with DILI were HIV-infected and 8 out of 138 controls were HIV-infected.
\textsuperscript{3}All remaining patients except one started ART during TB treatment.
\textsuperscript{4}HIV infection was an independent risk factor for development of serious adverse events (not DILI specifically) with aHR = 2.43 (95\% CI = 1.35-8.67; p-value = 0.009).
Table 2: Studies that directly compared tuberculosis treatment-associated drug-induced liver injury (TB DILI) in HIV-infected and HIV-uninfected patients (HIV testing routinely done):

<table>
<thead>
<tr>
<th>Reference Country</th>
<th>n</th>
<th>DILI among HIV positive</th>
<th>DILI among HIV negative</th>
<th>DILI Total</th>
<th>ART</th>
<th>HIV a significant risk factor for DILI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(30) Zaire</td>
<td>523</td>
<td>0/335</td>
<td>0/188</td>
<td>0</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>(31) Haiti</td>
<td>427</td>
<td>12% of 177</td>
<td>9% of 250</td>
<td>21% of 427</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>(32) United Kingdom</td>
<td>312</td>
<td>20/156</td>
<td>20/156</td>
<td>40</td>
<td>111</td>
<td>No</td>
</tr>
<tr>
<td>(33) Ethiopia</td>
<td>197</td>
<td>26/103</td>
<td>8/94</td>
<td>34</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td>2(34) Brazil</td>
<td>162</td>
<td>6/30</td>
<td>12/132</td>
<td>18</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>

Legend for table 2:
n=number of patients in study
DILI: Drug induced liver injury
DILI Total: Drug induced liver injury cases in total
NR: Not reported
129 on ART at the start of the study and 82 patients started on ART during study at a median of 2 months after initiating TB treatment.
2Three different definitions for DILI were used in this paper. The number of cases for definition b) reported in table, see detail in text.
Table 3: Identifying risk factors for DILI in HIV-TB co-infected patients: Studies that included only HIV-TB co-infected patients:

<table>
<thead>
<tr>
<th>Reference Country</th>
<th>n</th>
<th>ART</th>
<th>DILI Total</th>
<th>Factors associated with increased risk to develop DILI</th>
</tr>
</thead>
</table>
| United Kingdom    | 188 | 15% on ART; 45% started ART during TB treatment | 11 (5.9%)  | ¹Female sex: OR=2.03; 95% CI 1.09-3.77  
Concomitant TB treatment and ART: OR=1.88; 95% 1.03-3.42 |
| Malawi            | 579 | No ART                               | ≥8 (1.4%)  | Not reported                                         |
| France            | 144 | 25 on ART                            | 15 (10.4%) | Abnormal baseline ALT (p=0.028) and BR levels (p=0.033) 
Fluconazole use (p=0.008) |
| Malawi            | 156 | All patients started NVP based ART during TB treatment | 3 (2%)    | Not reported                                         |
| Thailand          | 142 | All patients started NVP or EFV based ART | 9 (6.3%)  | HCV co-infection (aOR 3.03; 95%CI 1.26-7.29)          |
| Ethiopia          | 353 | All patients started ART within 8 weeks of starting TB treatment | 106 (30%) 
106 (18.4%) | ³Female sex (p = 0.001), higher plasma EFV level (p = 0.009), efv/8-hydroxyefavirenz ratio (p = 0.036), 
raised baseline AST (p = 0.022), and ALT (p = 0.014), 
lower Hb (p = 0.008), and serum Alb (p = 0.007), 
NAT2 slow-acetylator genotype (p = 0.039)and 
ABCB1 3435TT genotype (p = 0.001) |

Legend for table 3:
n=number of patients in study  
ART: Antiretroviral therapy  
DILI: Drug induced liver injury  
DILI Total: Drug induced liver injury cases in total  
OR: Odds ratio; aOR: Adjusted odds ratio  
CI: Confidence interval  
ALT: Alanine transaminase; BR: Bilirubin; AST: aspartate aminotransferase;  
Alb: Albumin  
NVP: Nevirapine; EFV: Efavirenz  
HCV: Hepatitis C virus  
BMI: Body mass index  
Hb: Hemoglobin  
¹Predictors of adverse events reported in this study, not predictors of DILI.  
²Grade 2 and 3 hepatotoxicity reported here.  
³Unclear whether this was in univariate or multivariate analysis.
Table 4: Concomitant TB treatment as a risk factor for DILI in patients on ART: Comparing DILI in patients on ART alone vs. patients on ART and TB treatment:

<table>
<thead>
<tr>
<th>Reference Country</th>
<th>n</th>
<th>DILI among patients on ART only</th>
<th>DILI among patients on concomitant TB treatment and ART</th>
<th>DILI Total</th>
<th>Concomitant TB treatment and ART a significant risk factor for DILI?</th>
</tr>
</thead>
<tbody>
<tr>
<td>(43) South Africa</td>
<td>868</td>
<td>NR</td>
<td>NR</td>
<td>140</td>
<td>Yes</td>
</tr>
<tr>
<td>(44) Botswana</td>
<td>310</td>
<td>3%</td>
<td>9%</td>
<td>18</td>
<td>Yes</td>
</tr>
<tr>
<td>(45) South Africa</td>
<td>1809</td>
<td>22/?</td>
<td>4/?</td>
<td>26</td>
<td>No</td>
</tr>
<tr>
<td>(46) Uganda</td>
<td>240</td>
<td>7/227</td>
<td>3/13</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>(47) Tanzania</td>
<td>473</td>
<td>15/253 (5.9%)</td>
<td>22/220 (10%)</td>
<td>37</td>
<td>No</td>
</tr>
</tbody>
</table>

Legend for table 4:
n=number of patients in study
ART: Antiretroviral therapy
DILI: Drug induced liver injury
TB: Tuberculosis
DILI Total: Drug induced liver injury cases in total
NR: Not reported

1 Number of patients with grade 3 or 4 hepatitis reported here.
Burden of antituberculosis and antiretroviral drug-induced liver injury at a secondary hospital in South Africa

Charlotte Schutz, Zahiera Ismail, Charles John Proxenos, Suzaan Marais, Rosie Burton, Chris Kenyon, Gary Maartens, Robert J Wilkinson, Graeme Meintjes

Background. G F Jooste Hospital (GFJH) is a secondary-level referral hospital in a high HIV and tuberculosis (TB) co-infection setting. The TB prevalence is high at initiation of ART: 2 clinics in Cape Town reported concomitant TB treatment (TBT) in 25% and 40% of patients, respectively, at time of ART initiation.5,6 In SA, 42% of HIV-positive TB cases received both ART and TBT in 2009, compared with 18% in 2008.3

An estimated 34 million people are HIV-infected globally; South Africa (SA) carries the highest burden with an estimated 5.6 million people infected.1 A major scale-up of public sector antiretroviral therapy (ART) among patients presenting with liver dysfunction at GFJH and to describe management and outcomes.

Methods. A retrospective observational study was performed of all cases referred to GFJH with significant liver dysfunction from 1 January to 30 June 2009. Significant liver dysfunction was defined by alanine transaminase (ALT)≥200 U/l or total bilirubin (TBR)≥44 µmol/l. TBT- or ART-associated DILI was defined as significant liver dysfunction attributed to TBT and/or ART and which resulted in the halting of treatment or the adjustment thereof. Outcome measures included case numbers, descriptive data, and in-hospital and 3-month mortality.

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Results. A total of 318/354 cases of significant liver dysfunction were reviewed: 71 were classified as TBT- or ART-associated DILI, while liver dysfunction was attributed to other causes in the remainder. In-hospital and 3-month mortality of TBT- or ART-associated DILI patients was 27% (n=19) and 35% (n=25), respectively. The majority of deaths were related to sepsis or sepsis complicating liver dysfunction. Twenty-three patients (32%) were lost to follow-up; 23 (32%) were alive and in outpatient care 3 months after presentation.

Conclusions. TBT- or ART-associated DILI is a common reason for presentation at a referral hospital in South Africa. In-hospital and 3-month mortality are high. Prospective studies are needed to define optimal management.

Laboratory Service laboratory from 1 January to 30 June 2009 were reviewed. Hepatocellular injury is characterised by a marked rise in serum transaminases, aspartate aminotransferase (AST) and alanine transaminase (ALT). Cholestatic liver injury is characterised by a rise in alkaline phosphatase, gamma-glutamyltransferase and/or raised total bilirubin (TBR). Significant hepatocellular injury and cholestatic injury was defined as resulting in a Grade 3 or 4 elevation of ALT>200 U/l (>5 times the normal upper limit) and TBR>44 µmol/l (>2.5 times the normal upper limit), respectively. Patients who fulfilled one or both criteria were included. Sepsis was documented when clinical presentation was compatible and the admitting team managed infection as the primary cause of illness. Hepatic encephalopathy was documented by the admitting team.

Patients were reviewed and data recorded on a standardised form. DILI was attributed to TBT or ART if either regimen was interrupted or adjusted. Cases not classified as TBT- or ART-associated DILI were classified as ‘liver dysfunction due to other causes’. This included: (i) patients receiving TBT and ART and diagnosed with hepatic TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), (ii) patients presenting with untreated disseminated TB, (iii) patients receiving TBT and/or ART and presenting with liver injury with no subsequent change or discontinuation of TBT or ART, and (iv) patients diagnosed with alternative causes of liver dysfunction.

The University of Cape Town Human Research Ethics Committee approved the study (HREC ref: 522/2009). Statistical analyses were conducted with STATA 11.1 software (2009).

Management

Patients receiving TBT and ART were managed at primary care clinics according to national treatment guidelines. Patients with significant symptoms or signs suggestive of DILI were referred to GFJH. Patients were admitted or managed as outpatients depending on clinical severity and LFT results. GFJH has an infectious diseases referral clinic with capacity to manage stable DILI patients as outpatients.

In patients with TBT-associated DILI, a decision was made to cease treatment temporarily or to switch to alternative and less hepatotoxic treatment. Cesation of TBT was defined as discontinuation of all TBT for longer than a day. In patients whose treatment had been interrupted, a less hepatotoxic regimen, typically consisting of streptomycin, ethambutol and ofloxacin, was usually commenced once LFT results improved. Rifampicin and isoniazid was then ‘re-challenged’ in a stepwise manner after LFT results normalised. Rifampicin or isoniazid was started at a low dose and increased to full dose over a few days with concurrent monitoring of ALT. This was followed by similar introduction of the second drug. Once full-dose rifampicin and isoniazid were re-introduced, certain of the less hepatotoxic drugs were discontinued. Optimal TBT was defined as rifampicin-based therapy.

Depending on the suspected cause and severity of ART-associated DILI, generally either: (i) ART was ceased, (ii) a single drug substitution was made, or (iii) more hepatotoxic ART (e.g. nevirapine) was interrupted and replaced within a few days (e.g. by efavirenz 5 - 7 days later), while less hepatotoxic ART (e.g. stavudine and lamivudine) was continued. Optimal ART was defined as triple ART medication from at least 2 classes.

Outcome assessment

Clinical management and outcome data were ascertained by review of patient records. In-hospital and 3-month (within 90 days of presentation) mortality were recorded, including the cause of death where possible. Only in-hospital mortality was recorded for patients with liver injury due to other causes. Three-month retention in care was also recorded. In the case of TBT and/or ART-associated DILI, the Clinicom and eKapa electronic databases were consulted to ascertain follow-up and mortality documented elsewhere in the Western Cape. Loss to follow-up was defined as inability to trace any patient data after discharge, within 3 months of presentation.

Results

A total of 354 patients met the criteria for inclusion; 36 (10.2%) were excluded due to incomplete or missing records. Of 318 cases reviewed, 71 were classified as TBT- and/or ART-associated DILI. In 247 cases, liver injury was attributed to other causes (Fig. 1). Among many other causes of liver injury, the most common was sepsis-induced liver dysfunction, evident from clinical presentation and LFT results; 27 patients receiving TBT or ART were not diagnosed with TBT- or ART-associated DILI because no alteration was made to TBT or ART.

![Fig. 1. Hepatitis or cholestasis: description of the cohort. TB = tuberculosis; TBT = TB treatment; ART = antiretroviral therapy; DILI = drug-induced liver injury.](image)

Baseline characteristics

Of the 318 patients, 47% were women and 41% were HIV-infected (Table 1). At presentation, 18% were receiving ART, 26% were receiving TBT and 10% were receiving concomitant TBT and ART. ART regimens included: (i) stavudine (or zidovudine), lamivudine and efavirenz (n=17; 53%); (ii) stavudine (or zidovudine), lamivudine and nevirapine (n=9; 28%); and (iii) protease inhibitor (PI)-based ART (n=4; 13%). Three patients receiving TBT were treated with...
PI-based ART and thus double-dose lopinavir/ritonavir. In the TBT- or ART-associated DILI category, a history of cotrimoxazole prophylaxis was available in 48/60 (80%) of the HIV-seropositive patients, and of these, 28 (47%) were receiving cotrimoxazole at presentation. Fifty-seven (80%) patients in this category were screened for hepatitis B surface antigen; 8 (14%) were positive.

Clinical presentation and management

Median length of hospital stay was 13 days (interquartile range (IQR) 7 - 20) in the 87% of TBT- or ART-associated DILI patients who were admitted. Patients presented as follows: 56 (79%) with cholestasis (TBR≥44 µmol/l), 31 (44%) with hepatocellular injury (ALT≥200 U/l) and 18 (25%) with both. Fifteen (21%) had hepatic encephalopathy (Table 2). One or more possible alternate causes of liver dysfunction, including sepsis and TB-IRIS, were documented in 53 (75%) of patients.

TBT was ceased in 29 (49%) patients, with a median of 16.5 (IQR 14 - 26) days off optimal treatment. Less hepatotoxic TBT was initiated in 38 (64%) patients prior to re-challenge with rifampicin/isoniazid. Change in ART was individualised and varied widely.

Optimal rifampicin-based TBT was not re-introduced in 27/59 (45.8%) patients who presented while receiving TBT, for the following reasons: (i) death (n=14), (ii) transfer to another facility without particulars of subsequent re-challenge (n=5), (iii) absence of evidence for initial TB diagnosis (n=4), (iv) discharge with less hepatotoxic TBT and intention to re-challenge at a later stage (n=2), (v) presentation of DILI while receiving less hepatotoxic TBT which was continued while ART was adjusted (i.e. managed as ART-associated DILI) (n=1), (vi) completion of TBT (n=1), or (vii) patient absconded (n=1).

ART was interrupted in 11 patients (34%) and altered in 23 (74%). Patients spent a median of 25 (IQR 7 - 40) days off optimal ART (triple therapy). In 27 (38%) TBT- or ART-associated DILI patients, additional investigations were performed, including abdominal ultrasound (n=24), computed tomography (CT) of the abdomen (n=2), and liver biopsy (n=1); performed during DILI relapse. Patients who were discharged and followed up as outpatients (n=21, 29.6%) had a median of 4.5 visits in the 3 months following presentation. Seven (9.9%) patients had subsequent relapse of hepatitis.

**Table 1. Baseline characteristics of patients who presented with cholestasis or hepatitis**

<table>
<thead>
<tr>
<th></th>
<th>Total (N=318)</th>
<th>TB or ART* (n=71)</th>
<th>Other (n=247)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), median (IQR)</td>
<td>39 (30 - 50)</td>
<td>39 (30 - 43)</td>
<td>39 (29 - 54)</td>
</tr>
<tr>
<td>Sex: female, n (%)</td>
<td>165 (51.9)</td>
<td>44 (62)</td>
<td>121 (49)</td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tested for HIV, n (%)</td>
<td>190 (59.7)</td>
<td>69 (97.2)</td>
<td>121 (49)</td>
</tr>
<tr>
<td>HIV-positive, n (%)</td>
<td>144 (45.3)</td>
<td>60 (84.5)</td>
<td>84 (34)</td>
</tr>
<tr>
<td>HIV-negative, n (%)</td>
<td>46 (14.5)</td>
<td>9 (12.7)</td>
<td>37 (15)</td>
</tr>
<tr>
<td>CD4 count, median (IQR)</td>
<td>59 (26 - 179)</td>
<td>75 (28 - 189)</td>
<td>57 (26 - 174)</td>
</tr>
<tr>
<td>Tested for hepatitis B surface antigen, n (%)</td>
<td>-</td>
<td>57 (80.3)</td>
<td>-</td>
</tr>
<tr>
<td>Positive, n (%)</td>
<td>-</td>
<td>8 (11.3)</td>
<td>-</td>
</tr>
<tr>
<td>Receiving ART at presentation, n (%)</td>
<td>63 (19.8)</td>
<td>32 (45.1)</td>
<td>31 (12.6)</td>
</tr>
<tr>
<td>Days of ART, median (IQR)</td>
<td>60 (30 - 251)</td>
<td>41 (29 - 81)</td>
<td>105 (38 - 565)</td>
</tr>
<tr>
<td>Receiving TBT at presentation, n (%)</td>
<td>92 (28.9)</td>
<td>59 (83.1)</td>
<td>33 (13.4)</td>
</tr>
<tr>
<td>Days of TBT, median (IQR)</td>
<td>56 (20 - 129)</td>
<td>40 (15 - 89)</td>
<td>99 (32.5 - 158.5)</td>
</tr>
<tr>
<td>Regimen I TBT, n (%)</td>
<td>62 (19.5)</td>
<td>44 (62)</td>
<td>18 (54.6)</td>
</tr>
<tr>
<td>Regimen II TBT, n (%)</td>
<td>25 (7.8)</td>
<td>12 (17)</td>
<td>13 (39.4)</td>
</tr>
<tr>
<td>Concomitant TBT and ART, n (%)</td>
<td>36 (11.3)</td>
<td>20 (28.2)</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>Cotrimoxazole prophylaxis documented, n (%)</td>
<td>127 (39.9)</td>
<td>48 (67.6)</td>
<td>79 (32)</td>
</tr>
<tr>
<td>Receiving cotrimoxazole, n (%)</td>
<td>59 (18.6)</td>
<td>28 (39.4)</td>
<td>31 (12.6)</td>
</tr>
</tbody>
</table>

*Patients with TBT- and/or ART-associated DILI
†Regimen I TBT: 2 months of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 4 months of rifampicin and isoniazid.
‡Regimen II TBT: 2 months of rifampicin, isoniazid, pyrazinamide, ethambutol and streptomycin, followed by 1 month of rifampicin, isoniazid, pyrazinamide and ethambutol, followed by 5 months of rifampicin, isoniazid and ethambutol.
§Data were only captured for TBT- or ART-associated DILI.
¶TBT- or ART-associated DILI: 11 known HIV-infected patients with no available information about ART use. Other causes: 1 known HIV-infected patient with no available information about ART use.
|||8 patients with TBT- or ART-associated DILI: unknown duration of TBT.
**11 patients with TBT- or ART-associated DILI: unknown TB regimen.
††Cotrimoxazole prophylaxis documented in known HIV-infected patients.
### Table 2. Clinical presentation and management of TBT- or ART-associated DILI patients

<table>
<thead>
<tr>
<th>Admitted to hospital, n (%)</th>
<th>TBT- or ART-associated DILI (N=71)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>62</strong> (87.3)</td>
<td></td>
</tr>
<tr>
<td>Days in hospital, median (IQR)</td>
<td>13 (7 - 20)</td>
</tr>
<tr>
<td>Laboratory results at presentation</td>
<td></td>
</tr>
<tr>
<td>AST (U/l), median (IQR)</td>
<td>245 (117 - 628)</td>
</tr>
<tr>
<td>ALT (U/l), median (IQR)</td>
<td>157 (71 - 353)</td>
</tr>
<tr>
<td>Patients with ALT≥200 U/l, n (%)</td>
<td>31 (43.6)</td>
</tr>
<tr>
<td>GGT (U/l), median (IQR)</td>
<td>108 (61 - 292)</td>
</tr>
<tr>
<td>ALP (U/l), median (IQR)</td>
<td>110 (80 - 231)</td>
</tr>
<tr>
<td>TBR (µmol/l), median (IQR)</td>
<td>88 (50 - 128)</td>
</tr>
<tr>
<td>Patients with TBR≥44 µmol/l, n (%)</td>
<td>56 (78.9)</td>
</tr>
<tr>
<td>Patients with ALT≥200 U/l and TBR≥44 µmol/l, n (%)</td>
<td>18 (25.4)</td>
</tr>
<tr>
<td>INR performed at presentation, n (%)</td>
<td>42 (59.2)</td>
</tr>
<tr>
<td>INR, median (IQR)</td>
<td>1.7 (1.3 - 3)</td>
</tr>
</tbody>
</table>

#### Clinical features

- Hepatic encephalopathy, n (%) 15 (21.1)
- Case fatality rate, n (%) 8 (53.3)
- Differential diagnosis, n (%) 53 (74.7)
- Number of differential diagnoses, median (range) 2 (1 - 3)
- Patients receiving TBT, n (%) 59 (83)
  - Treatment completely interrupted, n (%) 29 (49.2)
  - Less hepatotoxic TBT initiated, n (%) 38 (64.4)
  - TB medication restarted, n (%) 32 (54.2)
  - Days off optimal TBT, median (IQR) 16.5 (14 - 26)
- Patients receiving ART, n (%) 32 (45)
  - Treatment completely interrupted, n (%) 11 (34.4)
  - Any change made to ART, n (%) 23 (71.9)
  - Days off optimal ART, median (IQR) 25 (7 - 40)
- Additional investigations performed, n (%) 27 (38)
  - USS abdomen 24 (33.8)
  - CT abdomen 2 (2.8)
  - Liver biopsy 1 (1.4)
- Outpatient follow-up visits, median (IQR) 4.5 (3 - 7)
- Relapse of hepatitis or cholestasis, n (%) 7 (9.9)
- Admitted to hospital, n (%) 5 (7)
- Days in hospital, median (IQR) 12 (12 - 21)
- Outpatient follow-up visits following relapse, median (IQR) 6 (5 - 8)

AST = aspartate aminotransferase; ALT = alanine transaminase; GGT = gamma-glutamyltransferase; ALP = alkaline phosphatase; TBR = total bilirubin; INR = international normalised ratio.

*Five (7.35%) patients had other reason contributing to high INR: warfarin therapy (n=2) and congestive cardiac failure (n=3).
*Case fatality rate in patients who presented with hepatic encephalopathy.
*Patients who had significant differential diagnoses at time of DILI.
*Significant differential diagnoses per patient.
*Rifampicin and isoniazid restarted.
**Rifampicin-based TBT.
***Including ART completely stopped.
††Triple therapy ART.
‡‡One patient had a liver biopsy at subsequent relapse of hepatitis.
§§Outpatient follow-up visits 3 months after presentation.
mortality of the cohort was 27% (The Kaplan-Meier survival estimate is shown in Fig. 3. In-hospital Patient outcomes and in care 3 months after presentation of relapse. 12 days (IQR 12 - 21); 1 died in hospital due to sepsis and 6 were alive with sepsis, of whom 14 were receiving TBT or ART.

patients died during admission. This included 34 patients admitted alive and in care, and 23 (32%) were lost to follow-up (Table 3).

months after presentation, 25 (35%) patients had died, 23 (32%) were and unknown (1, unexpected death after initial improvement). At 3 months after presentation, 25 (35%) patients had died, 23 (32%) were alive and in care, and 23 (32%) were lost to follow-up (Table 3).

In cases of ‘liver dysfunction due to other causes’, 71 (28.7%) patients died during admission. This included 34 patients admitted with sepsis, of whom 14 were receiving TBT or ART.

Table 3. Three-month outcomes of TB- or ART-associated DILI patients’ (N=71)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n (%)</th>
<th>Days, median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died during initial admission¹</td>
<td>19 (26.8)</td>
<td>8 (3 - 13)</td>
</tr>
<tr>
<td>Discharged; died within 3 months of presentation</td>
<td>6 (8.5)</td>
<td>59.5 (56 - 70)</td>
</tr>
<tr>
<td>Lost to follow-up within 3 months of presentation³</td>
<td>23 (32.4)</td>
<td>42 (18 - 57)</td>
</tr>
<tr>
<td>Discharged, alive and in care 3 months after presentation</td>
<td>23 (32.4)</td>
<td>-</td>
</tr>
</tbody>
</table>

¹Three months or 90 days from presentation with hepatitis or cholestasis.
²Days from presentation with hepatitis or cholestasis until death or loss to follow up.
³Lost to follow-up: no patient record available after discharge.
⁴Three patients who completed TB drug re-challenge died during admission.

Discussion
To our knowledge, this is the first study describing the management, outcome and high burden of TB- or ART-associated DILI at a referral hospital in a high TB/HIV prevalence community. Over 6 months there were 71 cases. This may reflect under-ascertainment, accepting that –

There are considerable risks associated with prolonged hospital stay in the context of advanced HIV infection, particularly nosocomial sepsis.⁵ We observed more cases of DILI related to TBT alone (n=39) than with ART alone (n=12) or concomitant ART and TBT (n=20), possibly reflecting that more patients were initiated on TBT than on ART in the hospital catchment area during the study period. Alternatively, TBT may be a more common cause of DILI.

Adding to the complexity, cotrimoxazole may also cause DILI; prophylactic treatment is often stopped during management of DILI, rendering patients vulnerable to opportunistic infections. Chronic hepatitis B is also an important co-factor in DILI; concomitant TBT significantly increases the risk of hepatotoxicity.⁹ Hepatitis B surface antigen was positive in a minority of cases in our study; 8/57 patients with TBT- or ART-associated DILI.

A striking finding was the high mortality associated with TBT- or ART-associated DILI (35% at 3 months after presentation) with a median time to death of 11 days (IQR 5 - 31). Mortality was likely under ascertained, as it is possible that some patients recorded as lost to follow-up really died. In comparison, mortality in a general cohort of patients with HIV-associated TB in our setting was only 8% during 6 months of TBT.⁸

In our study, the most common cause of death ascertained was sepsis, highlighting the vulnerability of patients with liver injury to bacterial and other infections. Close monitoring for community- and hospital-acquired bacterial infections and early diagnosis with appropriate antimicrobial treatment may improve outcome. Liver failure was the cause of death in only a minority of cases. Further studies are required to define reasons for the high mortality among DILI patients; this rate may reflect direct and indirect consequences
of DILI, or that DILI complicates poor prognoses owing to other disease-related factors.

We acknowledge several limitations of our study. The use of herbal, traditional or over-the-counter medication, all of which may cause liver injury, was poorly documented. A retrospective review has many limitations: data capture was limited to documentation by attending clinicians and 10% of records were not found for review.

**Conclusions**

Liver injury due to TBT- or ART-associated DILI necessitating referral to hospital was common and associated with high mortality in our study. The cause of liver injury in HIV-TB co-infected patients is likely multi-factorial and is complex to manage. Prospective studies are urgently needed to investigate optimal management strategies and improve outcomes of such patients. The use of early invasive investigations (e.g. liver biopsy) in the diagnosis and management of liver injury requires investigation.

**Acknowledgements.** Sources of support: Perinatal HIV Research Unit, the US Agency for International Development, and the President’s Emergency Plan for AIDS Relief (SM and CS), Wellcome Trust (RJW and GM, WT 081667, 084323 and 088316); a Fogarty International Center South Africa TB/AIDS Training Award (GM and CS, NIH/FIC 1U2RTW007373-01A1, U2RTW007373 ICORTA); a European Union Grant (RJW, SANTE/2005/105-061-102); and MRC (RJW, U1175.02.002.00014.01). The funders had no role in study design, data collection and analysis, decision to publish, or manuscript preparation.

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PART D: Appendices:

a. Acknowledgements:

Co-authors:

Graeme Meintjes, Robert J Wilkinson, Gary Maartens, Suzaan Marais, Rosie Burton and Chris Kenyon were all involved with study conception and planning of the study. Zahiera Ismail and Charles John Proxenos assisted with design and piloting of the data capture sheets. They also helped to capture data and with data entry. Graeme Meintjes and Suzaan Marais helped with reviews of the first rough drafts of the paper and Suzaan Marais helped with extensive reviewing of the second last draft of the paper. Graeme Meintjes reviewed the final draft extensively. This final draft was then reviewed by all co-authors and extensive input was given to finalize the paper for submission. All co-authors’ comments were incorporated into the paper prior to submission.

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Thank you:

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**b. Selected tables or figures:**

The following figure and table were prepared for the manuscript but was not submitted due to space constraints. Some of the information was included in the flow chart and the text in the manuscript.
Figure: Reasons treatment for tuberculosis was not restarted in patients who had treatment interruption for tuberculosis and or antiretroviral treatment associated liver dysfunction.

Legend:
n: Number of patients in this category.
TB: Tuberculosis treatment
ART: Antiretroviral treatment
Table: Other Causes of Liver Dysfunction:

<table>
<thead>
<tr>
<th>Cause</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Sepsis</td>
<td>66</td>
<td>26.5</td>
</tr>
<tr>
<td>**Viral Hepatitis</td>
<td>31</td>
<td>12.5</td>
</tr>
<tr>
<td>Alcohol</td>
<td>24</td>
<td>9.6</td>
</tr>
<tr>
<td>Gallbladder/Pancreas pathology</td>
<td>24</td>
<td>9.6</td>
</tr>
<tr>
<td>Disseminated TB</td>
<td>23</td>
<td>9.2</td>
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<tr>
<td>Other</td>
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<td>***Cardiac</td>
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<td>Cotrimoxazole</td>
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<tr>
<td>TB IRIS</td>
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<td>1.6</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>Toxins</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

TB: Tuberculosis
TB IRIS: TB Immune Reconstitution Inflammatory Syndrome.
* This includes patients who had bacteriologically proven sepsis and also patients with a clinical picture of sepsis who were managed as sepsis by the admitting team.
** This includes acute hepatitis A and acute and chronic cases of hepatitis B.
*** Cardiomyopathy or congestive cardiac failure causing liver congestion and abnormal liver function tests.