Liver and renal issues in HIV

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Thanks to Raj Gandhi, Viv Black, Andrew Black, Francesca Conradie, Mark Nelson, Trevor Gerntholtz
Liver then kidney
Most Common Grade 4 Events: CPCRA Cohort

Liver 2.6
Neutropenia 1.5
Anemia 1.1
CVD 0.9
Pancreatitis 0.9
Psychiatric 0.8
Renal 0.6

Incidence

Hazard Ratio For Death by Grade 4 Event (95% CI)

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>3.49</td>
<td>(2.38-5.12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.02</td>
<td>(0.61-1.72)</td>
<td>0.93</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.76</td>
<td>(0.99-3.09)</td>
<td>0.051</td>
</tr>
<tr>
<td>CVD</td>
<td>7.08</td>
<td>(4.14-12.05)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>3.40</td>
<td>(1.82-6.33)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>1.91</td>
<td>(0.79-4.63)</td>
<td>0.15</td>
</tr>
<tr>
<td>Renal</td>
<td>4.60</td>
<td>(2.45-8.66)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

n=2947; CPCRA=Terry Beirn Community Programs for Clinical Research on AIDS.

# Mechanism of HAART related Hepatotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Direct Toxicity</th>
<th>HSR</th>
<th>Mitochondrial Toxicity</th>
<th>IRIS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td>NNRTI/PI</td>
<td>Abacavir, NNRTIs, Fosamprenavir/ Darunavir</td>
<td>NRTI (AZT, D4T, DDI)</td>
<td>All</td>
</tr>
<tr>
<td><strong>Dose Dependance</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>2-12m</td>
<td>&lt;6 weeks</td>
<td>Late</td>
<td>Early</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Fever, Rash, Eosinophilia</td>
<td>AST&gt;ALT Lactic Acidosis</td>
<td>HBV, HCV</td>
<td></td>
</tr>
</tbody>
</table>
HIV and the Liver

• Underlying liver disease in common in HIV+ patients
  – In a South African cohort, 4% of HIV-infected patients had liver enzyme elevations >5 x upper limits of normal (ULN) prior to starting ARVs
  
  Hoffmann C, AIDS 21:1301

• Non-infectious & infectious processes may cause liver disease in HIV-infected patients
Non-infectious causes of liver disease in HIV+ patients

- Alcohol
- Traditional or herbal medications
  - In one South African cohort, 1/3 of HIV+ patients were taking traditional medications
- Iron overload
- Autoimmune hepatitis
- Malignancy
  - Kaposi’s sarcoma
  - Lymphoma
  - Hepatocellular carcinoma
Infectious causes of liver disease in HIV-infected patients

- Mycobacterial infection: TB, MAI
- Fungal infection: histoplasma, cryptococcus, penicillium, candida
- Bacterial infection: Syphilis, Bartonella (peliosis hepatis), Salmonella, Listeria
- Parasitic infection: *Schistoma mansoni*, visceral leishmaniasis
Infectious causes of liver disease in HIV-infected patients: Viral

- HIV, including HIV cholangiopathy
- Viral hepatitis: HAV, HBV, HCV, HDV, HEV
- CMV
- HSV
- EBV
Case study

• A 30-year old male taxi driver, CD4 count of 5 cells/ul
• Vague history of weight loss and night sweats
• A month of TB treatment (rifampicin, isoniazid, pyrazinamide, and ethambutol).
• He is initiated on antiretroviral therapy (tenofovir, lamivudine, efavirenz)
• The clinician involved was concerned; brought the patient back after 4 weeks.
• The patient said he felt much better. Objectively, he had gained 4 kilograms, and was slightly jaundiced. There was no hepatomegaly or any other clinical findings.
His baseline bloods and bloods done are as follows:

<table>
<thead>
<tr>
<th>Result</th>
<th>1 week before antiretrovirals started</th>
<th>4 weeks after</th>
<th>5 weeks after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dl) (normal 12-15)</td>
<td>9</td>
<td>8.5</td>
<td>8</td>
</tr>
<tr>
<td>Platelets (normal 140-400)</td>
<td>500</td>
<td>480</td>
<td>450</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Normal</td>
<td>10 x normal</td>
<td>10 x normal</td>
</tr>
<tr>
<td>AST</td>
<td>2x normal</td>
<td>8 x normal</td>
<td>10x normal</td>
</tr>
<tr>
<td>ALT</td>
<td>3x normal</td>
<td>8x normal</td>
<td>10x normal</td>
</tr>
<tr>
<td>Gamma -GTs</td>
<td>2 x normal</td>
<td>10 x normal</td>
<td>10 x normal</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>2xnormal</td>
<td>10 x normal</td>
<td>10 x normal</td>
</tr>
<tr>
<td>INR</td>
<td></td>
<td></td>
<td>Normal (1.1)</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Urine dipstix</td>
<td>Normal</td>
<td>Bilirubin, protein on dipstix</td>
<td>Bilirubin, protein on dipstix</td>
</tr>
<tr>
<td>Hepatitis B/C screening serology</td>
<td>Negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral load/CD4</td>
<td>1 million copies/ml and 5 cells/ul</td>
<td>2000 and 50</td>
<td></td>
</tr>
</tbody>
</table>
Locate your liver

1. **ANATOMY**

- Upper right quadrant deep to inferior ribs
- Dome of liver abuts against inferior diaphragm surface
- Left/right lobes
- Gall bladder is thin muscular sac on inferior surface where bile collects (1 above)
Percuss your liver

- Easiest organ to percuss
- Dense tissue gives rock-solid sound/feel on percussion
- Mid-clavicular line moving inferiorly from mid-chest to lower right quadrant

Measuring liver span by percussion: variation in liver span
Variation in liver span according to the vertical plane of examination. Since there is variability in where clinicians determine the mid-clavicular line to be, the inevitable consequence is that liver span may also vary even if multiple observers are perfectly accurate in measuring it.
What does the liver do?

Multi-function, blood-processing “factory”

- Temporary nutrient storage (glucose-glycogen)
- Remove toxins from blood
- Remove old/damaged RBC’s
- Regulate nutrient or metabolite levels in blood—keep constant supply of sugars, fats, amino acids, nucleotides (including cholesterol)
- Secrete bile via bile ducts and gall bladder into small intestines.

Needs blood supply laden with “stuff” to process
Dual blood supply to liver:
1. Hepatic portal system

- Main drainage of blood from gut
- Nutrient-rich, toxin-laden, oxygen-poor blood from gut via hepatic portal vein
Dual blood supply to liver

2. Hepatic artery

- Primary branch from celiac artery which is one of the three main visceral branches of aorta (review from circulation)
- Within liver lobules, blood mixes:
  - Oxygen-rich blood from hepatic portal artery
Cholesterol—one example of liver processing

• Our body needs cholesterol for
  – Cell membranes
  – Vitamin D
  – Hormones—progesterone and testosterone
  – Myelin (neuron axonal “wrapping”)
  – Component of bile salts

• 85% of cholesterol in our blood is “endogenous” or manufactured by our own cells (mostly liver)

• 15% comes from the food we eat

• So, is zero-cholesterol good…or even healthy?
Other liver cell functions

- Red blood cell decomposition and recycling of components
- Toxin neutralization
- Conversion of “substrates:” altering amino acids, amino acids to sugars, sugars to amino acids, etc....to insure adequate supply of necessary “molecules of life.”
LIVER FUNCTION TESTS

- USED TO
- Detect presence of liver disease
- Distinguish among different types
- Gauge the extent of known liver damage
- Follow the response of treatment
Disadvantages

• Rarely suggest a specific diagnosis
Tests based on detoxification & excretory functions

• Serum bilirubin
• Urine bilirubin
• Blood ammonia
• Serum enzymes: AST, ALT, GGT, 5’Nucleotidase, ALP
Tests that measure Biosynthetic function of liver

- Serum Albumin
- Serum Globulins
- PT, INR
LFT Abnormalities After Starting ARVs: Differential Diagnosis

- Progression of underlying liver disease
- Drug-induced liver injury
  - ARV hepatotoxicity
  - Antituberculous therapy hepatotoxicity
- TB Immune Reconstitution Inflammatory Syndrome (IRIS)
- Superinfection
  - HAV, HCV, HDV, HEV, EBV, CMV
- Hepatitis B flare
Drug-induced liver injury (DILI)

• Clinical diagnosis of exclusion
• If feasible, exclude other causes of liver injury, such as viral hepatitis
• Generally DILI occurs within a few months of initiating a new drug
• Treatment is usually withdrawal of drug and supportive care
  – N-acetyl cysteine used in acetaminophen (paracetamol) overdose
  – Intravenous carnitine used in valproate-induced mitochondrial injury
DILI: Pathogenesis

• May result from direct toxicity of the drug or from immunologically-mediated response

• **Predictable DILI**
  – Dose-related, high attack rate, occurs rapidly
  – Injurious free radicals cause hepatocyte necrosis
  – Example: acetaminophen (paracetamol)

• **Unpredictable or idiosyncratic DILI**
  – Hypersensitivity or metabolic reaction
  – Largely independent of dose; occurs rarely
  – May result in hepatocyte necrosis and/or cholestasis
  – Accounts for most cases of DILI
## Typical patterns of liver injury with drugs

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Mixed</th>
<th>Cholestatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVs</td>
<td>Sulfonamides</td>
<td>Amox/clav</td>
</tr>
<tr>
<td>Herbal meds</td>
<td>Bactrim</td>
<td>Macrolides</td>
</tr>
<tr>
<td>INH</td>
<td>Phenytoin</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>PZA</td>
<td>Phenobarbital</td>
<td>Tricyclics</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Nitrofurantoin</td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>NSAIDS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Navarro & Senior. NEJM 354: 7
DILI: ARV hepatotoxicity

- 14-20% of HIV+ pts starting ARVs have elevations in LFTs
- 2-10% need to interrupt ART because of significant hepatotoxicity
- Risk factors: elevated baseline transaminases; HBV or HCV; concomitant hepatotoxic drugs (anti-TB drugs, anticonvulsants, bactrim, dapsone, erythromycin, augmentin, azoles).
- All 3 classes of HIV medicines—protease inhibitors, non-nucleoside RT inhibitors and nucleoside RT inhibitors—have been associated with hepatotoxicity
ARV Hepatotoxicity: NNRTIs

- Both Nevirapine and Stocrin may cause hepatotoxicity
- Incidence may be higher with NVP than with Stocrin

Prospective 2NN study, grade 3 or 4 hepatotoxicity:
- NVP 400 mg qd: 13.6%*. NVP 200 mg bid: 8.3%. Stocrin: 4.5%
- Association between NVP hepatotoxicity and specific genetic polymorphisms in MDR gene

Van Leth Lancet 363:1253-1263
Haas et al, CID (2006), 43:783
# Nevirapine Hepatotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Timing</strong></td>
<td>6-18 weeks</td>
<td>&gt;18 weeks</td>
</tr>
<tr>
<td><strong>Systemic sx</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Hypersensitivity</td>
<td>?</td>
</tr>
<tr>
<td><strong>Risk factors</strong></td>
<td>F: CD4&gt;250</td>
<td>HBV, HCV</td>
</tr>
<tr>
<td></td>
<td>M: CD4&gt;400</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low BMI</td>
<td></td>
</tr>
</tbody>
</table>

http://www.fda.gov/medwatch/SAFETY/2003/03DEC_PI/Viramune_PI.pdf
ARV Hepatotoxicity: Nucleosides RTI

- NRTIs have been associated with lactic acidosis/hepatic steatosis syndrome
- NRTI-induced mitochondrial toxicity → Decreased fatty acid oxidation → Accumulation of fatty acids and metabolism to TGs

Pao, D et al. Sex Transm Infect 2001;77:381
NRTI-Based Liver Toxicity: Clinical Presentation

• Unspecific symptoms
  – Abdominal pain, vomiting, anorexia, pain (right upper quadrant)
• Hepatomegaly
• Mixed cholestatic/hepatocellular pattern of liver enzymes
• Evidence of extrahepatic mitochondrial toxicity
  – Amylase/lipase, CPK, lactate, metabolic acidosis, loss of bicarbonate
ARV hepatotoxicity: PIs

- 298 HIV+ subjects initiating PI-based ARV therapy
- Patients with HCV or HBV more likely to develop hepatotoxicity
- Still, 88% of coinfected individuals had no or minimal hepatotoxicity
- Kaletra has a relatively low rate of hepatotoxicity (6-9%)

Sulkowski et al. JAMA (2000) 283:74
DILI due to antituberculous therapy (ATT)

• DILI may occur with any of the 1st line antituberculous drugs, particularly INH, rifampin and PZA
• Overall rate: 5-33%
• Risk factors
  – Age >35
  – Abnormal baseline LFTs
  – Malnutrition
  – HIV
  – Hepatitis B, especially if HBeAg+
  – Hepatitis C
DILI: INH

• Reactive metabolites may cause liver injury
• Usually occurs within weeks to months
  – Median interval 4 months
  – Differs from hypersensitivity reactions which may occur in days-weeks
• Rate: 0.1 to 4%.
• Risk factors:
  – Older age
  – Pregnancy
  – Use of EtOH, other hepatotoxic drugs (inc. rifampicin)
  – Active hepatitis B or C infection
  – Elevated baseline transaminases
  – Malnutrition
DILI: Rifampicin

• May cause dose-dependent interference with bilirubin uptake
  – Results in subclinical hyperbilirubinemia or jaundice without hepatocellular damage.
• May also cause hepatocellular injury and potentiate toxicities of other anti-TB medications
• Hypersensitivity may cause liver injury.
  – Presents with nausea, vomiting, fever, mildly elevated ALT, elevated bili in 1st few months of treatment
• Rate of symptomatic hepatitis with combination of INH and Rif higher than with regimens with either drug alone.
  – Rif may promote formation of toxic INH metabolites
DILI: PZA

- May cause both dose-dependent and idiosyncratic hepatotoxicity
- May have shared mechanism of toxicity with INH
  - Patients who had previous hepatotoxicity with INH more likely to have toxicity with PZA-containing regimens
- May also induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis
- Allopurinol decreases PZA clearance, and may increase its hepatotoxicity
Hepatotoxicity during ATT: Interventions

- Consider stopping medications if:
  - Serum transaminases are > 5 X ULN with or without symptoms
  - Transaminases are > 3 X ULN with jaundice or hepatitis symptoms

- Rechallenge:
  - When ALT returns to < 2 x ULN, rifampicin may be restarted with or without ethambutol
  - After 3-7 days, reintroduce INH, and subsequently check ALT
  - If symptoms recur or ALT increases, the last drug added should be stopped.

LFT Abnormalities After Starting ARVs: Differential Diagnosis

- Progression of underlying liver disease
- Drug-induced liver injury
  - ARV hepatotoxicity
  - Antituberculous therapy hepatotoxicity
- TB Immune Reconstitution Inflammatory Syndrome (IRIS)
- Superinfection
  - HAV, HCV, HDV, HEV, EBV, CMV
- Hepatitis B flare
TB IRIS

• 30% of patients in South Africa receive overlapping TB therapy during 1\textsuperscript{st} year of ART.
  Lawn et al. AIDS 20:1605.

• TB IRIS is characterized by clinical worsening soon after initiation of ART
  – Occurs in 10-30% of patients commencing ART
  – Fever, adenopathy, worsening respiratory symptoms, increasing pulmonary infiltrates or effusions, intracranial tuberculomas, ascites, splenomegaly, psoas abscess, intra-abdominal adenopathy

• Two types:
  – Paradoxical TB IRIS
  – ART-associated TB/”Unmasking” TB IRIS
LFT Abnormalities After Starting ARVs: Differential Diagnosis

- Progression of underlying liver disease
- Drug-induced liver injury
  - ARV hepatotoxicity
  - Antituberculous therapy hepatotoxicity
- TB Immune Reconstitution Inflammatory Syndrome (IRIS)
- Superinfection
  - HAV, HCV, HDV, HEV, EBV, CMV
- Hepatitis B flare
Other causes of liver enzyme elevation in HIV-HBV subjects receiving ART

- Discontinuation of a 3TC-containing regimen may lead to a flare in hepatitis B
  - 3TC has activity vs. HBV
  - Incidence after 3TC-withdrawal may be as high as 22%
    - Wit et al, JID (2002) 186:23
- Development of HBV resistance to 3TC may be associated with flares in hepatitis
- A flare in liver enzymes may signal HBeAg seroconversion
- HBV IRIS after initiation of ART
Other causes of liver enzyme elevation in HIV-HBV subjects receiving ART

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- A flare in liver enzymes may signal HBeAg seroconversion
- HBV IRIS after initiation of ART
HIV and HBV

- Patients with HBV/HIV have a 17-fold increased risk of liver-related mortality compared with patients with HIV or HBV alone.
- All HIV-infected patients should be tested for HBV with a HBsAg.
- Both 3TC and tenofovir have excellent activity against HBV (in addition to HIV).
Conclusions

• In a HIV+ patient with liver test abnormalities after starting ART, consider:
  – Worsening of an underlying liver disease, e.g. alcohol-related
  – Drug-induced liver injury
    • ARVs
    • ATT
    • Other drugs
  – TB IRIS
    • Particularly if fever, adenopathy, hepatomegaly, other sites of disease
  – Viral superinfection
  – Flare of HBV or HBV IRIS
  – Herbs!
What happened?

- Continued the antiretrovirals and TB continuation phase treatment
- phoned the patient daily to make sure he was OK. I was a little
- Suspicious about traditional medication use
- Showed him his liver function numbers and how they were deteriorating. I was worried about his driving a taxi (on efavirenz, potentially encephalopathic)
- No objective signs of liver failure, his INR remained normal suggesting his liver synthetic function was still OK
- An ultrasound three weeks later showed liver and splenic microabscesses, so it could also have been an IRIS reaction.
- He is fine now, CD4 over 300 and VL undetectable a year later, still driving his taxi, but we never proved TB.
- Continuation phase, I presume- he had had 2 months of TB treatment already at the 4th week of ART.
Liver toxicity of TB drugs

ALT ≤ 5x ULN and/or bilirubin ≤ 2x ULN and asymptomatic

- Check baseline LFT
- TB proven?
- Reconsider TB diagnosis
- Exclude other causes, e.g. viral hepatitis

- Reassurance
- Repeat LFT weekly until improving or stable

ALT > 5x ULN and/or persistent or increasing bilirubin > 2x ULN or
ALT > 3x ULN and/or persistent or increasing bilirubin > 2x ULN and symptomatic

- Check baseline LFT
- TB proven?
- Reconsider TB diagnosis
- Intensive or continuation phase?
- Patient ill or not ill?

- Admission
- Stop all drugs
- If in liver failure manage accordingly
- Check for hepatotoxins (alcohol, co-medication, herbs)
- Check pregnancy
- Check hepatitis B/C, HIV serology
- Abdominal sonar
- Liver biopsy (if no contraindications)**

* right-sided abdominal pain, nausea, vomiting, jaundice, anorexia

** indications for liver biopsy: LFT not improving or worsening, if need to exclude other opportunistic infections or IRIS

Guideline Helen Joseph Hospital/TB focal point (April 2012)
Reintroduction of TB drugs (liver toxicity): Intensive phase

STEP 1: Start EMB/ Streptomycin

Repeat LFT after 1 week (outpatients), 3 days (inpatients)

STEP 2: Start INH (if predominantly cholestatic pattern), start RIF (if predominantly transaminitis)

Repeat LFT after 1 week (outpatients), 3 days (inpatients)

STEP 3.A: If LFT stable or improving:
Add RIF if INH started on previous step
Add INH if RIF started on previous step

STEP 3.B: If LFT worsening stop last introduced drug, wait for LFT to improve. If stable or improving: reintroduce RIF (if INH reintroduced on STEP 2) or INH (if RIF reintroduced on STEP 2) with ofloxacin as the fourth drug.

Repeat LFT in 3-7 days

STEP 4.A: If LFT stable or improving: Continue RIF, INH, EMB and streptomycin

STEP 4.B: If LFT worsening, stop last introduced drug, start ofloxacin

STEP 4.C: If LFT improving: continue all introduced drugs during intensive phase

STEP 4.D: If LFT worsening: consider liver biopsy if no C/I, discuss with ID

Repeat LFT in 3-7 days

STEP 5.A: If LFT stable or improving: continue regimen

STEP 5.B: If LFT worsening: consider liver biopsy if no C/I, discuss with ID

Repeat LFT in 3-7 days

- If patient critically ill (whether TB is confirmed or suspected) contact ID consultant/registrar for appropriate regimen
- Never reintroduce pyrazinamide (PZA)
- If no RIF included in the final regimen and fully sensitive TB add ofloxacin as fourth drug, continue INH/EMB/Strep/Oflox to complete intensive phase of 2/12, continue INH/EMB/Strep/Oflox for 10-16 months (total treatment duration 12-18 months)
- If no INH included in final regimen and fully sensitive TB continue RIF/EMB/Strep/Oflox to complete intensive phase of 2/12, continue RIF/EMB/Strep/Oflox for 7-10 months (total treatment duration of 9-12 months)
- Ciprofloxacin and macrolides should not be used due to hepatotoxicity and inferior anti-TB activity
- If HIV+ and CD4 <200 start ARVs within 2-4 weeks after start of TB treatment if LFT stable, if HIV+ and CD4 >200 defer ARVs until completion of intensive phase (consult ID)
- Contact infectious diseases consultant/registrar in case of questions
Reintroduction of TB drugs (liver toxicity): Continuation phase

**STEP 1:** Start EMB/INH (if predominantly cholestatic pattern), start EMB/RIF (if predominantly transaminitis)

- Repeat LFT after 1 week (outpatients), 3 days (inpatients)

**STEP 2.A:** If LFT stable or improving:
- Add RIF if INH started on previous step
- Add INH if RIF started on previous step

- Repeat LFT in 3-7 days

**STEP 3.A:** Continue RIF/INH, stop EMB

- If no RIF included in the final regimen and fully sensitive TB continue INH/EMB/oflox for the remaining treatment duration (total treatment duration 12-18 months)

- If no INH included in final regimen continue RIF/EMB/oflox for the remaining treatment duration (total treatment duration 9-12 months)

- If HIV+ (any CD4 cell count) refer for antiretroviral therapy

- Contact infectious diseases consultant/registrar in case of questions

**STEP 2.B:** If LFT worsening stop last introduced drugs, wait for LFT to improve. If stable or improving:
- reintroduce EMB/RIF (if INH reintroduced on STEP 1) or EMB/INH (if RIF reintroduced on STEP 1).

- Repeat LFT in 3-7 days

**STEP 3.B:** If LFT improving:
- add oflox as third drug, continue all introduced drugs during continuation phase

**STEP 3.C:** If LFT worsening:
- consider liver biopsy if no C/I, discuss with ID

Guideline Helen Joseph Hospital/TB focal point (April 2012)
Renal
The nephron

- Filtration: blood to lumen
- Reabsorption: lumen to blood
- Secretion: blood to lumen
- Excretion: lumen to external environment
Characterized by tubule proteinuria (Urine protein/creat ratio < 1), and electrolyte imbalance

**Proximal Tubule**
- Ischemia
- Prerenal azotemia
- Crystalluria
- Nephrotoxicity
  - Aminoglycosides
  - Fanconi Syndrome (TDF)

**Distal Tubule**
- Nephrotoxins: Amphotericin

**Collecting Duct**
- SIADH
- Nephrogenic diabetes insipidus

**Interstitium**
- Interstitial Nephritis (NSAIDS)
- Fibrosis
HIV and the kidney...

- **Direct Effects**
  - HIV associated nephropathy (HIVAN)
  - Immune complex mediated nephropathy
  - ?other GN’s
  - TTP/HUS
  - Interstitial nephritis
  - Electrolyte disorders

- **Indirect Effects**
  - HIV related infections
  - HIV related drugs
  - Dehydration
The scale of the problem:

- Epidemiology unknown in Africa – rely on stats from the USA
- HIVAN most common cause of CKD 5 in HIV infected people
- 3\textsuperscript{rd} biggest cause of CKD 5 in Blacks in the USA
- 40 million HIV + people in the world
- 30 million in sub Saharan Africa
- 4-5 million in South Africa
- 1-10\% (40 000 – \(\frac{1}{2}\) million) potential patients
So what should be done?

- Estimate GFR with either Cockcroft-Gault or MDRD formulae
- Then adjust all drug dosages according to renal function

Adapted from Brenner & Rector, Saundar Ed, 2001
Estimating GFR from Serum Creatinine

**Cockcroft-Gault**
- Derived in 249 hospitalised males
- GFR Reference: 24-hour urine creatinine clearance
- Adjustment for female gender added later

Equation¹:
\[(1.23\times(140-\text{age}) \times \text{weight (kg)} \times (0.85 \text{ if female})) / \text{creat (µmol/l)}\]

**MDRD**
- Derived in 1,628 patients with CKD (GFR 20-60 ml/min/1.73m2)
- GFR Reference: iothalamate clearance
- 2 variables eliminated ("abbreviated MDRD")

Equation¹:
\[
\text{GFR (mL/min/1.73 m2)} = 186 \times (\text{plasma creatinine}/88.1 (\mumol/l))^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \\
x 1.21 \text{ if Afro-Caribbean}
\]

---

5. Cockcroft DW, Gault MH Nephron 1976;16(1):31-34
Serum creatinine and GFR

Serum creatinine is not the safest way to determine whether renal function is normal or not.

Patients with «normal» creatininemia

Proteinuria

Abnormal amount of protein in the urine

- Glomerular
  - High in albumin
    - HIVAN
    - Hypertension
    - Diabetic nephropathy
    - GN

- Tubular proteinuria
  - Not Albumin
    - Drug-induced tubular damage
How to assess proteinuria

- Dipstick (15p)
- 24 urine collection (always difficult)
- Spot sample – Urine protein/creatinine ratio (uPCR)
HIVAN

• First described in 1984 by Rao et al from NYC and Pardo et al from Miami
• Prior to the isolation of HIV even
• FSGS pattern similar to heroin nephropathy
• Affects all compartments of the kidney:
  - glomeruli
  - FSGS
  - tubules
  - cystic dilatation
  - interstitium
  - t cell infiltrate
Clinicopathological Findings

• Affects blacks predominantly
• Nephrotic syndrome with heavy proteinuria
• Rapid progression to end stage disease
• **LM:** visceral epithelial cell hypertrophy collapse
  obliterated cap lumina with foam cells
  marked interstitial infiltrate immunofluorescence negative
• **EM:** effacement, visceral cell enlargement tubuloreticular inclusions
HIVAN- focal area of collapse with prominent overlying epithelial cells
Tubulo-interstitium

Cystic dilatation with fibrosis
Pathogenesis

HIV virus vs Host susceptibility

- **DIRECT HIV infection:**
  - HIV DNA found in renal tissue of affected and unaffected kidneys
  - *replication in mesangial cells* -> TGF-β, PDGF -> fibrosis
  - *reservoir* mesangial cell proliferation

- **APOPTOSIS:** increased amounts of apoptotic cells in HIV kidneys (?TNF-α)
Treatment

• NO randomised controlled trials
• Steroids
• Ace inhibitors
• Anti-retrovirals
Impact of HAART on HIVAN
Survival of 60 Patients with HIVAN

Survival was similar for patients with biopsy proven or clinically defined HIVAN (logrank test: p=0.57)

90% survival at 5 years

HAART ERA

PRE-HAART ERA

Success of Dialysis (next: Transplantation)

Post et al (King’s College Hospital, London)
Renal survival in 60 patients with HIVAN

ESRD: n=30 (50%)
Never required dialysis: n=24 (40%)

HAART sustains survival but cannot prevent all ESRD

Post et al (King’s College Hospital, London)
Drug-related renal dysfunction in HIV infection

Prerenal
- ACE inhibitors
- Amphotericin B
- COX-2 inhibitors
- Cyclosporine
- Diuretics
- Interferon
- NSAIDs

Tubule Dysfunction
- Adefovir
- Cidofovir
- Aminoglycosides
- Amphotericin B
- Foscarnet
- Pentamidine
- Tenofovir DF
- Didanosine
- Abacavir
- Lamivudine
- Cocaine

Acute Interstitial Nephritis
- Abacavir
- Atazanavir
- Indinavir
- Ritonavir
- Aciclovir
- Cefhalosporins
- Cimetidine
- Ciprofloxacin
- Cocaine
- NSAIDs
- Penicillins
- Rifampin
- Sulfonamides
- TMP-SMX

TTP-HUS
- Indinavir
- Cocaine
- Cyclosporine
- Valacyclovir

Obstructive
- Indinavir
- Aciclovir
- Foscarnet
- Sulfadiazine
- Sulfonamides
- Aminoglycosides
- Amphotericin B
- COX-2 inhibitors
- Diuretics

Chelsea and Westminster Cohort Analysis
Rate Ratio of Abnormal Creatinine
Cohort N=1175 Vs. TDF Case Control N=1058

Renal failure is not more common with TDF than with other anti-retroviral drugs

The critical question: Is it Fanconi syndrome?

Proteinuria ≤ 2 g/day
Hypophosphatemia
Acidosis
Glycosuria
Hypokalemia
Aminoaciduria
Hypouricemia

Proximal Tubulopathy

Na, K, Cl, UFCa (70%), HCO3 (>80%), Phosphates (>75%), Uric Acid (∼90%), Glucose (>99%), Amino acids (>95%), Small proteins (>95%)
HIV drug-related Fanconi syndrome

- Tenofovir DF (n>50 published cases*)
- Didanosine (3 cases)
- Abacavir (1 case)

*From various published sources including: Izzedine H et al AIDS 2004;18:1074-1075
Crowther MA et al AIDS 1993;7(1):131-2
Izzedine H et al AIDS 2005;19(8):844-845
Biological features of Fanconi syndrome

- Glycosuria with normal blood glucose level
- Proteinuria (not albuminuria)
- Hypophosphatemia
- Acidosis
- Hypokalemia
- Hypouricemia
- Polyuria-polydipsia syndrome
- Bone Pain (if chronic)

Izzedine H et al AIDS 2004;18:1074-1075
### Incidence of Renal Diseases in HIV: Clinical Diagnosis Versus Biopsy Confirmation

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Biopsy</th>
<th>No Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIVAN</td>
<td>45.9% (17)(^a)</td>
<td>69.8% (30)(^a)</td>
</tr>
<tr>
<td>Membranoproliferative glomerulonephritis</td>
<td>10.8% (4)</td>
<td>4.7% (2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.4% (2)</td>
<td>14.0% (6)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5.4% (2)</td>
<td>4.7% (2)</td>
</tr>
<tr>
<td>Amyloid</td>
<td>5.4% (2)</td>
<td>2.3% (1)</td>
</tr>
<tr>
<td>Chronic focal glomerulonephritis</td>
<td>2.7% (1)</td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>5.4% (2)</td>
<td></td>
</tr>
<tr>
<td>Membranous glomerulopathy</td>
<td>2.7% (1)</td>
<td></td>
</tr>
<tr>
<td>Nonspecific</td>
<td>2.7% (1)</td>
<td></td>
</tr>
<tr>
<td>No tissue obtained</td>
<td>8.1% (3)</td>
<td></td>
</tr>
<tr>
<td>Mesangial glomerulonephritis</td>
<td>5.4% (2)</td>
<td></td>
</tr>
<tr>
<td>Heroin abuse</td>
<td></td>
<td>2.3% (1)</td>
</tr>
<tr>
<td>Nephrotoxic drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>37</strong></td>
<td><strong>43</strong></td>
</tr>
</tbody>
</table>

\(^a\) P = 0.03 (HIVAN vs. all others)


HIVAN is HIV-associated nephropathy
## NRTI Dosing in Renal Insufficiency or Hemodialysis: Combination

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Standard Initial Dose</th>
<th>Dosing in Renal Insufficiency or Hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir/lamivudine</td>
<td>1 tablet qd</td>
<td>By creatinine clearance &lt;50 mL/min: not recommended*</td>
</tr>
<tr>
<td>Emtricitabine/tenofovir</td>
<td>1 tablet qd</td>
<td>By creatinine clearance &gt;50 mL/min: standard initial dose &lt;50 mL/min: not recommended; 30-49 mL/min: 1 tablet q48 hours &lt;30 mL/min†: not recommended</td>
</tr>
<tr>
<td>Zidovudine/lamivudine</td>
<td>1 tablet bid</td>
<td>By creatinine clearance &lt;50 mL/min: not recommended*</td>
</tr>
<tr>
<td>Zidovudine/lamivudine/abacavir</td>
<td>1 tablet bid</td>
<td>By creatinine clearance &lt;50 mL/min: not recommended*</td>
</tr>
</tbody>
</table>

*Not recommended because one or more of the components of the fixed-dose combination requires dose adjustment. Substitute individual component drugs and adjust dose accordingly.
†Including patients requiring hemodialysis.
In conclusion . . .

- HIV can affect the kidney in protean ways, not just HIVAN
- Substantial disease burden
- ACE –i appear to have a clear role
- Effective prevention strategies need to be studied further
- Chronic renal replacement therapy SHOULD be offered in the South African context