Southern African HIV Clinicians Society

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Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
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Tuberculosis in renal and liver disease

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Southern African HIV Clinicians Society Conference
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Mr HL – 56 year old man from Alex

- **Main complaint**:

  3 month history:

  marked loss of weight (20kg in 3mo.)

  Generalised abdominal pains

  Fever/ nightsweats

- **Background:** HPT, dyslipidemia

  newly diagnosed HIV: CD4 = 13

  Started on AZT/ 3TC/ EFV 2 weeks ago

- **Clinical examination**

  vitals – normal, generalised shotty nodes, bipedal oedema

  All other systems - normal

Investigations

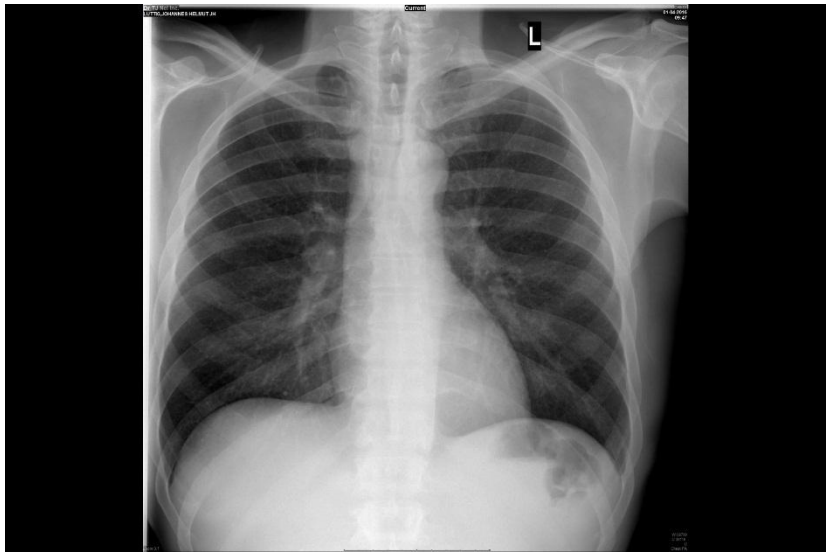
FBC: WCC – 5.97/ Hb - 7.2/ Plt 316

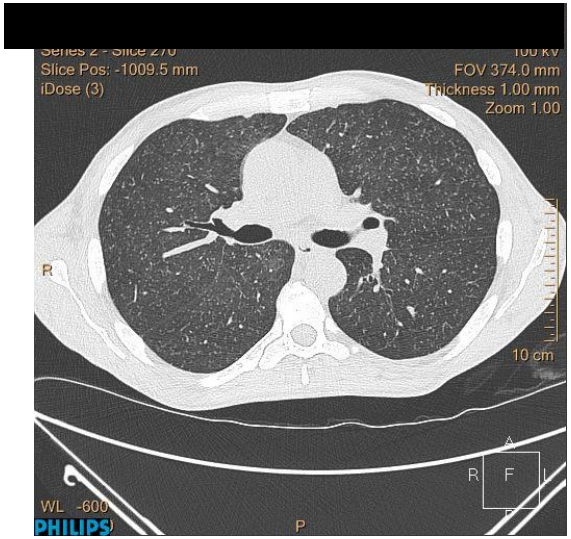
U+E: Na – 130/ K – 3.4/ urea – 14.1/ creat – 203

LFT: TB – 18/ CB – 8/ TP – 73/ Alb – 22/ ALP – 182/ GGT – 176/ ALT – 139/ AST – 170

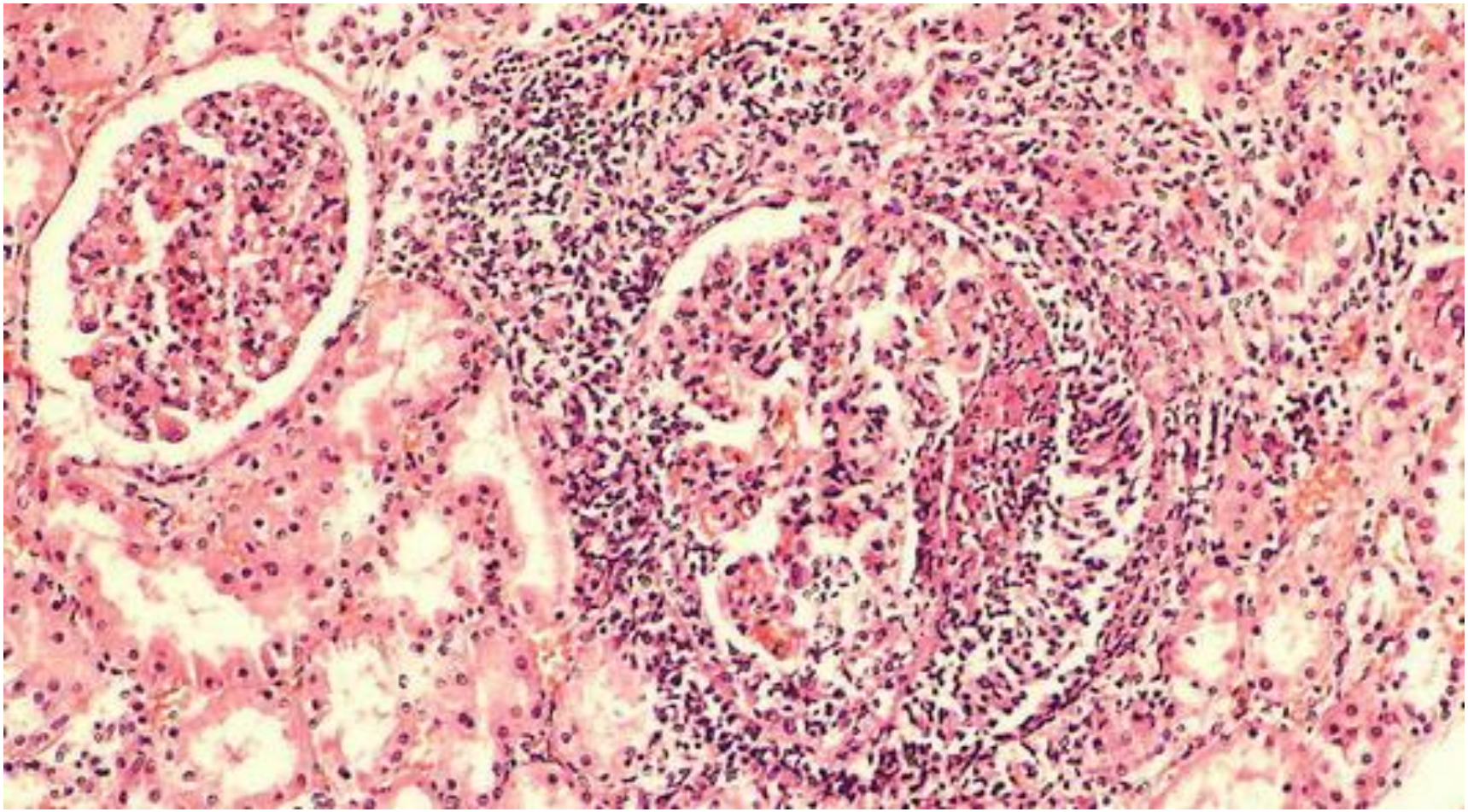
Renal biopsy: necrotising granulomata

Urine: PCR – Mtb+^{ve}, RIF/ INH sensitive





Tuberculosis in renal disease



TB in patients with renal disease

Epidemiology

- Increased incidence and prevalence of TB in ESRD and dialysis patients
- Increased rates of OIs especially TB in HIV-positive haemodialysis patients vs HIV-negative
- ?increased mortality

Fabian J, *et al. S Afr Med J* 2015;105(2):110-114

Clinical picture

- **<u>Atypical clinical presentation</u>**:
- Pulmonary TB less common - <25%
- Disseminated forms predominate:
- Pleural effusions/ lymphadenopathy/ ascites/ hepatomegaly
- Tuberculous peritonitis in PD patients

- Often delayed diagnosis -
  with atypical presentation

Is TB treatment nephrotoxic?

- **First line therapy:**
- INH/ Rif/ EMB – all nephrotoxic – RIF most commonly implicated in AKI (0.05%)

- Recovery rates around 90% by 120 days
- Common pathologies:

  a) acute interstitial nephritis b) acute tubular necrosis
- **Second line therapy:**
- Aminoglycosides – daily vs 3 x/ week regimens?

  No difference in ototoxicity and nephrotoxicity

Chang CH, *et al. BMC Infectious Diseases* 2014;14(23):1471
Peloquin CA, *et al. Clinical Infectious Diseases* 2004;38:1538-44

Treating TB in renal disease

- **Choice of drugs:**

  unchanged

  use standard drugs

  EXCEPT

  With dose intervals

- **Standard duration:**

  as per normal guidelines

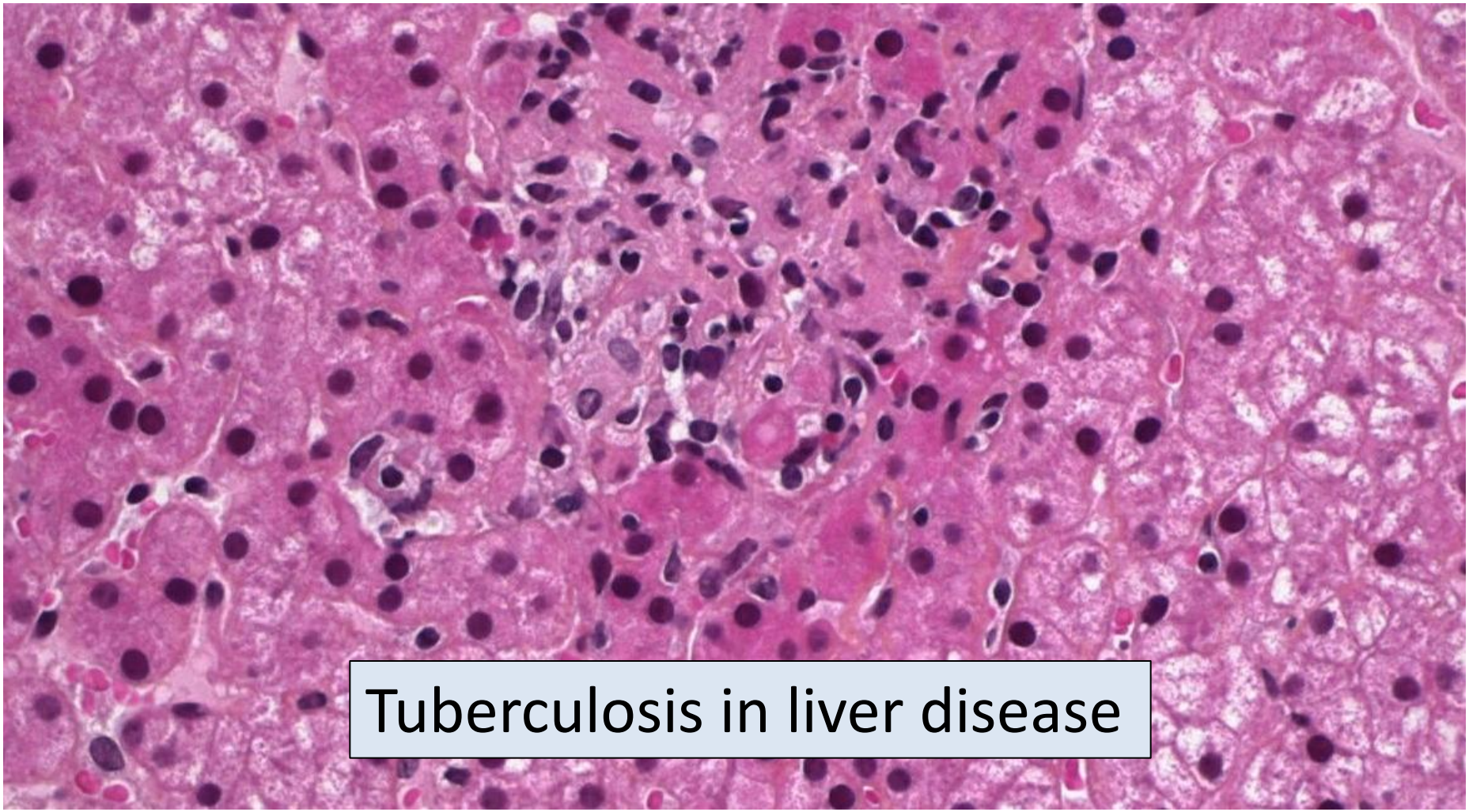
Milburn H*, et al. Thoarx* 2010;65:559-570

Dosing adjustments in renal disease (BTS guideline)

- **Isoniazid:** full dose in all stages of renal failure
  (increase pyridoxine to 100mg to avoid risk of neuropathy)
  - not removed by dialysis
- **Rifampicin**: full dose in renal failure, not removed by dialysis

- Stage 4 (CrCl 15 – 30) and Stage 5 (CrCl <15) Chronic Kidney Disease – dosing intervals increased to 3x weekly for EMB/ PZA (In drug-resistant: aminoglycosides)
- **EMB:** mainly excreted in urine – increased ocular toxicity in renal failure

Milburn H, *et al. Thoarx* 2010;65:559-570


Tuberculosis in liver disease

TB in the setting of established liver disease

- Incidence of TB increased with chronic liver disease and liver cirrhosis
- Main challenge is decision regarding therapy – hepatotoxicity of first-line agents
- Risk of severe liver failure is markedly increased if hepatotoxicity develops in liver cirrhosis
- Clinical features similar to in renal failure – atypical presentations, increased dissemination/ extrapulmonary disease

Approach to starting TB therapy in patients with abnormal LFTs

- Confirm TB diagnosis

- Take extensive drug history – hepatotoxic HAART? TMP-SMX? Other chronic medication?

- Basic blood work up for raised liver enzymes
  - Blood count for bone marrow involvement
  - characterise pattern of liver dysfunction
  - viral hepatitis screen

- Abdominal u/s – looking for liver infiltration, splenic lesions, intra-abdominal nodes

- Consider IRIS
- Seldom: liver biopsy

Defining
Drug Induced Liver Injury

Table 2. DILI definition advocated in the SA setting

- ALT level >120 IU/l **and** symptomatic (nausea, vomiting, abdominal pain, jaundice); **or**
- ALT level >200 IU/l **and** asymptomatic; **or**
- Total serum bilirubin concentration >40 µmol/l

Jong E, *et al. S Afr J HIV Med* 2013;14(3):113-119

Hepatotoxic potential of first line TB regimen

- Risk factors: polymorphisms - slow acetylators,
- levels of drug, low baseline albumin, low BMI
- Age: >35 years old
- Men: higher incidence of DILI vs. Women: more severe DILI
- More disseminated disease – higher risk
- Underlying chronic Hepatitis B and C, other chronic liver disease
- HIV

Satyaraddi A, *et al. Int J Tuberc Lung Dis* 2014;18(2):188-95 Rana SV, *et al. J Clin Pharm Ther* 2014;39(1):91-6
Devarbhavi H. *Trop Gastro* 2011;32(3):167-174

Hepatic TB

- Clinically: hepatomegaly – 80%

  Ascites – 20%

  Jaundice – 20%

❑ If HIV+ - more likely to have pulmonary TB infection concurrently

❑ Bloods: commonly ALP/ GGT raised

  ALP: up to 750 GGT: up to 400

  occasionally: ALT/ AST raised up to 200

Treatment: standard anti-TB regimen

Hickey AJ, *et al. BMC Infect Dis* 2015;15:209

Which first-line drugs are implicated and how?

Isoniazid	**transient enzyme increase is common** **frank hepatitis in <2%**
Pyrazinamide	**dose related hepatotoxicity** **variable picture: from reversible raised ALT/ AST to frank hepatitis**
Rifampicin	**raised enzymes common but frank hepatitis uncommon** **isolated raised bilirubin – subsides with continued Rx**
Ethambutol	**generally considered safe**

South African Medicines Formulary (SAMF), 2014; 11th Ed.

What constitutes a “liver friendly” regimen?

- Ethambutol
- Aminoglycoside: streptomycin/amikacin/ kanamycin
- Fluoroquinolones: moxifloxacin

- SA HIV Clinicians Society Consensus statement:

  EMB/ Sm/ Mfx
- NICE Guidelines 2016:

  EMB/ Sm ± quinolone: Mfx/ Lfx

Jong E, *et al. S Afr J HIV Med* 2013;14(3):113-119
NICE Guideline nice.org.uk/guidance/ng33

What about treating TB with other liver disorders in the mix?

- Calculate dose according to weight and avoid exceeding dose
- Consider a PZA-free regimen, means longer duration: PTB 9/12, EPTB 12/12
- Regular LFT checks: weekly initially then monthly
- Avoid alcohol – sounds simple but major predisposing factor
- Monitor closely for clinical deterioration, features of hepatitis – urgent bloods then stop Rx

Vasakova M. *Clin Respir J* 2015;9:143-152

Hepatotoxicity of drug-resistant regimens

- Not as common as standard TB Rx (about 16%)
- Mean time until onset >6 months
- One or more drugs stopped permanently in <2% of pts
- Rare to stop treatment entirely
- Doesn't necessarily equate to poor prognosis

Loddenkemper R, Schaberg T. *Int J Tuberc Lung Dis* 2012;16(5):571

Hepatotoxicity of drug-resistant treatment – implicated agents

- Ethionamide – few%
- Quinolones – numerous case reports
- Para-aminosalicylic Acid (PAS) 0.5%

Re-introduction of TB treatment

- Many Different ways to skin a cat
- Durban, KZN: no difference in safety with re-introduction method (full rechallenge vs stepwise)
- Safe to monitor for recovery from DILI while holding treatment
- Johannesburg, GP: significant % will need modified regimens; ARVs & TB-DILI: longer, more severe DILI
- SA Guidelines: Start with full dose Rif,

  check LFTs

  add full dose INH

  check LFTs

Costiniuk CT, *et al. J Glob Infect Dis* 2015;7(4):151-156
Naidoo S, *et al. S Afr Med J* 2015;105(5):393-396

Thank you