HIV Infection and Liver Disease

Introduction

- the scope of the problem

- Most common non-AIDS-related cause of death
- Accounts for 14 to 18% of all deaths
- Responsible for some 50% of deaths in hospitalized patients
- Landscape of liver disease has changed
  - ~ pre-ART OIs: CMV, mycobacteria, NHL & KS
  - ~ post-ART: HCV, HBV, DILD, alcohol abuse, NAFLD

Viral Hepatitis – Hepatitis C

- Prevalence of coinfection: 10% among high-risk sexual behaviours to 90% among IVDAs
- Overall 30% in USA (in SA 2%)
- Effect of HIV on HCV (cfd with HIV –ves):
  - ~ less likely to clear HCV
  - ~ higher HCV viral load
  - ~ accelerated fibrosis and more cirrhosis (2-fold)
  - ~ higher risk of liver failure once cirrhotic (5-fold)
  - ~ probably higher risk of HCC
  - ~ less likely to respond to Rx
- Effect of HCV on HIV less clear

Diagnosis & Treatment Recommendations

- Screen for anti-HCV
- May be anti-HCV –ve
  ~ HCV RNA by RT-PCR among high risk
- LFTs insensitive – need biopsy
- Rx with fibrotic disease
- Rx G2 and 3 regardless
- Early Rx for acute infection
- ESLD referred for LTx
- Screen for HCC every 6 to 12 months
- Vaccinate against HAV and HBV

- SOC: combo of pegylated IFN and ribavirin
  - ~ SVR 14 – 38% G1
    44 to 73% G2,3
  - ~ No ddI □ mitochondrial damage
  - ~ No AZT □ anaemia
  - ~ No d4T □ steatosis
  - ~ Abacavir □ SVR

Viral Hepatitis – Hepatitis B

- Worldwide ~ 10% coinfection (RSA 20%)
- Effect of HIV on HBV:
  - ~ 3 – 6 x risk of chronicity after first exposure
  - ~ □HBeAg clearance
  - ~ □viral load
  - ~ □cirrhosis and death
- Effect of HBV on HIV unclear

Diagnosis & Treatment Recommendations

- Screen all for HBV infection: HBsAg, anti-HBs & anti-HBc
- Vaccinate if not exposed (response poor if CD4< 200)
- Isolated anti-HBc common (42% in one study)
- Occult infection = HBV DNA +, HBsAg – described
- Reverse HBeAg seroconversion seen
- Stage liver disease with biopsy

- Rx: initiation depends on meeting criteria for either virus
  - ~ dual activity of antivirals: TDF, LAM, emtricitabine, entecavir
- Rx if HBV DNA $\geq$ 2000 iu/ml & > mild disease on Bx
- Use Truvada or TDF and LAM
- Use entecavir if TDF contraindicated
- If ART not feasible try pIFN, adefovir, telbivudine
- Worsening ALTand AST during ART:
  - ~ DILD, HBV reactivation on drug withdrawal esp LAM, HBeAg loss or IRIS
- Screen for HCC

Medication Toxicity -DLID

- Most common serious AE of ART
- Mild asymptomatic to ALF
- Incidence 10% severe
- A life-threat in 2.6 / 100 person-years
- 4 primary mechanisms:
  - ~ hypersensitivity
  - ~ idiosyncrasy
  - ~ mitochondrial injury
  - ~ IRIS (immune response hepatitis virus infection)

Risk factors for DILD:

- ~ HBV or HCV coinfection
  - ~ advanced hepatic fibrosis
  - ~ pre-Rx □ALT, AST
  - ~ alcohol
  - ~ older age
  - ~ first exposure to ART
  - ~ □□CD4
  - ~ concomitant anti-TB rx
  - ~ cocaine use

Monitoring

- Check LFTs @ start
- Recheck every 3 months
- Educate Sxs of hepatitis
- STOP ART if:
  - ~ symptomatic
  - ~ jaundiced
  - ~ grade 4 hepatotoxicity
  - ~ severe lactic acidosis
- Mild ↑ALT/AST usually resolve spontaneously

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Hypersensitivity reaction

Associated drugs

NVP, ETR, RTV, T20, MVC

Onset

Greatest risk in first 6 weeks

Can present through 18 weeks

Clinical manifestations

Abrupt onset flu-like symptoms, abdominal pain, jaundice, fever, with or without skin rash

Prevention/monitoring

Educate patients on signs/symptoms

Check ALT/AST if rash develops

NVP

- Avoid in women with CD4 >250 cells/mm^3, men with CD4 >400 cells/mm^3
- Two-week dose escalation might decrease incidence
- Check ALT/AST every 2 weeks × first month, then monthly × 2 months, then every 3 months

ABC

- Screen for HLA-B*5701 before initiation; do not start ABC if positive

Management

- Discontinue all ART and all other potentially hepatotoxic medications
- Rule out other causes of symptoms
- Management is supportive
- Unknown whether other NNRTIs can be used safely after NVP-associated hepatotoxicity
- After ABC-associated hepatotoxicity, switch to another NRTI. ABC contraindicated in future use

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Mitochondrial toxicity

- Associated drugs
  - NRTIs: ddI > D4T > AZT/ZDV > 3TC = FTC = ABC = TDF
- Onset
  - Weeks to months
- Clinical manifestations
  - Anorexia, abdominal pain, nausea, vomiting, weight loss, fatigue
  - Might progress to tachycardia, tachypnea, jaundice, muscle weakness, altered mental status, multi-organ failure
  - Lab abnormalities include increased lactate, low arterial pH, low bicarbonate, increased anion gap
- Prevention/monitoring
  - Check lactate in symptomatic patients or in patients with elevated anion gap or low bicarbonate
- Management
  - Mild symptoms
    - Change ART regimen to NRTI with lower risk of mitochondrial toxicity or to NRTI-sparing regimen
    - Closely monitor lactate after resuming NRTI
  - Severe symptoms
    - Discontinue ART
    - Supportive care, which might include hemodialysis or hemofiltration, mechanical ventilation
    - Intravenous thiamine and/or riboflavin

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Direct drug toxicity/metabolism

Associated drugs

All NNRTIs, all PIs, most NRTIs, MVC

Onset

Weeks to months

Clinical manifestations

Might present with asymptomatic transaminase elevation

Clinical hepatitis might present with anorexia, weight loss, fatigue, jaundice, abdominal pain, nausea, vomiting

Prevention/monitoring

Monitor LFTs in NVP as above

For other agents, monitor LFTs every 3 months, more frequently in at-risk patients (HBV or HCV coinfection, elevated transaminases at baseline, underlying liver disease, alcohol abuse, cocaine use, use of other potentially hepatotoxic drugs, first exposure to ART)

Management

- Rule out other causes of hepatotoxicity, including viral hepatitis or HBV reactivation

Symptomatic patients

- Discontinue ART and other potentially offending medications
- Once symptoms and LFT abnormalities resolve, resume ART without offending agent(s)

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

IRIS

- Associated drugs
  - Any ART
- Onset
  - First 2 months
- Clinical manifestations
  - Nonspecific symptoms (fever, night sweats, fatigue, jaundice, nausea)
  - Might be difficult to distinguish from hepatitis due to drug toxicity without liver biopsy
  - If performed, liver biopsy shows hepatic necrosis with CD8+ T-cell infiltration
- Prevention/monitoring
  - Screen for HCV and HBV before ART initiation (should be done in all HIV-positive patients regardless of ART)
  - In HIV-HBV, treat HBV when initiating HAART
  - Consider diagnosis in patients with HBV or HCV coinfection and robust response to ART
  - In patients with HBV or HCV, monitor LFTs at least every month × first 3 months of ART initiation
- Management
  - Symptomatic patients
    - Discontinue ART
  - Asymptomatic patients
    - Discontinue ART if AST/ALT >10 × ULN
    - Closely monitor patients with less severe increases in AST/ALT

Hepatitis B reactivation

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Associated drugs

3TC, FTC, TDF

Onset

After withdrawal of medication with anti-HBV activity or development of HBV resistance (usually months to years of therapy)

Clinical manifestations

Ranges from asymptomatic increase in LFTs to severe fulminant hepatitis

Median onset 12–16 weeks after withdrawal

Prevention/monitoring

In setting HBV, ART regimen should include TDF and FTC (Truvada) or TDF and 3TC

If 3TC is withdrawn because of HIV resistance, replace it with an agent with anti-HBV activity

Management

- Resume anti-HBV therapy with appropriate agent on basis of resistance profile

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Asymptomatic patients

- Mild elevations usually resolve without drug discontinuation
- If ALT >5–10 × ULN and elevated direct bilirubin, discontinue ART
- If ALT >10 × ULN, discontinue ART
- Once LFT abnormalities resolve, resume ART without offending agent(s)

Medication	Pattern of liver injury
Antifungals	
Ketoconazole, fluconazole, amphotericin B	Hepatocellular injury
Antibiotics	
Ciprofloxacin	Hepatocellular injury
Azithromycin, dapsone	Cholestatic injury
Trimethoprim-sulfamethoxazole	Mixed hepatocellular-cholestatic injury
Tuberculosis treatment	
Isoniazid, rifampin, pyrazinamide	Hepatocellular injury
Ethambutol	Cholestatic injury
Antivirals	
Ganciclovir, acyclovir	Hepatocellular injury
Anabolic/androgenic steroids	
Testosterone, nandrolone, oxandrolone	Cholestatic injury, liver tumors, peliosis hepatis

Source: Price JC, Thio CL. Clin Gastro Hepatol 2010,8:1002-1012

Alcohol

- HIV+ more likely to drink

  USA study: 8% classified as heavy drinkers -2x general population
- Accelerates fibrosis in HCV monoinfection
- 10% of hazardous drinkers ↑surrogate markers for fibrosis
- A modifiable risk factor
- Counsel

Nonalcoholic Fatty Liver Disease

- NAFLD / NASH (steatohepatitis)
- Estimated prevalence 40 - 69% vs 17 – 33% (gen pop)
- Esp if HCV + or on NRTIs
- Metabolic derangements on ART
  - ~ NRTI-PI combos
  - ~ insulin resistance, dyslipidaemia
  - ~ hypertriglyceridaemia
  - ~ lipodystrophy
- Natural Hx unknown
- Exacerbate underlying chronic LD

Nodular Regenerative Hyperplasia

- Rare disorder multiple small regenerative liver nodules
- A cause of cryptogenic LD in HIV
- ? Aetiology – ddI, thrombophilia
- Consider in idiopathic portal HT

AIDS Cholangiopathy

- Infection-related strictures in biliary tree
- RUQ pain, ↑ALP, GGT usually not jaundiced
- Fever, N&V, diarrhoea
- CD4 < 100
- Less common after ART
- Infections: *Cryptosporidium parvum, CMV, Microsporidia, Cyclospora, MAC, Histoplasmosis*
- *Diagnose by US, MRCP, ERCP*
- *Rx with ART*

Acalculous Cholecystitis

- Associated with CMV or Cryptosporidium
- Isospora and microsporidium also seen
- RUQ pain, fever, cholestasis, no leucocytosis
- Imaging = thickened, big GB, no stones
- HIDA scan non-functioning GB
- Rx = cholecystectomy

AIDS-related Cancers

- Hepatic involvement with NHL 33%
- Hepatic involvement with KS 9%

OIs

- MAC common – N&V, doarrhoea, abdo pain, high ALP, poorly formed granulomata with AFB
- TB common – granulomata, abscess
- CMV present in liver without clinical clues
  - ~ mild xaminitis, fever, malaise, LOW, hepar
- Fungal infection – cryptococcus, histoplasmosis, candida, aspergillus
- PJP in liver described
- Peliosis hepatis with Bartonella
- HSV hepatitis
- HHV6
- VZV
- EBV
- Toxoplasmosis
- Strongyloides

Vanishing Bile Duct Syndrome

- Loss of small to medium sized intrahepatic bile ducts
- Many causes
- CMV and drug toxicity
- Cholestatic presentation
- Diagnose by histology
- First rule out large duct disease
- Prognosis ominous