HIV and the Liver

• Liver disease common in HIV+ patients
  – In a S. African cohort, 4% had LFT elevations >5 x upper limits of normal (ULN) prior to ARVs
    Hoffmann C, AIDS 21:1301

• Liver disease increasing cause of death in HIV+ patients

Outline

• Evaluation of chronically elevated transaminases

• Evaluation of acutely elevated transaminases (acute hepatitis)

• Evaluation of elevated alkaline phosphatase
Liver function tests

- **Misnomer:**
  - Don’t always measure liver function
  - May be abnormal even in patients with healthy liver

- **Aminotransferases:**
  - Sensitive indicators of hepatocellular injury; elevated in hepatitis
  - Also present in other tissues; elevated after hemolysis, exercise, muscle or cardiac injury
Liver function tests

- **Alkaline phosphatase (AP)**
  - Derived from liver and bone
  - Elevated levels of liver-derived AP suggest cholestasis or infiltrative hepatic process

- **GGTP**
  - Inducible enzyme expressed in hepatic cholangioles
  - Elevated levels suggest cholestasis, infiltrative process

- **Bilirubin**: measures ability to detoxify metabolites, transport organic anions into bile

- **Albumin, PT**: tests of liver’s synthetic function
Case

- 37 yo M with HIV. CD4 cell count 50; VL >750,000. ALT and AST initially elevated
- Started on TDF/FTC/EFV.
- CD4 cell count increased to 322; VL dropped to <50 c/mL. LFTs normalized

<table>
<thead>
<tr>
<th>Yr</th>
<th>Meds</th>
<th>CD4</th>
<th>HIV RNA</th>
<th>ALT</th>
<th>AST</th>
<th>AP</th>
<th>Bili</th>
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<tr>
<td>0</td>
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<td>50</td>
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<td>206</td>
<td>181</td>
<td>102</td>
<td>3.4</td>
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<td>1</td>
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<td>322</td>
<td>&lt;50</td>
<td>46</td>
<td>29</td>
<td>122</td>
<td>5.1</td>
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</tbody>
</table>
Case

- Over the next 3 years, he gained close to 50 kg
- Weight increased from 95 kg to 143 kg (BMI 49)
- ALT, AST became chronically elevated

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<td>97</td>
<td>89</td>
<td>125</td>
<td>5.1</td>
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</table>

- Platelets fell to 75 K. Noted to have splenomegaly
Outline

- Evaluation of chronically (>6 mo.) elevated transaminases
- Evaluation of acutely elevated transaminases (acute hepatitis)
- Evaluation of elevated alkaline phosphatase
Elevated transaminases: The 4 steps

- **Step 1:**
  - Review meds, supplements
  - Alcohol use
    - AST:ALT ≥ 2:1. AST < 8 x ULN
  - Viral hepatitis (B, C)
  - Hemochromatosis: Fe/TIBC >0.45
  - Fatty liver disease: U/S
    - ALT, AST <4x ULN: AST:ALT < 1

Pratt DS and Kaplan MM, NEJM, 2000
Elevated transaminases: The 4 steps

- **Step 2:**
  - Rule out non-hepatic causes: muscle, thyroid, celiac, adrenal disease; anorexia nervosa

- **(Step 3):**
  - Rule out rare causes: autoimmune hepatitis, Wilson disease, α-1-antitrypsin deficiency)

- **Step 4**
  - Liver biopsy
Case

- 37 yo HIV+ M, BMI 49
- ALT, AST slightly elevated (97, 89). Platelets fell to 75 K.
- Abdominal U/S: fatty liver and splenomegaly

Image from Afdhal, JAMA, 2012
Case

- Patient underwent gastric-bypass surgery. In OR, liver noted to be nodular, consistent with cirrhosis
- Liver bx: steatohepatitis, cirrhosis
- Childs class A (well-compensated)
- After surgery, lost 50 kg!
- F/U: Vitamin E; HCC screening
Non-alcoholic fatty liver disease

• Most common cause of abn. transaminases in U.S.
• Subset of those with hepatic steatosis develop steatohepatitis, fibrosis
• Risks: obesity, meds (steroids), metabolic disorders (DM, insulin resistance), lipodystrophy, HCV, HIV
• Tests: Imaging (U/S, MRI); liver biopsy
• Treatment:
  – Weight loss, exercise, treat metabolic disorders (DM)
  – In HIV pts, switch to “metabolically friendly” ART
  – Vitamin E
  – Pioglitazone
Case

• 31 year old male → female transgender.
• Takes estrogen. Works as an escort.
• HIV+. CD4 cell count 18 (3%). HIV RNA: 63,000
• Started on trim/sulfa and azithromycin
• 3 weeks later, develops fever, diarrhea, myalgias
Case

- AP: 49; ALT 186; AST 601; CK 10,615
- HBsAg+, HBeAg+, anti-HBc+ (IgG), HBV DNA 97,000,000
- Dx: trim/sulfa-induced rhabdomyolysis
- LFTs, CK normalize after changing trim/sulfa to atovoquone.
Case

- Started on TDF/FTC/EFV

<table>
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<th>Bili</th>
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<tr>
<td>0</td>
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<td>15</td>
<td>10 million</td>
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<td>nl</td>
<td>5.1</td>
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<tr>
<td>4</td>
<td>TDF/FTC/EFV; ATQ</td>
<td>126 (6%)</td>
<td>507</td>
<td>329</td>
<td>234</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>TDF/FTC/EFV; ATQ</td>
<td></td>
<td>1802</td>
<td>1147</td>
<td>283</td>
<td>34/20.5</td>
<td></td>
</tr>
</tbody>
</table>

- PT, CK normal. Patient has no symptoms!
What do you do now?

- Take additional history
- Do additional testing
- Stop all or some medications
- All of the above!

<table>
<thead>
<tr>
<th>Day</th>
<th>Meds</th>
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<th>HIV RNA</th>
<th>ALT</th>
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<td>15</td>
<td>10 m</td>
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</tbody>
</table>
Outline

• Evaluation of chronically elevated transaminases

• Evaluation of acutely elevated transaminases (acute hepatitis)

• Evaluation of elevated alkaline phosphatase
LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug-induced liver injury
- Super-infection
- Immune reconstitution Inflammatory Syndrome (IRIS)/HBV flare
LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug induced liver injury
- Super-infection
- Immune reconstitution Inflammatory Syndrome (IRIS)/HBV flare
Drug-induced liver injury (DILI)

- Hepatocellular: ALT >> AP
- Cholestatic: AP >> ALT.
- Mixed

• **Hy’s law**: drug-induced hepatocellular injury accompanied by jaundice has a high mortality
### DILI: Typical Patterns

<table>
<thead>
<tr>
<th>Hepatocellular</th>
<th>Mixed</th>
<th>Cholestatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>(ALT/AP &gt;5)</td>
<td></td>
<td>(ALT/AP &lt;2)</td>
</tr>
<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></td>
<td></td>
<td>PZA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ketoconazole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenobarbital</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tricyclics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anabolic steroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NSAIDS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Allopurinol</td>
</tr>
</tbody>
</table>

**Internet resource on DILI:**

National Library of Medicine’s LiverTox


Navarro & Senior. NEJM 354: 7
Antiretroviral (ARV) DILI

- 14-20% of HIV+ pts starting ARVs have elevations in LFTs
  - 2-10% need to interrupt ART

- Risk factors:
  - Elevated baseline transaminases
  - Concomitant hepatotoxic drug (anticonvulsants, bactrim, amox/clav, azoles, antituberculous therapy)
  - HCV
  - HBV

Hoffmann et al. CID (2008) 47:1479
Audsley J, 17th CROI (2010), abs 691
Risk factors for ARV Hepatotoxicity: HBV and TB

• 868 HIV+ patients in S. Africa
  – 94% male, most treated with AZT/3TC/EFV

• ~5% developed severe hepatotoxicity after ARVs
  – TB treatment increased risk 8.5-fold
  – Positive HBsAg increased risk 3-fold (mainly in those with HBV DNA >10,000 c/mL)
  – Highest risk if patient was HBV+ and receiving antituberculous therapy

## Mechanisms of ARV DILI

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
<th>Characteristic/Time of onset</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reaction</td>
<td>NVP Abacavir</td>
<td>Rash, fever, &lt; 8 weeks</td>
<td>Female, High CD4 (&gt;250 in F; &gt;400 in M)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Genetics</td>
</tr>
<tr>
<td>Mitochondrial Toxicity</td>
<td>ddI&gt;d4T&gt;AZT&gt;ABC/TDF/FTC/3TC</td>
<td>Lactic acidosis/Weeks to months</td>
<td>Female, obesity</td>
</tr>
<tr>
<td>Steatosis</td>
<td>NRTIs PIs</td>
<td>Prolonged exposure</td>
<td>Metabolic syn, lipodystrophy, HCV (gt 3)</td>
</tr>
<tr>
<td>Immune reconstitution</td>
<td>Any</td>
<td>Usually in first few months</td>
<td>Low CD4 HBV</td>
</tr>
</tbody>
</table>

McGovern B, Sulkowski M, Sterling R, in Boyer, Chapter 38
Risk of hepatotoxicity of ARVs

Caution

- ddi
- d4T
- AZT
- NVP
- EFV
- RTV
- TPV

Safe

- ABV
- TDF
- 3TC
- FTC
- APV
- DRV
- ATV
- LPV
- SQV
- NFV
- T20

In a series of 218 HIV+ patients (40% coinfected with HCV), no cases of grade 3/4 hepatotoxicity were attributed to raltegravir.

Rate of raltegravir hepatotoxicity in randomized studies is low.

Mena A, 5th IAS (2009); Rockstroh J, 17th CROI (2010), abstract 662
DILI due to antituberculous therapy (ATT)

• Overall rate: 5-33%

• Risk factors:
  – Older age (>35 yo)
  – Pregnancy
  – HIV
  – HBV or HCV
  – Elevated baseline LFTs
  – Use of concomitant hepatotoxins (prescribed or not!)
DILI: Frequency with 1\textsuperscript{st} line drugs

- 430 patients with active TB initiating therapy
- Incidence of major adverse events:
  - PZA: 14.8/1000 person-months
  - INH: 4.9/1000
  - Rif: 4.3/1000
  - ETH: 0.7/1000

LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug-induced liver injury
- Super-infection
- Immune reconstitution Inflammatory Syndrome (IRIS)/HBV flare
Superinfection

- **Viral infections:**
  - HAV
  - HCV (check RNA and Ab)
  - HDV (in HBV+)
  - HEV
  - Herpes viruses
    - HSV
    - CMV, EBV: may be associated with mono-like syndrome, atypical lymphs

- **Bacterial infections:** e.g. syphilis
HSV Hepatitis

- **Risk groups:** neonates, malnourished children, pregnancy, malignancy, immunosuppression (e.g. steroids), organ transplant, AIDS

- **Presentation**
  - Fulminant picture, resembling septic shock
  - Fever, N/V, abdominal pain, leukopenia, thrombocytopenia, coagulopathy, marked rise in transaminases

- **Diagnosis:** liver bx; serum HSV PCR

- **Treatment:** acyclovir

Kaufman B, CID, 1997; Levitsky J, Liver Transplantation, 2008
What do you do now?

• Take additional history
• Stop all or some medications
• Do additional testing
• All of the above!

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<td>15</td>
<td>10 mnl</td>
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</tr>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
What do you do now?

- HBV DNA 93,000 (down from 97 million)
- HCV RNA, EBV PCR, CMV PCR, HSV PCR negative, HDV negative
- Abdominal ultrasound normal
ART continued;
EFV changed to raltegravir

<table>
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<td>0</td>
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<tr>
<td>7</td>
<td>TDF/FTC/RAL</td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>TDF/FTC/RAL</td>
<td>182</td>
<td>54</td>
<td>130</td>
<td>8.5</td>
</tr>
</tbody>
</table>
But the story’s not over. . .

- After LFTs normalized, patient rechallenged with TDF/FTC/EFV. No recurrence of hepatitis.

- Seroconverted:
  - HBsAg negative, anti-HBs positive

- Diagnosis: HBV IRIS!
LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug-induced liver injury
- Super-infection
- Immune reconstitution Inflammatory Syndrome (IRIS)/hepatitis B flare
Liver enzyme elevation in HIV/HBV coinfection

- Discontinuation of hepatitis B-active drugs (3TC, FTC, TDF) may lead to HBV flare

- Flares in transaminases may also be due to:
  - Drug-induced liver injury
  - Superinfection
  - Breakthrough of drug-resistant HBV
  - Seroconversion of HBeAg
  - HBV IRIS

- Liver histology may distinguish drug toxicity (eosinophils) from viral hepatitis (portal inflammation)
HBV IRIS

• Hepatic flare because of an increase in HBV-specific T cell responses
  – Due to reduction in HBV viremia plus ART-associated immune reconstitution

• Risk factors: high baseline ALT and HBV DNA

HBV IRIS

• After ART initiation, interferon-\(\gamma\) inducible cytokines remain elevated in those with hepatic flares, suggesting immune-mediated mechanism

• Role of steroids controversial
  – Steroids associated with reactivation of HBV infection
  – Although immune system is responsible for hepatocyte injury, it is also vital to virus clearance

Crane M JID (2009) 199:974
35 yo F with HIV diagnosed in 1996
- History of PCP, cryptococcal fungemia, acyclovir resistant genital HSV
- CD4 cell count 1, HIV RNA 302,000
- Initiated TDF/FTC/ATV/r
- 1 week later, developed fever, abdominal pain, nausea, diarrhea
- AP: 1400; Bilirubin 85; AST 100; ALT 80.
- U/S: hepatic steatosis, prominent intra-abdominal LN, splenomegaly; no biliary dilatation
Evaluation of the Elevated AP

- Cholestatic or infiltrative liver disease
  - Consider drug-induced cholestasis or viral hepatitis
  - U/S: intra- or extra-hepatic biliary dilatation
  - Antimitochondrial Ab (+ suggests primary biliary cirrhosis)
  - If unrevealing and AP persistently and significantly elevated, consider ERCP/MRCP and liver bx
Differential Diagnosis

- AIDS Cholangiopathy
- Atazanavir-induced cholelithiasis
- Mycobacterial IRIS: MAC, TB
Curious Case of Atazanavir-induced Cholelithiasis

- 14 patients on ATV who had complicated cholelithiasis (cholecystitis, cholangitis)
- Median duration of ATV: 42 mo.
- Abd pain, elevated bili
- ATV found in biliary calculi in 8 of 11 cases
  - 1 pt had persistent ATV stones 11 mo. after stopping drug

Mycobacterial IRIS

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

• In 19 patients with TB-IRIS, 7 (37%) had intra-abdominal manifestations and 4 (21%) had hepatic involvement.

• All 4 had hepatomegaly and elevated LFTs without evidence of biliary obstruction on U/S
  – Median AP 495, GGTP 338, ALT 66, AST 68.

• In all 4 cases, there was evidence of TB-IRIS at another anatomic site, e.g. intra-abdominal adenopathy, increased respiratory disease.

Case

- BCx positive for MAC. Received clarithromycin, ethambutol and rifabutin
- Complicated course with hypercalcemia, recurrent fevers
- Ultimately, liver biopsy showed granulomatous hepatitis, consistent with MAC-IRIS
Elevated AP in patients with AIDS

• In 24 patients in France with fever and elevated AP, liver biopsy revealed a microbiologic diagnosis in 13 (54%); most common etiology was mycobacterial infection

• In 501 HIV patients in the U.S. who underwent liver biopsy (mostly for LFT abnormalities, fever, hepatomegaly), mycobacterial infection found in 26% (MAC, M. tb, other mycobacteria)

Cavicchi M, CID, 1995; Poles, M, JAIDS, 1996
Bringing It All Back Home: Summary
Summary

• 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, other drugs
  – Superinfection
  – HBV flare (if patient HBV coinfected)
  – IRIS, e.g. TB, MAC
    • Particularly if fever, adenopathy, hepatomegaly, other sites of disease and elevated AP/GGTP
Acknowledgements

• Barbara McGovern
• Chinwe Ukomadu
• Florencia Pereyra
• Kimon Zachary
• Azure Makadzange
• Seth Glassman
• Nesli Basgoz

• AWACC
  • Henry Sunpath
  • Yunus Moosa
  • Francois Venter
Extra Slides
# HBV treatment in the HIV+ patient

<table>
<thead>
<tr>
<th>Virus Needing Treatment</th>
<th>Preferred option</th>
<th>Avoid</th>
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<tbody>
<tr>
<td>HIV or HBV</td>
<td>TDF+ FTC/3TC+</td>
<td>3TC/FTC/TDF/ETV monotherapy</td>
</tr>
<tr>
<td></td>
<td>3rd HIV agent</td>
<td></td>
</tr>
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</table>

Continue nucleoside/nucleotide therapy indefinitely

If HIV therapy not an option, pegylated IFN can be used for treatment of HBV infection
Monitoring Therapy

- Monitor HBV DNA every 3 months
- If patient is HBeAg (+): monitor HBeAg, anti-HBe, HBsAg
- If patient originally HBeAg (-): check HBsAg after HBV DNA is undetectable
- Only about 10% of patients clear HBsAg; the majority who clear, do so in the first year

Goal of Therapy

• Complete virologic response:
  – HBV DNA < 60 IU/mL at 6-12 months
  – Continue therapy

• Inadequate virologic response:
  – HBV DNA ≥ 2000 IU/ml (~10,000 c/ml) at 6-12 mo.
  – Assess adherence. If pt adherent, consider possibility of drug-resistant HBV
## HBV Diagnosis

<table>
<thead>
<tr>
<th>Phase</th>
<th>HBsAg</th>
<th>HBeAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>Anti-HBe</th>
<th>HBV DNA</th>
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<tbody>
<tr>
<td>Acute</td>
<td>+</td>
<td>+</td>
<td>IgM</td>
<td></td>
<td></td>
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<tr>
<td>Chronic &gt; 6 mo.</td>
<td>+</td>
<td>+/-</td>
<td>IgG</td>
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<tr>
<td>Recovery</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Vaccine recipient</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
ART for HIV/HBV Coinfection

- Cross-sectional study of 122 HIV/HBV coinfected patients, most with prior 3TC exposure
- Patients on TDF + FTC or 3TC more likely to have undetectable HBV DNA than those on TDF or 3TC monotherapy

Matthews GV et al, AIDS, 2009
Lamivudine (3TC)

- Lamivudine reduces HBV DNA by an average of 3 log in coinfected patients Benhamou CID 38:S101; Dore JID 180:607
- Mutations in HBV YMDD motif: ~25%/yr in HIV+

Leung, *J Hepatol* 1999;30:59A
Liver enzyme elevation in patients with HBV/HIV: “HBV flares”

- Flares in transaminases may also be due to:
  - Breakthrough of drug-resistant HBV
    - rtV173L/L180M/M204V
  - Seroconversion of HBeAg
  - Immune reconstitution against HBV
  - Superinfection with HDV, HCV or HAV

- Liver histology may be helpful in distinguishing drug toxicity (presence of eosinophils) from viral hepatitis (portal inflammation).
HBV IRIS

- HBV IRIS may be caused by an increase in HBV-specific T cell responses due to reduction in HBV viremia plus ART-associated immune reconstitution. McGovern, CID (2004) 39:133
- Hepatic flares are particularly dangerous in patients with underlying cirrhosis and poor hepatic reserve.
- Risk factors for hepatic flares include high baseline ALT and HBV DNA levels. Crane M (2009) JID 199:974
- After initiation of ART, interferon-γ inducible cytokines remain elevated in patients who had hepatic flares compared with those who did not, suggesting an immune-mediated mechanism
- The role of steroids in HBV IRIS is controversial
  - Steroids associated with reactivation of HBV infection
  - Although the immune system is responsible for hepatocyte injury, it is also vital to virus clearance