Outline

• Evaluation of chronically elevated transaminases

• Evaluation of acutely elevated transaminases (acute hepatitis)

• Evaluation of newly elevated alkaline phosphatase

• Bonus mystery case!
Liver function tests

• Aminotransferases:
  – 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)
  – Found in liver, bone, intestine
  – Elevated levels of liver AP suggest cholestasis or infiltrative hepatic process

• Gamma-glutamyl transpeptidase (GGTP)
  – Elevated: cholestasis, infiltrative process, but non-specific (increased with alcohol use, renal failure, other conditions)

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

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

- Middle-aged HIV+ M. CD4 count 50; VL >750,000.
- Started on TDF/FTC/EFV.
- VL undetectable; CD4 cell count increased to 760
- Over the next 3 years, he gained 50 kg: his weight increased to 143 kg (BMI 49)
- Developed glucose intolerance
- ALT, AST became persistently elevated: ALT 97, AST 89. AP 125, Bili 0.3
- 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

• Bonus mystery case!
Causes of Chronically Elevated Aminotransferases

Pratt DS and Kaplan MM, NEJM, 2000

• Hepatic causes
  – Alcohol abuse
  – Medication
  – Chronic HBV or HCV
  – Steatosis and non-alcoholic steatohepatitis
  – Autoimmune hepatitis
  – Hemochromatosis
  – Wilson’s disease (in <40yo)
  – Alpha-1 antitrypsin deficiency

• Non-hepatic causes
  – Muscle diseases
  – Strenuous exercise
  – Celiac sprue
  – Thyroid disease
  – Anorexia nervosa
Elevated transaminases: The 4 steps

- **Step 1:**
  - Review meds, supplements
  - Assess for alcohol use
    - Clue: AST:ALT ≥ 2:1; AST<8x ULN
  - Test for viral hepatitis (B, C)
  - Consider hemochromatosis
    - Fe/TIBC > 0.45
  - Fatty liver disease: ultrasound
    - Clue: ALT, AST<4x ULN. AST:ALT<1

**TABLE 1. Causes of Chronically Elevated Aminotransferase Levels.**

<table>
<thead>
<tr>
<th>Hepatic causes</th>
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<tbody>
<tr>
<td>Alcohol abuse</td>
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<tr>
<td>Medication</td>
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<tr>
<td>Chronic hepatitis B and C</td>
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<tr>
<td>Steatosis and nonalcoholic steatohepatitis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
</tr>
<tr>
<td>Hemochromatosis</td>
</tr>
<tr>
<td>Wilson’s disease (in patients ≤40 years old)</td>
</tr>
<tr>
<td>Alpha1-antitrypsin deficiency</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonhepatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac sprue</td>
</tr>
<tr>
<td>Inherited disorders of muscle metabolism</td>
</tr>
<tr>
<td>Acquired muscle diseases</td>
</tr>
<tr>
<td>Strenuous exercise</td>
</tr>
</tbody>
</table>

Pratt D, Kaplan M, NEJM, 2000;
AGA Position Statement, Gastroenterology, 2002
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

- HIV+ M, BMI 49
- ALT, AST persistently elevated (97, 89).
- No alcohol or other medication use
- Viral hepatitis testing negative

- Abdominal U/S: fatty liver, splenomegaly

Image from Afdhal, JAMA, 2012
Case

- Pt had gastric-bypass surgery. In OR, liver noted to be nodular
- Biopsy: steatohepatitis, cirrhosis
- Childs class A (well-compensated)
- After surgery, lost 50 kg! LFTs normalized
- F/U: Vitamin E; liver cancer screening

Image from Afdhal, JAMA, 2012
Non-alcoholic fatty liver disease (NAFLD)

• Most common cause of abnormal transaminases in the U.S.
• Frequently present in HIV pts (30-40%)
• Risks: age, obesity, diabetes, dyslipidemia
• Rule out common causes of secondary hepatic steatosis:
  – Excessive alcohol, HCV (gt 3), medications (e.g. steroids)

HIV, Insulin Resistance, and NAFLD

HIV

Chronic inflammation

Abnormal fat distribution
Visceral adiposity
Lipoatrophy

Antiretrovirals
PI, Thymidine analogues

HCV

Puri P, Sanyal A, Clinical Liver Disease, 2012;
Stanley T, Grinspoon S, JID, 2012
Assessing risk of NAFLD

– Patients > 45 years old, diabetes, obesity (BMI >30)

– High NAFLD Fibrosis Score
  (http:nafldscore.com)
    Age, BMI, DM, aminotransferases, platelets, albumin

NAFLD: Management

• Weight loss, exercise, treat metabolic disease (diabetes; lipids – statin if elevated)
• Vitamin E
  – Not yet recommended in patients with cirrhosis, DM, or NAFLD without liver biopsy
• Pioglitazone (possibly)
• Hepatocellular cancer screening (U/S, AFP) in patients with advanced fibrosis
• In HIV pts, switch to “metabolically friendly” ART

Metabolically “Friendly” ART

Propensity to cause dyslipidemia

High: Less “Friendly”
- d4T
- AZT
- IDV/r, NFV
- TPV/r, LPV/r, FPV/r

Low: More “Friendly”
- 3TC
- FTC
- TDF
- ABC
- DRV/r, SQV/r
- ATV/r
- NVP
- RAL
- EVG/cobi

Based on Dube and Cadden, 2011
Case

• Middle-aged 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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<tr>
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<td>1.8/0.9</td>
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</table>

- PT, CK normal. Patient has no symptoms!
What is going on?

A. Drug-induced liver injury due to efavirenz
B. Drug-induced liver injury due to tenofovir
C. Superinfection
D. Hepatitis B flare

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What do you do now?

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

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Outline

• Evaluation of chronically elevated transaminases

• Evaluation of acutely elevated transaminases (acute hepatitis)

• Evaluation of elevated alkaline phosphatase

• Mystery bonus case!
LFT Abnormalities After Starting ART: Differential Diagnosis

• Drug-induced liver injury
• Super-infection
• Hepatitis flare in setting of Immune Reconstitution Inflammatory Syndrome (IRIS)
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

*ALT or AST > 3x ULN; bilirubin > 2x ULN
DILI: Typical Patterns

Hepatocellular 
(ALT/AP >5) 

ARVs 
Herbal meds 
INH 
Ketoconazole 
Valproate 
NSAIDS 
Allopurinol

Mixed 

Sulfonamides 
Bactrim 
Phenytoin 

Cholestatic 
(ALT/AP <2) 

Amox/clav 
Macrolides 
Phenothiazines 
Oral contraceptives

Internet resource on DILI: 
National Library of Medicine’s LiverTox 

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

• Risk factors:
  – Elevated baseline transaminases
  – Alcohol, malnutrition: decreased glutathione levels (reduces ability to scavenge free oxygen radicals)
  – Concomitant hepatotoxic drug (anticonvulsants, trim/sulfa, azoles, TB therapy)
  – HCV or HBV (increases risk about 3-fold)

Hoffmann et al. CID (2008) 47:1479
Audsley J, 17th CROI (2010), abs 691
# Mechanisms of ARV DILI

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
<th>Features/Time of Onset</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity reaction</td>
<td>Nevirapine (NVP)</td>
<td>Rash, fever, &lt; 8 weeks</td>
<td>NVP: Female, High CD4 (&gt;250 in F; &gt;400 in M); HIV viremia; Genetics</td>
</tr>
<tr>
<td></td>
<td>Abacavir</td>
<td></td>
<td></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>HCV ddI + ribavirin</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 antiretroviral</td>
<td>Usually in first few months</td>
<td>Low CD4 HBV</td>
</tr>
</tbody>
</table>

Adapted from McGovern B, Sulkowski M, Sterling R, in Boyer, Chapter 38
Risk of Hepatotoxicity of ARVs

Caution

*Full-dose ritonavir

Integrase Inhibitors

RAL  EVG/cobi

Safe

When should medication be stopped in suspected DILI?

Consider stopping drug(s) if patient has:

• Symptomatic hepatitis
• Acute hepatitis with jaundice (Hy’s law)
• Symptoms of drug hypersensitivity (rash, fever)
• Mitochondrial toxicity/lactic acidosis
• Marked ALT, AST elevation even if asymptomatic (particularly if patient has advanced liver disease)

• Close monitoring is essential
LFT Abnormalities After Starting ART: Differential Diagnosis

• Drug-induced liver injury

• Super-infection

• Hepatitis flare in setting of Immune Reconstitution Inflammatory Syndrome (IRIS)
Superinfection

- Viral infections:
  - HAV (check IgM)
  - HCV (check RNA and Ab)
  - HDV (serology, RNA in HBsAg + pts)
  - HEV
  - Herpes viruses
    - HSV: fulminant picture; marked transaminase elevation; rash present in <50%
    - CMV, EBV: mono-like syn, atypical lymphs, hepatitis
- Bacterial infections: e.g. syphilis

What do you do now?

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

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Tests!

- HBV DNA 93,000 (down from 97 million)
- HAV IgM, HCV RNA, HDV negative
- EBV PCR, CMV PCR, HSV PCR negative
- Abdominal ultrasound normal
## EFV changed to Raltegravir

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<td>7</td>
<td>TDF/FTC/RAL</td>
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<tr>
<td>9</td>
<td>TDF/FTC/RAL</td>
<td>182</td>
<td>54</td>
<td>130</td>
<td>0.5</td>
</tr>
</tbody>
</table>
But the story’s not over. . .

- About one year later, patient rechallenged with TDF/FTC/EFV (at her request). No recurrence of hepatitis.

- Patient had previously seroconverted: HBsAg negative, anti-HBs positive

- Hepatitis flare, likely because of HBV IRIS
Acute elevation of transaminases in HIV/HBV Patient

- Drug-induced liver injury
- Superinfection

HBV-related:
- Discontinuation of HBV-active drugs (3TC, FTC, TDF)
- Breakthrough of drug-resistant HBV
- Hepatitis flare during HBeAg seroconversion
- HBV IRIS
HBV IRIS

- Hepatitis flare because of increase in T cell responses and interferon-\( \gamma \) inducible cytokines after initiation of ART
- Risk factors: high baseline ALT and HBV DNA
- Role of steroids controversial
  - Steroids can cause HBV reactivation
  - Immune system responsible for hepatocyte injury, but also vital for HBV clearance

HBV in HIV-infected Patients

- HBV/HIV patients have higher HBV DNA levels and ~17-fold higher rate of liver-related mortality than HIV monoinfected patients\(^1\)
- HBeAg+ patients most likely to have high HBV DNA – may be the highest priority group to treat\(^2\)
- Treatment Goals:
  - Prevent end-stage liver disease, liver cancer
  - Prevent transmission (e.g. during pregnancy)
  - Reduce risk of drug-induced hepatotoxicity
  - Reduce risk of IRIS

HBV Drugs: Potency and Genetic Barrier to Resistance

Potency

Genetic Barrier

3TC, FTC
LAM
FTC
LdT
ETV
TDF
Tenofovir Entecavir
ADV
IFN

M. Levrero (2006)
HBV treatment in HIV+ patient

Preferred option

- TDF+ FTC/3TC+
- 3rd HIV agent

Avoid

- 3TC/FTC/TDF/ETV monotherapy

Continue nucleoside/nucleotide therapy indefinitely
What if patient has renal failure?

- Evaluate cause of kidney disease; if HIV-associated nephropathy or HBV-associated cryoglobulinemia, may improve with renally-dosed therapy
- If renal dysfunction is due to tenofovir, change to a tenofovir-sparing regimen, e.g. abacavir/3TC/efavirenz or AZT/3TC/efavirenz
- Start entecavir, a potent anti-HBV agent.
- Because entecavir has anti-HIV activity and can select for drug-resistant HIV (M184V), best to introduce entecavir when HIV RNA undetectable
Case

- Middle-aged F with HIV diagnosed in the 1990s
- History of cryptococcemia
- CD4 cell count 1, HIV RNA 302,000
- Initiated TDF/FTC/atazanavir/ritonavir
- 1 week later, developed fever, abdominal pain, nausea, diarrhea

- AP: 1400; Bilirubin 5; AST 100; ALT 80.
What is going on?

A. AIDS Cholangiopathy
B. Atazanavir-induced cholelithiasis
C. HSV hepatitis
D. Mycobacterial Immune Reconstitution Inflammatory Syndrome (IRIS)
E. Cryptococcal IRIS
Evaluation of the Elevated AP

- Cholestatic or infiltrative liver disease
  - Consider drug-induced cholestasis or viral hepatitis (fibrosing cholestatic variant)
  - U/S to look for intra- or extra-hepatic biliary dilatation
  - If initial testing unrevealing and AP persistently and significantly elevated, consider further evaluation
Differential Diagnosis

- AIDS Cholangiopathy
  - Cryptosporidium; also Microsporidium
  - CD4 cell count <100/mm³
  - Abdominal pain, diarrhea, fever
  - U/S, ERCP: papillary stenosis, bile duct stricture, sclerosing cholangitis

- Atazanavir-induced cholelithiasis
  - Presents as cholecystitis, cholangitis, pancreatitis

- Mycobacterial IRIS

Markedly dilated CBD with distal stricture (red arrow), suggestive of papillary stenosis.
Case - continued

- U/S: no biliary dilatation; notable for prominent intra-abdominal lymphadenopathy, splenomegaly
- BCx positive for MAC. Received clarithromycin, ethambutol and rifabutin
- Complicated course with hypercalcemia, recurrent fevers
- Liver biopsy showed granulomatous hepatitis, consistent with MAC-IRIS
Mycobacterial IRIS of Liver

• After initiation of ART, hepatic IRIS due to mycobacterial infection (TB, MAC) may occur—often accompanied by other sites of worsening disease (e.g. adenopathy, pulmonary disease)

Bonus Mystery Case!

- Middle-aged HIV+ M
- CD4 cell count >500, HIV RNA <50 for many years on ABC/3TC/atazanavir/ritonavir
- Patient presented with 3-4 weeks of abdominal pain and chest wall discomfort
- Admitted to an outside hospital for evaluation of chest discomfort. Found to have a pulmonary nodule and rim-enhancing lesions in the liver
Case - continued

- Past medical history: secondary syphilis several years ago, s/p treatment; non-reactive RPR 4 months prior to presentation. HAV/HBV immune.
- Multiple sexual partners, does not always use condoms. No TB exposures.
- On exam, appears well. Afebrile. No rash or adenopathy. No abdominal tenderness or HSM.
- AP 695. ALT 119. AST 70. Bilirubin 2.5/0.3 (LFTs had been normal 4 months ago)
Multiple rim-enhancing lesions in the liver

Multiple pulmonary nodules, measuring 2-10 mm
What is going on?

A. Malignancy
B. Syphilis
C. Peliosis hepatis due to Bartonella
D. Fungal infection
E. Mycobacterial infection
Tests

- Blood cultures negative.
- Negative tests for Cryptococcus, Histoplasma, Bartonella, Brucella, Coxiella, latent TB
- HIV RNA undetectable. CD4 cell count 500
- HCV RNA and antibody undetectable.
Liver biopsy

- Periportal inflammation and edema; granulomas; microbiologic stains negative

Slides courtesy of Dr. Joseph Misdraji, Mass. General
Follow-up

- RPR + 1:64
- Treated with 3 weekly shots of IM penicillin
- AP declined from 695 to normal
- ALT declined from 119 to normal
- Repeating imaging revealed markedly decreased size of pulmonary nodules and liver lesions!
Syphilitic hepatitis

- LFT abnormalities may occur during secondary syphilis
- AP may be disproportionately elevated, but not always
  - In one case series, median AP 186 (129-1836), median ALT 105 (82-614)
  - LFTs normalized after penicillin (within 5 d to 3 mo.)
- Pathology: pericholangiolar inflammation, periportal hepatocyte necrosis; spirochetes seen on liver biopsy in some but not all cases
- Rare cases of hepatic gumma mimicking cancer have been reported

Bringing It All Back Home: Summary
Summary

• In approaching a HIV patient with abnormal LFTs, consider both the pattern and tempo of the changes.

• In a HIV patient with liver test abnormalities after starting ART, consider:
  – Worsening of underlying liver disease, e.g. alcohol-related, steatohepatitis
  – Drug-induced liver injury: ART, other drugs
  – Superinfection (hepatitis viruses, herpes viruses, syphilis)
  – HBV flare (if patient HBV coinfected)
  – IRIS
Kathleen Corey
Barbara McGovern
Chinwe Ukomadu
Florence Pereyra
Kimon Zachary
Azure Makadzange
Seth Glassman
Joseph Misdraji
Nesli Basgoz
Kelsey Han

**AWACC:**
Henry Sunpath, Yunus Moosa, Francois Venter, Karen Moodley, all our sponsors

Haruspicy or hepatoscopy: divination by inspecting entrails, esp. the liver

*Etruscan Bronze Mirror of Chalchas the Seer Reading a Liver (Vatican: Gregorian Museum, Rome), 5th century BCE*