

Abnormal Liver Function Tests in HIV+ Patients



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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
 - Tend to be higher in men, those with greater muscle mass

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

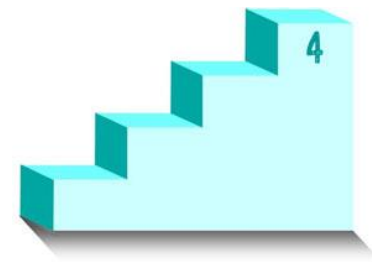
Outline

- 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

- 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: $AST:ALT \geq 2:1$; $AST < 8x$ 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.

Hepatic causes

Alcohol abuse

Medication

Chronic hepatitis B and C

Steatosis and nonalcoholic steatohepatitis

Autoimmune hepatitis

Hemochromatosis

Wilson's disease (in patients ≤ 40 years old)

Alpha₁-antitrypsin deficiency

Nonhepatic causes

Celiac sprue

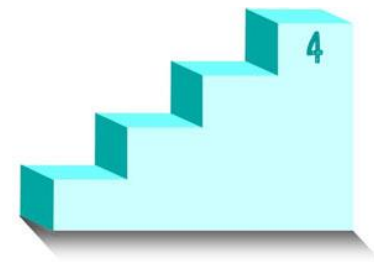
Inherited disorders of muscle metabolism

Acquired muscle diseases

Strenuous exercise

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**



Ultrasound image showing diffuse increased echogenicity consistent with fatty liver.

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

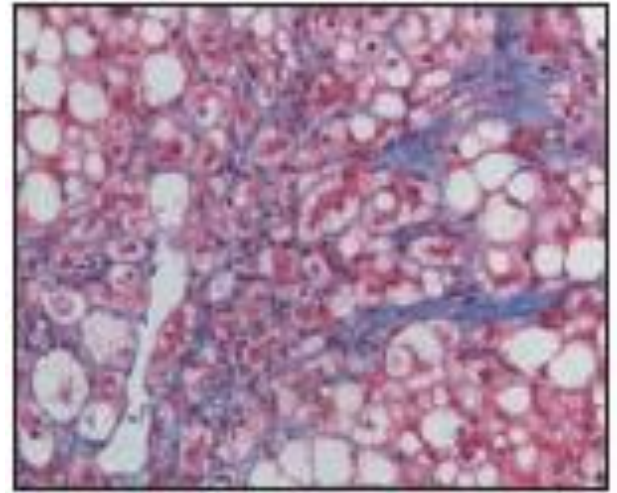
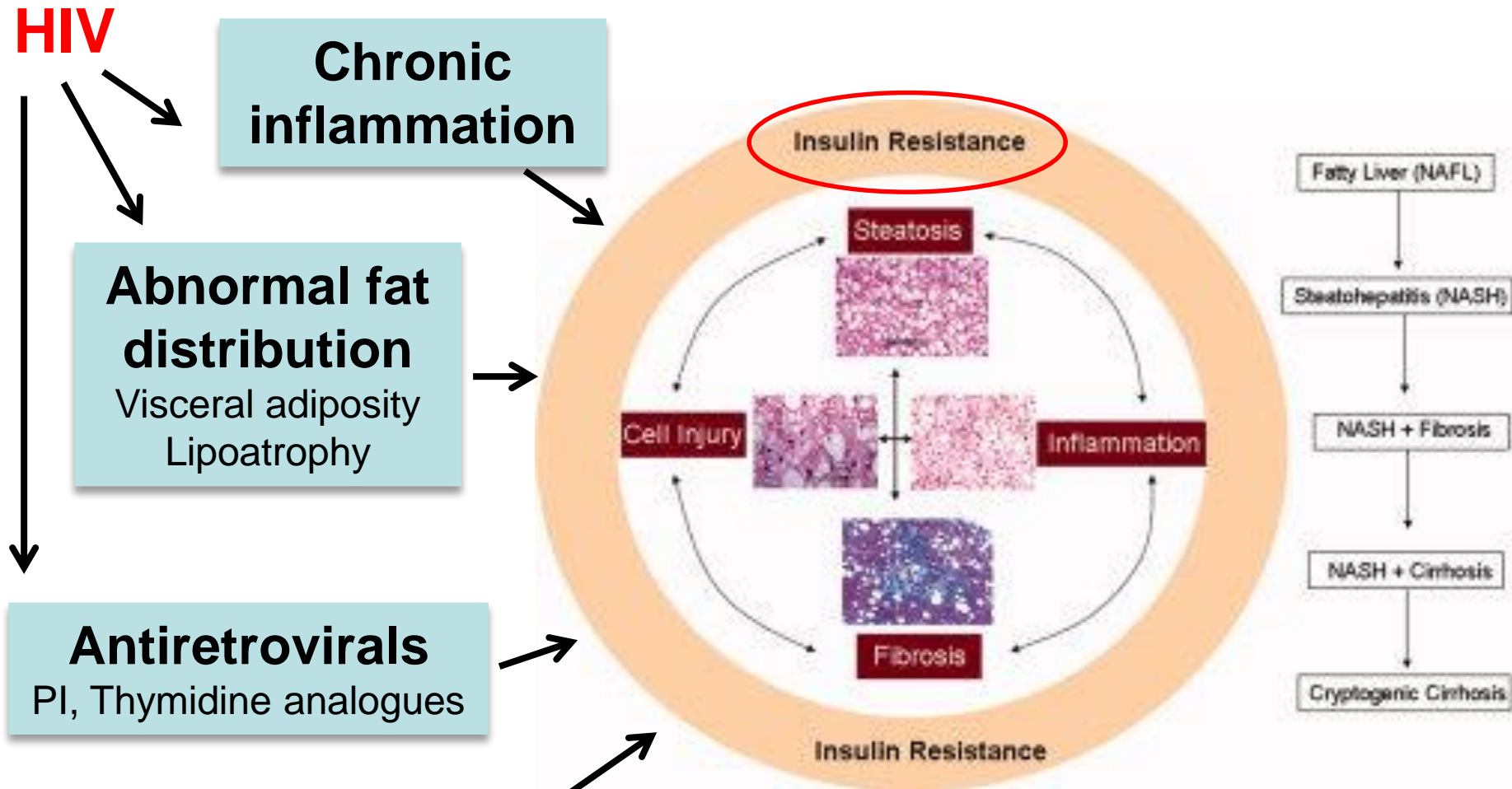


Image from Afdhal, JAMA, 2012

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, HBV, HCV (gt 3), medications (e.g. steroids)

HIV, Insulin Resistance, and NAFLD



HCV

Assessing risk of significant liver disease with NAFLD

- Consider liver biopsy in patients with:
 - evidence for liver disease: peripheral stigmata, splenomegaly, cytopenias
 - elevated ferritin
 - age >45 yrs, diabetes, obesity (BMI >30)
- High NAFLD Fibrosis Score (<http://nafldscore.com>)

Age, BMI, DM, aminotransferases, platelets, albumin

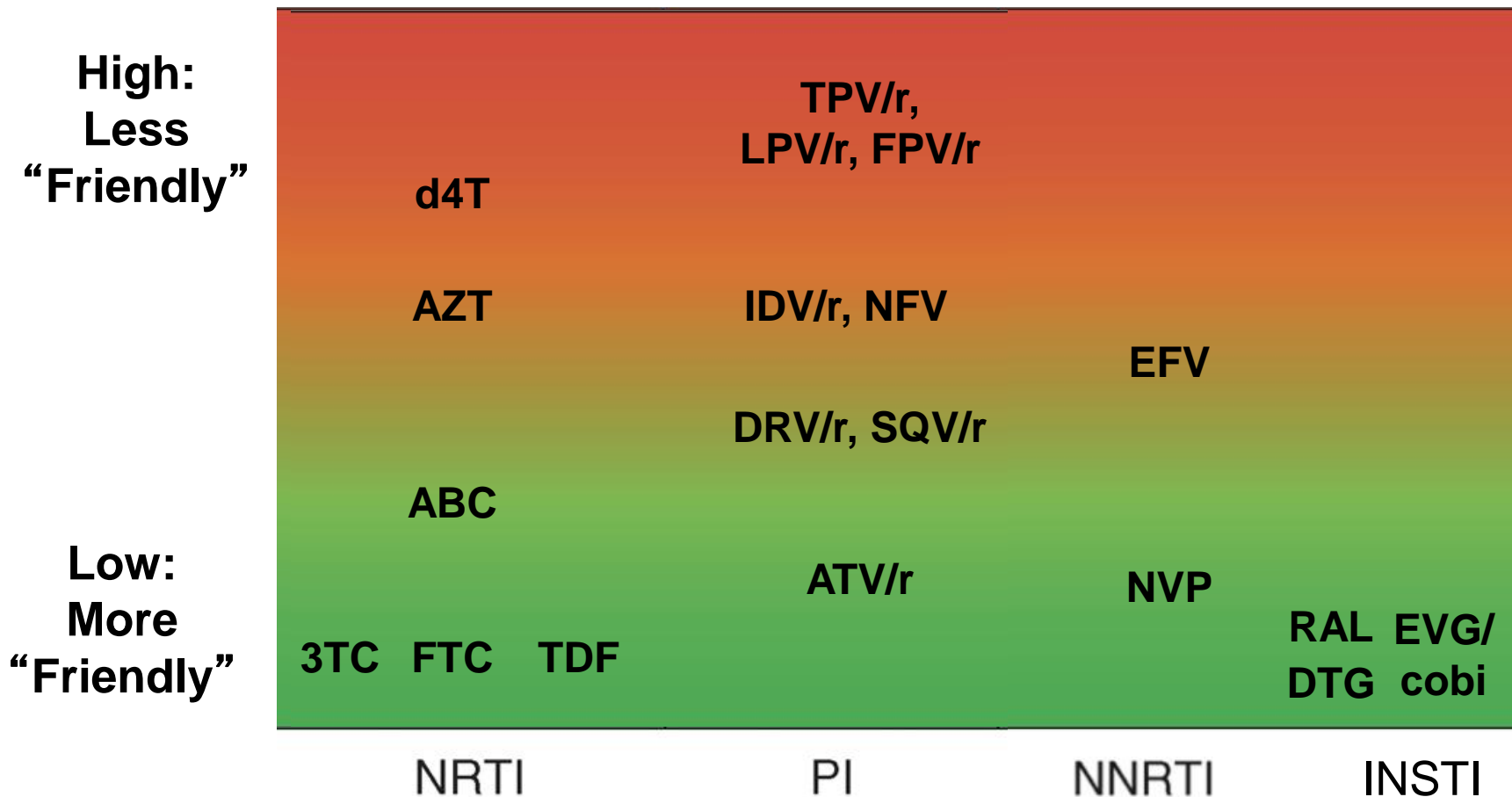
NAFLD: Management



- Weight loss, exercise, treat metabolic disease (diabetes; lipids – statin if elevated)
- CV disease preventive measures, avoid alcohol
- Hepatitis A and B vaccination (if non-immune)
- Vitamin E: NASH or fibrosis without DM
- Pioglitazone: consider in those with DM
- Hepatocellular cancer screening (U/S, AFP) in patients with advanced fibrosis
- In HIV pts: “metabolically friendly” ART

Metabolically “Friendly” ART

Propensity to cause dyslipidemia



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

Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV	15	10 million	nl	nl	nl	0.3
4	TDF/FTC/EFV	126 (6%)	507	329	234	104	
6	TDF/FTC/EFV			1802	1147	283	1.8/ 0.9

- 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

Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV	15	10 m	nl	nl	nl	0.3
4	TDF/FTC/EFV	126	507	329	234	104	
6	TDF/FTC/EFV			1802	1147	283	1.8

What do you do now?

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



Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV	15	10 m	nl	nl	nl	0.3
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Outline

- Evaluation of chronically elevated transaminases
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- 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

valproate

NSAIDS

Allopurinol

Mixed

Sulfonamides

Bactrim

Phenytoin

Navarro & Senior. NEJM 354: 7

Cholestatic

(ALT/AP <2)

Amox/clav

Macrolides

Phenothiazines

Oral

contraceptives

Internet resource on DILI:

National Library of Medicine's LiverTox

<http://livertox.nih.gov/php/searchchem.php>

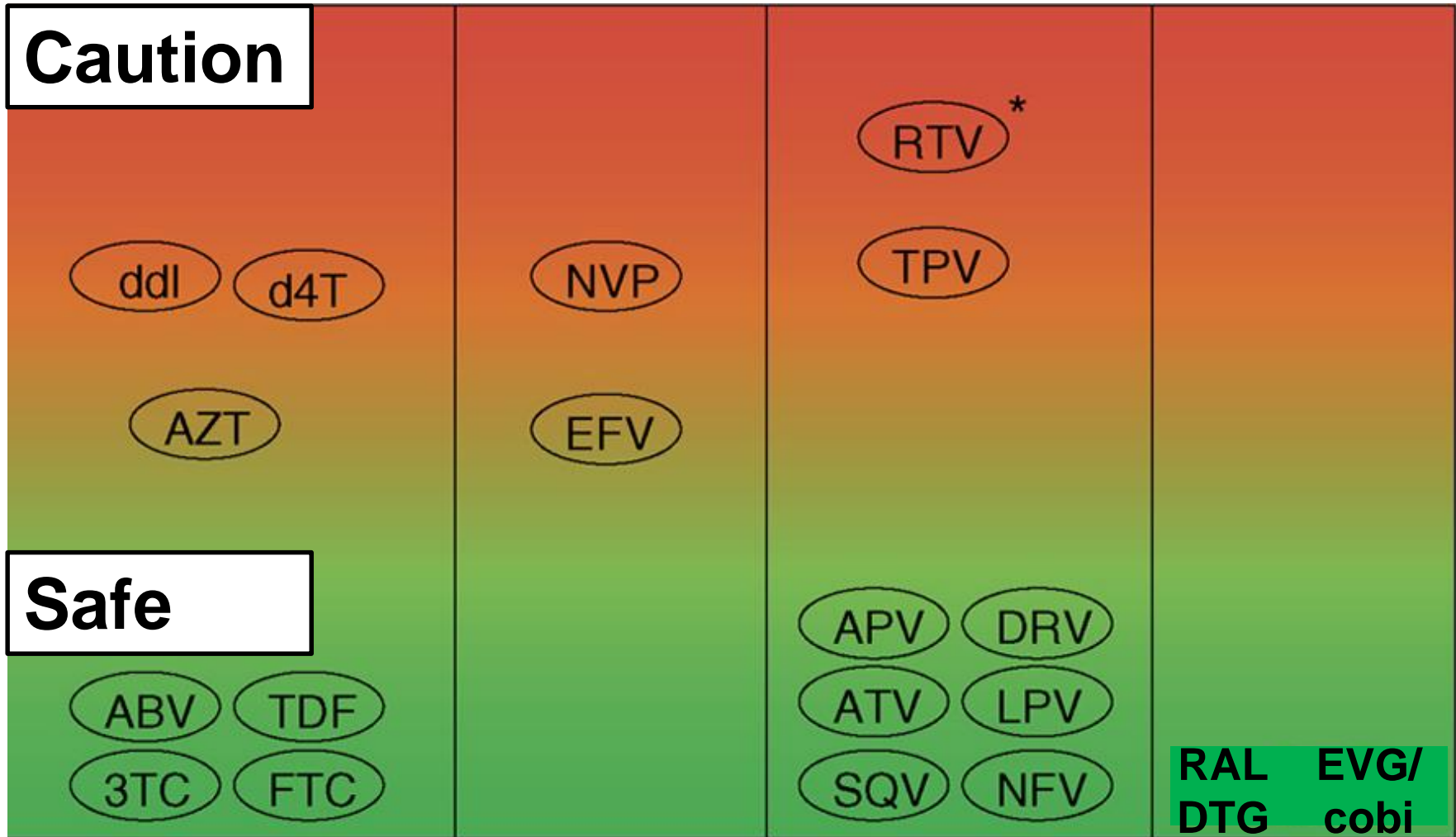
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Antiretroviral (ARV) DILI

- 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)

Risk of Hepatotoxicity of ARVs



NRTI

NNRTI

PI

Integrase Inhibitors

*Full-dose ritonavir

Adapted from Soriano, AIDS, 2008. Also: Vispo J Antimicrob Chemother, 2010; Rockstroh HIV Medicine, 2011 DeJesus, Lancet, 2012; Sax, Lancet, 2012

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!



Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV	15	10 m	nl	nl	nl	0.3
4	TDF/FTC/EFV	126	507	329	234	104	
6	TDF/FTC/EFV			1802	1147	283	1.8

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

Wk	Meds	ALT	AST	AP	Bili
0	TDF/FTC/EFV	nl	nl	nl	0.3
4	TDF/FTC/EFV	329	234	104	
6	TDF/FTC/EFV	1802	1147	283	1.8
7	TDF/FTC/RAL				
9	TDF/FTC/RAL	182	54	130	0.5

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- γ 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

Case

- Middle-aged F with HIV diagnosed in the 1990s
- History of cryptococemia
- 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

- Confirm AP is liver-derived (check GGTP or 5 'nucleotidase)
- 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 (ERCP/MRCP, liver biopsy)

Differential Diagnosis

- AIDS Cholangiopathy

- Cryptosporidium; also Microsporidia
- CD4 cell count $<100/\text{mm}^3$
- Abdominal pain, diarrhea, fever; ϵ
- U/S, ERCP: papillary stenosis, bilateral sclerosing cholangitis

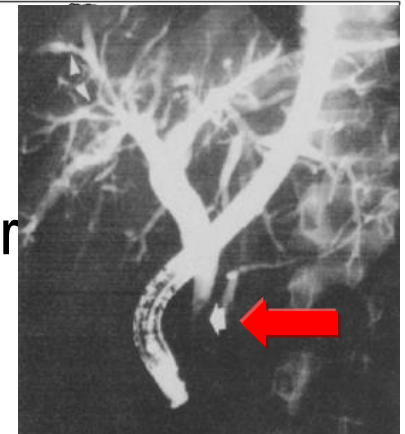
Atazanavir-induced cholelithiasis.



- 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)

Cavicchi M, CID, 1995; Poles, M, JAIDS, 1996; Lawn et al. AIDS 21:335. Lawn and Woods, AIDS 21: 2362. Verma S. AIDS Res Hum Retroviruses. 22:1052; Ratnam I, CID, 2006

Bonus Mystery Case!



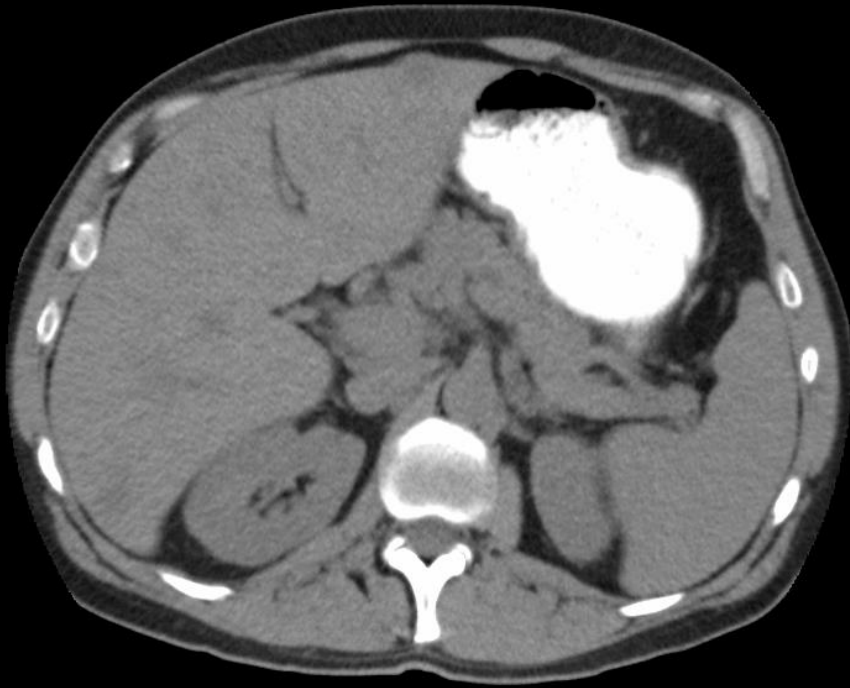
- Middle-aged HIV+ M
- CD4 cell count >500, HIV RNA <50 for many years on ABC/3TC/atazanavir/ritonavir
- Patient presented with 3-4 weeks of abdominal pain and chest wall discomfort
- Admitted to an outside hospital for evaluation of chest discomfort. Found to have a pulmonary nodule and rim-enhancing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

Case - continued

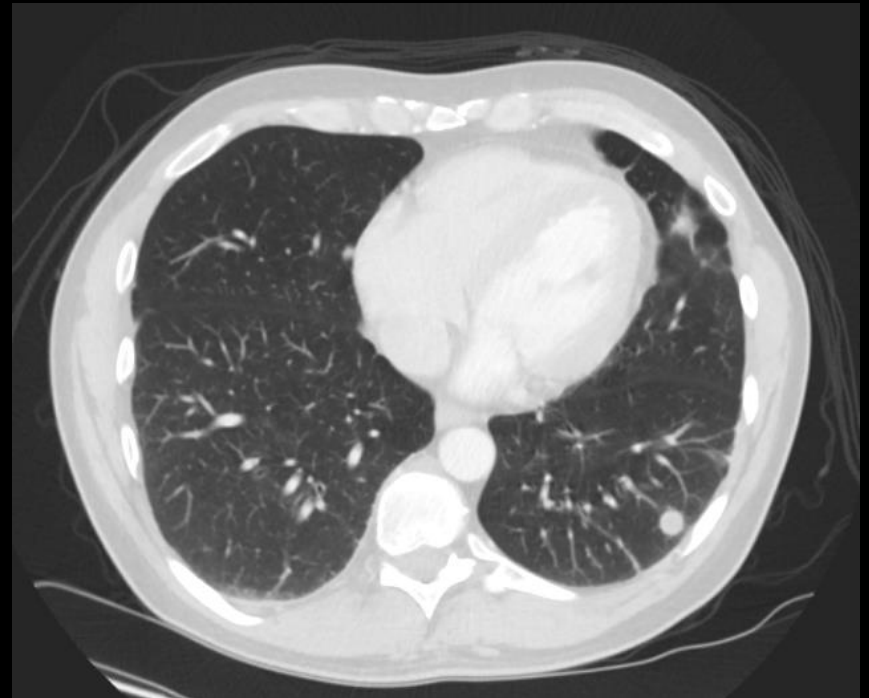
- Past medical history: secondary syphilis several years ago, s/p treatment; non-reactive RPR 4 months prior to presentation. HAV/HBV immune
- Multiple sexual partners, does not always use condoms. No TB exposures.
- On exam, appears well. Afebrile. No rash or adenopathy. No abdominal tenderness or HSM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

Imaging

Multiple rim-enhancing lesions in the liver



Multiple pulmonary nodules, measuring 2-10 mm



What is going on?



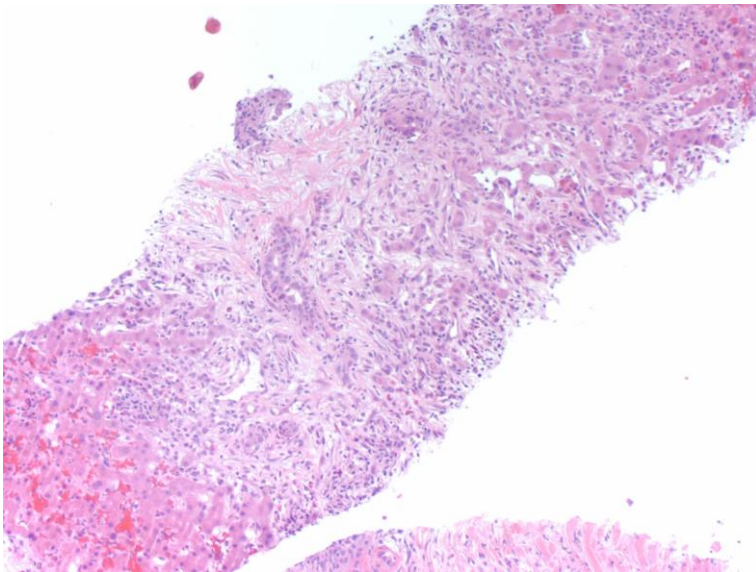
- A. Malignancy
- B. Syphilis
- C. Peliosis hepatis due to Bartonella
- D. Fungal infection
- E. Mycobacterial infection

Tests

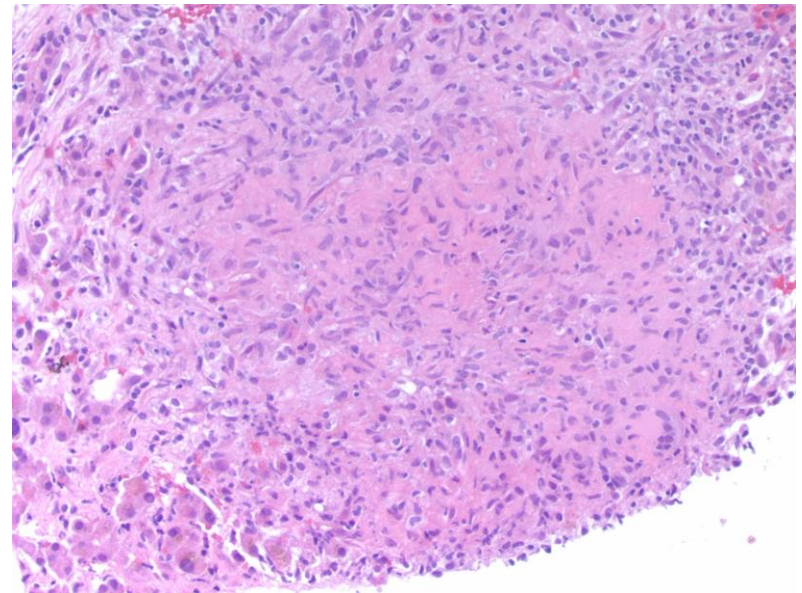
- Blood cultures negative.
- Negative tests for Cryptococcus, Histoplasma, Bartonella, Brucella, Coxiella, latent TB
- HIV RNA undetectable. CD4 cell count 500
- HCV RNA and antibody undetectable.

Liver biopsy

- Periportal inflammation and edema; granulomas; microbiologic stains negative



Periportal inflammation and edema



Granuloma

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 coinfecting)
 - IRIS

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**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*