

Abnormal Liver Tests in People with HIV



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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 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
- ALT levels more specific indicator of liver injury than AST

Liver tests



- **Alkaline phosphatase (AP)**
 - Found in liver, bone, intestine
 - Elevated levels of liver AP: cholestasis or infiltrative hepatic process
- **Gamma-glutamyl transpeptidase (GGTP)**
 - Elevated: cholestasis, infiltrative process, but non-specific (increased with alcohol use, renal failure)
 - Given lack of specificity, should not be used as a screening test in absence of other abnormal LFTs
- **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 (body mass index, 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

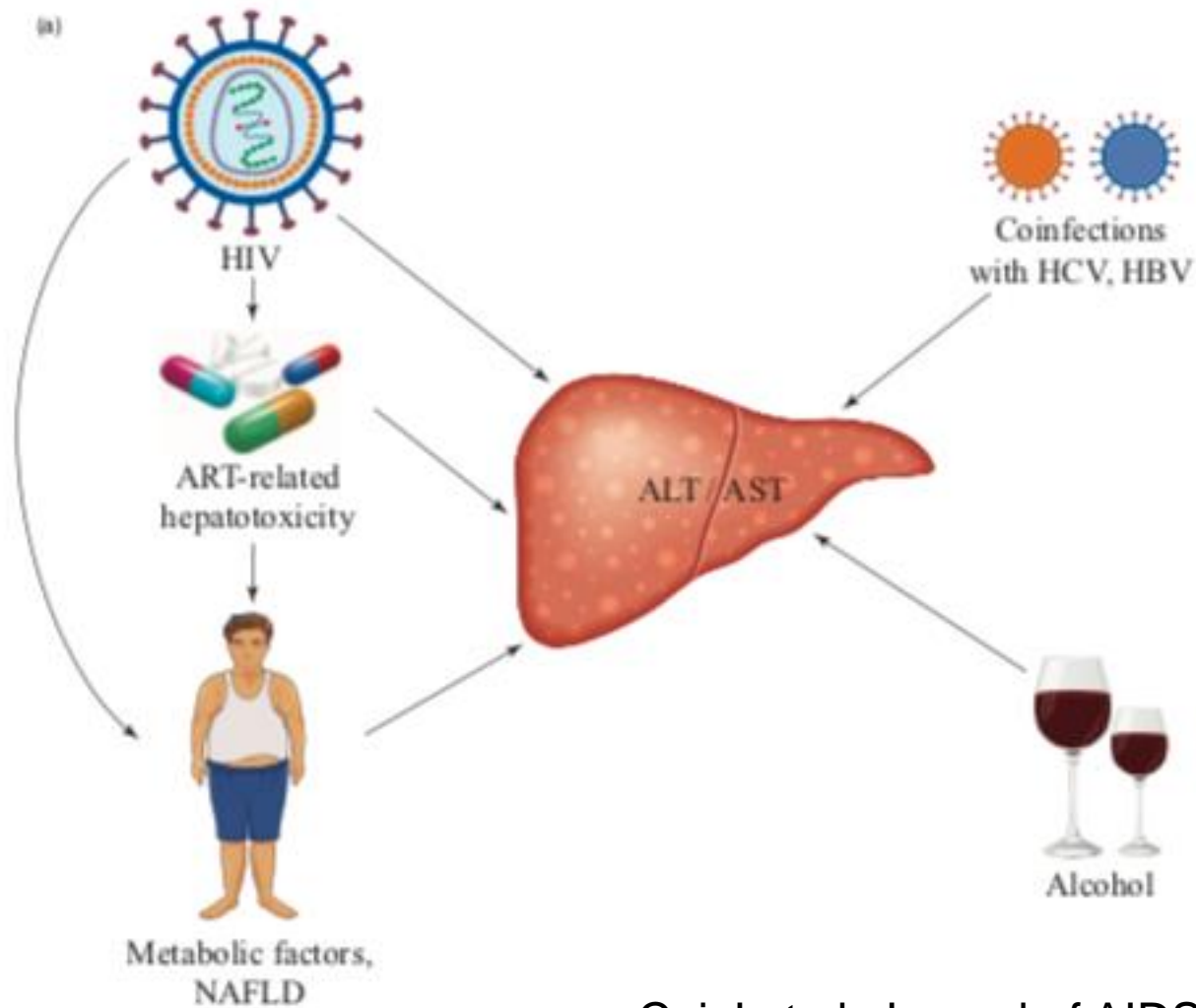
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- Evaluation of chronically (>6 mo.) elevated transaminases
- Evaluation of acutely elevated transaminases (acute hepatitis)
- Evaluation of elevated alkaline phosphatase
- Bonus mystery case!

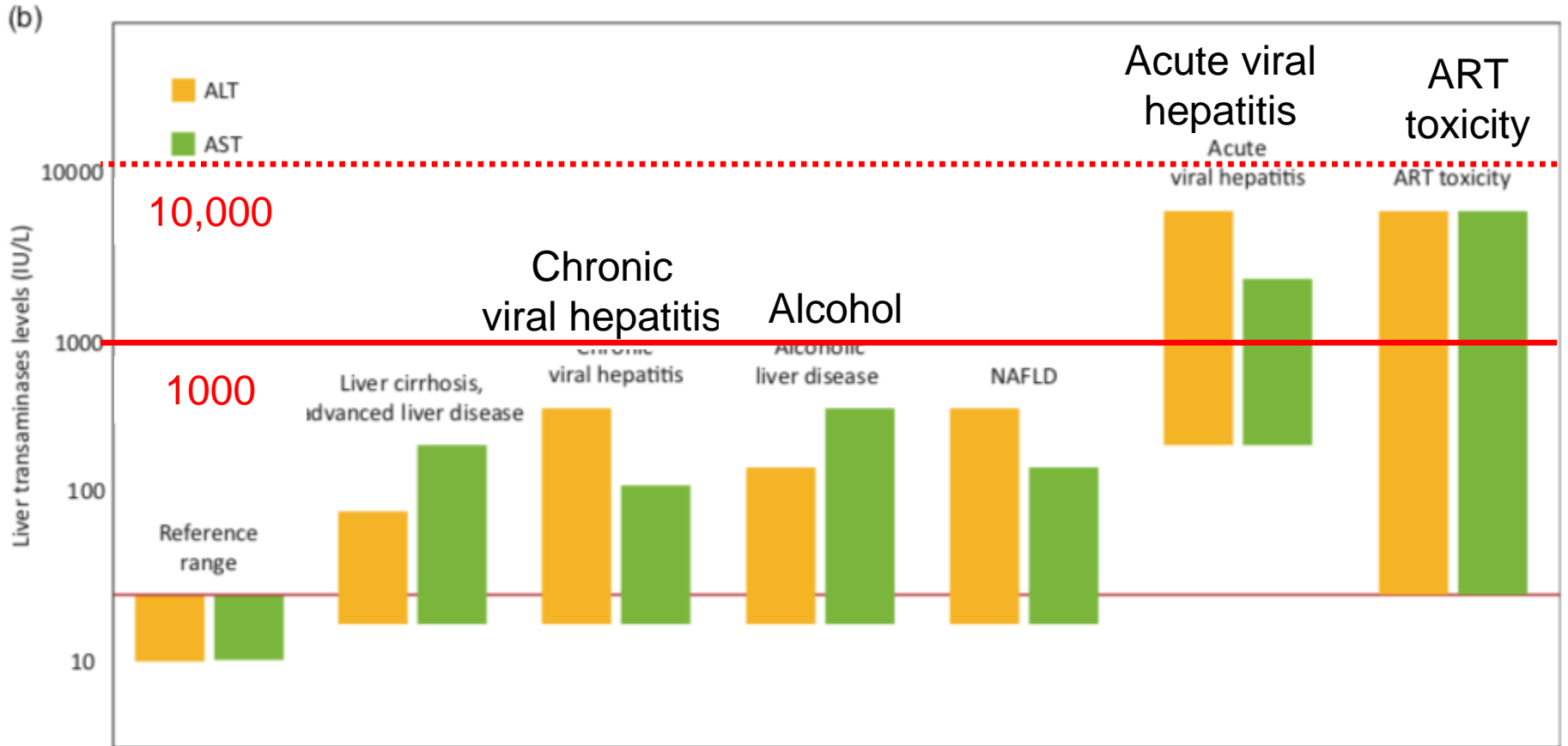
Causes of Chronically Elevated Aminotransferases

- 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

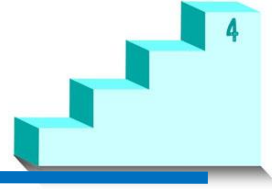
Transaminase Elevation in People with HIV



Transaminase Elevation in People with HIV



Elevated transaminases



- Review meds, supplements
- Assess for alcohol use
 - Clue: AST:ALT \geq 2:1; AST usually $<$ 300
- 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 \leq 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

Case

- HIV+ M, body mass index 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

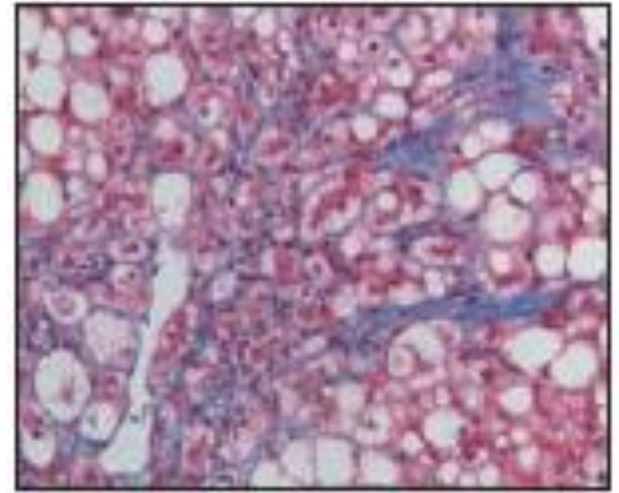


Image from Afdhal, JAMA, 2012

Non-alcoholic fatty liver disease (NAFLD)

- Most common cause of abnormal transaminases in the U.S.
- Frequently present in HIV pts (13 – 65%)
- Risks: age, obesity, diabetes, dyslipidemia
- Rule out common causes of secondary hepatic steatosis:
 - Excessive alcohol, HBV, HCV (gt 3), medications (e.g. steroids)

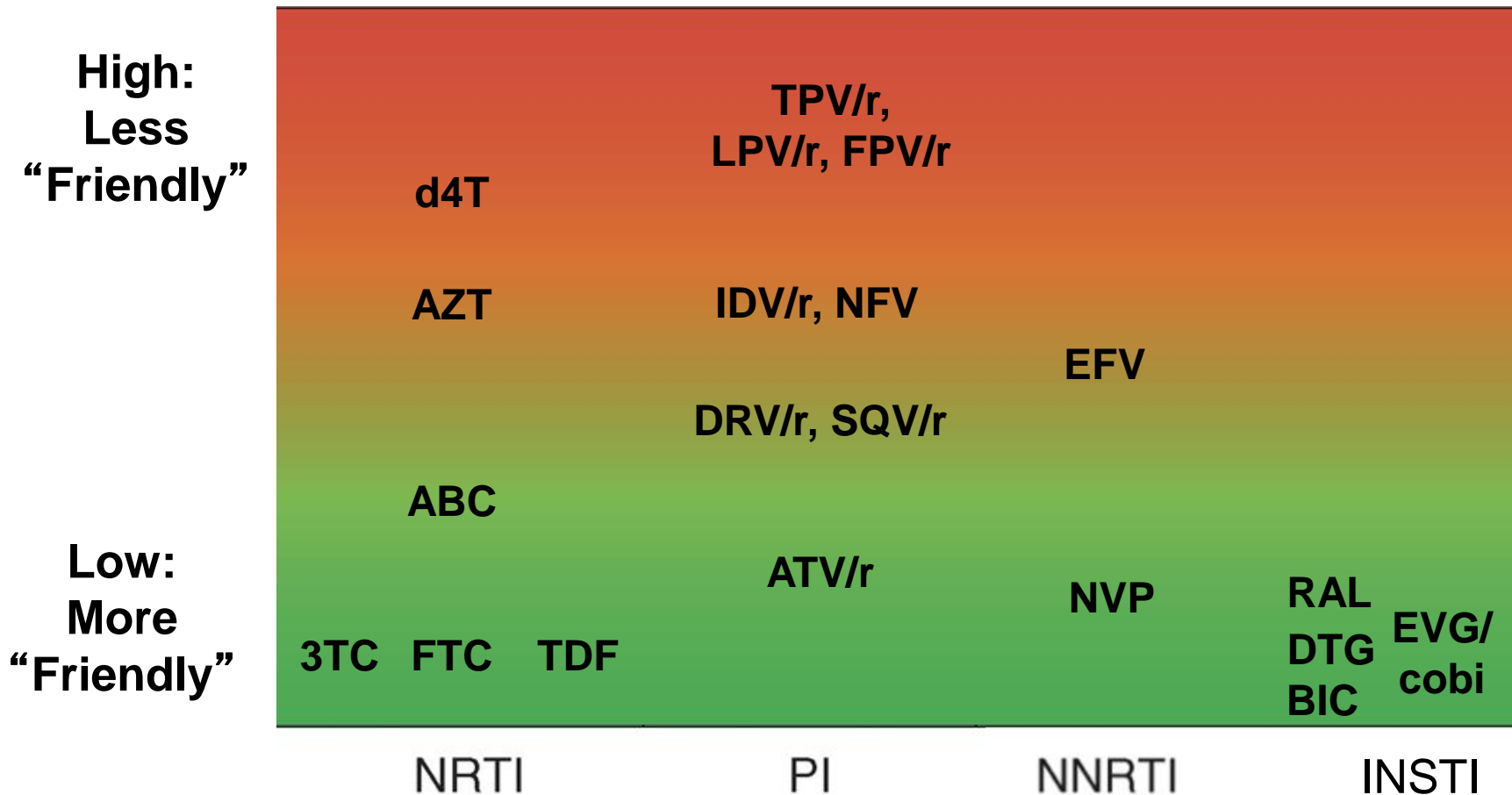
NAFLD: Management



- 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

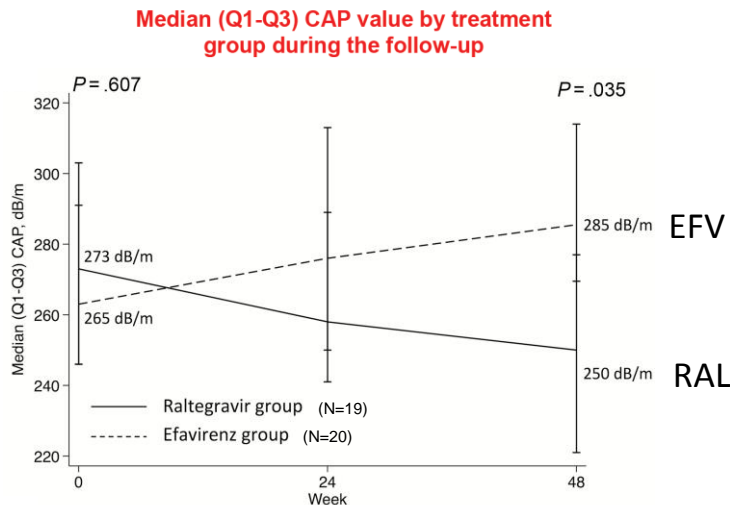
Metabolically “Friendly” ART

Propensity to cause dyslipidemia

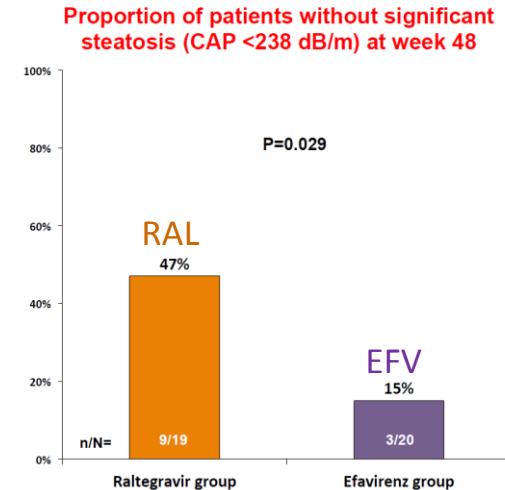


Switching EFV to RAL: Decrease in Hepatic Steatosis

- Patients on EFV + TDF/FTC or ABC/3TC with virologic suppression and hepatic steatosis
 - Controlled attenuation parameter (CAP) >238 dB/m (CAP: software added to transient elastography; provides information on ultrasound attenuation due to fat)
- Randomized to continue EFV (n=20); switch to RAL (n=19)



P-values show comparison between groups of treatment at baseline and at 48 weeks



Separate study: Hepatic steatosis biomarker and adipokine decrease when NNRTI or PI switched to RAL.

Offor O et al, PLoS ONE, 2018

Macías J et al, Clinical Infectious Diseases, 2017

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 IRIS

Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
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Outline

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- Evaluation of elevated alkaline phosphatase
- Mystery bonus case!

Liver Test 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)

Variable	Direct Hepatotoxicity	Idiosyncratic Hepatotoxicity	Indirect Hepatotoxicity
Frequency	Common	Rare	Intermediate
Dose-related	Yes	No	No
Predictable	Yes	No	Partially
Latency	Rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes	Acute hepatic necrosis; sinusoidal obstruction; acute fatty liver; nodular regeneration	Acute hepatocellular hepatitis; mixed or cholestatic hepatitis; immunoallergic features	Acute hepatitis; immune mediated hepatitis; chronic hepatitis
Common agents	Acetaminophen, niacin, aspirin, cocaine	Amox/clav, INH, macrolides, nitrofurantoin	Glucocorticoids; Antibodies against TNF, checkpoints

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

PZA

Mixed

Sulfonamides

Bactrim

Phenytoin

Phenobarbital

Cholestatic (ALT/AP <2)

Amox/clav

Macrolides

Phenothiazines

Tricyclics

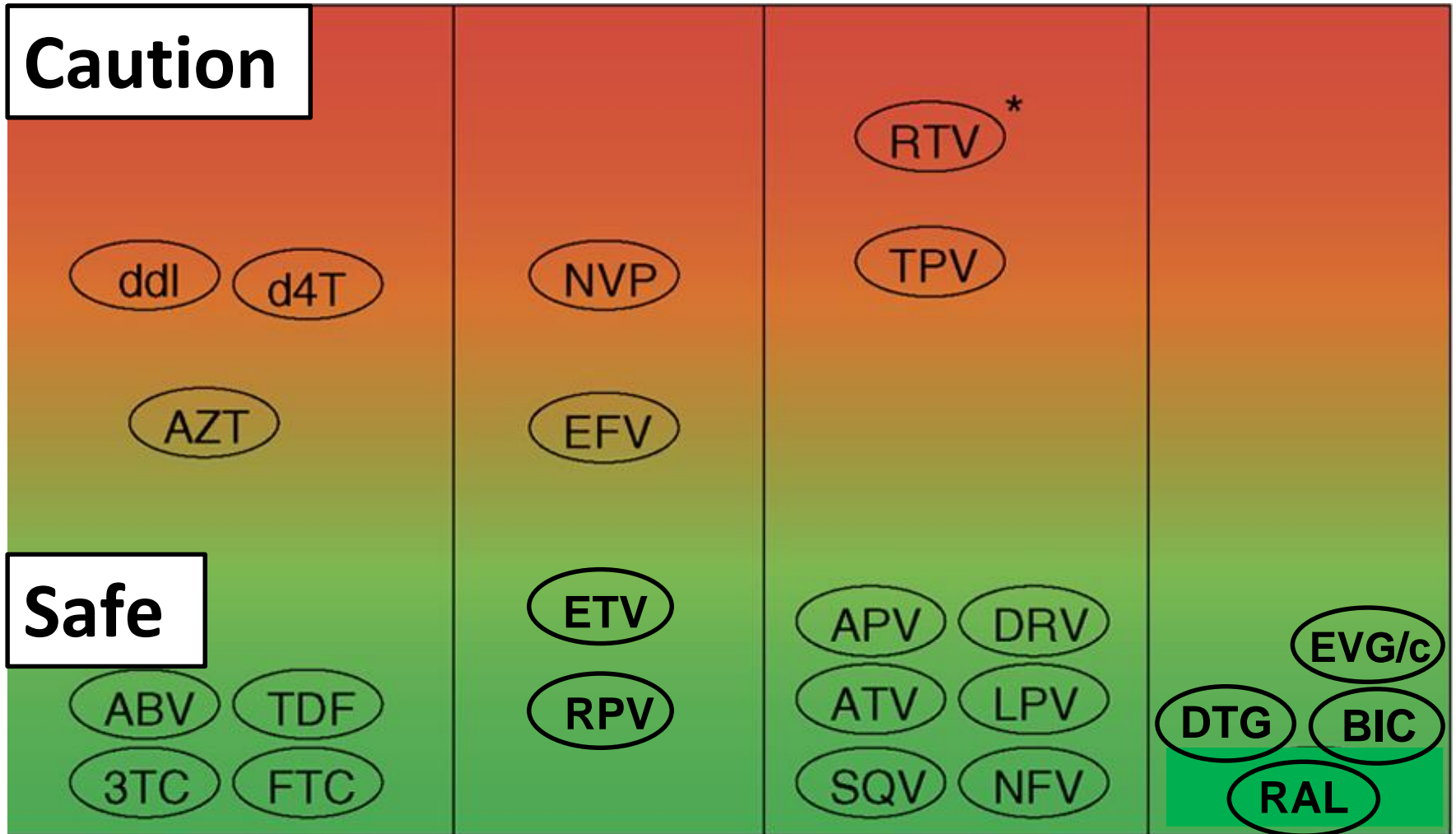
**Internet resource on DILI:
National Library of Medicine's LiverTox
<https://livertox.nih.gov/>**

Allopurinol

Nitrofurantoin

Minocycline

Risk of Hepatotoxicity of ARVs



NRTI

NNRTI

PI

Integrase Inhibitors

*Full-dose ritonavir

Hepatic safety of EFV and DTG: Randomized trial

EFV vs DTG (ADVANCE)

Grade 3 or 4 lab abnormalities			
Abnormality	Subjects, n (%)		
	DTG+ FTC/TAF (n=351)	DTG+ FTC/TDF (n=351)	EFV+ TAF/FTC (n=351)
ALT (increased)	10 (3)	7 (2)	18 (5)
AST (increased)	6 (2)	6 (2)	14 (4)
GGT (increased)	4 (1)	6 (2)	35 (10)

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Which ARVs should you use in someone with liver disease?

- **Raltegravir**

- Major mechanism of clearance: UGT1A1 glucuronidation
- Mild to moderate hepatic insufficiency: no clinically important effect on PK; no dosage adjustment
- RAL PK in End-stage liver disease (n=10) or liver transplant (n=5): increased RAL exposure but well tolerated
 - ESLD: C_{min} 36-8148 ng/mL. Normal liver function: 15-2223 ng/mL

Dolutegravir in Liver Disease

- **Dolutegravir**

- Primary metabolism: UGT1A1; CYP3A4 (10-15%)
 - DTG levels similar in healthy adults and pts with Childs-Pugh B
 - No dosage adjustment for those in Child-Pugh Class A or B
 - Insufficient data in severe hepatic disease

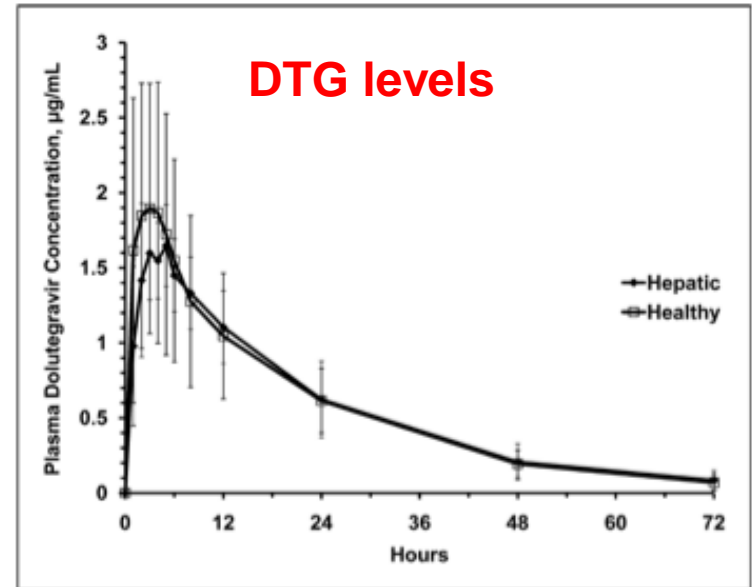


Figure 1. Mean plasma dolutegravir linear concentration-time plots. Error bars represent standard deviation.

Song I et al, Clin Pharm Drug Develop, 2013

Efavirenz in Liver Disease

- Metabolism: CYP2B6 (primary), 3A4, and 2A6
- EFV excreted as glucuronides in the urine
- No dose recommendation for those with hepatic impairment; use with caution
- Not recommended in patients with hepatic insufficiency (Child-Pugh class B or C)

DILI due to antituberculous therapy (ATT)

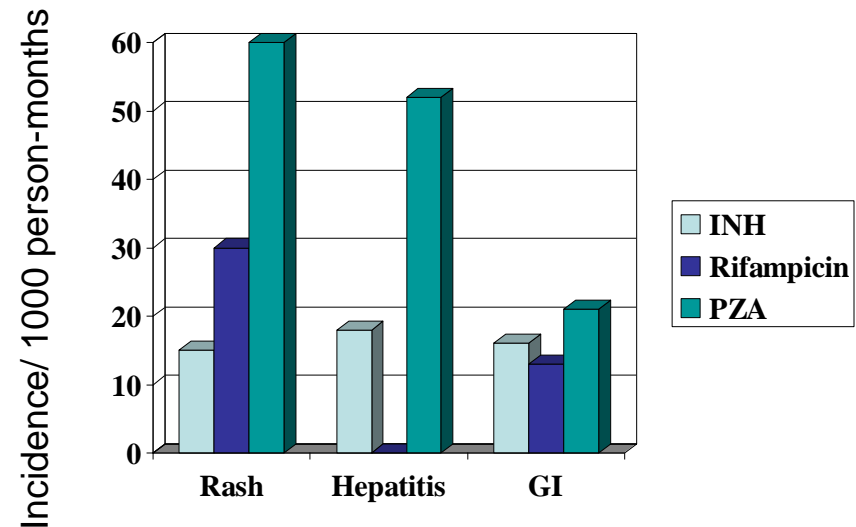
- Overall rate: 5-33%
- INH
 - Reactive metabolites may cause liver injury
 - Median interval 4 months
 - Differs from hypersensitivity reactions which may occur in days-weeks
- Rifampicin
 - Dose dependent interference with bilirubin uptake: subclinical hyperbilirubinemia or jaundice without hepatocellular damage
 - May also cause hepatocellular injury
 - Hypersensitivity: N/V, fever, elevated liver tests

DILI: PZA

- May cause both dose-dependent and idiosyncratic hepatotoxicity
- May also induce hypersensitivity reactions with eosinophilia and liver injury or granulomatous hepatitis
- Allopurinol decreases PZA clearance, and may increase its hepatotoxicity

DILI: Frequency with 1st 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



When should medication be stopped in suspected DILI?

- Symptomatic hepatitis (transaminases >3 ULN)
- Acute hepatitis with jaundice (Hy's law)
- Symptoms of drug hypersensitivity (rash, fever)
- Marked ALT, AST elevation (>5 ULN) even if asymptomatic (particularly if patient has advanced liver disease)
- Close monitoring is essential

Liver Test 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?

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	
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Tests!

- HBV DNA 93,000 (down from 97 million)
- Testing for super-infection negative
 - 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
- Initial liver test elevations likely due to 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^A
- CD4 cell count $<100/\text{mm}^3$
- Abdominal pain, diarrhea, fever; ϵ
- U/S, ERCP: papillary stenosis, bilateral sclerosing cholangitis

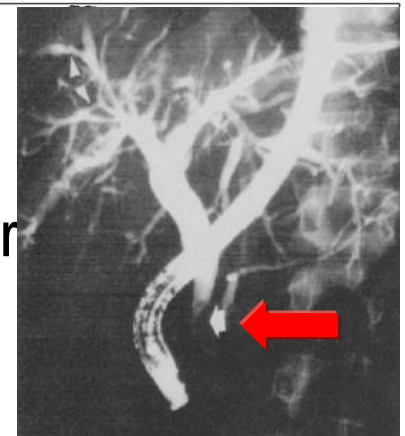
Atazanavir-induced cholelithiasis.



- 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
- Blood cultures 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 fever, other sites of worsening disease (e.g. adenopathy, pulmonary infiltrates or effusions, intracranial tuberculomas, ascites, splenomegaly, psoas abscess)

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!



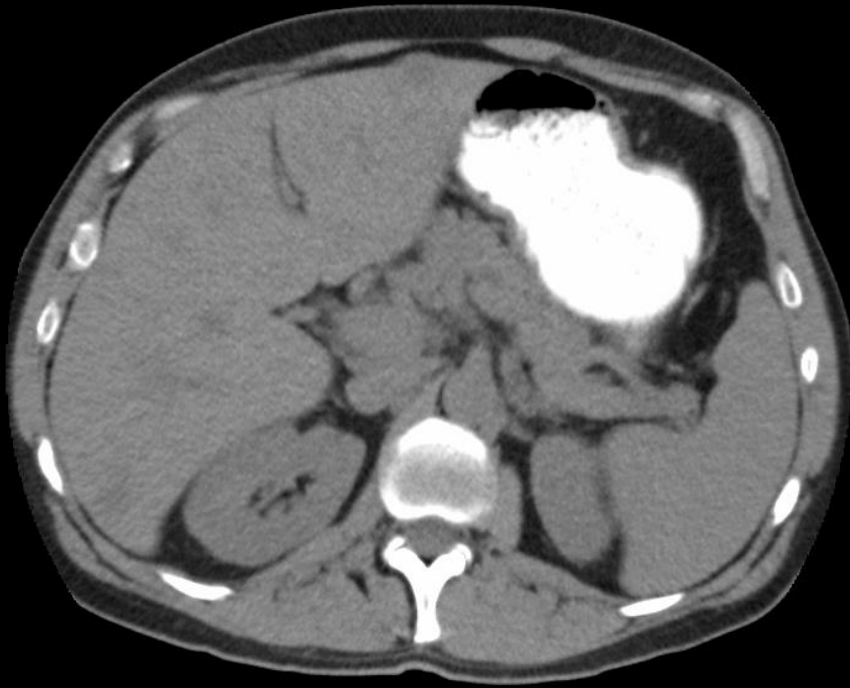
- Middle-aged HIV+ M
- CD4 cell count >500, HIV RNA <50 for many years on ABC/3TC/atazanavir/ritonavir
- Patient presented with 3-4 weeks of abdominal pain and chest wall discomfort
- Admitted to an outside hospital for evaluation of chest discomfort. Found to have a pulmonary nodule and rim-enhancing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

Case - continued

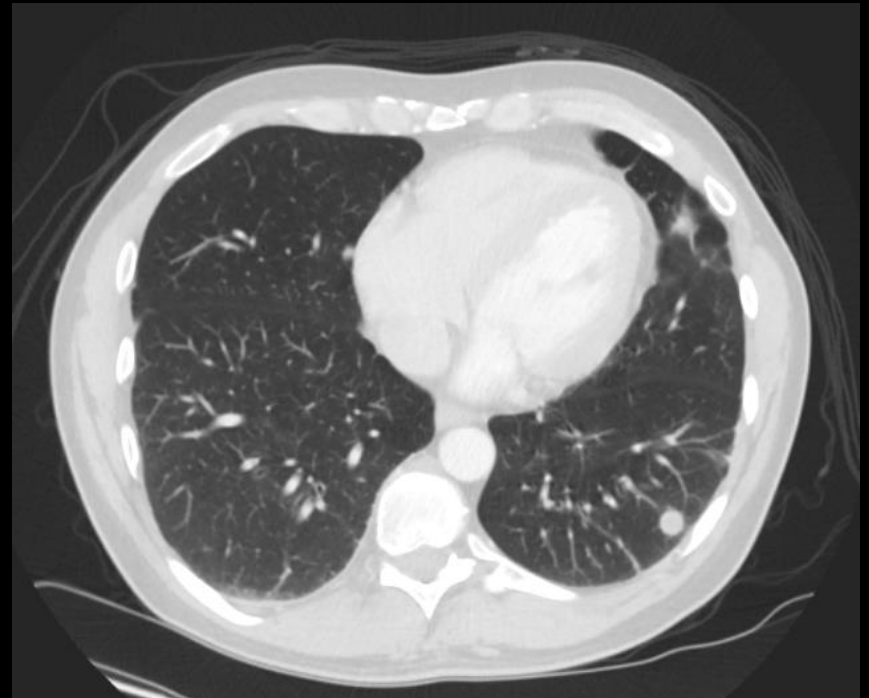
- Past medical history: secondary syphilis several years ago, s/p treatment; non-reactive RPR 4 months prior to presentation. HAV/HBV immune
- Multiple sexual partners, does not always use condoms. No TB exposures.
- On exam, appears well. Afebrile. No rash or adenopathy. No abdominal tenderness or HSM
- 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?



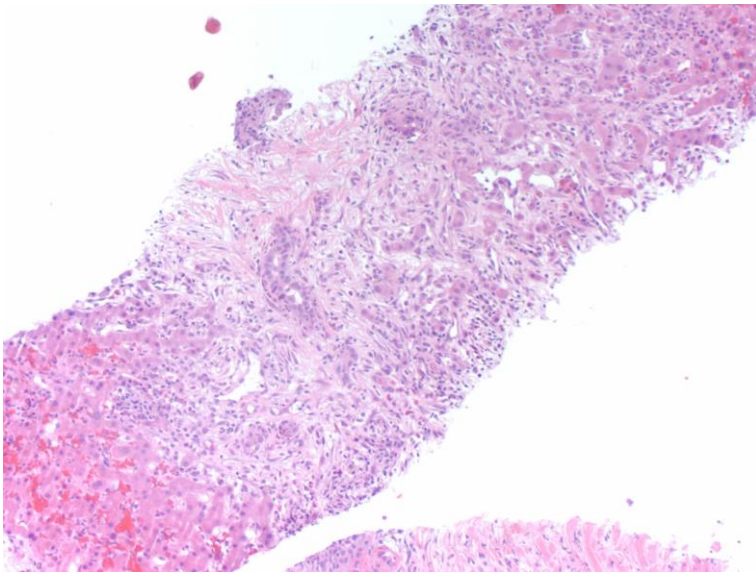
- A. Malignancy
- B. Syphilis
- C. Peliosis hepatis due to Bartonella
- D. Fungal infection
- E. Mycobacterial infection

Tests

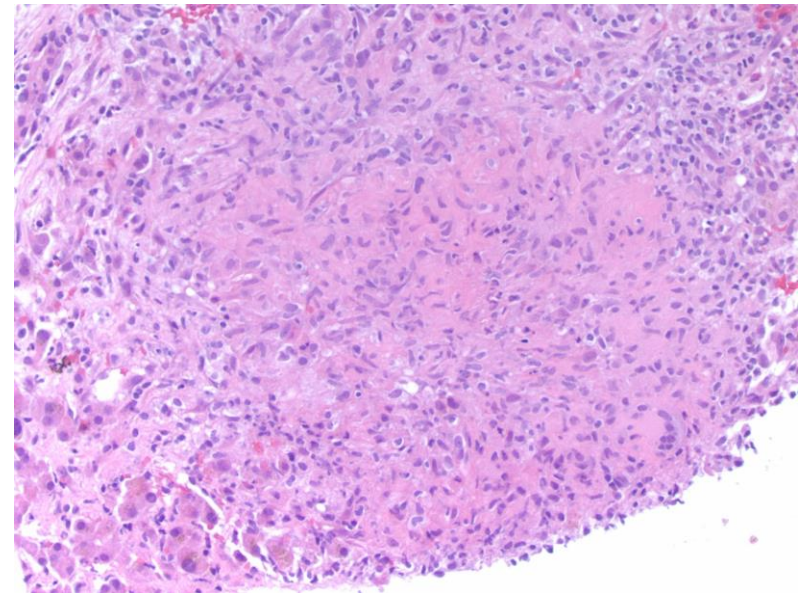
- Blood cultures negative.
- Negative tests for Cryptococcus, Histoplasma, Bartonella, Brucella, Coxiella, latent TB
- HIV RNA undetectable. CD4 cell count 500
- HCV RNA and antibody undetectable.

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)
 - IRIS
 - Don't forget syphilis.

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Selvan Pillay**

Harvard CFAR, 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*