Abnormal Liver Function Tests in HIV+ Patients

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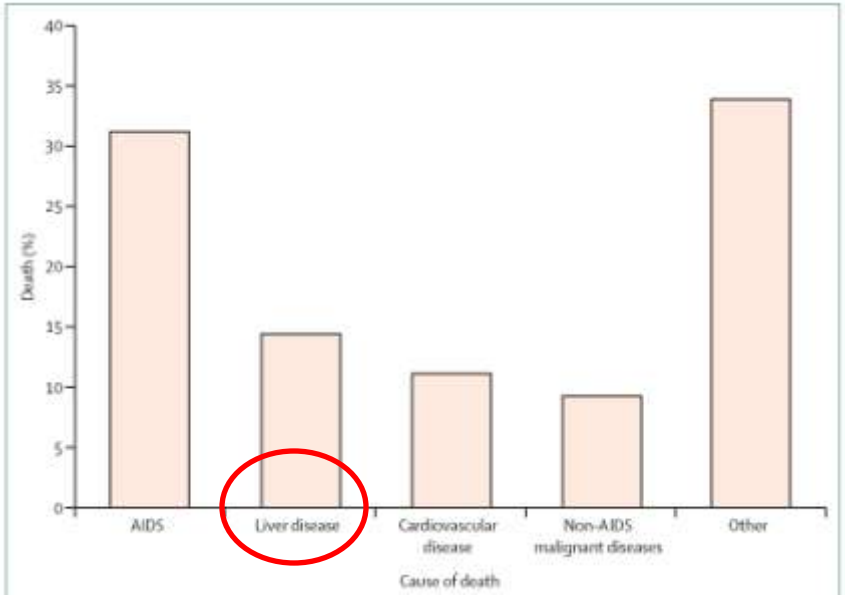
October 4th, 2012

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



Weber R, Arch Int Med, 2006

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

Yr	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0		50	>750K	206	181	102	3.4
1	TDF/FTC/EFV	322	<50	46	29	122	5.1

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

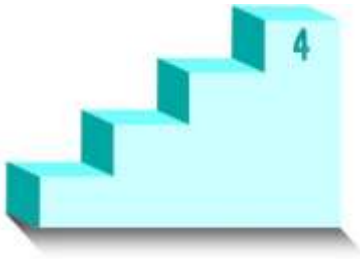
Yr	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0		50	>750K	206	181	102	3.4
1	TDF/FTC/EFV	322	<50	46	29	122	5.1
3	TDF/FTC/EFV	760	<50	97	89	125	5.1

- 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



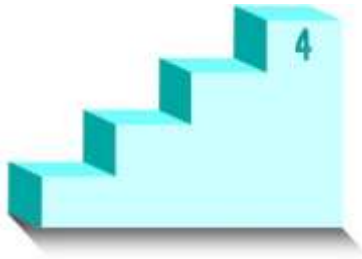
- Step 1:
  - Review meds, supplements
  - Alcohol use
    - AST:ALT ≥ 2:1. AST < 8 x ULN
  - Viral hepatitis (B, C)
  - Hemochromatosis: Fe/TIBC >0.45
  - Fatty liver disease: U/S
    - ALT, AST <4x ULN: AST:ALT < 1

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)
Alpha$_1$-antitrypsin deficiency
Nonhepatic causes
Celiac sprue
Inherited disorders of muscle metabolism
Acquired muscle diseases
Strenuous exercise

Pratt DS and Kaplan MM, NEJM, 2000

Elevated transaminases: The 4 steps

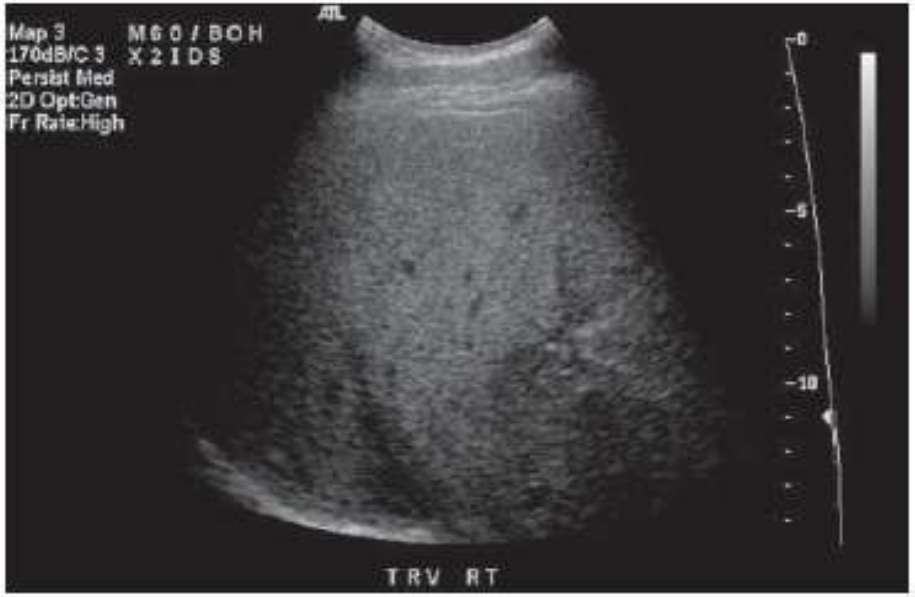


- Step 2:
  - Rule out non-hepatic causes: muscle, thyroid, celiac, adrenal disease; anorexia nervosa
- (Step 3:
  - Rule out rare causes: autoimmune hepatitis, Wilson disease, α-1-antitrypsin deficiency)
- Step 4
  - Liver biopsy

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



Ultrasound image showing diffuse increased echogenicity consistent with fatty liver.

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

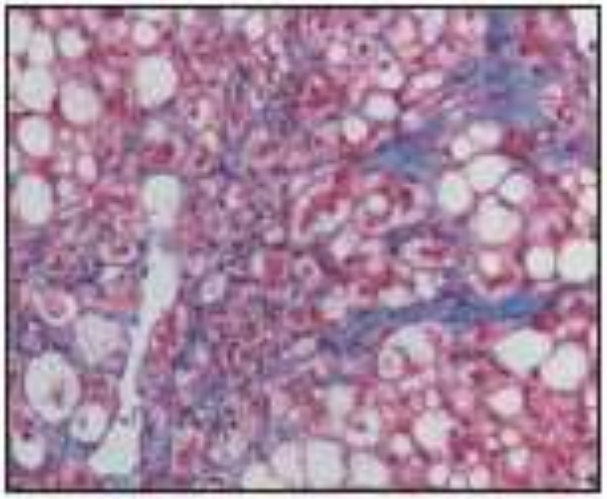
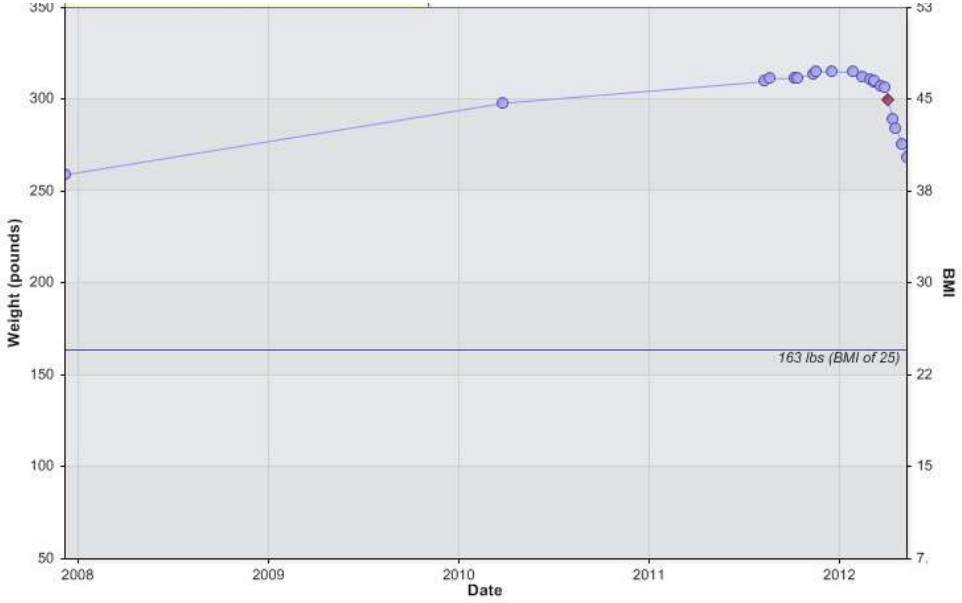


Image from Afdhal, JAMA, 2012



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

Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV; ATQ	15	10 million	nl	nl	nl	5.1
4	TDF/FTC/EFV; ATQ	126 (6%)	507	329	234	104	
6	TDF/FTC/EFV; ATQ			1802	1147	283	34/ 20.5

- 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!

Day	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV; ATQ	15	10 m	nl	nl	nl	5.1
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Outline

- Evaluation of chronically elevated transaminases
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LFT Abnormalities After Starting ART: Differential Diagnosis

- Drug-induced liver injury
- Super-infection
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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

Hepatocellular (ALT/AP >5)	Mixed	Cholestatic (ALT/AP <2)
ARVs	Sulfonamides	Amox/clav
Herbal meds	Bactrim	Macrolides
INH	Phenytoin	Phenothiazines
K		s
		roids
Valproate		Oral
NSAIDS		contraceptives
Allopurinol		

Internet resource on DILI:
National Library of Medicine's LiverTox
http://livertox.nih.gov/php/searchchem.php

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. AIDS (2007) 21: 1301
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

Hoffmann et al. AIDS (2007) 21: 1301

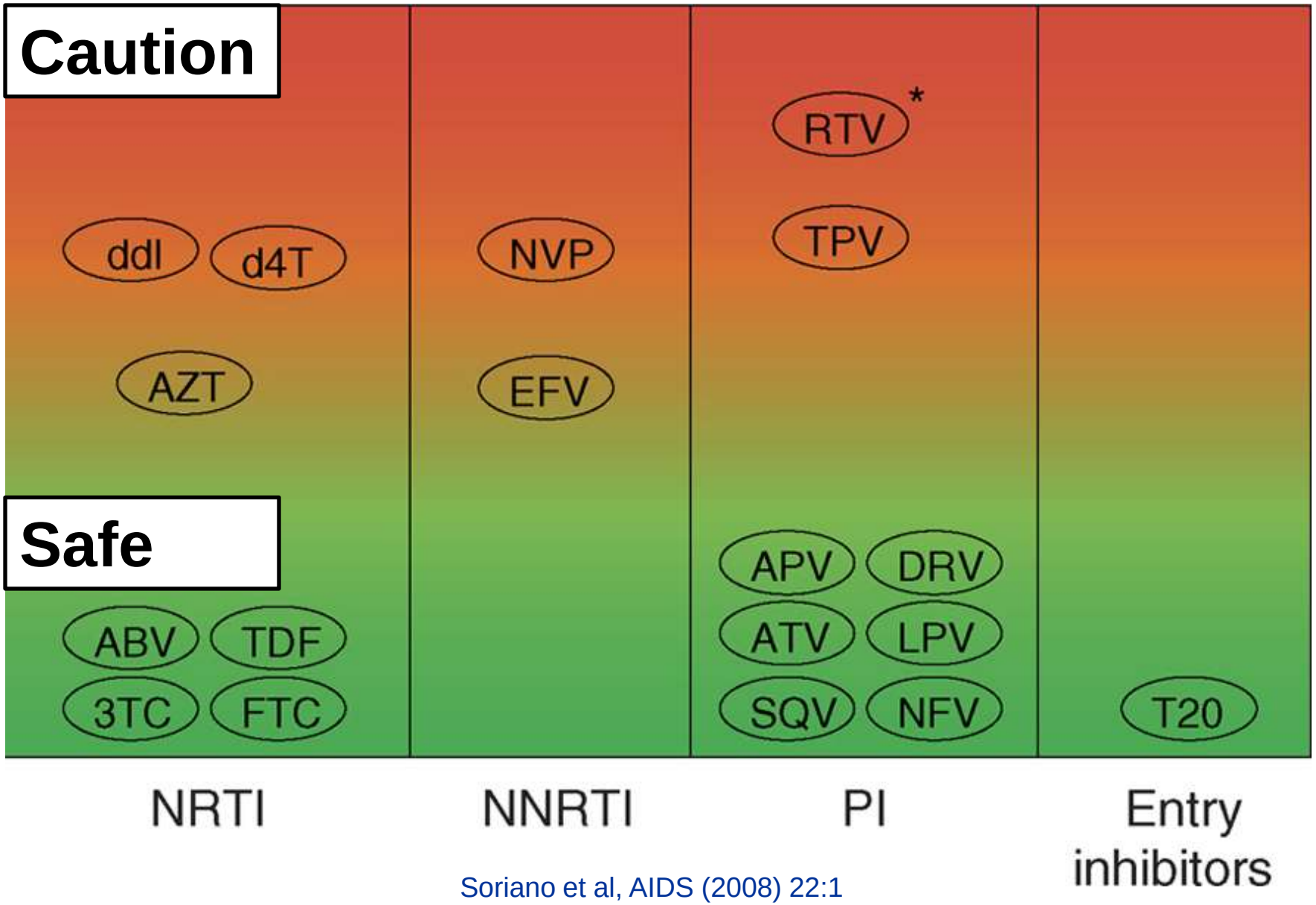
Hoffmann et al. CID (2008) 47:1479

Mechanisms of ARV DILI

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

McGovern B, Sulkowski M, Sterling R, in Boyer, Chapter 38

Risk of hepatotoxicity of ARVs



Soriano et al, AIDS (2008) 22:1

Raltegravir

- 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

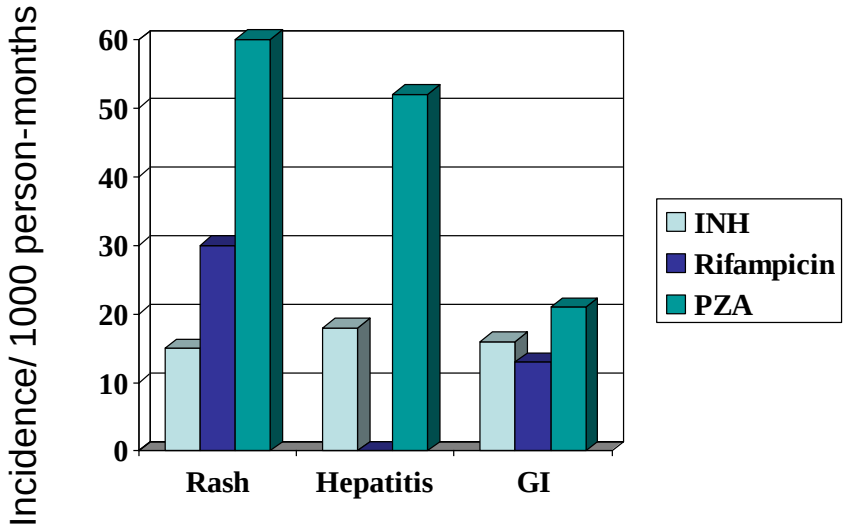
Mena A, 5th IAS (2009) ; Rockstroh J, 17th CROI (2010), abstract 662

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 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



Yee D et al. Am J Respir Crit Care Med. 167: 1472.

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!

Day	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV; ATQ	15	10 m	nl	nl	nl	5.1
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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

Wk	Meds	ALT	AST	AP	Bili
0	TDF/FTC/EFV	nl	nl	nl	5.1
4	TDF/FTC/EFV	329	234	104	
6	TDF/FTC/EFV	1802	1147	283	34
7	**TDF/FTC/RAL**				
9	**TDF/FTC/RAL**	182	54	130	8.5

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

McGovern, B, CID, 2004; Crane M JID, 2009; Ofotokun et al. Am J Med Sci 2007

HBV IRIS

- After ART initiation, interferon-γ 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

Case

- 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

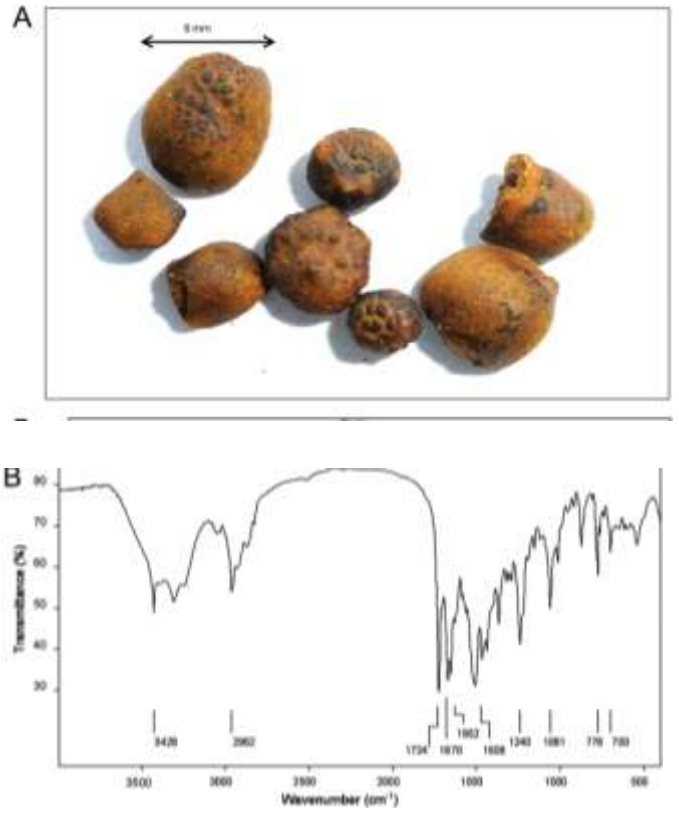
Differential Diagnosis

- 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

Atazanavir-induced cholelithiasis.



Rakotondravelo S et al. Clin Infect Dis. 2012

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.

Lawn et al. AIDS 21:335. Lawn and Woods, AIDS 21: 2362. Verma S. AIDS Res Hum Retroviruses. 22:1052

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

Virus Needing Treatment	Preferred option	Avoid
HIV or HBV	TDF+ FTC/3TC+ 3rd HIV agent	3TC/FTC/TDF/ETV monotherapy

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

Lok & McMahon. Chronic Hepatitis B: Update 2009. Hepatology 50:661. Keefe, Clin Gastro Hepatol 2007. Zoutendijk R, JID, 2012.

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

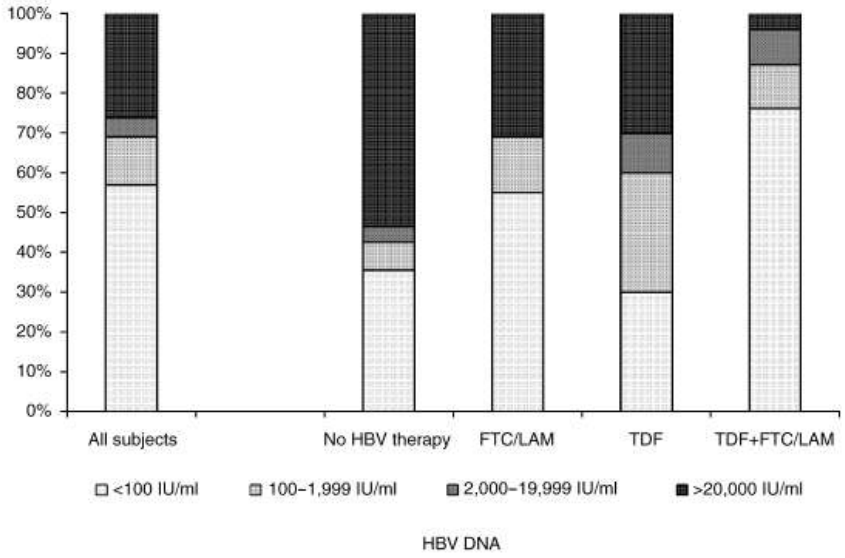
J Hepat (2009) 50(2): 227-242. Lok & McMahon. Chronic Hepatitis B: Update 2009. Hepatology 50:661. Keefe, Clin Gastro Hepatol 2007

HBV Diagnosis

Phase	HBsAg	HBeAg	Anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute	+	+	IgM			+
Chronic	+ > 6 mo.	+/-	IgG			+
Recovery	-	-	+	+	+	-
Vaccine recipient	-	-	-	+	-	-

ART for HIV/HBV Coinfection

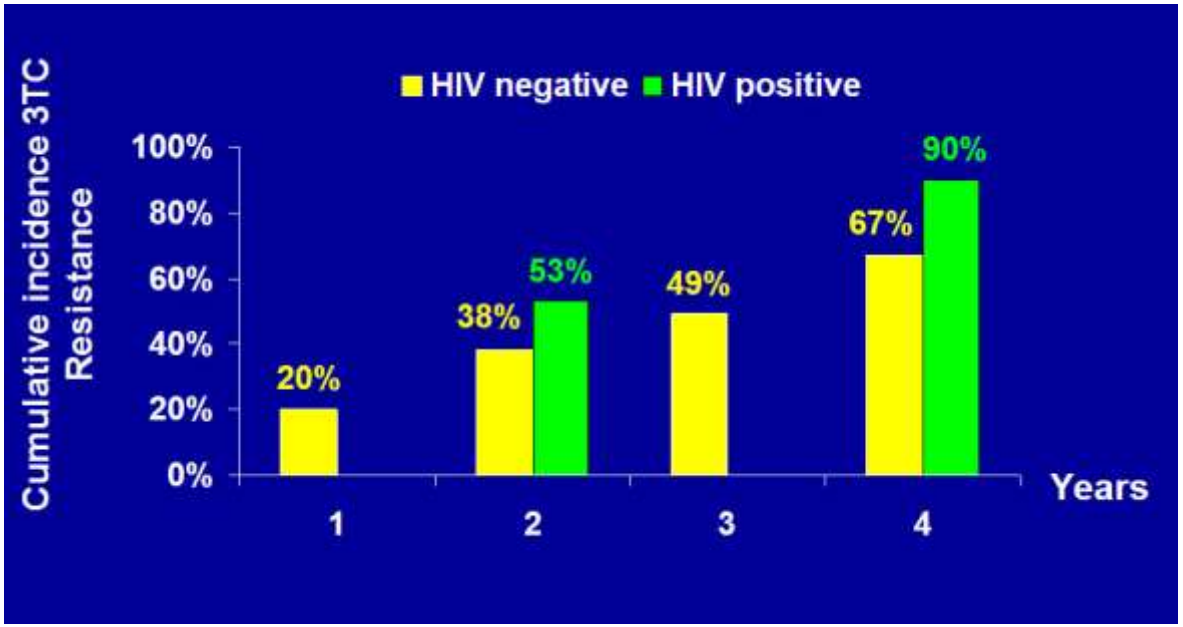
- Cross-sectional study of 122 HIV/HBV coinfected patients, most with prior 3TC exposure
- Patients on TDF + FTC or 3TC more likely to have undetectable HBV DNA than those on TDF or 3TC monotherapy



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+



Benhamou, *Hepatology* 1999; 30:1302

Lai, *NEJM 1998;339:61*

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