HIV, HBV and the Liver

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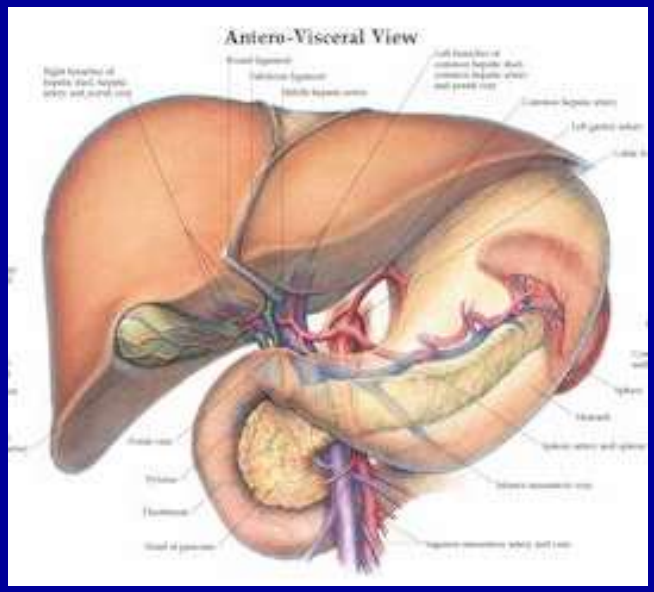
HIV and the Liver

- Underlying liver disease in common in HIV+ patients
  - In a South African cohort, 4% of HIV-infected patients had liver enzyme elevations >5 x upper limits of normal (ULN) prior to starting ARVs

    Hoffmann C, AIDS 21:1301
- Non-infectious & infectious processes may cause liver disease in HIV-infected patients



Non-infectious causes of liver disease in HIV+ patients

- Alcohol
- Traditional or herbal medications
  - In one South African cohort, 1/3 of HIV+ patients were taking traditional medications
- Iron overload
- Autoimmune hepatitis
- Malignancy
  - Kaposi's sarcoma
  - Lymphoma
  - Hepatocellular carcinoma

Infectious causes of liver disease in HIV-infected patients

- Mycobacterial infection: TB, MAI
- Fungal infection: Histoplasma, Cryptococcus, Penicillium, Candida
- Bacterial infection: Syphilis, Bartonella (peliosis hepatis), Salmonella, Listeria
- Parasitic infection: Schistosomiasis, visceral leishmaniasis

Infectious causes of liver disease in HIV-infected patients: Viral

- HIV, including HIV cholangiopathy
- Viral hepatitis: HAV, HBV, HCV, HDV, HEV
- CMV
- HSV
- EBV

Case

- 32 yo man presents with cough, fever and weight loss
- No other medical problems. Denies use of alcohol, herbal or traditional medicines.
- Physical exam notable for temperature of 39, oral thrush and temporal wasting
- CXR shows a right upper lobe infiltrate.
- Sputum AFB smear is positive, consistent with a diagnosis of pulmonary TB.

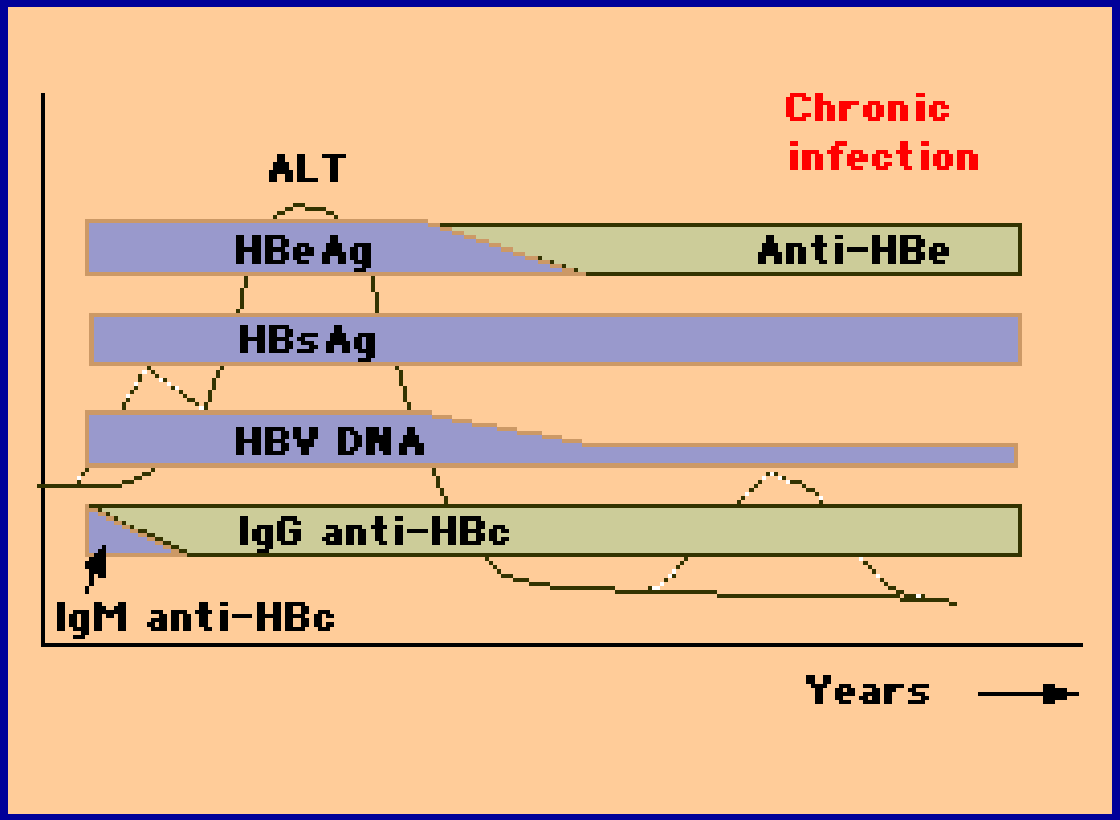
Case (continued)

- Baseline labs reveal elevated ALT 100 U/L, AST of 80 U/L, normal alkaline phosphatase (AP) and bilirubin
- HIV-positive. CD4 cell count 137, HIV RNA 123,000

- To evaluate his elevated transaminases, you decide to test him for hepatitis B.
- What diagnostic tests would be useful in determining whether he is infected with HBV?

HBV Diagnosis

- Positive HBsAg is the hallmark of infection
- HBsAg+ >6 months: chronic hepatitis B (CHB)



Anna Lok, Serologic Diagnosis of HBV, UpToDate, 2005

HBV Diagnosis

Phase of infection	HBsAg	HBeAg	Anti-HBc	Anti-HBs	Anti-HBe	HBV DNA
Acute	+	+	IgM			+
Chronic	+	+/-	IgG			+
Recovery	-	-	+	+	+	-

Case (continued)

- 32 yo man with HIV, pulmonary TB, CD4 cell count 137, Viral load 123,000, elevated ALT and AST.
- His test for HBsAg is positive. He also tests positive for HBeAg.
- He is started on bactrim for PCP prophylaxis and on INH/Rifampicin/PZA/ETH for pulmonary TB.
- One month later, he initiates antiretroviral therapy with d4T/3TC/Efavirenz (EFV or Stocrin)

Case (continued)

- Four months after starting ARVs, presents with nausea, vomiting, abdominal pain

Mo.	Meds	CD4	VL	ALT	AP
0	d4T/3TC/EFV; INH/Rif. Bactrim	137	123,000	100	69
3	d4T/3TC/EFV; INH/Rif. Bactrim	194	<400	47	79
4				793	173

What's going on?

LFT Abnormalities After Starting ARVs: Differential Diagnosis

- Drug-induced liver injury
  - ARV hepatotoxicity
  - Antituberculous therapy hepatotoxicity
  - Other: alcohol, traditional medications
- Immune Reconstitution Inflammatory Syndrome
  - TB
  - Opportunistic infections, e.g. MAC (granulomatous hepatitis)
- Superinfection
  - HAV, HCV, HDV, HEV, EBV, CMV
- Hepatitis B flare

Drug-induced liver injury (DILI)

- May result from direct toxicity of the drug or from an immunologically-mediated response
- Clinical diagnosis of exclusion
  - If feasible, exclude other causes of liver injury, such as viral hepatitis
- Generally occurs within a few months of initiating a drug
- Treatment is usually withdrawal of drug and supportive care
  - N-acetyl cysteine used in acetaminophen (paracetamol) overdose
  - Intravenous carnitine used in valproate-induced mitochondrial injury

Typical patterns of liver injury with drugs

Hepatocellular (ALT/AP >5)	Mixed	Cholestatic (ALT/AP <2)
ARVs	Sulfonamides	Amox/clav
Herbal meds	Bactrim	Macrolides
INH	Phenytoin	Phenothiazines
PZA	Phenobarbital	Tricyclics
Ketoconazole	Nitrofurantoin	Anabolic steroids
Valproate		Oral contraceptives
NSAIDS		
Allopurinol		

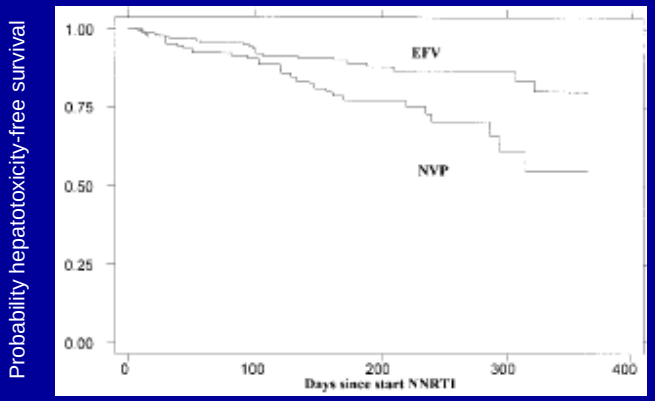
Navarro & Senior. NEJM 354: 7

DILI: ARV hepatotoxicity

- 14-20% of HIV+ pts starting ARVs have elevations in LFTs
- 2-10% need to interrupt ART because of significant hepatotoxicity
- Risk factors: elevated baseline transaminases; HBV or HCV; concomitant hepatotoxic drugs (anti-TB drugs, anticonvulsants, bactrim, dapsone, erythromycin, amox/clav, azoles).
- All 3 classes of HIV medicines—protease inhibitors, non-nucleoside RT inhibitors and nucleoside RT inhibitors—have been associated with hepatotoxicity

ARV Hepatotoxicity: NNRTIs

- Both Nevirapine and Stocrin may cause hepatotoxicity
- Incidence may be higher with NVP than with Stocrin



Sulkowski Hepatology (2002) 35: 182

- Prospective 2NN study, grade 3 or 4 hepatotoxicity: NVP 400 mg qd: 13.6%*. NVP 200 mg bid: 8.3%. Stocrin: 4.5%.
- Association between NVP hepatotoxicity and specific genetic polymorphisms in MDR gene

Van Leth Lancet 363:1253-1263

Haas et al, CID (2006), 43:783

Ritchie et al, CID (2006), 43:779

Nevirapine Hepatotoxicity

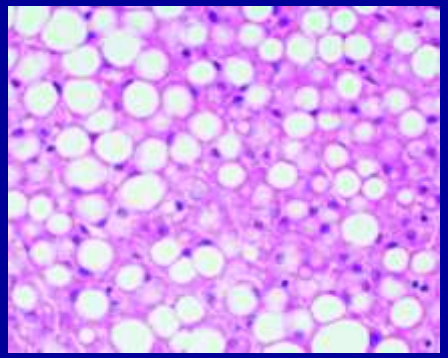
	Early	**Late**
Timing	6-18 weeks	>18 weeks
Systemic sx	Yes	No
Rash	Yes	No
Mechanism	Hypersensitivity	?
Risk factors	F: CD4>250 M: CD4>400 Low BMI	HBV, HCV

Dieterich et al, Clin Infect Dis (2004) 38: S80. Sanne, J Infect Dis (2005); 191:825

http://www.fda.gov/medwatch/SAFETY/2003/03DEC_PI/Viramune_PI.pdf

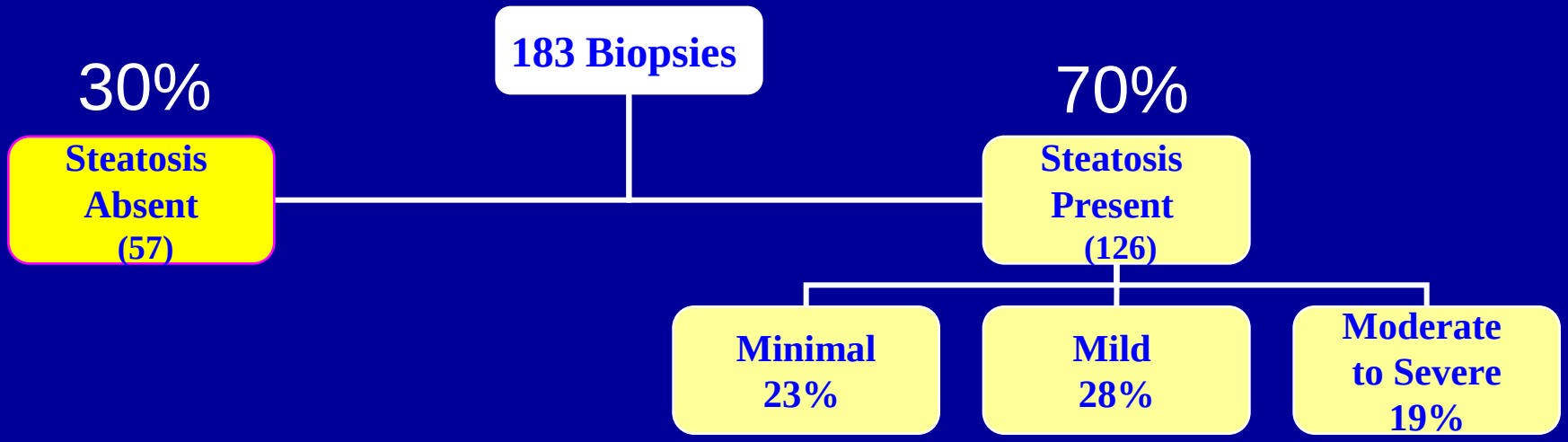
ARV Hepatotoxicity: Nucleosides RTI

- NRTIs have been associated with lactic acidosis/hepatic steatosis syndrome
- NRTI-induced mitochondrial toxicity → Decreased fatty acid oxidation → Accumulation of fatty acids and their metabolism to TGs
- Results in hepatic steatosis
- Inhibition of mitochondrial DNA polymerase-γ: d4T, ddI>AZT>3TC, Abacavir, Tenofovir



Pao, D et al. Sex Transm Infect 2001;77:381

Frequency of hepatic steatosis on liver biopsy in HIV/HCV co-infected patients



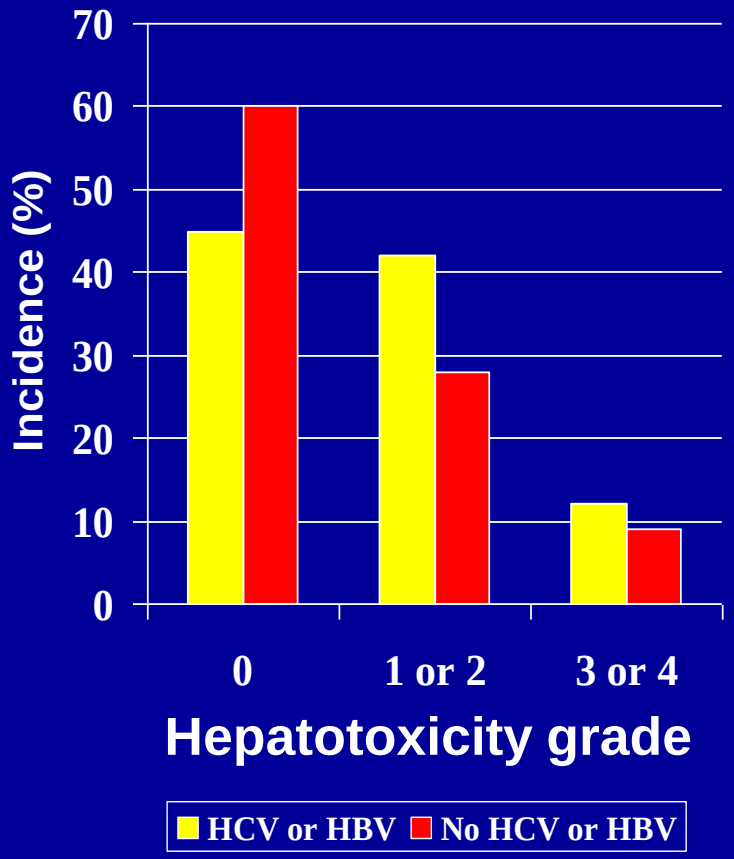
NRTI	Multivariate OR	p=
None	1.00	
Non-D	2.65 (0.98-7.41)	0.062
D-NRTI	4.63 (1.55-13.8)	0.006

D-NRTI=d4T or ddI

McGovern B et al, Clinical Infectious Diseases. 43: 365.

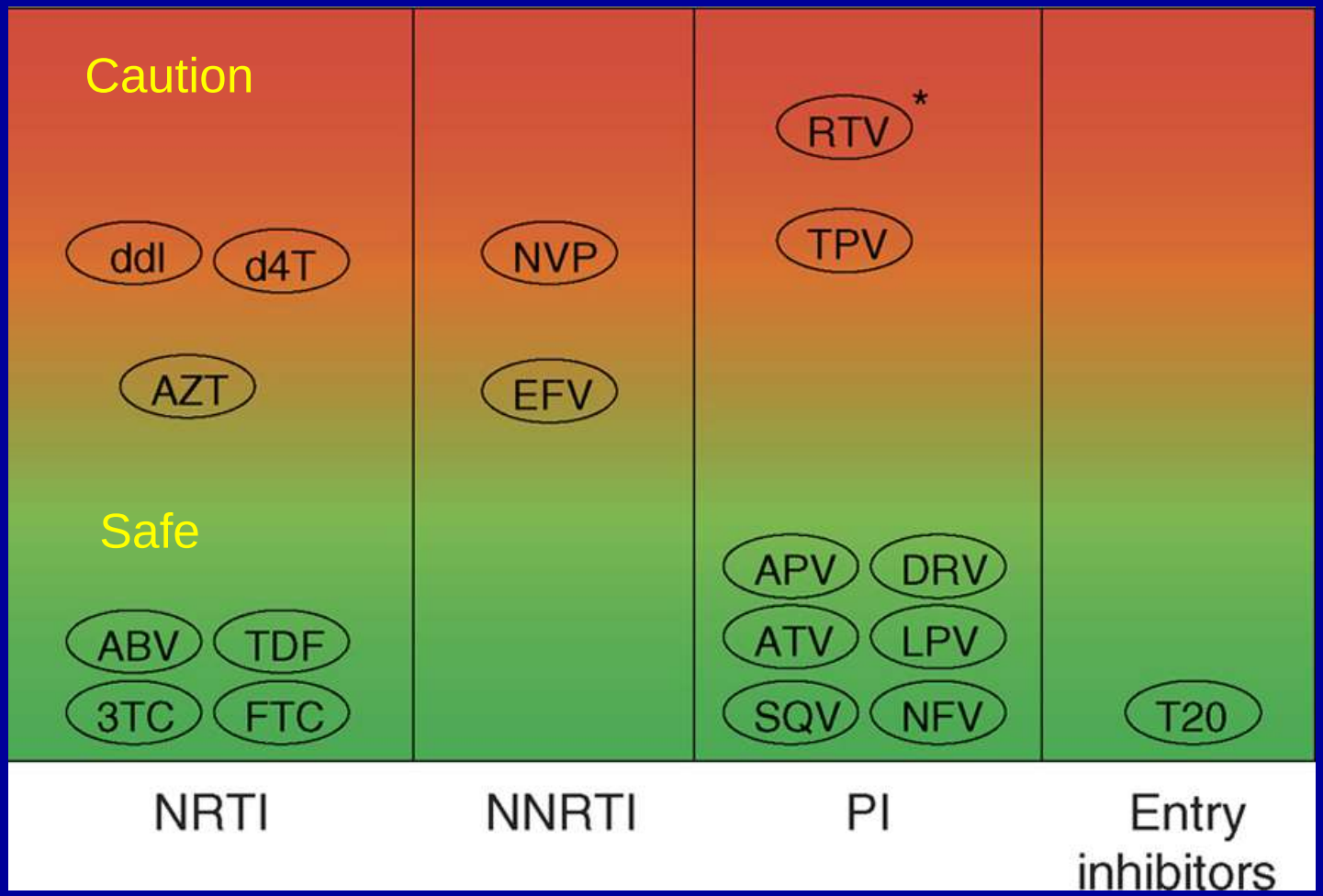
ARV hepatotoxicity: PIs

- 298 HIV+ subjects initiating PI-based ARV therapy
- Patients with HCV or HBV more likely to develop hepatotoxicity
- Still, 88% of coinfected individuals had no or minimal hepatotoxicity
- Kaletra has a relatively low rate of hepatotoxicity (6-9%)



Sulkowski et al. JAMA (2000) 283:74
Sulkowski et al. AIDS (2004) 18:2277

ARV hepatotoxicity: Summary



Soriano et al, AIDS (2008) 22:1

Risk factors for ARV Hepatotoxicity

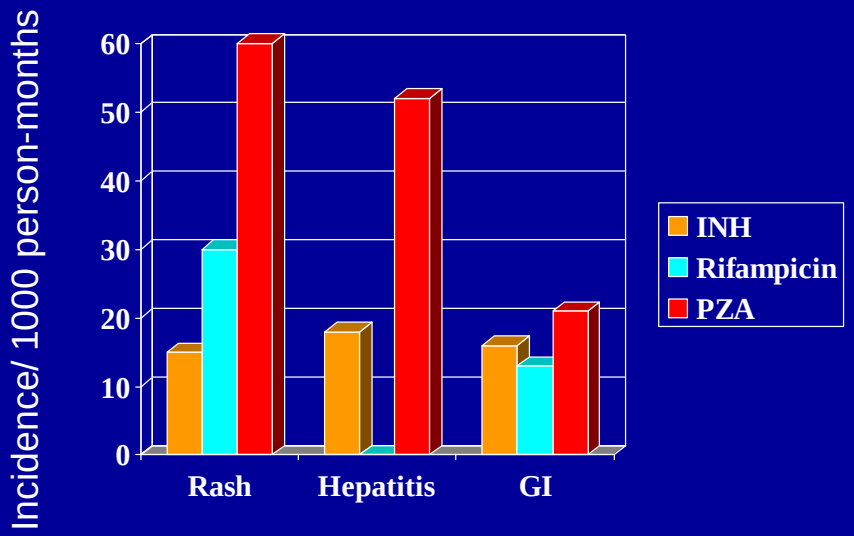
- 868 HIV+ patients in a workplace in S. Africa
  - 94% male, most treated with AZT/3TC/EFV
  - 17% of a randomly selected subset were HBsAg+
- 40 patients (4.6%) developed severe hepatotoxicity after initiating ARVs
  - TB treatment increased risk 8.5-fold
  - Positive HBsAg increased risk 3-fold
  - Highest risk if patient coinfected with HBV and receiving antituberculous therapy Hoffmann et al. AIDS (2007) 21: 1301
- Subsequent study revealed increased risk of hepatotoxicity was primarily in the group with high HBV DNA levels (>10,000 c/mL) Hoffmann et al. CID (2008) 47:1479

DILI due to antituberculous therapy (ATT)

- May occur with any of the 1st line drugs, particularly INH, rifampicin and PZA
- Overall rate: 5-33%
- Risk factors:
  - Older age (>35 years)
  - Pregnancy
  - Elevated baseline LFTs
  - Malnutrition
  - HIV
  - Active Hepatitis B or C infection
  - Alcohol use
  - Concurrent use of other hepatotoxic medications
    - Allopurinol decreases PZA clearance, 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



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

Hepatotoxicity during ATT: Interventions

- Consider stopping medications if:
  - Serum transaminases are > 5 X ULN with or without symptoms
  - Transaminases are > 3 X ULN with jaundice or hepatitis symptoms
- Rechallenge:
  - When ALT returns to < 2 x ULN, rifampicin may be restarted with or without ethambutol
  - After 3-7 days, reintroduce INH, and subsequently check ALT
  - If symptoms recur or ALT increases, the last drug added should be stopped.

Saukkonen et al. Official ATS Statement: Hepatotoxicity of Antituberculosis Therapy. Am J. Respir Crit Care Med 174:935 (2006)

Case (continued)

- 32 yo M with HIV, hepatitis B, pulmonary TB on INH/Rif
- Four months after starting ARVs, presents with nausea, vomiting, abdominal pain
- Denies use of alcohol, traditional meds. INH/Rif and bactrim held, but symptoms and LFT abnormalities persist.

Mo.	Meds	CD4	VL	ALT	AP
0	d4T/3TC/EFV; INH/Rif. Bactrim	137	123,000	23	39
3	d4T/3TC/EFV; INH/Rif. Bactrim	194	<400	47	79
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TB IRIS

- TB IRIS is characterized by clinical worsening soon after initiation of ART
  - Occurs in 10-30% of patients commencing ART
  - Fever, adenopathy, worsening respiratory symptoms, increasing pulmonary infiltrates or effusions, intracranial tuberculomas, ascites, splenomegaly, psoas abscess, intra-abdominal adenopathy
- Two types:
  - Paradoxical TB IRIS
  - ART-associated TB/"Unmasking" TB IRIS

Meintjes et al. Lancet ID (2008). 8: 516.

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 levels of biliary cannicular hepatic enzymes 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 (continued)

- 32 yo M with HIV, hepatitis B, pulmonary TB on INH/Rif
- Four months after starting ARVs, presents with nausea, vomiting, abdominal pain
- Afebrile. No adenopathy. RUQ tenderness.
- CXR: improved pulmonary infiltrates. Abd U/S: normal

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Superinfection

- Testing:
  - HAV IgG positive, IgM negative (consistent with remote infection)
  - HCV Ab and RNA negative
  - HDV and HEV Ab negative
  - EBV serology consistent with remote infection
  - CMV IgG positive, IgM negative, consistent with remote infection
- Conclusion: no evidence for superinfection

LFT Abnormalities After Starting ARVs: Differential Diagnosis

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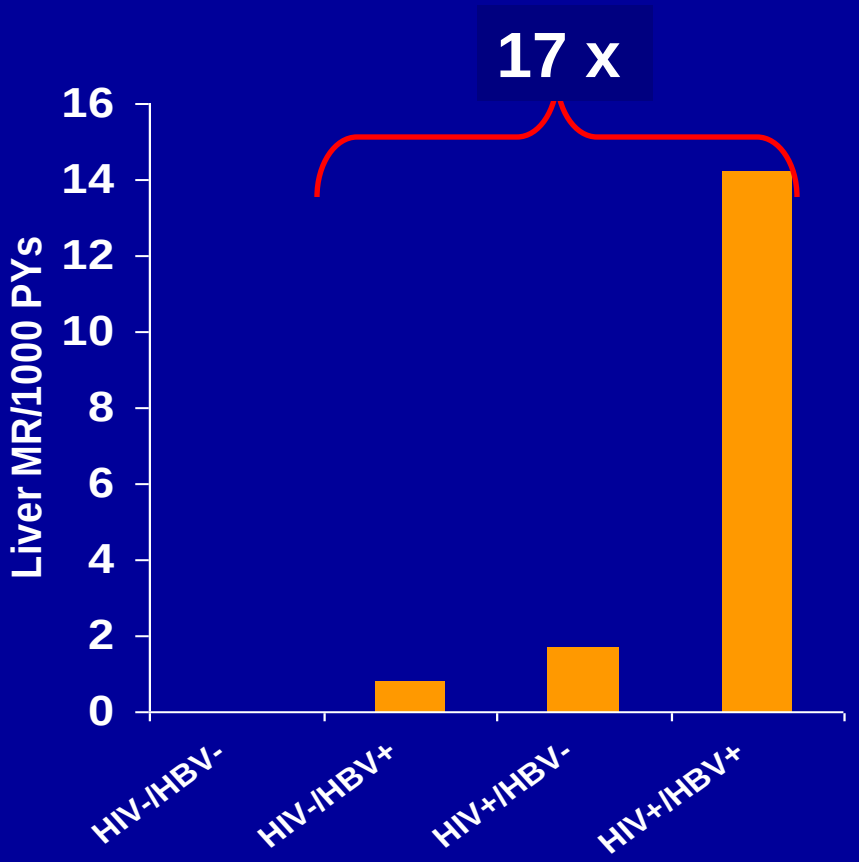
- Hepatitis B flare

HIV and HBV

- Following infection with HBV in HIV(-) subjects, 1-5% develop chronic hepatitis B (CHB)
- HIV+ patients may have increased risk of CHB after exposure: ~25% in one study Badsworth JID 163:1138.
- HIV associated with a decrease in the rate of HBeAg clearance and with higher HBV DNA levels
- HIV+ patients may have a higher rate of reactivation of HBV (reappearance of HBsAg and HBeAg , a.k.a. “reverse seroconversion”) than HIV-negative individuals
- Prevalence of chronic HBV in HIV+ subjects in the U.S. is 7.6% (0.4% in the general pop). Kellerman et al, JID (2003) 188:571

HBV/HIV Coinfection

- HBV/HIV+ patients have a higher rate of liver-related mortality than HIV or HBV monoinfected patients



Kellerman et al, JID (2003) 188:571

Thio C et al. *Lancet.* 2002;360:1921

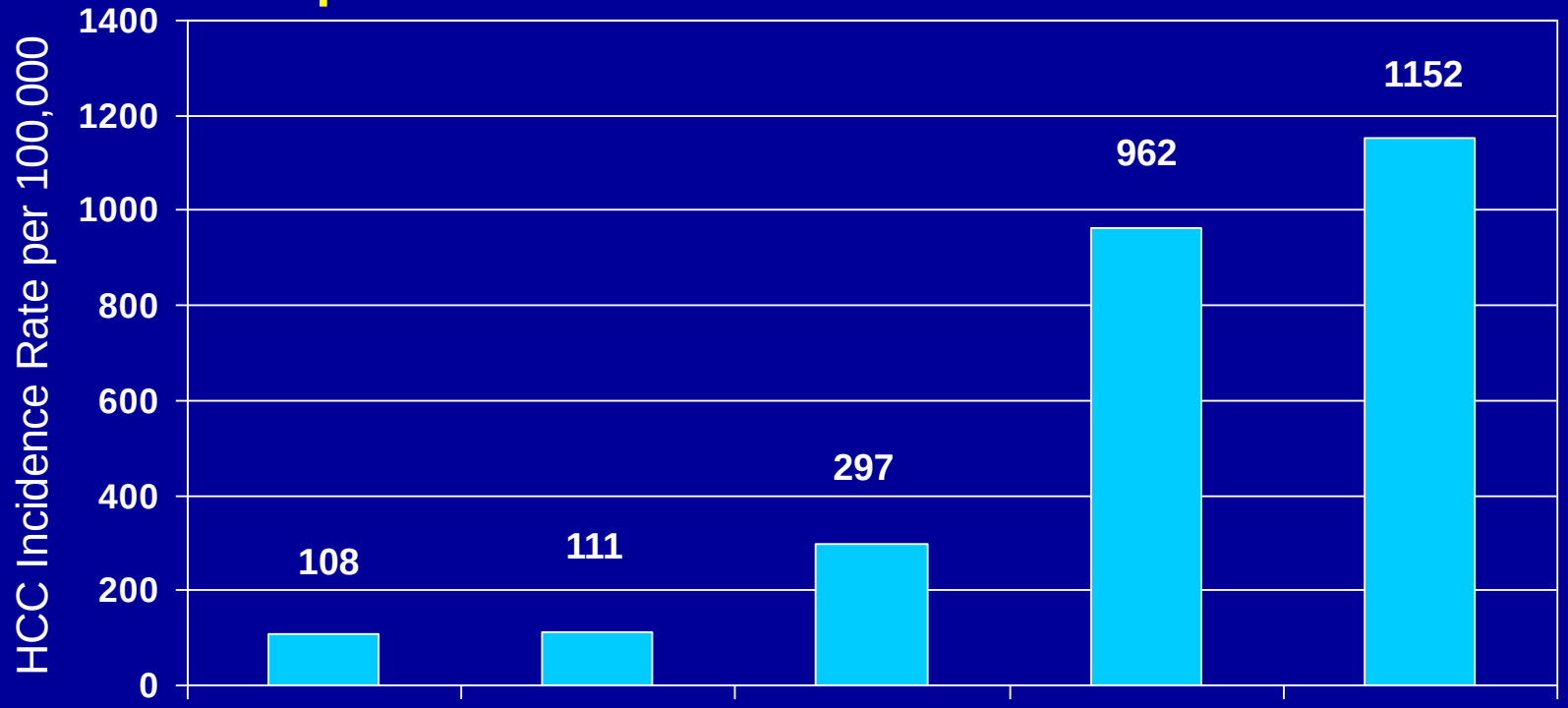
HBV and HIV: Recommendations

- All HIV+ patients should be tested for HBV
- Test for anti-HBs, HBsAg +/- anti-HBc
- HBV vaccine if negative for anti-HBs, HBsAg.
- HAV vaccine if non-immune
- For patients who test persistently + for HBsAg:
  - Check HBeAg, anti-HBe, HBV DNA
  - Check ALT, bilirubin, albumin, PT and platelet count
  - Screen for HCC with U/S and AFP every 6-12 mo. in patients at high risk
  - Counsel avoidance of alcohol
- Infants born to HBsAg positive women should receive hepatitis B Ig and HBV vaccine at birth and then complete the HBV vaccine series.

Why treat hepatitis B in an HIV-infected patient?

- Prevent transmission
- Prevent complications:
  - Cirrhosis
  - End-stage liver disease
  - Hepatocellular carcinoma
- Reduce risk of ART-related hepatotoxicity

REVEAL-HBV: Baseline HBV DNA predicts incidence of HCC



HBV DNA (copies/mL)	<300	300 to <10^3	1.0-9.9x10^4	1.0-9.9x10^5	≥1.1x10^6
Adjusted HR (95% CI)	1.0	1.1 (0.5-2.3)	2.3 (1.1-4.9)	6.6 (3.3-13.1)	6.1 (2.9-12.7)
P value	--	NS	.02	<.001	<.001

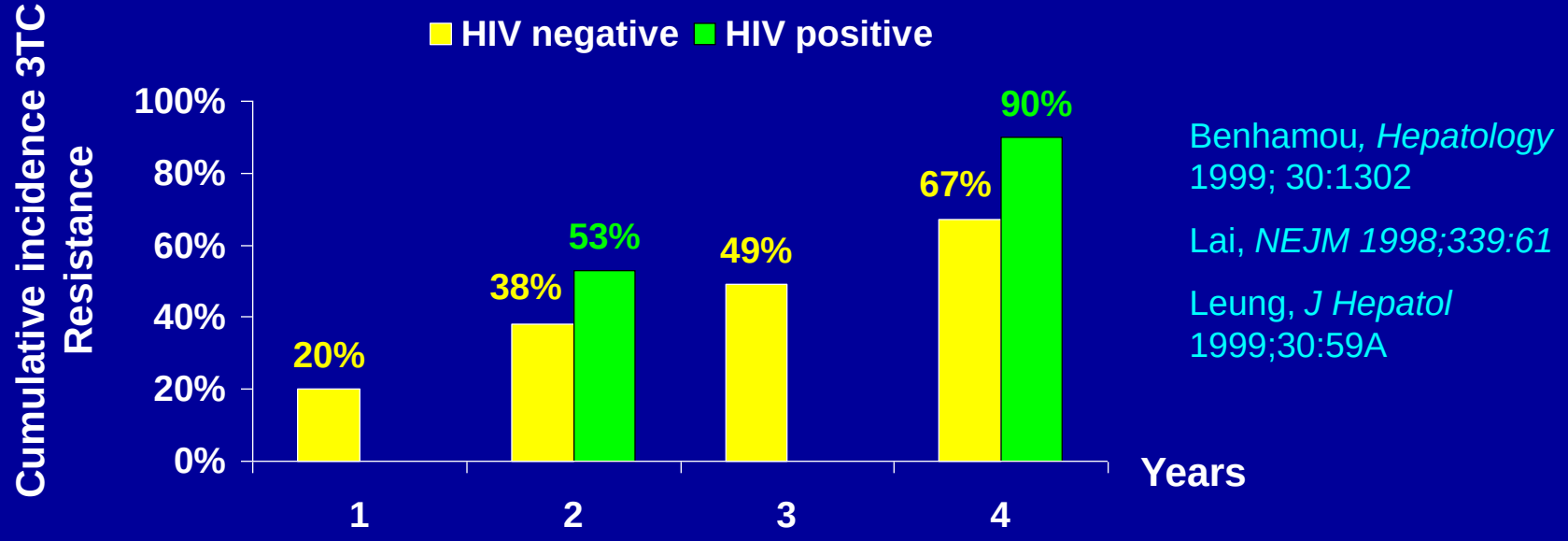
Chen CJ, et al. JAMA 2006; 65

Treatment options for HBV infection

FDA-approved	Not FDA-approved
IFN-α–2b	Emtricitabine
Pegylated IFN-α-2a	Pegylated IFN-α-2b
Lamivudine*	
Tenofovir*	
Entecavir	
Adefovir	
Telbivudine	

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+



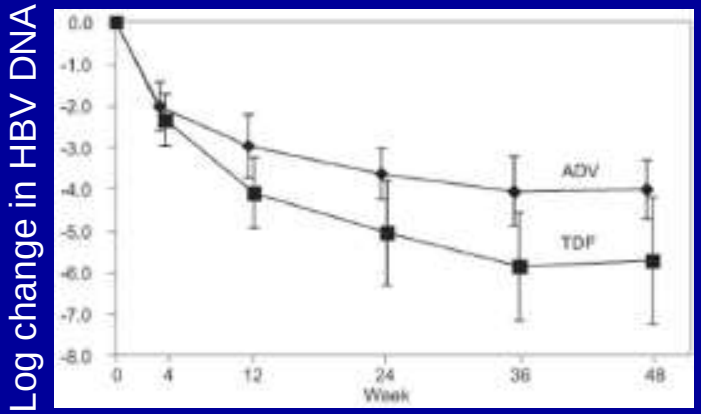
Benhamou, *Hepatology* 1999; 30:1302

Lai, *NEJM 1998;339:61*

Leung, *J Hepatol* 1999;30:59A

Tenofovir (TDF)

- Active against both HIV and HBV
- Average 4 log reduction in HBV DNA, even in patients with lamivudine resistance
- In ACTG 5127, larger mean decrease in HBV DNA with TDF than with ADV Peters et al, Hepatology (2006) 44:1110



- Combination of TDF and 3TC may be more effective than 3TC alone. Dore et al, JID (2004) 189:1185. Matthews et al., CROI 2005.

Treatment of HBV in HIV+ subjects

- Patient needs treatment for both HIV and HBV: TDF + 3TC or FTC as the backbone for ART
- Patient needs treatment for HIV but not HBV: TDF + 3TC or FTC as the backbone for ART
- Patient needs HBV treatment but not HIV: Controversial.
  - Consider starting ART with 2 drugs active against HBV or treating with peg-interferon

Case (continued)

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- Four months after starting ARVs, presents with nausea, vomiting, abdominal pain

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4				793	173

What's going on?

Case (continued)

Mo.	Meds	CD4	VL	ALT	AP
0	d4T/3TC/EFV; IRZE. Bactrim	137	123,000	49	80
3	d4T/3TC/EFV; INH/Rif. Bactrim	194	<400	57	99
4	None	123	149,000	793	134

- Patient admitted he had stopped taking ARVs about 4 weeks ago
- HBV DNA: 3 million IU/mL

Liver enzyme elevation in patients with HBV/HIV: “HBV flares”

- Discontinuation of 3TC, FTC or TDF-containing regimen may lead to a flare in hepatitis B
  - Incidence after 3TC-withdrawal may be as high as 22% Wit, JID (2002) 186:23
  - ~5% have elevation of ALT >5x ULN
    - ALT usually peaks 1-3 months after stopping 3TC

      Bellini, HIV Med (2009) 10:12

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

Bringing It All Back Home: Summary

Conclusions (1)

- 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
    - ATT
    - Other drugs
  - IRIS, e.g. TB
    - Particularly if fever, adenopathy, hepatomegaly, other sites of disease
  - Superinfection
  - Flare of HBV or HBV IRIS

Conclusions (2)

- HBV coinfection is common in HIV-infected patients
- Test HIV-infected patients for HBsAg and anti-HBs
- If HBsAg and anti-HBs negative, immunize patient for HBV
- If HBsAg-positive, initiate ARVs that include tenofovir and 3TC (or FTC)
- Warn patient not to stop ARVs as this can precipitate a HBV flare

Questions or comments?

The Johnson Treatment