Update on HBV Management: 2017

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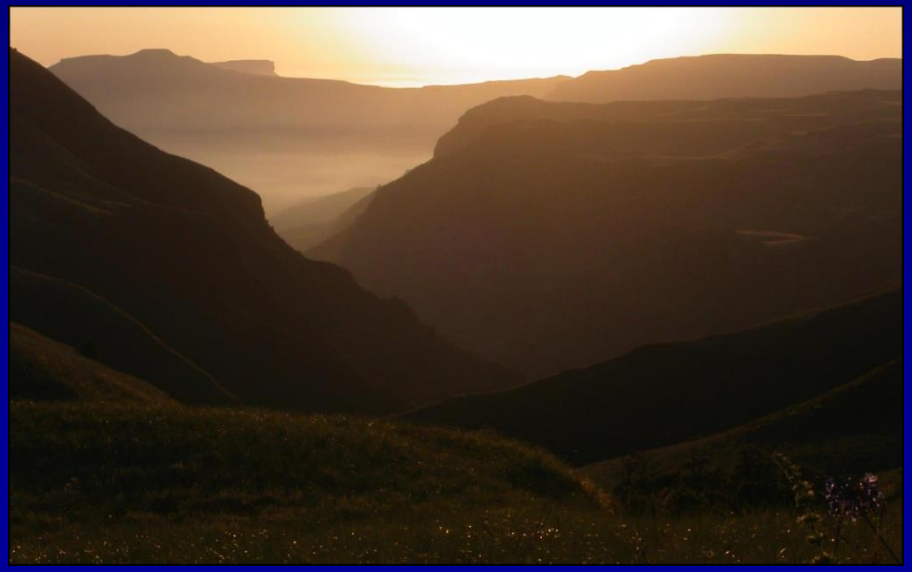

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Theratechnologies

Outline

- Treatment of HBV in HIV+ patients
- Antiretroviral hepatotoxicity in HIV/HBV: Case study

Case

- 52 yo HIV+ M, CD4 cell count 700, HIV RNA 23,000, ALT 170.
- HBsAg, HBeAg positive. HBV DNA: 90,000 IU/mL.
- Patient interested in receiving treatment for HBV
- You recommend:
    a. Continued observation until HBV DNA is >100,000 IU/mL
    b. Continued observation until ALT is > 5 x ULN
    c. Liver biopsy
    d. Initiation of HBV and HIV treatment

Classification of Chronic Hepatitis B

Immune tolerant phase

Mother-to-child tx

ALT normal

HBeAg (+)

HBV DNA >20,000 IU/ml

Liver bx usually normal or with minimal inflammation

May last for decades

Liver disease does not seem to progress

→

Immune active phase

Person-to-person tx

ALT > 2x or liver inflammation/fibrosis on bx

HBeAg (+) or (-)

HBV DNA >2,000 IU/ml

Highest risk for cirrhosis and HCC (risk factors: elevated ALT, HBV DNA; also older age, male sex, HIV, HCV)

⇄

Inactive carrier phase

ALT <2x/no liver disease

HBeAg (-)

HBV DNA <2000 IU/mL

May revert back to the immune active phase

Approach to patients depends on hepatitis B classification

Hepatitis B classification	Approach to patient
Immune tolerant	ALT testing every 3-6 months. If becomes elevated, recheck in 1-3 months.
Immune active chronic carrier	Evaluate for treatment Screen for HCC
Inactive chronic carrier	ALT every 6-12 months. Some recommend HCC screening for those at higher risk (male >45, cirrhosis, FHx HCC)

Treatment goals

- Prevent disease: End stage liver disease (ESLD); hepatocellular carcinoma (HCC)
- Prevent transmission
- Reduce risk of ARV-related hepatotoxicity
- Reduce risk of immune reconstitution inflammatory syndrome

Treatment of HBV in HIV-negative patients

When to Start?

Who should be treated for hepatitis B? 2016 AASLD Guidelines

- Immune active disease
  - ALT > 2 ULN* or histologic disease plus
  - Elevated HBV DNA: >2000 IU/mL for eAg (-); >20,000 IU/mL for eAg (+)

*ULN for ALT: >30 for males; >19 for females

- Immune-active CHB and cirrhosis if HBV DNA >2,000 IU/mL, regardless of ALT level
- Factors supporting treatment at lower ALT and HBV DNA: age over 40; family history of HCC; extra-hepatic manifestation

Terrault NA et al, Hepatology, 2016

When to Start in HBV/HIV Patients

- HBV/HIV patients have higher HBV DNA levels and a higher risk of cirrhosis and HCC than HIV monoinfected patients
- HBV/HIV+ patients have an ~17-fold higher rate of liver-related mortality than HIV or HBV monoinfected patients Thio C et al. *Lancet.* 2002;360:1921
- Since ART now recommended for all HIV patients, HBV treatment (which includes drugs used for HIV), should be given to all HBV/HIV patients

Case (continued)

- 52 yo HIV+ M, CD4 cell count 700, HIV RNA 23,000, ALT 170.
- Patient interested in receiving treatment
- You recommend:
  a. Continued observation until HBV DNA is >100,000 IU/mL
  b. Continued observation until ALT is > 5 x ULN
  c. Liver biopsy
  d. Initiation of HBV and HIV treatment

What to Start?

FDA approved

IFN-α-2b*

Pegylated IFN-α-2a*

Lamivudine* (LAM)

Entecavir* (ETV)

Adefovir dipivoxil (ADV)

Telbivudine (LdT)*[1?]

Tenofovir disoproxil fumarate (TDF)*

Not FDA approved

Emtricitabine*

Tenofovir alafenamide (TAF)*

***Active against HIV at doses used to treat HBV**

[1]Lo E et al, AIDS (2009) 23:546

Response Rates in Patients with HBeAg+ HBV Monoinfection

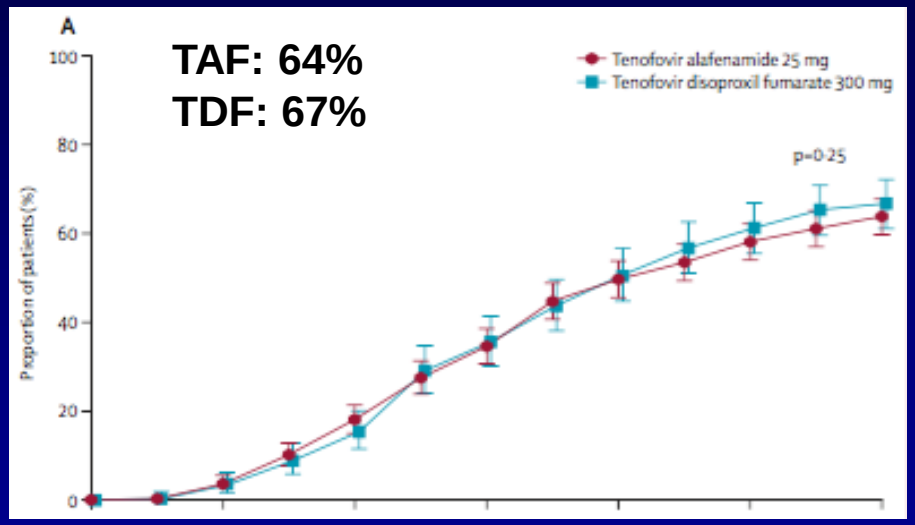
	PEG-IFN	LAM	ADV	ETV	L-dT	TDF
DNA loss (%) 1 yr	25	44	21	67	60	76
HBV DNA log decline	4.5	N/A	3.5	6.9	6.5	
HBeAg SC (%)	27 wk 48 32 wk 72	16-18	12	21	22	21
Resistance	0%	70% at 5 y	29% at 5 y	1.2% @ 6 y if naïve 57% if LAM-R	17% 2 y	0% 8 y

Tenofovir alafenamide (TAF)

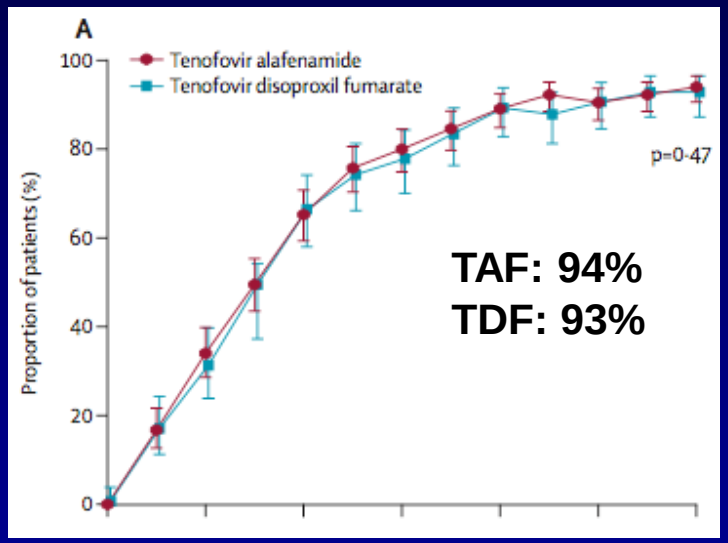
- Formulation of tenofovir that concentrates in cells
- 90% lower levels of tenofovir in plasma with TAF as compared with tenofovir disoproxil fumarate (TDF)
- In treatment of HIV:
  - TAF is non-inferior to TDF in terms of achieving HIV suppression
  - TAF has less deleterious effects on markers of bone and renal health than TDF

TAF vs. TDF for Chronic HBV: Phase 3 Randomized Clinical Trials

HBeAg (+)
Wk 48 HBV DNA <29 IU/mL



HBeAg (-)
Wk 48 HBV DNA <29 IU/mL

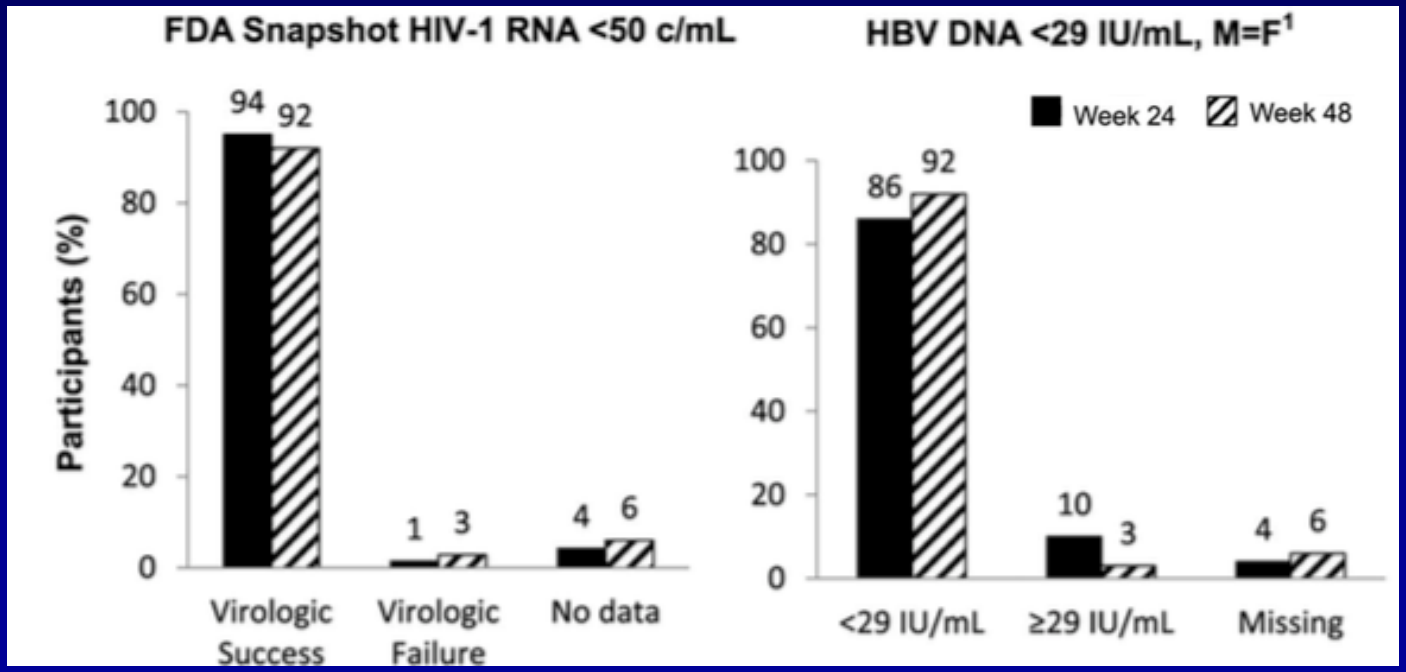


- TAF non-inferior to TDF for HBeAg (+) and eAg (-) CHB
- TAF associated with smaller decline in bone mineral density; less deleterious effects on renal markers

Buti M et al, Lancet Gastroenterol Hepatol, 2016; Chan HLY et al, Lancet Gastroenterol Hepatol, 2016

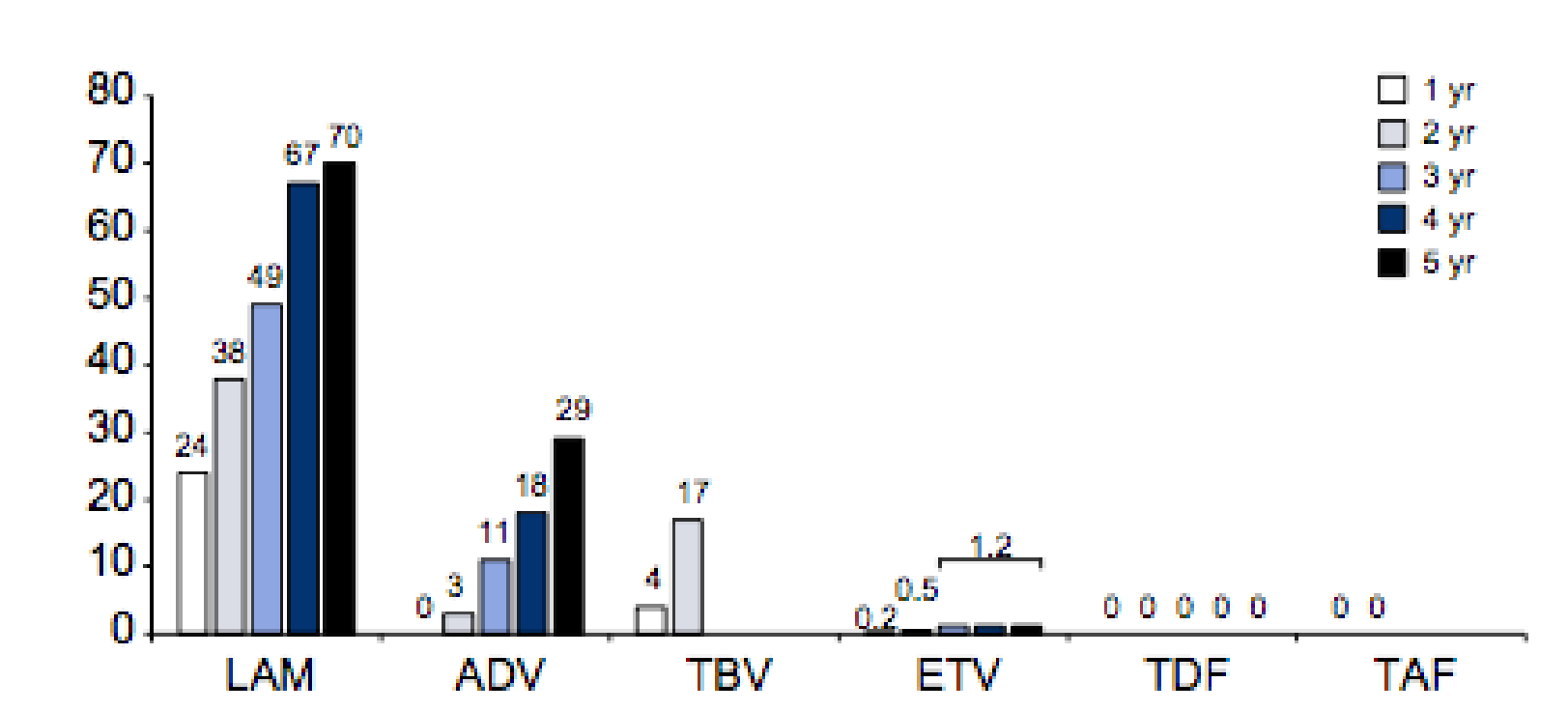
Switching to Elvitgegravir/cobi/FTCTAF in HIV/HBV Adults

- Open label switch study in 72 HIV/HBV adults
- Prior to switch, 71 (99%) had HIV RNA <50; 69 (96%) were on TDF ART; 62 (86%) had HBV DNA <50



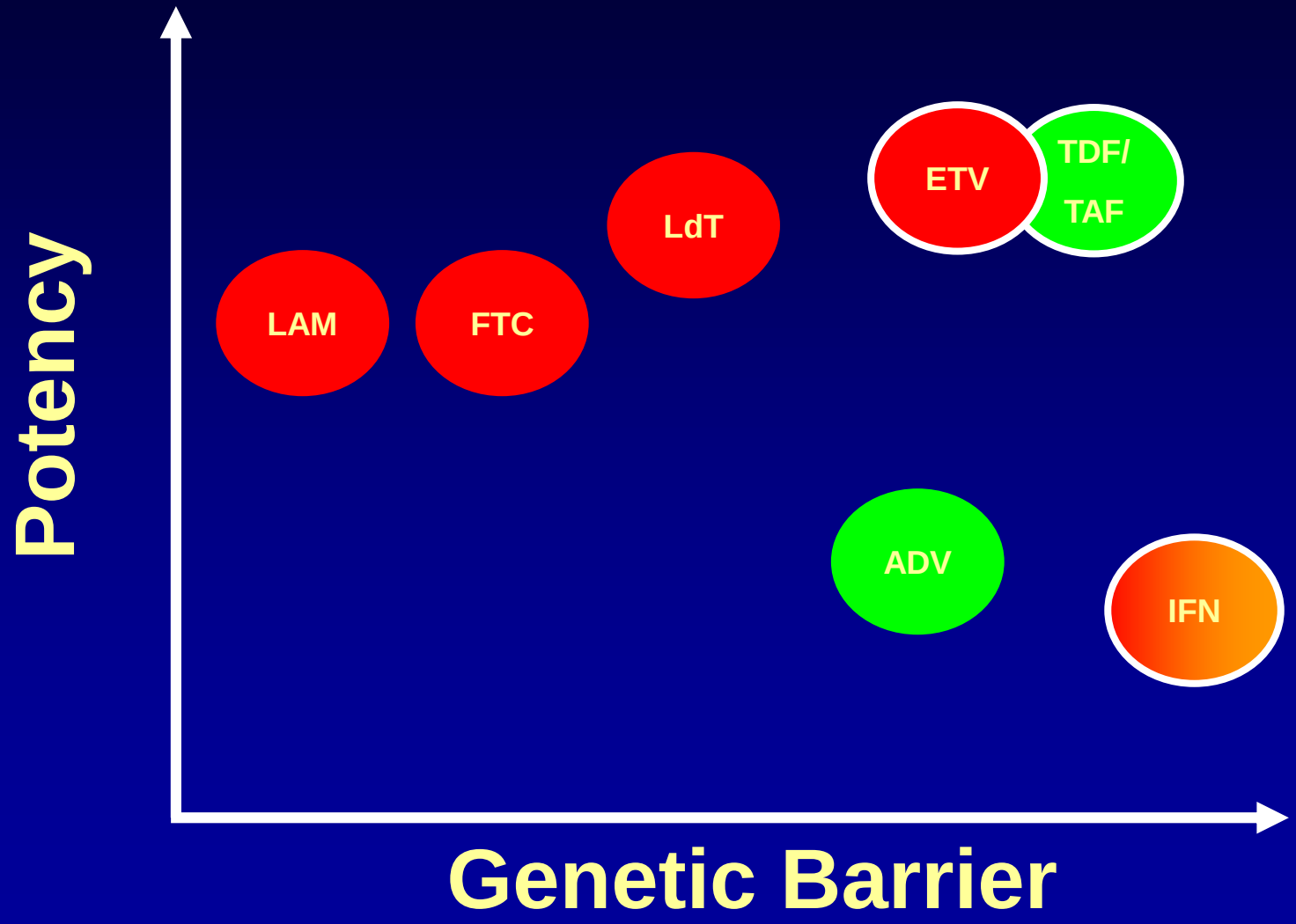
Gallant J et al, JAIDS, 2016

Cumulative Incidence of Resistance for Different HBV Drugs



EASL 2017 Clinical Practice Guidelines on Management of Hepatitis B virus infection, J Hepatol, 2017

HBV Drugs: Potency and Genetic Barrier to Resistance



M. Levrero (2006)

Preferred 1st line treatment options in HBV monoinfected patients

- Entecavir
- Tenofovir – either TDF or TAF

EASL 2017 Clinical Practice Guidelines on Management of Hepatitis B virus infection, J Hepatol, 2017

HBV treatment in the HIV patient

Virus Needing Treatment	Preferred option	Avoid
HIV or HBV	TDF/TAF+ FTC/3TC+ 3rd HIV agent	3TC/FTC/tenofovir/ 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 until undetectable x 2; then every 6 months
- ALT every 3 months until HBV DNA undetectable
- If patient is HBeAg (+): monitor HBeAg, anti-HBe every 6 months
- HBsAg yearly
- Only about 10% of patients clear HBsAg; the majority who clear, do so in the first year

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

Outline

- Treatment of HBV in HIV+ patients
- Antiretroviral hepatotoxicity in HIV/HBV coinfected patients: Case study

Case

- Middle-aged woman
- 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	750,000	nl	nl	nl	0.3
4	TDF/FTC/EFV; ATQ	126 (6%)	507	329	234	104	
6	TDF/FTC/EFV; ATQ			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; ATQ	15	750 K	nl	nl	nl	0.3
4	TDF/FTC/EFV; ATQ	126	507	329	234	104	
6	TDF/FTC/EFV; ATQ			1802	1147	283	1.8

What do you do now?

A. Take additional history
B. Do additional testing
C. Stop all or some medications
D. All of the above!

Wk	Meds	CD4	HIV RNA	ALT	AST	AP	Bili
0	TDF/FTC/EFV; ATQ	15	750 K	nl	nl	nl	0.3
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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)	Mixed	Cholestatic (ALT/AP <2)
ARVs	Sulfonamides	Amox/clav
Herbal meds	Bactrim	Macrolides
INH	Phenytoin	Phenothiazines
K		oids
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

Alcoholic Hepatitis

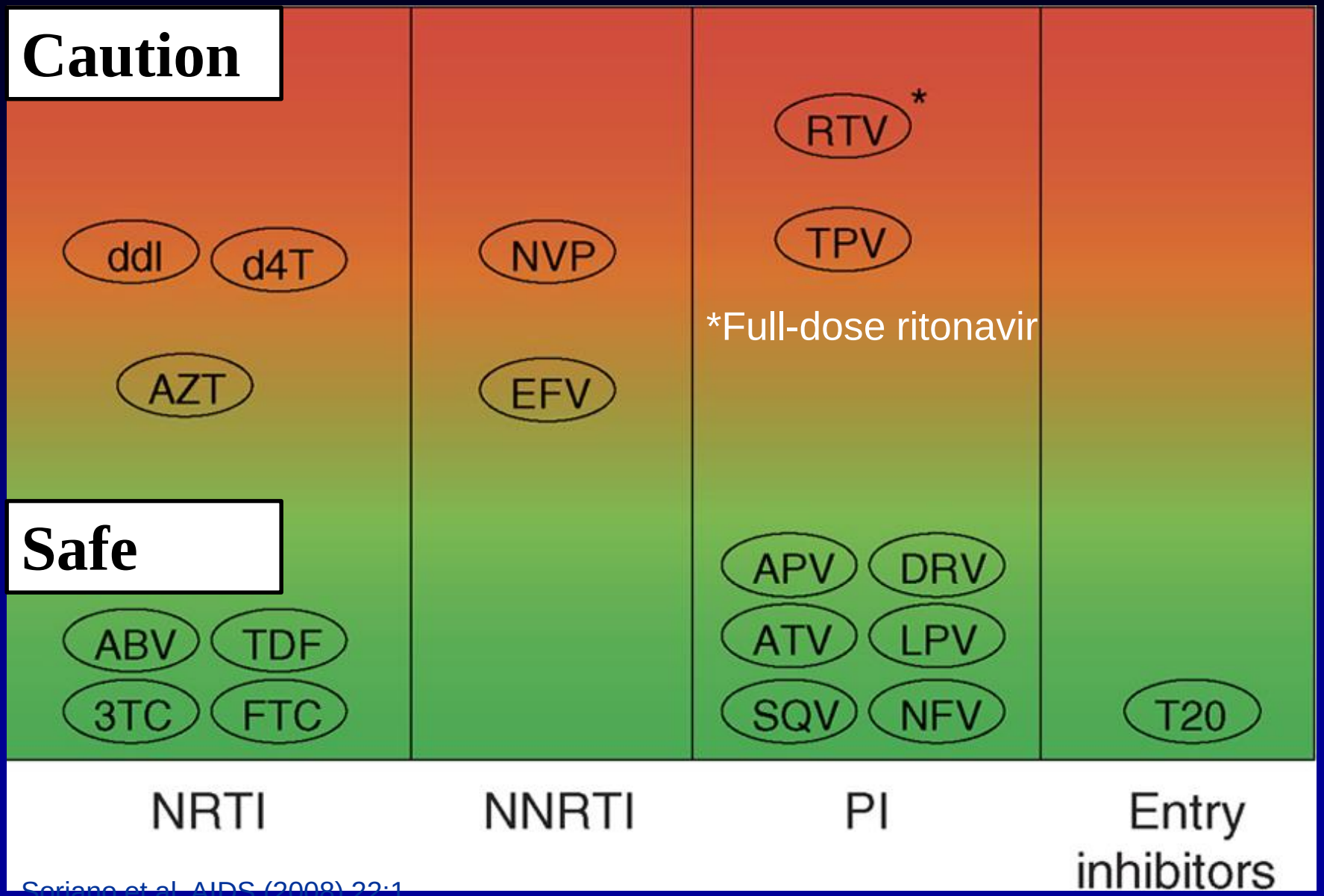
- Assess all patients with elevated LFTs for alcohol use
- Clues:
  - AST:ALT ≥ 2:1; AST <8x ULN
  - GGTP usually elevated
- Patient denies any alcohol use, herbal supplements, acetaminophen use

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. AIDS (2007) 21: 1301
Hoffmann et al. CID (2008) 47:1479

Risk of Hepatotoxicity of ARVs



Soriano et al, AIDS (2008) 22:1

Integrase Inhibitors and the Liver

- Raltegravir:
  - Rate of raltegravir hepatotoxicity in randomized studies and case series is low
- Elvitegravir (EVG)/cobicistat
  - LFT abnormalities less common with EVG/cobi than with EFV or ATV/r
- Dolutegravir
  - Low rate of hepatotoxicity

Vispo E et al, J Antimicrob Chemother, 2010; Rockstroh J et al, HIV Medicine, 2011

DeJesus E et al, Lancet, 2012; Sax PE et al, 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)

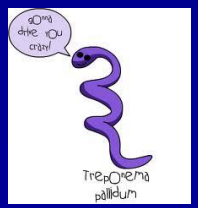
Close monitoring is essential

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 syndrome, atypical lymphs, hepatitis
- Bacterial infections: e.g. <u>syphilis</u>



Kaufman B, CID, 1997; Norvell JP et al, Liver Transp, 2007; 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!

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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

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

HBV IRIS

- Hepatitis flare because of increase in T cell responses, 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 (immune-mediated hepatitis flare associated with virus clearance)

McGovern, B, CID, 2004; Crane M JID, 2009; Ofotokun, Am J Med Sci 2007; Nair S & Perrillo RF, Hepatology, 2001; Liaw C, J Gastro Hepatol, 2003; Andrade, JID, 2013

Summary

- When to treat HBV monoinfected patient?
  - Immune active phase: elevated ALT and HBV DNA
- What to use?
  - In HBV monoinfected: tenofovir or entecavir
  - In HIV/HBV coinfected: tenofovir + 3TC/FTC + 3rd HIV agent
- Hepatotoxicity in an HIV/HBV patient. Consider:
  - Drug induced liver injury
  - Super infection
  - HBV IRIS

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Questions or comments