Hepatitis B Management in Immunosuppressed Patients

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Immunosuppressed Patients with

• HIV
  – When to start
  – How to monitor
  – Liver transplant

• Transplant

• Chemotherapy
HBV and Immunosuppression

- Increases HBV chronicity
- Increases HBV replication
- Decreases anti-HBe and anti-HBs seroconversion
- Increases hepatitis flares
- Increases progression to cirrhosis
- Increases hepatocellular carcinoma
- Diminishes efficacy of anti-HBV treatment
- Decreases response to interferon-alpha
- Increases lamivudine resistance mutations
Overlapping HIV and HBV Epidemics

HIV
40 million

HBV
400 million

HBsAg+
4 million
HBV-HIV Epidemiology

- HBV alone >400 million infected worldwide
- HIV 5%-30+% depending upon cohort, country
- Adult transmission is sexual or parenteral: genotype A>>G
  - IV drug use 5%–10%
  - US 9-10%
  - EuroSIDA 8.7% HBsAg
- Resource limited countries are often those with high HBV endemicity (vertical or childhood transmission) then acquisition of HIV:
  - Sub saharan Africa varies: Tanzania 9.2%; Nigeria 25.9%, Ghana 16.7%, Malawi 16.9%

Causes of Death Among HIV+ Persons with Access to ARVs

Multivariate model for liver death:
- HCV 6.7 (3.9 – 11.2)
- HBV 3.7 (2.4 – 5.9)
- HCC 82/10,000
- Low CD4 1.23 (1.2 - 1.3)
- IDU 2.0 (1.2 – 3.4)
- Older age 1.3 (1.2 – 1.5)
HIV Coinfection Increases the Risk of ESLD Due to HBV

- Multicenter Cohort Study
  - 4967 HBsAg negative MSM
    - HIV: 47% (n=2346)
  - 326 HBsAg positive
    - HIV: 65% (n=213)

- HIV/HBV coinfection
  - 19-fold higher risk of liver death compared with HBV monoinfection
  - Risk of liver-related mortality increased with:
    - Alcohol consumption
    - Low nadir CD4+ cell counts
    - Antiretroviral therapy

Liver Disease in HIV Infection

Alcohol Drugs Medications

HCV / HBV Other Liver Diseases

NAFLD

Drug-related Hepatotoxicity

– Antibiotics; TB, fungal, bacterial
– NSAIDS
– Neuropsychiatric medications
– OTC e.g. herbal medications
HBV HIV and HAART: abnormal LFTs

- Reactivation of HBV with improved immune response
  - Immune reconstitution - continue therapy
  - HAART without anti-HBV therapy
  - HAART holiday: continued need for HBV therapy
- Hepatotoxicity
- Development of drug resistance e.g. 3TC/ lamivudine after 4 yrs 90%
- Spontaneous HBV clearance occurs rarely in HIV
- Other liver disease
HIV / HBV Treatment: Choices

HBV with ART

• Treat HBV regardless of HBV DNA level
• Nucleoside + nucleotide analogues:
  • 3TC/ FTC/ ETV + TDF/ADV (*DHHS FTC + TDF*)
  • Use in combination
• Do not stop therapy as flare will occur which can be life threatening
  • STACCATO: 5/6 STI with HBV HIV “flared”, 1 severe

*Sherman, McGovern, Nguyen, Peters 2007 DHHS IDSA guidelines*
HIV Treatment Interruption Leads to HBV Flares

- STACCATO: multinational RTC of continuous versus CD4 cell count-guided treatment (threshold CD4 350 cells/µl)
- STI: structured treatment interruptions occurred in those randomized to STI when CD4 above 350
- antiretroviral therapy (ART) containing tenofovir/emtricitabine
- 362 Thai patients of whom 16 were HBsAg positive (f/u in study 48-96w)

AIDS. 2008 Jan 2;22(1):152-4
HIV Treatment Interruption Leads to HBV Flares

- 362 Thai patients 16 HBsAg positive (f/u 48-96w)
- On continuous therapy, 15/16 became HBV DNA neg; 1 HBeAg neg, 1 HBsAg neg; all decreased ALT
- STI occurred in 6/10 with mean of 1.3 STI per subject
  - 5/6 had rise in ALT and HBV DNA
  - One severe: AST 408 U/l, ALT 218 U/l, bilirubin 23.1 µmol/l, HBV DNA log 7.61 copies/ml
  - Reinstitution of ART resolved flare in all subjects

AIDS. 2008 Jan 2;22(1):152-4
HBV and HIV therapy in resource limited settings

- Types of ART therapies available varies between countries
- Many countries have TDF as 1\textsuperscript{st} line (Nigeria, South Africa)
- Most countries do not test HBsAg, but if 1\textsuperscript{st} line ART therapy failes, they test patient for HBsAg then- more cost effective
- Some countries use D4T or 3TC as 1\textsuperscript{st} line (high arte of HBV resistance)
TDF f/u 5 years in HBV HIV patients

- Retrospective study of 102 patients, at baseline
  - 80% detectable HBV DNA
  - 70% HBeAg positive
- At 5 years of f/u: 92% had control of HBV
  - No difference between baseline 3TC R or not
  - 2 patients lost HBsAg
  - 3 patients increased serum Cr (9 ml/min)

De Vries-Sjuijs Gastro 2010
Entecavir Intensification

- 92% of patients on TDF-based HBV treatment will have undetectable HBV at year 5
- No TDF mutations described in those with persistent viremia (usually low level)
  - TDF mutations still not characterized
- Entecavir intensification is an option in failure to suppress
- 2 series of ETV intensification (addition) reported:
  - 4 out of 4 suppressed with 36 weeks of Entecavir (Luetkemeyer CROI 2009)
  - 4 out of 4 suppressed with 3-12 months of ETV (DeVries-Sluijs 2010)
- Thus addition of ETV can be considered if persistent HBV viremia is seen after 1-2 years on TDF therapy

Luetkemeyer AF et al CROI 2009 # 636
DeVries Sluis Gastroenterology 2010
### Nucleos(t)ide Agents With Activity Against HIV and HBV

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<tr>
<th>HBV</th>
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<th>YMDD</th>
<th>HIV TREAT</th>
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<td>S (1 mg)</td>
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* FDA warning in patients not on ART
High incidence of treatment-induced and vaccine-escape hepatitis B virus mutants among HIV-hepatitis B infected patients

- Prospective cohort study of 171 HIV HBV patients with HBV viremia who had ≥ 1 visit. All had HBV viral genome sequences analyzed q 12-mos x3

- HBV DNA time 0 36 mos
  - >190 IU/mL 91.8% 40.3%
- LAM FTC 71.9%
- TDF use 17.5% 66.7%
- Cumulative duration of TDF was significantly associated with a reduction in the occurrence of immune-associated S-gene mutations (HR/month=0.88, 95%CI=0.79-0.98).

Lacombe Hepatology. 2013
Reactivation of HBV

• High rate of reactivation in immunosuppressed patients
  – Chemotherapy
  – HIV after immune reconstitution
  – Lymphoma increased in HIV patients
  – Post organ transplant
  – Biologic response modifiers: rituximab (anti-CD20), TNF-α inhibitors: GI, hematologists, rheumatologists, dermatologists

• Reactivation can occur in immunocompetent treated with steroids, BRMs
Chemotherapy-induced HBV Reactivation

Definition:

- Loss of HBV immune control in a patient with inactive or resolved HBV infection
- Abrupt reappearance or increase in viral replication with liver damage occurring during and/or following immune reconstitution
- Clinically:
  - Range from subclinical to severe or even fatal hepatitis
  - Rise in HBV DNA +/- return of HBeAg
  - ALT increase (may be mild or very dramatic)
  - May progress to liver failure and death
Consequences of Delayed Recognition/Treatment of Reactivated HBV

• Hepatitis
  – May be severe or even fulminant
  – Occasionally may miss HBV DNA spike if not followed routinely during treatment because HBV DNA falls when ALT rises
  – This may lead to misdiagnosis and subsequent flares

• Delay or stop of chemotherapy
  – Potential for poorer cancer-related outcome
Rituximab: A Particular Problem

- Monoclonal antibody against CD20 - B cell marker
- Reduces B cell numbers and antibody levels
- Increasingly used as part of CHOP-R, EPOCH-R

- Increased risk of HBV reactivation, including HBsAg-negative patients
- Reverse Seroconversion: Reappearance of HBsAg in previously HBsAg-negative patient
- Can occur very late after last dose
Lymphoma in HIV HBV patient

- 24 yo MSM HIV diagnosed 1990
- HBsAg positive 1997 (HBV DNA 9.62 log c/mL)
- ART with LAM became anti-HBc positive alone
- 2004 diffuse large B cell lymphoma treated with steroids and CHOP
- 6 weeks later he reverse seroconverted to HBsAg positive
- Delay in chemotherapy
- Adefovir added with dramatic decline in HBV DNA load and a normalisation of hepatic enzyme levels.

Patient and Graft Survival
HBV vs HBV-HIV*

*No deaths due to recurrent HBV

Survival Post-Transplantation (mos)

Terrault 2007
HBV-HIV Summary

• Immune response predicts HBV outcome
• Flares in HBV/HIV patients are common
  – Many HIV medications are hepatotoxic
  – Other causes of ALT elevations in HBV/HIV should be sought
  – Less common causes of flares in US in 2014 are ART without HBV therapy and stopping ART
• Atypical serologies may occur in HIV patients during ART
  – Reverse seroconversion occurs
  – Loss of HBsAg – can still serorevert to HBsAg under strong immune suppresssion (rituximab or Stem cell transplant)