Hepatitis B in HIV Patients Pt.II

Mamta K. Jain, M.D., M.P.H.
UT Southwestern Medical Center
Prevention of Hepatitis B
Comparison of Standard vs. Double Dose or recombinant HBV vaccine

<table>
<thead>
<tr>
<th>dose</th>
<th>Number</th>
<th>schedule</th>
<th>Anti-Hbs &gt;10mIU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 µg</td>
<td>94</td>
<td>0,1,6 months</td>
<td>34%</td>
</tr>
<tr>
<td>40 µg</td>
<td>98</td>
<td>0, 1, 6 months</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Those with CD4 >350 cells/µL had significantly higher rates of response (64% vs. 39%, p=0.01)

**No difference occurred in those with CD4 <350 cells/µL

Fonseca  *Vaccine* 2005; 23: 2902-2908
# HBV Vaccine Response in HIV patients

<table>
<thead>
<tr>
<th>Intervention CD4 &gt;200</th>
<th>Dose</th>
<th>Schedule</th>
<th>route</th>
<th>Response at 28 weeks; Response (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>recombinant vaccine A (n=145)</td>
<td>20μg</td>
<td>0, 4, 24 weeks</td>
<td>IM</td>
<td>65% (56-72%)</td>
</tr>
<tr>
<td>recombinant vaccine B (n=148)</td>
<td>40μg</td>
<td>0, 4, 8, 24 weeks</td>
<td>IM</td>
<td>82% (77-88%)*</td>
</tr>
<tr>
<td>recombinant vaccine C (n=144)</td>
<td>4μg</td>
<td>0, 4, 8, 24 weeks</td>
<td>interdermal</td>
<td>77% (69-84%)**</td>
</tr>
</tbody>
</table>

* p<.001 (A vs B)  
** p=0.02 (A vs. C)

Launay JAMA 2011; 305: 1432-1440
New HBV Vaccination Guidelines

- All immunosuppressed patients
  - HBV vaccine 40 mcg
  - 3 doses at 0, 1, and 6 months (Recombivax)
  - Or 4 doses of 40 mcg at 0, 1, 2, and 6 months (Engerix-B)
  - Check anti-HBs 1 month after completion of series
Vaccination Against Anti-HBc Ab

- 54 patients
- Given 1 dose 20μg of recombinant HBV vaccine
  - Those with anti-HBS <10mIU/ml at 4 weeks received 3 additional double dose (40 μg at 5, 9, 24 weeks)
- At wk 4, 46% were responders
- Non-responders at wk 4 who received further vaccination:
  - 89% had anti-HBS≥10mIU/mL at 28 weeks

Piroth *J Infect Dis* 2016;213:1735-42
Strategies to Increase HBV Vaccination Response

- reduction in HIV viral load
- Increase in CD4 cell count
- Make sure pts receive 3 or more doses
- Re-vaccinate those who are initial non-responders to vaccination series
  - No trials to show that double dose increases response rates in prior non-responders

Whitaker *Lancet Infect Dis* 2012; 12:966-976
Okulicz *Plos One* 2014; 9: e105591
<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>HIV-Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age &lt;40 vs. ≥40 y</td>
<td>2.3 (1.7-3.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.3 (0.9-1.8)</td>
<td>0.140</td>
</tr>
<tr>
<td>Multiple vs. 0-1 sexual partners in previous 6 mo</td>
<td>3.1 (2.3-4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ever IDU vs. never IDU</td>
<td>1.7 (1.0-2.7)</td>
<td>0.040</td>
</tr>
<tr>
<td>≥1 dose vs. no doses of HBV vaccine</td>
<td>0.3 (0.2-0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HIV infected vs. uninfected</td>
<td>2.4 (1.8-3.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CD4 cell count &lt;0.350 vs. ≥0.350 × 10^9 cells/L</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>Antiretroviral use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No HAART</td>
<td>Not tested</td>
<td></td>
</tr>
<tr>
<td>HAART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV RNA level ≥400 copies/mL</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HIV RNA level &lt;400 copies/mL</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

HAART = highly active antiretroviral therapy; HBV = hepatitis B virus; IDU = injection drug use; IRR = incidence rate ratio; NA = not applicable.

Model also adjusted for Multicenter AIDS Cohort Study site. All covariates except race and Multicenter AIDS Cohort Study site were used as time-varying covariates in the model. P values for all participants from negative binomial regression models to assess for overdispersion = 0.24; those for HIV-infected participants = 0.49.

Incident Hepatitis B Virus Infection in HIV-Infected and HIV-Uninfected Men Who Have Sex With Men From Pre-HAART to HAART Periods

A Cohort Study

HBV active ART To Prevent Incident HBV

Hazard ratios (HRs) of the different factors influencing hepatitis B virus (HBV) incidence.

Treatment of HBV
FDA-Approved HBV Therapies

1990 - Interferon alfa-2b
1998 - Lamivudine
2002 - Peginterferon alfa-2a
2005 - Entecavir
2006 - Tenofovir
2008 - Telbivudine
Goals of Treatment

- HBV DNA suppression
  - Decreased risk of HCC
  - Decreased progression to ESLD
- HBeAg+: HBeAg seroconversion
- HBeAg-: HBsAg loss
- HBsAg loss (ultimate goal)
HBV Treatment: Interferon

- Long term follow up limited
- Delayed clearance of HBsAg: 12-65% within 5 yrs
  - Lower incidence of HCC and higher survival rate
- HBeAg-: 20% cleared HBsAg in 5 yr f/u
  - Reduced risk HCC and liver deaths
## HBV/HIV: YMDD Resistance

<table>
<thead>
<tr>
<th>Author, yr</th>
<th>Resistance</th>
<th>Time Interval</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pillay, 2000</td>
<td>14%</td>
<td>Est. 1 yr</td>
<td>CAESAR sub-analysis</td>
</tr>
<tr>
<td>Benhamou, 1999</td>
<td>50%; Annual incidence of 20%</td>
<td>After 2 years</td>
<td>Resistance only in HBeAg carriers</td>
</tr>
</tbody>
</table>
## Treatment of HBV in HIV-Infected

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Log Reduction</th>
<th>HBeAg Seronversion</th>
<th>Resistance (YMDD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>2.7 log</td>
<td>22-29%</td>
<td>14-38% at 1 yr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>50% at 2 yr</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>3-5 log</td>
<td>25%</td>
<td>Active against YMDD; 1 reported case</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>2.92 log*</td>
<td>33%*</td>
<td>9% at 48 weeks*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18% at 96 weeks*</td>
</tr>
</tbody>
</table>

* Data not available in HIV/HBV

Combination pills: Combivir (lamivudine and zidovudine)
Trizivir (lamivudine, abacavir, and zidovudine)
Truvada (tenofovir and emtricitabine)
Atripla (efavirenz, tenofovir, and emtricitabine)

Gish. *Arch Int Med* 2006;166:49-56
Complications During Therapy
Acute Flares in Chronic HBV

- Spontaneous reactivation of chronic HBV
- Reactivated hepatitis due to immunosuppressive medications
  - Cancer chemotherapy
  - Antirejection drugs
  - Corticosteroids
- Resulting from antiviral therapy
  - Interferon
  - Nucleoside analogues
  - Corticosteroid withdrawal

- Induced by HBV genotypic variation
  - Precore mutant
  - Core promoter mutant
  - HBV DNA polymerase mutant

- Due to superimposed infection with other hepatotropic viruses
  - Hepatitis A,C,delta viruses

- Caused by interaction with HIV infection
  - Reactivated hepatitis
  - Effect of immune reconstitution therapy

Perrillo Gastroenterology 2001
Acute Flare

- Withdrawal of HBV treatment
- Never stop lamivudine/emtricitabine/tenofovir in pt with HBV if you are changing HIV regimen due to HIV resistance.
Hepatitis B IRIS

ALT (I/U)

CD4 Count

0 100 200 300 400 500 600 700 800

0 100 200 300 400 500 600 700 800

baseline 1mo 2mo 3mo 5mo

Jain et al., AIDS Patient Care & STDs, 2006
Drug-Induced Hepatotoxicity
- ALT increase
- 3-12 weeks after initiation of meds
- High likelihood for hepatotoxicity i.e. Nevarapine
- Hep B core IgM negative
- HBe Ag serconversion not seen
- Rash and fever may be seen

Immune Reconstitution/HBV flare
- Increase in CD4
- Decrease in HIV VL
- ALT increase
- 6-12 weeks after initiation of meds
- Hep B core IgM often positive
- HBeAg seroconversion may be seen during or following flare
Mutations

- HBeAg-negative variants occur naturally (HBV DNA +)
  - Precore stop codon G1896A
  - Basal core promoter A1762T/G1764A
- Mutations abolish or decrease HBeAg production
Entecavir Activity Against HIV

On entecavir

Wild type HIV

M184V HIV

---

Jain and Zoellner AIDS, 2007
## Resistance

### Nucleos(t)ide therapy and potential mutations in RT polymerase gene

<table>
<thead>
<tr>
<th>Drug</th>
<th>RT Polymerase mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamivudine, telbivudine, emtricitabine</td>
<td>rtM204V/I+rtL180M; rtV173L</td>
</tr>
<tr>
<td>adefovir</td>
<td>rtA181V; rtN236T</td>
</tr>
<tr>
<td>entecavir</td>
<td>rtM204V+rt180M plus rt184A/C/F/G/I/L/M/S or rtS202C/G/I or rtM250V/L</td>
</tr>
<tr>
<td></td>
<td>rtM204I plus rt184I/S or rtM250I/L</td>
</tr>
</tbody>
</table>
Monitoring During HBV Treatment
Evaluation of HBV

- We asked how well do HIV providers evaluate and monitor HBV in HIV/HBV patients?
- To evaluate response to HBV therapy, measurement of HBV DNA is needed at baseline and then during therapy.
### Baseline Characteristics (n=155)

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 (cells/μL), median [range]</strong></td>
<td>137 [1-1089]</td>
</tr>
<tr>
<td><strong>CD4&lt;200 cells/μL</strong></td>
<td>90 (58)</td>
</tr>
<tr>
<td><strong>Log HIV viral load (copies/mL), median [range]</strong></td>
<td>4.81 [1.69-6.11]</td>
</tr>
<tr>
<td><strong>ALT (IU/L) , median [range]</strong></td>
<td>34 [6-481]</td>
</tr>
<tr>
<td><strong>AST (IU/L), median [range]</strong></td>
<td>37 [13-389]</td>
</tr>
</tbody>
</table>

# Active HBV Therapy

<table>
<thead>
<tr>
<th>HBV Therapy</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any active HBV therapy</td>
<td>142 (92)</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>137 (88)</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Adefovir</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

Monitoring of HBV in HIV/HBV Patients

- Testing for HBV or HIV prior to starting HAART
  - HIV RNA prior to HAART 99%
  - HBV DNA prior to HAART 16%

- Monitoring of HIV and HBV during the first year of HAART
  - HIV RNA 1st year of Rx 497 (median 3/pt)
  - HBV DNA 1st year of Rx 85 (median <1/pt)

HBV Tests: HBV DNA or HBeAg/anti-HBe
HIV Tests: HIV RNA

HIV vs. HBV Kinetics

- HIV viral load becomes undetectable in 2-8 weeks
- HBV viral load may take >6 months
  - Much higher baseline HBV DNA level
Management of Hepatitis B

- HIV/HBSAg+ to begin ART:
  - Hepatitis B DNA
    - quantify HBV viral load prior to initiation of ART
  - Hepatitis B e Antigen
    - indicates ongoing viral replication and can be used as a marker of active disease
  - Hepatitis B e Antibody
    - will become positive when patient has seroconverted
  - Ultrasound of liver
    - Cirrhosis and HCC
  - Consider Liver biopsy to stage disease
Management of HBV

- Confirm HBV viremia

- Start HAART
  - Truvada should be used as back-bone
  - If tenofovir can not be used then entecavir should be added to ART regimen

- Stage Liver Disease
  - US
  - Fibroscan
  - Liver biopsy
  - Fibrasure/APRI/FIB-4
Management of HBV

- Monitor HBV DNA
  - Every 3-4 months
  - Once HBV DNA suppressed
    - Check HBeAg to determine if seroconversion has occurred

- Monitor for HCC
  - Ultrasound and AFP yearly
  - If cirrhotic then every 6 months
Special Request

- Longitudinal study of HIV/HBV
  - Via HIV/HBV Research Network

- Please refer all HIV/HBV patients to this study
  - Staging of liver disease
  - Liver disease progression monitored