Hepatitis B/HIV coinfection: updates in prevention and care
HIV Breakfast Club, Albany Medical Center

Elizabeth Reddy, MD, MSc
Upstate Medical University Hospital
Infectious Disease
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Overview

- Scope of the problem
- Prevention of hepatitis B in HIV infected persons
- Optimize treatment and monitoring in HIV/HBV coinfected persons
- Describe alternate options for therapy in cases of drug resistance or intolerance
- Data from Tanzania

Scope of the problem: HBV

- 350-400 million people worldwide estimated to be living with chronic hepatitis B virus (HBV) (Hepatitis B Foundation: http://www.hepb.org/pdf/hepb_fast_facts.pdf)
  - WHO estimates 780,000 people die each year due to complications of HBV infection
- 800,000-1.4 million people with chronic hepatitis B in the U.S. (CDC)
  - 18,000 estimated new cases per year (~5000 documented)
HBV: Progress in the U.S.

Incidence of acute hepatitis B, by year
United States, 1980-2011

Vaccine introduced
Infant vaccination initiated

CDC: http://www.cdc.gov/hepatitis/HBV/StatisticsHBV.htm#section4

Scope of the problem worldwide: HBV

Global infant vaccine coverage now estimated at 81% (WHO)

* For multiple countries, estimates of prevalence of hepatitis B surface antigen (HBsAg), a marker of chronic HBV infection, are based on limited data and might not reflect current prevalence in countries that have implemented childhood hepatitis B vaccination. In addition, HBsAg prevalence might vary within countries by subpopulation and locality.
Epidemiology of HIV/HBV coinfection

- In U.S. approximately 5-10% of patients with HIV are coinfected with hepatitis B
- Abroad estimates of HBV coinfection among patients with HIV typically range from 6-20%
  
  (Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Int J Infect Dis. 2010)


  - Reported prevalence as high as 60% in one study
    

- Common modes of infection
- Possible role of immune dysfunction contributing to persistence

Risks of HBV coinfection in HIV

- Multicenter AIDS Cohort study (MACS) 8 fold higher rates of death among HIV/HBV coinfected patients
  
  - Compared to monoinfection with either virus
- HIV appears to worsen HBV related liver disease
  
  - Increased risk of chronicity and progression to cirrhosis
- HBV related liver disease may also worsen HIV progression
  
  - SMART study demonstrated more rapid progression to low CD4 in coinfect ed patients randomized to drug conservation
- Coinfected patients can develop flares at initiation of antiretroviral therapy (ART), with changes in ART, or with worsening of immune status
Case 1: HBV prevention

- A 48 year old business man who has recently transferred care presents for routine follow up. He is receiving TDF/FTC/EFV and HIV RNA is not detected. CD4 is 186 cells/µL which he says is typical for him as he had a nadir <50. He received the hepatitis B vaccine about 5 years ago, a year after he initiated HIV care. Labs are as follows:
  - Hepatitis B surface antibody (HBsAb) 4 IU/mL
  - Hepatitis B surface antigen (HBsAg) negative
  - Hepatitis A antibody negative

Case 1 cont.

- Which of the following would you recommend to him?
  A. Obtain further history to determine risk factors and, if demonstrable risk, vaccinate with Twinrix (3 dose series)
  B. Obtain further history, and if demonstrable risk vaccinate with hepatitis A (2 dose series) and hepatitis B 40mcg/mL (4 dose series)
  C. Vaccinate with hepatitis A (2 dose series) and hepatitis B 40mcg/mL (3 dose series)
  D. No indication for re-vaccination given low CD4
HBV screening among HIV-infected persons

- All patients with HIV should have HBsAg and HBsAb tested at care presentation
  - Routine testing of hepatitis B core antibody (HBcAb) is controversial but many HIV experts recommend this; will discuss further
- Levels of HBsAb < 10 IU/mL are considered negative
  - All patients with HIV are recommended for HBV vaccination
  - Hepatitis A vaccination is still risk-based (MSM, foreign travel) even among those with HIV

Response to HBV vaccine in HIV coinfection

- Compared with 90% of the general population, about 40-70% of HIV-infected persons are expected to respond to the HBV vaccine
- At least 4 studies have demonstrated increased vaccine response with higher doses/more doses of vaccine; 1 study showed no difference
- Suppressed viral load and CD4 count (>200 or >350) significantly associated with seroconversion
Clinical trials of response to high dose vs. standard dose HBV vaccine among HIV coinfected patients

Current CDC HBV vaccination guidelines for coinfected patients

- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive
  1 dose of 40 mcg/mL (Recombivax HB) administered on a 3-dose schedule at 0, 1, and 6 months or
  2 doses of 20 mcg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 months

Figure 1: Odds ratios (OR) and 95% CIs of individual studies and pooled OR from the fixed-effects model for response rates of the increased dose vaccination compared with standard dose vaccination in HIV-infected patients in this meta-analysis.
Does ART prevent HBV infection?

- Chun et al followed 1885 HIV-infected patients, HBV-uninfected patients between 1998-2008
  - 9.7% (181) developed HBV infection, 2.0% (37) chronic
  - Previous receipt of >1 dose of HBV vaccine and any HBV-active ART were both significantly protective against HBV infection
  - Greatest risk of infection was male gender (HR 8.8)

Significance of positive HBCaAb in HIV-infected patients

- Isolated HBCaAb [HBCaAb positive with all other markers negative (I-HBCaAb)] common in patients with HIV (15-30%)
- Controversial significance
  - Past HBV infection with loss of HBsAb
  - Autoimmune phenomenon
- Typically associated with low or undetectable levels of HBV DNA
- Has been associated with reactivations in severe immune compromised state
  - 17 (11.1%) of 150 patients with I-HBCaAB and lymphoma in Taiwan developed HBV viremia during chemotherapy; 4 with severe, life-threatening disease (Hsu, C., et al. (2014). "Hepatology 59(6): 2092-2100")
Significance of positive isolated HBcAb in HIV-infected patients cont.

- Many HIV specialists recommend checking HBcAb in all HIV-infected patients and assuring that at least one agent active against HBV is using in their ART
  - Some recommend assessing baseline HBV DNA levels in these patients
- Many experts also recommend that this pattern should be assessed prior to chemotherapy in ALL patients regardless of HIV status
- Patients who are I-HBcAb positive and HIV coinfection should preferentially receive dual-active therapy against HBV
- Patients with I-HBcAb should be vaccinated against HBV

Additional investigations for patients with HBV infection

- HBeAg and HBeAb
- HBcAb (if not already done)
- HBV DNA
- Hepatitis delta antigen
- Full measure of hepatic inflammatory and synthetic function
- Consideration of liver biopsy or non-invasive measure of hepatic fibrosis
  - Transient elastography increasingly used to assess fibrosis in this population. Better validated for HCV but has some role in HBV monoinfection
Natural history of HBV infection

HBV exists in 9 genotypes A-I. Associations exist between genotypes and progression, response to therapy however specific genotype-based guidelines are not yet available.

Characterization of Common Hepatitis B Virus (HBV) Serologic Test Result Patterns and recommendation

<table>
<thead>
<tr>
<th>Characterization of Test Result</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Occult HBV infection</td>
<td>HBcAb+, HbcAg- Detectable HBV DNA, usually low levels (&lt;10,000 copies/mL) Generally benign course unless severe immune suppression Treat coinfected patients with at least 1 HBV-active agent and preferably 2.</td>
</tr>
<tr>
<td>Chronic carrier (inactive carrier state)</td>
<td>HBsAg+, may be HBcAb- HVB not detected or low level (&lt;10,000 copies/mL) Treat coinfected patients with at least 1 HBV-active agent and preferably 2.</td>
</tr>
<tr>
<td>Immune tolerant HBeAg-seropositive hepatitis</td>
<td>HbsAg+, HbcAg- Generally normal AST/ALT and no evidence of fibrosis. Found often in early stage adult and perinatally/childhood acquired infection. Definitely treat coinfected patients with 2 active agents and tenfuro should preferentially remain in their regimen.</td>
</tr>
<tr>
<td>Chronic active HBeAg-seropositive hepatitis</td>
<td>High HBV DNA and signs of hepatic inflammation, possibly fibrosis/cirrhosis. Definitely treat coinfected patients with 2 active agents and tenfuro should preferentially remain in their regimen.</td>
</tr>
<tr>
<td>Chronic active HBeAg-seronegative hepatitis</td>
<td>HBsAg+, HbcAg-, HbcAb- Low to moderately high HBV DNA but high risk of cirrhosis, fibrosis, and elevated risk of hepatocellular carcinoma. Definitely treat coinfected patients with 2 active agents and tenfuro should preferentially remain in their regimen.</td>
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</table>
Treatment of patients with HBV

- Algorithms available from American Association for the Study of Liver Diseases (last update 2009) for monoinfected patients
- Interferon has been associated with seroconversion to HBeAb positivity and control of viremia
  - Overall less popular choice in the era of well tolerated oral agents
  - Some efficacy demonstrated in HIV coinfected patients but rarely indicated
- **Strong recommendation for treatment of all HIV/HBV coinfected patients at the time of diagnosis with fully suppressive ART that includes 2 nucleos(t)ides active against HBV**

Oral agents for treatment of HBV (1)

- **Entecavir**
  - One of the preferred agents for HBV monotherapy due to its low barrier to resistance but only partially active against HIV
  - Associated with development of M184V when used outside of a fully suppressive ART regimen
  - Patients with HBV resistance to lamivudine often also have resistance to entecavir
- **Lamivudine**
  - Monotherapy associated with a high likelihood of resistance over 1-5 years of therapy (as much as 90% in U.S. patients)
- **Emtricitabine**
  - Development of resistance also common with monotherapy however more potent that 3TC
- **Telbivudine**
  - Less commonly used; theoretically may elicit M184V but not demonstrated to do so
Oral agents for the treatment of HBV (2)

- **Tenofovir**
  - Has become the mainstay of oral therapy for HBV
  - Effective as monotherapy
    - Mixed data on superiority as part of combination therapy with lamivudine, emtricitabine, or entecavir
  - Head-to-head with entecavir demonstrates similar to superior viral efficacy
  - NO drug resistance for patients on therapy after up to 7 years (!!!)
  - Rare renal insufficiency/tubulopathy primary effect limiting its use

- **Adefovir**
  - Similar mechanism of action, efficacy and side effects to tenofovir; little reason to use in coinfected population

Hepatic flare after ART initiation

- 25-30% of HIV/HBV coinfected patients exhibit a transient rise in serum AST and ALT with initiation of ART with at least one active agent against HBV
  - Typical range from Grade I – II
    - Transaminases 5x ULN were common in Thai study (*Matthews et al, Hepatology*, Vol. 48, No. 4, 2008)
  - Mean 56 days post ART initiation
  - May coincide with development of HBeAb
  - *Can occur more frequently and be more severe if ART without activity against HBV is initiated*
Hepatic flare after withdrawal of ART

- 2008 Swiss cohort study analyzed liver function/inflammation tests after withdrawal of lamivudine in 109 coinfected patients
  - 42 (29%) developed elevation in transaminases to at least 2x ULN
    - 3 had Grade III
    - 5 had Grade IV
    - 3 fulminant hepatitis including 1 death


Transitioning patients with HBV on ART

- Patients with HBV who require changes in/discontinuation of ART should remain on at least 1 agent active against HBV at all times
- Telbivudine has been proposed as an option in the event that all active ART needs to be discontinued due to questions about drug toxicity or drug resistance—however this would rarely be indicated
Trajectory of HBV virologic suppression in coinfectected patients

- HBV DNA in the millions is common, especially in the setting of HBeAg positivity
- Time to undetectable typically 1 year and can be longer

Serologic response to treatment in HIV/HBV coinfection

- HBeAg seroconversion ranges from 5-30% over 2-5 years of continuous therapy in coinfectected patients
- HBsAg loss occurs in 8-30%
- HBsAb seroconversion rare (1-2%)

(Kosi, L., et al. (2012); J Viral Hepat 19(11): 801-810)
Case 2-HBV viremia in a coinfected patient

- You are seeing a patient who has HBeAg-positive HBV and HIV infection who has been taking elvitegravir/cobicistat/tenofovir/emtricitabine for 2.5 years. Her HBV level was $10^6$ copies/mL prior to the initiation of therapy and her CD4+ cell count was 190 cells/µL. After 11 months of therapy, her HBV level became undetectable and remained so for 12 months. Recently, she was noted to have an HBV DNA of 1693 while her HIV RNA level was undetectable.

Case 2- cont.

- What should your next steps be?
  A. Inform the patient that she likely has resistance to tenofovir and add entecavir to her current ART regimen
  B. Continue current therapy but perform genotypic resistance testing for HBV
  C. Perform testing for anti-Hbe
  D. Continue current therapy and reassess the patient’s HBV level in 3 months while encouraging adherence
Persistent viremia on dual active oral therapy


Fig. 1. Flow chart of HBV replication profiles.

Case 3 – medication intolerance

- A 38 year old man with HIV/HBV coinfection initiates ART with Truvada and dolutegravir
- Baseline viral load for HIV is 628,000 copies/mL and for HBV is 2.38 million copies/mL
- Six months after ART initiation, HIV RNA is not detected and HBV DNA is 8000 copies/mL.
- Creatinine is found to have increased from 1.0 to 1.3 and the patient exhibits proteinuria, phosphaturia and glycosuria
  - GFR by Cockcroft-Gault equation is 56
Case 3 cont.

- What is the next best step?
  - A. Change the Truvada to every other day and continue dolutegravir at the current dose
  - B. Continue current regimen with cautious renal monitoring
  - C. Change to ABC + 3TC + entecavir 50mg daily + dolutegravir
  - D. Change to ABC + 3TC + entecavir 50mg BID + dolutegravir
  - E. Change to Triumeq (ABC/3TC/dolutegravir)

Medication intolerance cont.

- Entecavir is the preferred option for HBV therapy after tenofovir
- Development of resistance may occur over a period of years but is significantly less common than with lamivudine or emtricitabine alone
- Entecavir needs to be given as part of a fully suppressive regimen for HIV
- Patients who have had any documented HBV resistance to lamivudine or those with cirrhosis should receive twice daily dosing
- Interferon may be an option for patients who are intolerant to all HBV-active nucleos(t)ides
Tenofovir drug resistance in HIV

- *Tenofovir is the optimal agent for treatment of chronic HBV and resistance has not been documented*
- Patients with HIV/HBV coinfection and history of HBV viremia who develop HIV resistance with a K65R while on tenofovir should remain on tenofovir even if it is not used as part of their HIV active regimen
- If the patient has NEVER had documented HBV viremia, using 3TC or FTC is the only active agent against HBV is probably reasonable

Long term outcomes on oral therapy for HBV

- Regression of fibrosis and cirrhosis can occur with long term tenofovir therapy for HBV
  - 70-80% of patients demonstrate improvement in fibrosis measured by biopsy over 3-5 years of therapy
  - 50-80% of patients demonstrate regression of cirrhosis
    - In one monoinfection study, 71 (74%) of 96 patients with cirrhosis no longer had cirrhosis at 5 years
    - 3 of 252 (1.1%) without cirrhosis at baseline progressed to cirrhosis

Hepatocellular carcinoma (HCC) and HBV

- Early data from Taiwan demonstrated HCC incidence of 11.6/1000 among HBsAg positive patients not receiving therapy (Beasley et al, Lancet. Volume 318, Issue 8256, 21 November 1981, 1129–1133)
- Incidence in the era of oral therapy has declined to 2-3/1000 with much higher rates among patients with cirrhosis (2-3/100)
- Few data available for coinfectected patients
- Higher levels of viremia, earlier age at infection, origin from an HBV endemic country, male gender all associated with increased risk of HCC
  - New emergence of lamivudine resistance has also been associated with development of HCC
- Currently annual ultrasound is recommended for all chronically infected patients
HIV/HBV coinfection globally

- About 3.5 million coinfected individuals worldwide
- Not all countries routinely screen HIV-infected individuals prior to ART
- Not all countries start tenofovir-based regimens as first line ART
- What is the significance of lamivudine resistance in this population?
  - Genotypes more commonly found in East Africa previously thought to be associated with lower levels of HBV DNA

A few data from Moshi, Tanzania

- 431 patients
  - 2 largest treatment centers in Northern Tanzania
  - Tested with HBsAg with reflex to HBV DNA & HBeAg for positives between 2010-2011
  - Average time on ART was 2.8 years
  - Most common regimen was AZT/3TC/NVP
    - What was the prevalence of HBsAg+?
    - How many would have HBV viremia on regimens with 3TC as the only active agent against HBV?
Brief assessment of suspected lamivudine resistance in Northern Tanzania, results

- 29 (6.7%) were HBsAg positive
  - 9.8% if indeterminates included
  - All positives and indeterminates were sent for HBV DNA and HBeAg
  - ART history and HIV RNA was recorded

Results, cont.

All of these patients had undetectable HIV RNA

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>TDF + 3TC or FTC</th>
<th>3TC only</th>
<th>no HBV active agents</th>
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<tr>
<td>not detected or detected &lt;20IU/mL</td>
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<td>10^2-10^5</td>
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<td>10^6 and above</td>
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Results, cont.

- 1/3 of HBsAg positive patients in Tanzania had detectable HBV viremia while on ART for HIV
- Treatment with tenofovir eliminated high grade viremia
- Simple HBV screen highly recommended in this population

Summary

- Hepatitis B prevention remains important with thousands of incident cases/year in the U.S.
  - High dose vaccine regimens, vaccination while virologically suppressed, and re-vaccination promote immunity in persons with HIV
- Hepatitis B affects approximately 1/20 HIV-infected patients in the U.S.
Summary cont.

- Consider routine testing of hepatitis B core Ab in HIV-infected patients
  - Definitive testing if chemotherapy is indicated
- Perform HBV DNA and HBeAg on all HBsAg positive patients
- Immediate treatment of all coinfected patients; dual active therapy is optimal
- Anticipate elevation in AST/ALT in 1/3 of patients after ART start

Summary, cont.

- Avoid withdrawal of HBV active agents once initiated
- Entecavir can be added to a fully suppressive regimen in TDF-intolerant patients
- Patients whose HIV is resistant to TDF should generally stay on it for HBV
- Chronic or slow-to-respond viremia may occur
- Screen regularly for HCC
- Cirrhosis can regress after treatment
Questions?