

# ICAP GRAND ROUNDS WEBINAR

## **An Overview of HIV-Hepatitis B Co-infection**

**Oladipo Alao, MD, MPH  
Clinical Advisor  
ICAP, NY**

**30 September 2010**

# Objectives-1

- **Describe the current burden of Hepatitis B virus (HBV) co-infection among HIV infected patients across sub-Saharan Africa;**
- **Explain how HBV co-infection impacts HIV disease, and how HIV infection impacts HBV disease progression;**
- **Describe clinical syndromes associated with HBV infection;**

# Objectives-2

- **Discuss an approach to diagnosis of HBV among HIV- infected patients (including those in resource-limited settings [RLS]);**
- **Discuss on-going monitoring of HIV/HBV co-infected patients;**
- **Review eligibility of HIV-HBV co-infected patients for HBV treatment;**
- **Discuss issues around co-infection in special populations (e.g., pregnant women);**
- **Describe HBV prevention strategies for HIV-infected patients**

# Outline

- **Background and epidemiology;**
- **Impact of HBV co-infection on HIV disease progression and impact of HIV on HBV progression;**
- **Clinical syndromes;**
- **Diagnosis and treatment eligibility;**
- **Treatment and monitoring of HIV-HBV co-infection;**
- **Prevention of HBV**

# Background and Epidemiology

- Chronic HBV (persistence of HBV surface antigen, HBsAg for greater than 6 months);
- Worldwide, 33.4 million PLWHIV and 350 million people with HBV (WHO);
- 5-10% ( 2-4 million) of HIV-infected patients are co-infected with HBV<sup>1</sup> ;
- In areas with high endemicity (>8% HBsAg), including sub-Saharan Africa, HBV may be no more prevalent in HIV-infected individuals compared with the HIV uninfected<sup>2</sup> (because of transmission early in life).

# Background and Epidemiology

- Less prenatal, more early childhood transmission in sub-Saharan Africa vs. East and SE Asia;
- attributed to lower prevalence of HBeAg+ disease<sup>2</sup>;
- Paucity of data and little evidence of higher prevalence of HIV-HBV co-infection in children<sup>3,4</sup>;
- Data suggests prevalence of HBV among HIV infected individuals varies widely (2.4 - 25.9%) compared with HIV uninfected individuals (5.4-14.3%) in sub-Saharan Africa<sup>5-10</sup>;
- Higher prevalence of HBV observed in studies that tested for occult HBV infection (HBsAg- HBV DNA+).<sup>7</sup>

# Impact of HBV Co-infection on HIV Disease Progression

- HBV does not appear to affect the course of HIV disease significantly
- HBV had no impact on new AIDS diagnosis, % with HIV viral suppression and increases in CD4 counts after 6 to 12 months of HAART.<sup>11, 12</sup> (low endemic area)
- In a study from Taiwan, co-infected patients had similar risks new HIV related opportunistic illnesses, similar increases in CD4 counts after 6-12 months of HAART, increased risks of virologic failure and death.<sup>13</sup>

# Impact of HIV

- Acute HBV eliminated in 95% of HIV-uninfected adults but (3-6x) increased risk of progression to chronic HBV in persons with HIV infection<sup>12</sup>;
- Lower risk of spontaneous loss of HbsAg and HbeAg, also higher risk of reactivation of HBV;
- Co-infected patients have increased risk of liver fibrosis, cirrhosis, hepatocellular carcinoma and liver-related death(17x);
- HBV-related liver disease due to immunological response. HIV may minimize this response;
- Immune reconstitution with HAART could be favorable or deleterious: HbsAg and HbeAg seroconversion vs. hepatitis and progressive liver damage (more common with advanced immunosuppression [CD4<200]).<sup>11</sup>

# Clinical Syndromes

- **Acute HBV:**
  - Most patients with acute or chronic HBV are asymptomatic;
  - Incubation period about 1 to 6 months (mean=90 days)
  - Symptoms of acute HBV may include fatigue, RUQ abdominal pain, nausea, vomiting, fever, arthralgias, jaundice;
  - Clinical recovery takes about 6 weeks though laboratory abnormalities may persist;
  - Younger age at the time of acute HBV is associated with a higher risk progression to chronic HBV.<sup>2</sup>

**Table 1: Spectrum of Hepatitis B infection: serologic and virologic patterns<sup>14</sup>**

Stage	HbsAg	HbsAb	HbcAb IgG	HbcAb IgM	HbeAg	HbeAb	HBV DNA (viral load)
Incubation	+	-	-	-	+/-	-	Low
Acute hepatitis B	+	-	+	+	+	-	High
HbsAg-negative Acute hepatitis B	-	-	+	+	+/-	-	High
Inactive carrier	+	-	+	+/-	-	+	Low
Precore mutant	+	-	+/-	+/-	-	+	High
Occult Infection	-	-	+	+/-	-	-	High or Low
Chronic hepatitis B	+	-	+	+/-	+/-	-	High or Low
Resolved Infection	-	+	+	+/-	-	-	-
Vaccination	-	+	-	-	-	-	-

# Chronic HBV

- Persistence of HbsAg for more than 6 months
- Asymptomatic/non specific symptoms;
- Spectrum: an immune-tolerant phase, an immune-active phase, an inactive carrier phase, a phase of reactivation of HBV and occult HBV
- Transition to the inactive carrier phase occurs at the rate of 8-15%/year in HBV mono-infected patients but much less frequently among HIV-HBV co-infected patients<sup>2</sup>;
- Reactivation of HBV and occult HBV appear to occur more common among HIV-HBV co-infected individuals.

# Chronic HBV

- **Chronic (active) HBV can be categorized by HBV replication (associated with HbeAg):**
  - **HbeAg positive disease, which is associated with high replication, high levels of HbsAg, HBV DNA and liver enzymes (ALT);**
  - **HbeAg negative disease, associated with low levels of HbsAg, HBV DNA and low or normal liver enzymes (a variant of HbeAg negative disease 'pre-core mutant' is associated with high HBV DNA levels).**

# Screening

- Routine testing for HBV in all HIV patients is desirable, especially before starting ART;
- Test for HBsAg, HBcAb, and HBsAb;
- Unclear if routine testing for HbsAg in patients starting ART will prove cost effective in RLS (cost, high % of occult HBV);
- Targeted HbsAg testing of certain groups about to start ART (e.g., ↑ALT, pregnant women, etc.) may be an alternative, yet untested, strategy.

# Initial Laboratory Tests

- **Test for HbeAg, HbeAb, HBV DNA to determine phase of disease (see: Table 1);**
- **Hematocrit, platelet count, ALT, albumin, PT, bilirubin, AFP at baseline and every 6 months (ultrasound annually);**
- **Screen for hepatitis A virus (HAV) and vaccinate if non-immune.**

**Table 1: Spectrum of Hepatitis B infection: serologic and virologic patterns<sup>14</sup>**

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HbsAg-negative Acute hepatitis B	-	-	+	+	+/-	-	High
Inactive carrier	+	-	+	+/-	-	+	Low
Precore mutant	+	-	+/-	+/-	-	+	High
Occult Infection	-	-	+	+/-	-	-	High or Low
Chronic hepatitis B	+	-	+	+/-	+/-	-	High or Low
Resolved Infection	-	+	+	+/-	-	-	-
Vaccination	-	+	-	-	-	-	-

# Determination of Hepatitis B treatment eligibility

- HBV treatment is indicated in HIV-HBV co-infected patients when ALT is elevated and HBV DNA > 2,000 IU/mL (irrespective of HbeAg status) <sup>18</sup> ;
- Liver biopsy is indicated to determine treatment eligibility in the absence of either (significant fibrosis may be present);
- When determination of HBV DNA may not be possible and liver biopsy may not be feasible, treatment decisions may have to be made based on ALT alone.

# Goals of therapy

- HbsAg seroconversion;
  - HbeAg seroconversion;
  - ALT normalization;
  - Improvement in liver histology;
  - Sustained suppression of serum HBV DNA;
- Treatment is more likely to be successful with:
- positive HbeAg
  - low serum HBV DNA
  - elevated ALT
- (all three are less common in HIV-HBV co-infected patients)<sup>18</sup>.

# Treatment of HIV-HBV Co-infection-1

- According to WHO guidelines<sup>17</sup>, ART indicated in all HIV-HBV co-infected patients who require HBV treatment irrespective of CD4 counts;
- Treatment with an HIV regimen with at least two HBV-active agents (lamivudine [3TC] or emtricitabine [FTC] with tenofovir [TDF]) is recommended;
- Pegylated interferon alpha-2a (for 48 weeks), an alternative if a patient declines ART, is associated with lower rates of success and higher rates of toxicity among HIV-HBV co-infected patients.<sup>18</sup>

# Treatment of HIV-HBV Co-infection-2

- Adefovir and entecavir are also options for HBV therapy;
- None of these therapies should be used in the absence of suppressive combination ART regimens because of possible HIV ART resistance mutations.

# Treatment of HIV-HBV

## Co-infected Patients in Pregnancy-1

- Routine testing for HBV (with HbsAg) should be considered for HIV infected pregnant women;
- Treatment with an HIV regimen with at least two HBV-active agents, lamivudine with tenofovir, should be considered in pregnant women with HIV-HBV co-infection;
- When ART is not indicated, prophylaxis with a regimen containing only one HBV-active agent (lamivudine) should be avoided because of the risk of selecting lamivudine-resistant HBV;

# Treatment of HIV-HBV

## Co-infected Patients in Pregnancy-2

- When ART with an HBV active agents is employed for prophylaxis, discontinuation post-partum may result in acute hepatitis;
- If ART is prescribed for prophylaxis then close clinical and laboratory monitoring is indicated if/when discontinued post-partum;
- Hepatitis B immune globulin (and vaccine) should be administered to infants born to mothers with HIV-HBV co-infection within 12 hours of delivery.

# Monitoring Treatment Response

- After initiation of HBV treatment; HBV DNA levels, ALT, HbeAg and HbsAg seroconversion should be assessed at least every 6 months<sup>14</sup>;
- ALT elevation may suggest one of the following<sup>18</sup>:
  - ART related drug injury;
  - immune reconstitution (HbSAg positive patients);
  - HbeAg/HbsAg seroconversion;
  - HBV reactivation (in patients who have resolved HBV infection or are inactive carriers);
  - HBV drug resistance;
  - super infection with Hepatitis A, C or D (Delta) virus.

These possibilities should be considered and ruled-out with additional tests (may not be possible in RLS).

# Counseling

- All HBV patients should avoid alcohol intake (no safe threshold established);
- Counseling about risk for transmission to household, sexual, and needle-sharing contacts;
- should avoid sharing potentially contaminated objects such as razors, needles and toothbrushes;
- Use of effective barrier protection (latex condoms) should be encouraged;
- Household contacts should be offered vaccination.

# Prevention of HBV infection

- **Vaccinate all HIV-infected patients without evidence of prior immunity;**
- **Response suboptimal at lower CD4 counts but do not defer;**
- **If no response, consider revaccination (double dose?, at higher CD4 counts?).**

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