HIV and Hepatitis B Coinfection

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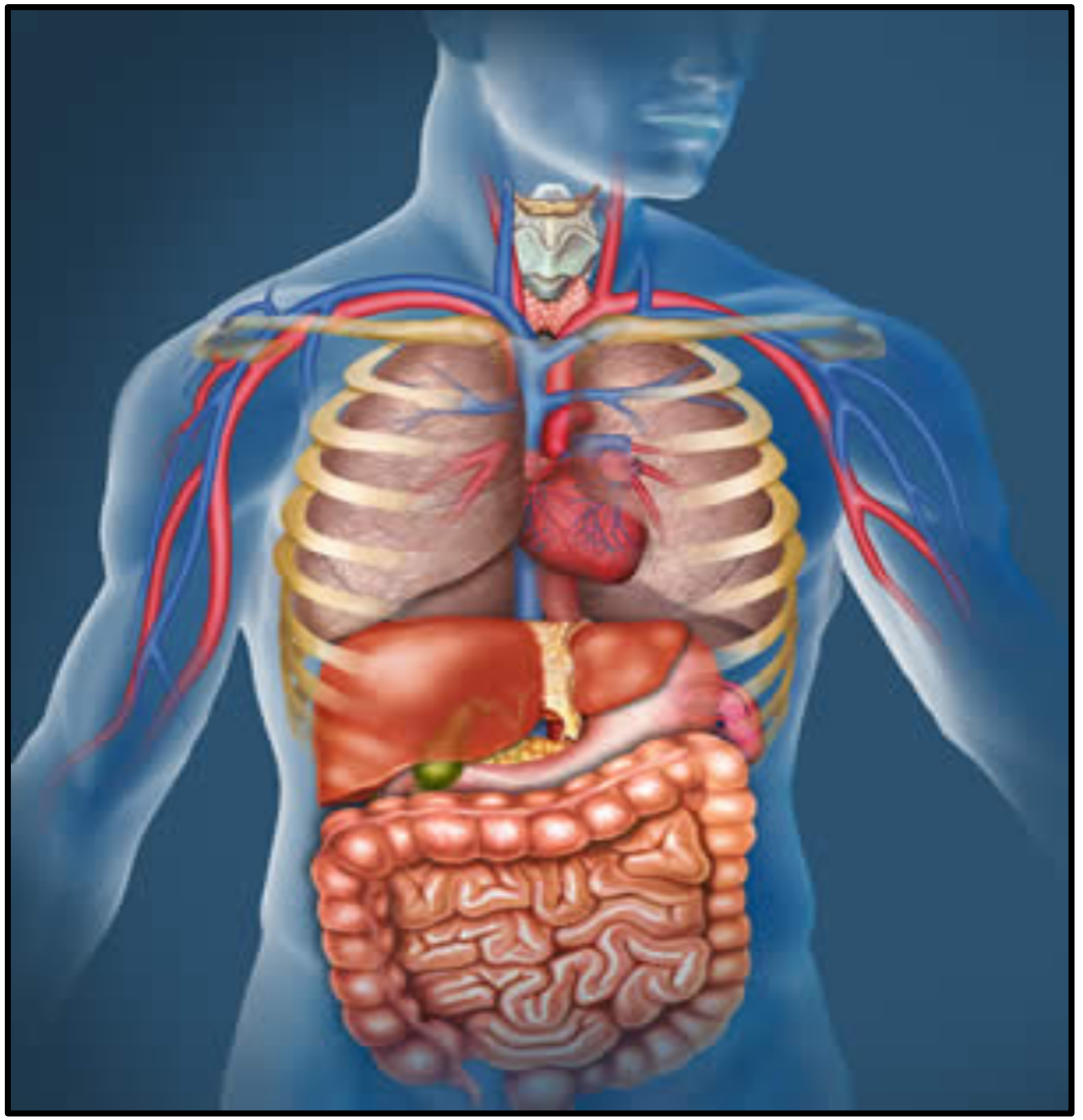
HIV and Hepatitis B Coinfection



Hepatitis B Epidemiology

- **Hepatitis B virus is the leading cause of chronic liver disease worldwide**
  - **Globally- estimated 240 million persons have chronic Hepatitis B (CHB)**
    - Prevalence highest in Africa and Asia
  - **United States**
    - Survey between 1999-2008 identified approximately 704,000 adults with CHB
    - After adjusting for foreign-born persons for hepatitis B infection, the upper estimated of CHB in the US may be as high as 2.2 million
  - **Global deaths from cirrhosis and hepatocellular carcinoma (HCC) are estimated at 310,000 and 340,000 per year, respectively.**
  - **Approximately 10% of HIV infected patients have evidence of CHB**

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full
https://www.cdc.gov/hepatitis/hbv/bfaq.htm#bFAQc09

Modes of Transmission

- **High Prevalence countries**
  - Perinatal
  - Childhood exposure
- **Low Prevalence countries**
  - Sexual contact
  - Injection Drug Use (IDU)
- **HBV is transmitted more efficiently than HIV by 100 fold**
  - HBV virus remains viable outside the host for up to 7 days

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full
https://www.cdc.gov/hepatitis/hbv/bfaq.htm#bFAQc09

Risk of Progression to CHB

- **Varies with age**
  - <1 year, 90%
  - 1-5 years of age, 20-50%
  - Adults, <5%
- **Hepatitis B genotypes identified (A-J)**
  - Genotype A is most common in North America, and Western Europe

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Clinical Manifestations – Acute Infection

- **~70% of patients with acute HBV are asymptomatic**
- **<1% of patients develop hepatic failure**

- **Typical Symptoms of acute HBV include:**
  - RUQ abdominal pain
  - Nausea
  - Vomiting
  - Fever
  - Arthralgia with or without jaundice

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Clinical Manifestations – Chronic Infection

- **HBV incubation phase**
  - 90 days (range 60-150 days) from exposure to onset of jaundice AND 60 days (range 40-90 days) from exposure to onset of abnormal liver enzymes
- **Most patients with CHB will clinically present:**
  - Asymptomatic
  - Non specific symptoms, i.e. fatigue
- **15-40% of Patients with CHB**
  - Cirrhosis
  - Hepatocellular carcinoma (HCC)
  - Liver failure
- **25% of people die prematurely from complications of CHB**

Baseline Labs for Person with HIV (PWH)

- **The following laboratory tests performed during the initial patient visit can be used to stage HIV disease and to assist in the selection of antiretroviral therapy (ART):**
  - HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) (AI);
  - CD4 T-cell count (CD4 count) (AI);
  - Plasma HIV RNA (viral load) (AI)

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/baseline-evaluation?view=full

Baseline Labs in Person with HIV (PWH) cont.

- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN), and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses (AIII);
- Fasting blood glucose and serum lipids (AIII); and
- Genotypic resistance testing at entry into care, regardless of whether ART will be initiated immediately (AII).
  - For patients who have HIV RNA levels <500 to 1,000 copies/mL, viral amplification for resistance testing may not always be successful (BII)

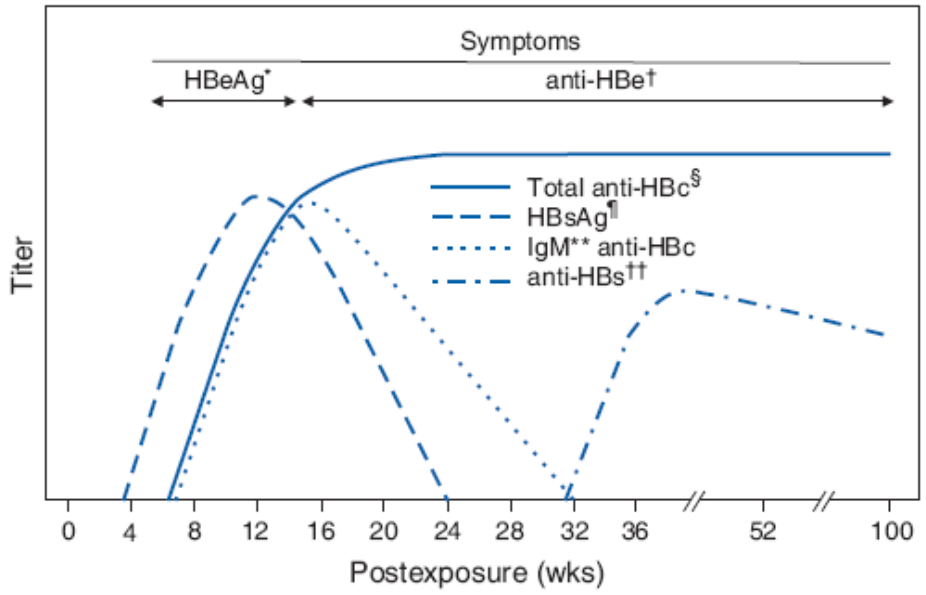
https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/baseline-evaluation?view=full

Interpretation of Hepatitis B Serologic Test Results

- **Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV) specific antigens and antibodies**
  - **Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient:**
    - Has acute or chronic HBV infection
    - Is immune to HBV as a result of prior infection or vaccination, or
    - Is susceptible to infection

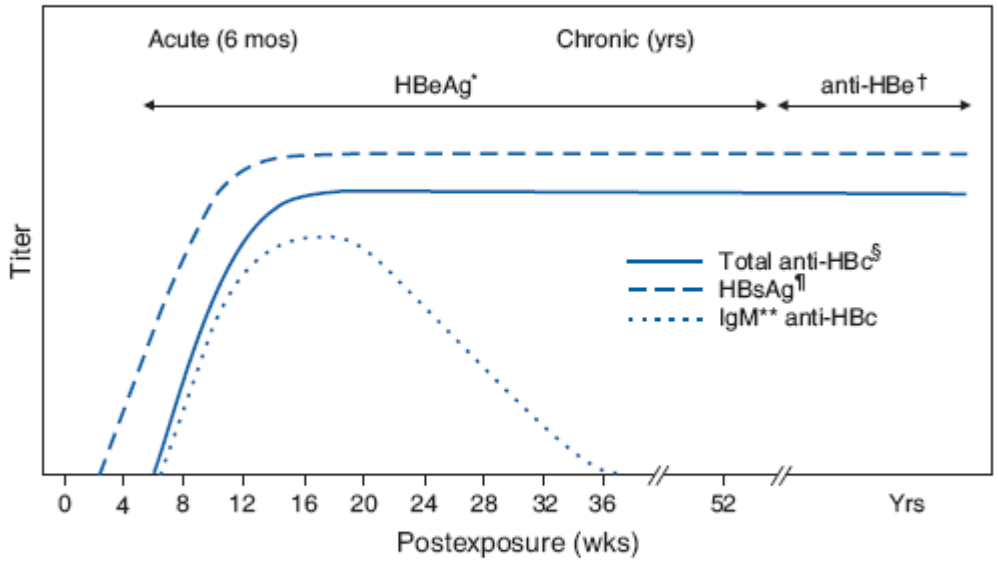
Hepatitis B Serology Overview

FIGURE 1. Typical serologic course of acute hepatitis B virus infection with recovery



* Hepatitis B e antigen.
† Antibody to HBeAg.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
** Immunoglobulin M.
†† Antibody to HBsAg.

FIGURE 2. Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection



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Centers for Disease Control and Prevention. (2008, September 19). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *Morbidity and Mortality Weekly Reports.* Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm

Interpreting Hepatitis B Serologic Test Results

- **Hepatitis B surface antigen (HBsAg):**
  - A protein on the surface of hepatitis B virus
  - It can be detected in high levels in serum during acute or chronic hepatitis B virus infection
- **The presence of HBsAg indicates that the person is infectious**
  - The body normally produces antibodies to HBsAg as part of the normal immune response to infection
  - HBsAg is the antigen used to make hepatitis B vaccine

Interpreting Hepatitis B Serologic Test Results

- **Hepatitis B surface antibody (anti-HBs):**
  - The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection
  - Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B

Interpreting Hepatitis B Serologic Test Results

- **Total hepatitis B core antibody (anti-HBc):**
  - The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame
  - Appears at the onset of symptoms in acute hepatitis B and persists for life

Interpreting Hepatitis B Serologic Test Results

- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):**
  - Positivity indicates recent infection with hepatitis B virus (<6 mos)
  - Its presence indicates acute infection

Interpreting Hepatitis B Serologic Test Results

Serology	Result	Interpretation
HBsAg anti-HBc anti-HBs	negative negative negative	Susceptible
HBsAg anti-HBc anti-HBs	negative positive positive	Immune due to natural infection
HBsAg anti-HBc anti-HBs	negative negative positive	Immune due to hepatitis B vaccination
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive positive negative	Acute infection

www.cdc.gov/hepatitis

Interpreting Hepatitis B Serologic Test Results

Serology	Result	Interpretation
HBsAg anti-HBc IgM anti-HBc anti-HBs	positive positive negative negative	Chronic Infection
HBsAg anti-HBc anti-HBs	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. “Low level” chronic infection 4. Resolving acute infection

www.cdc.gov/hepatitis

Hepatitis B Acute Infection

- **HBsAg**
  - Can be detected in 4 weeks (range 1-9 weeks) after exposure
- **Anti-HBc IgM**
  - Usually detected at onset of symptoms

Hepatitis B Chronic Infection

- **Characterized by persistent HBsAg; 2 occasions at least 6 months apart**
  - Further testing is warranted
  - Check HBV e-antigen (HBeAg)
  - Check antibody to HBeAg (anti-HBe)
  - Check HBV DNA
- **Active disease**
  - HBeAg negative or HBeAg positive
  - Can be distinguished from inactive disease by the presence of serum HBV DNA and persistent or fluctuating alanine transaminase (ALT) elevations

Hepatitis B Chronic Infection

- **Patients whose past infections are resolved**
  - HBsAg negative
  - Anti-HBs positive and/or anti-HBc
- **Although covalently closed circular DNA (cccDNA) may remain in hepatocyte nuclei**
  - **Patient may become HBsAg positive again**
  - **HBV viremia may occur under severe immune suppression**
    - Rituximab therapy
    - After stem cell transplant

Hepatitis B Chronic Infection

- **Isolated anti-HBc positive result**
  - Usually represents past HBV infection with subsequent loss of anti-HBS
  - Occurs in 7-19% of of PWH
  - Incidence of HBV viremia in PWH with the isolated anti-HBc pattern ranges from 1-36%
- **Clinical Significance of isolated anti-HBc**
  - Unknown
  - May indicate chronic or, more likely resolved infection in PWH
  - In low prevalence countries, i.e. U.S.A., may represent a false positive
  - ↑ frequency in PWH with underlying HCV coinfection

Clinical Features in HIV/HBV Coinfection

- **HIV coinfection with Hepatitis B compared to mono-infected HBV**
  - ↑ levels of HBV viremia
  - ↓ likelihood of resolved infection following acute HBV infection
  - More likely to have detectable HBeAg
  - ↓ rates of seroconversion to anti-HBe
  - ↑ risk of HCC
  - ↑ risk of liver related mortality and morbidity

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Exposure to Hepatitis B Virus

- **Hepatitis B Virus transmission**
  - Percutaneous
  - Mucosal exposure to infectious blood or body fluids
- **Persons with HIV**
  - **Counsel about transmission risks for HBV**
  - **Encourage patients to avoid behaviors associated with HBV transmission**
    - Sexual transmission
    - Sharing needles and syringes
    - Body-piercing

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Hepatitis B Infection

- **Recommended screening**
  - All family members of patients with HBV
  - Sexual contacts of patients with HBV
- **Recommended HBV Vaccination**
  - All susceptible contacts of patients with HBV regardless of HIV status
- **Hepatitis B vaccination is the <u>MOST EFFECTIVE WAY</u> to prevent HBV infection and its consequences**
- **All PWH who are susceptible to HBV**
  - Should receive hepatitis B vaccine series
  - May receive combined hepatitis A and hepatitis b vaccine

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Hepatitis B Infection

- **Screening tests include:**
  - HBsAg
  - Anti-HBs
  - Anti-HBc
- **Patients with seropositive anti-HBc and anti-HBs has resolved infection**
  - Do not need vaccination
- **Patients with presence of anti-HBs alone at levels ≥ 10 IU/mL, consistent with seroprotection, usually from vaccination**
  - Do not need vaccination

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Hepatitis B Infection

- **PWH with isolated anti-HBc pattern: HBsAg -, anti-HBc +, anti-HBs –**
  - **False positive**
  - **May signify distant infection with subsequent loss of anti-HBs**
  - **Usually HBV DNA-negative and not immune to HBV infection**
    - Therefore routine checking of HBV DNA is not recommended
- **Recommend 1 standard dose of hepatitis B vaccine**
  - Check anti-HBs titers in 1-2 months
  - If anti-HBs titer > 100 IU/mL, no further vaccination
  - If anti-HBs titer < 100 IU/mL, a complete series of HBV vaccine (single or double dose) should be completed followed by anti-HBs testing

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Hepatitis B Infection

- **Adult PWH**
  - Magnitude and duration of immunogenicity to Hepatitis B vaccine is significantly lower compared to healthy adults without HIV
- **Factors associated with poor response**
  - ↓ CD4 counts
  - Detectable HIV RNA
  - Coinfection with Hepatitis C Virus
  - Occult Hepatitis B infection
  - General health status of the person
- **Vaccine Recommendation**
  - Early in course of HIV infection before CD4 count < 350 cells/mm^3

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing Hepatitis B Infection

- **PWH with CD4 counts < 350 cells/mm³**
  - Do not defer hepatitis B vaccination
  - Some PWH with CD4 counts < 200 cells/mm³ do respond
- **Non Responders (anti-HBs titers <10 IU/mL) with 3-dose vaccine series**
  - 25-50% respond to an additional dose
  - 44-100% respond to a 3-dose revaccination series
  - Some HIV Specialists might delay revaccination until after a sustained ↑ in CD4 cell count on ART

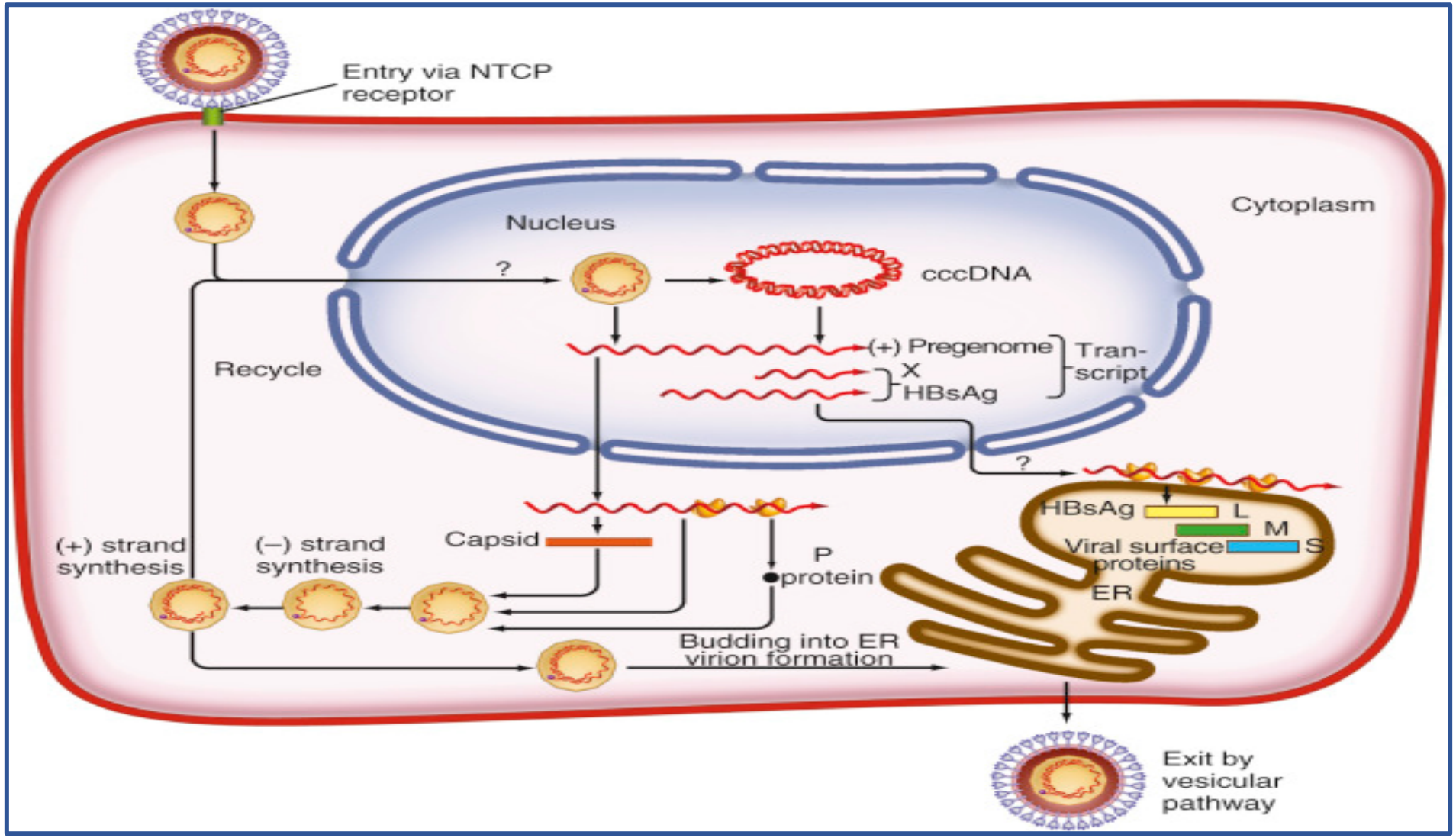
https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Preventing other Liver Diseases

- **HAV Vaccination recommendations**
  - All HAV antibody-negative patients who have chronic liver disease
  - Injection and non-injection drug users
  - Men who have sex with men (MSM)
- **PWH**
  - Response to HAV vaccination are reduced when CD4 <200
  - Assess antibody response 1 month after completion of vaccination
  - If HAV antibody immunoglobulin (HAV Ab IgG) is negative, revaccinate when CD4 count is >200 cells/mm^3

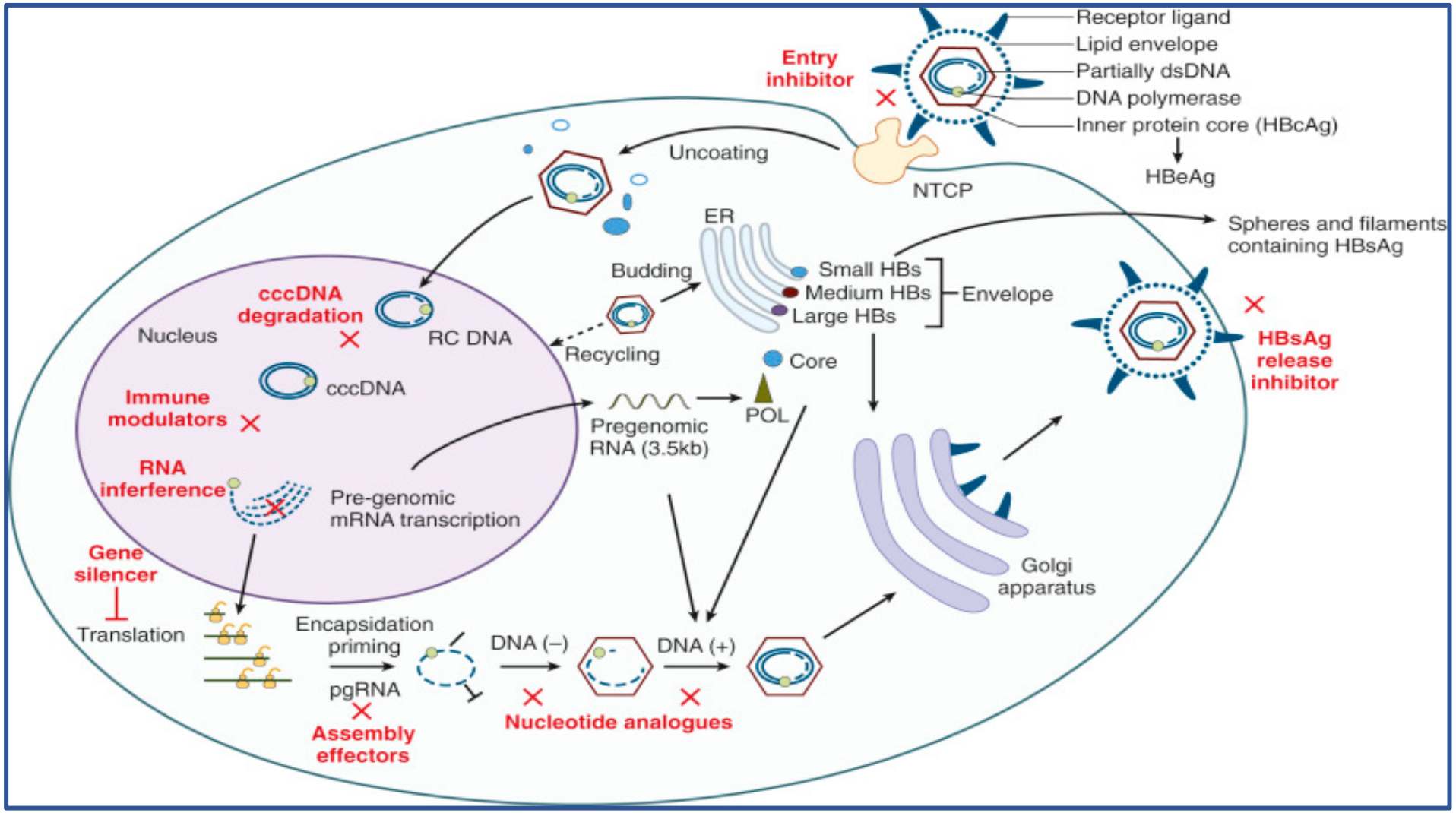
https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Hepatitis B Life Cycle



CITATION

Hepatitis B Life Cycle with Drug Targets



CITATION

DHHS Guidelines: What to Start in Treatment Naïve Adult and Adolescent

Recommended Initial Regimens for Most People with HIV

Recommended regimens are those with demonstrated durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of use.

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- BIC/TAF/FTC **(AI)**
- DTG/ABC/3TC **(AI)—if HLA-B*5701 negative**
- DTG plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- RAL plus (TAF or TDF)[a] plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)

INSTI plus 1 NRTI:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive?view=full

DHHS Guidelines: What to Start in Certain Scenarios

Recommended Initial Regimens in Certain Clinical Situations

These regimens are effective and tolerable but have some disadvantages when compared with the regimens listed above or have less supporting data from randomized clinical trials. However, in certain clinical situations, one of these regimens may be preferred (see Table 7 for examples).

INSTI plus 2 NRTIs:

Note: For individuals of childbearing potential, see Table 6b before prescribing one of these regimens.

- EVG/c/(TAF or TDF)[a]/FTC **(BI)**

Boosted PI plus 2 NRTIs:

- In general, boosted DRV is preferred over boosted ATV
- (DRV/c or DRV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(AI)**
- (ATV/c or ATV/r) plus (TAF or TDF)[a] plus (FTC or 3TC) **(BI)**
- (DRV/c or DRV/r) plus ABC/3TC —**if HLA-B*5701 negative (BII)**

NNRTI plus 2 NRTIs:

- DOR/TDF[a]/3TC **(BI)** or DOR plus TAF[a]/FTC **(BIII)**
- EFV plus (TAF or TDF)[a] plus (FTC or 3TC)
  - EFV 600 mg plus TDF plus (FTC or 3TC) **(BI)**
  - EFV 400 mg/TDF/3TC **(BI)**
  - EFV 600 mg plus TAF/FTC **(BII)**
- RPV/(TAF or TDF)/FTC **(BI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**

Regimens to Consider when ABC, TAF, and TDF Cannot be Used or Are Not Optimal:

- DTG/3TC **(AI)**, except for individuals with HIV RNA >500,000 copies/mL, HBV coinfection, or in whom ART is to be started before the results of HIV genotypic resistance testing for reverse transcriptase or HBV testing are available
- DRV/r plus RAL twice a day **(CI)—if HIV RNA <100,000 copies/mL and CD4 count >200 cells/mm^3**
- DRV/r once daily plus 3TC[a] **(CI)**

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/what-start-initial-combination-regimens-antiretroviral-naive?view=full

FDA Approved Hepatitis B Antiviral Medications

- **Approved Antiviral Therapies for HBV in Adults and Children**
  - **Children - Interferon Alfa-2b and adefovir dipivoxil**
  - **Adults -**
    - **Peginterferon Alfa-2a**
    - **Lamivudine**
    - **Telbivudine**
    - **Entecavir**
    - **Adefovir**
    - **Tenofovir**
      - Disoproxil Fumarate (TDF)
      - Alafenamide (TAF)
    - **Emtricitabine***
      - *Not FDA Approved but has anti-HBV activity

Antivirals Active Against HIV and HBV

Medication	HBV Activity	HIV Activity	Selection of HIV Resistance Reported
Lamivudine	Yes	Yes	Yes
Adefovir	Yes	No[a]	No
Entecavir	Yes	Partial	Yes
Emtricitabine	Yes	Yes	Yes
Telbivudine	Yes	Partial[b]	No
Tenofovir alafenamide	Yes	Yes	Yes
Tenofovir disoproxil fumarate	Yes	Yes	Yes

[a] = anti-HIV activity at higher doses; more potent against HBV
[b] = No in vitro activity observed against HIV, but HIV RNA decline reported

https://www.hiv.uw.edu/go/co-occurring-conditions/hepb-coinfection/core-concept/all

Treating Disease HIV/HBV Coinfection

- **DHHS Recommendations**
  - All treatment naïve PWH who are ready to begin lifelong therapy for HIV should begin combination Antiretroviral Therapy (ART) per guidelines regardless of HIV-1 Viral Load or CD4 count
  - Those with Hepatitis B coinfection should begin ART regardless of CD4 cell count or need for HBV treatment
  - Tenofovir and Emtricitabine both have anti-HBV activity, this combination is the treatment of choice for HIV/HBV coinfection (AIII)
    - Regardless of CD4 count
    - Regardless of HBV DNA level
  - TDF and TAF are both active against the wild-type and Lamivudine resistant HBV strains
  - TDF and TAF both have a high genetic barrier for development of resistance mutations

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Treating Disease HIV/HBV Coinfection: Renal Dosing Consideration

- **Creatinine Clearance ≥ 60 mL/min**
  - TAF/emtricitabine
  - TDF/emtricitabine
- **Creatinine Clearance 30-59 mL/min**
  - TAF/emtricitabine is preferred
- **Creatinine Clearance <30 mL/min**
  - A fully suppressive ART regimen without tenofovir should be used, with the addition of renally dosed entecavir to the regimen *or*
  - ART with renally dose-adjusted TDF and FTC can be used (BIII) <u>when recovery of renal function is unlikely</u>
  - Guidance for TAF use in persons with CrCl <30 is not yet established.

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Treating Disease HIV/HBV Coinfection

- **Switching from a primarily TDF-based ART regimen to a single tablet TAF/emtricitabine/elvitegravir/cobicistat regimen**
  - Patients maintained or achieved HBV suppression
  - Improved estimated glomerular filtration rate eGFR
  - Improved bone turnover markers
- **In HBV monotherapy:**
  - **TAF 25 mg was non-inferior to TDF 300 mg based on the % patients with HBV DNA levels <29 IU/mL at 48 weeks of therapy**

    94% for TAF vs 93% TDF; P = 0.47

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Treating Disease HIV/HBV Coinfection

- **Lamivudine or Emtricitabine in HIV/HBV coinfection**
  - **Chronic use as the only active drug against HBV <u>should be avoided</u>**
    - High rate of selection of HBV drug-resistant mutations
- **People receiving ART for HIV/HBV Coinfection**
  - Should continue therapy indefinitely because relapses after response occurs if stopped, especially w/ ↓ CD4 cell counts
  - Discontinuing nucleos(t)ide analogues is associated with HBV flares (30%)
    - Loss of benefit accrued from previous anti-HBV treatment
    - Possible decompensation of liver disease

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Treating Disease HIV/HBV Coinfection

- **What to do if anti-HBV and ART must be discontinued**
  - Monitor transaminase levels every 6 weeks for 3 months
  - Monitor transaminase levels every 3-6 months after initial 3 months of monitoring
- **Hepatitis B disease flare of antiviral therapies**
  - Restart anti-HBV and ART therapies
  - Resuming antiviral therapies can be potentially life saving

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Alternative Treatment of HBV in PWH Who Are Not Receiving ART

- **<u>HBV and HIV co-treatment are essential and recommended</u>**
- **Few options available for treatment of HBV alone in HIV/HBV coinfection**
  - Do not give directly acting HBV drugs in the absence of a fully suppressed ART regimen
  - Only option remains pegylated interferon-alfa-2a monotherapy

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Coinfection HBV/HIV/HCV

- **HBV/HIV/HCV coinfection**
  - Have accelerated progression of liver fibrosis
  - Higher risk of HCC
  - Increase mortality
  - Should attempt to treat both hepatitis viruses, if feasible
  - If ART is administered, then anti-HBV therapy must be included with anti-HCV therapy introduced as needed
- **Treatment for HCV with direct-active antivirals (DAAs) can lead to HBV reactivation in the absence of HBV active drugs**
  - Patients should be on HBV-active ART at the time of HCV treatment initiation

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Regimens that are Not Recommended in HBV/HIV coinfection

- **<u>Do not use</u> the following drugs as monotherapy in the absence of a fully suppressive ART regimen: will develop HIV-resistance mutations**
  - Tenofovir (TDF and TAF)
  - Entecavir
  - Lamivudine
  - Emtricitabine
  - Telbivudine
- **<u>Do not use</u> these regimens for HBV in addition to a fully suppressive ART regimen due to toxicity and higher rates of HBV failure**
  - Adefovir with Lamivudine or Emtricitabine, ↑ incidence renal disease
  - Telbivudine, ↑ incidence of myopathy and neuropathy

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Monitoring Response to Therapy and Adverse Events

- **Goal of Pharmacotherapy**
  - Durable suppression of HBV DNA viral load, decrease liver toxicity
  - Prevent emergence of HBV and HIV drug-resistant variants
    - ✓ HBV DNA every 3-6 months
- **Treatment Response Definitions**
  - Primary non-response, HBV DNA < 1 $\log_{10}$ decline at 12 weeks
  - Complete virologic response, HBV DNA undetectable at 24-48 weeks
  - Partial virologic response, ≥1 $\log_{10}$ decline but still detectable at 24 weeks
  - Maintained virologic response, HBV DNA remains undetectable on therapy
  - Sustained virologic response, HBV DNA remains undetectable 6 months after stopping therapy

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Monitoring Response to Therapy and Adverse Events

- **HBV/HIV in persons who are HBeAg-positive**
  - Loss of HBeAg is also a measure of virologic response
- **Other markers indicating treatment success**
  - Improvement in liver histology per biopsy
  - Transient elastography or noninvasive markers
  - Normalization of serum aminotransferases
  - Patients with loss of HBeAg, development of anti-Hbe
  - Sustained loss of HBsAg is considered by some to be a complete response
    - This is uncommon (<1% per year)

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Monitoring Response to Therapy and Adverse Events

- **IFN-alfa (pegylated or standard)**
  - Flu-like symptoms
  - Fatigue
  - Pyrexia
  - Myalgia
  - Headache
  - Psychiatric reactions
    - Depression
    - Insomnia
    - Irritability
    - Anxiety
- **Other common reactions:** anorexia, nausea, vomiting, diarrhea, arthragia, injection site reactions, alopecia, pruritis

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Monitoring Response to Therapy and Adverse Events

- **Nucleos(t)ide Analogs**
- **Tenofovir Disoproxil Fumarate (TDF)**
  - ↑ SCr or Renal tubular dysfunction
  - More frequent in PWH with underlying CKD
  - More frequent in older patients
  - More frequent in those treated for prolonged periods
  - Biochemical changes are typically reversible with discontinuation or change to TAF
- **Monitoring Drug Therapy**
  - Electrolytes, SCr @baseline, and every 3-6 months
  - Urinalysis every 6 months
  - Perform renal dose adjustments, do not use TAF with CrCl < 30 mL/min

https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

Monitoring Response to Therapy and Adverse Events

- **Nucleos(t)ide Analog**
- **Entecavir**
  - Lactic acidosis is uncommon but has been reported in HBV monoinfection with advanced cirrhosis

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **IRIS leading to reactivation of HBV-associated liver disease**
  - With immune competence after ART
  - After steroid withdrawal
  - Chemotherapy
  - ↑ serum aminotransferases, “hepatic flare” in HIV/HBV coinfection
- **Manifestations of IRIS**
  - Dramatic ↑ serum aminotransferases as CD4 ↑ within 6-12 weeks after ART
  - Signs/Symptoms characteristic of acute hepatitis w/o other cause for flare
- **Monitoring Parameters**
  - Closely monitor serum ALT, at 6 & 12 weeks, then q3-6 months thereafter
  - Consult hepatologist if Jaundice, ↑ INR, ↓ Albumin, and ↑ LFT’s

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Patients who are at increased risk for more severe flares**
  - Severe liver disease
  - Cirrhosis
- **Assess for other causes of non-ART-associated hepatotoxicity**
  - Acute hepatitis A,C,D, or E virus
  - Epstein-Barr virus
  - Herpes Simplex virus
  - Cytomegalovirus
- **ART-associated hepatotoxicity**
  - May be dose dependent
  - Idiosyncratic
  - Risk ↑ with elevated pre-ART aminotransferases (ALT, AST) AND HBV or HCV

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Predictors of Hepatotoxicity**
  - HIV/HBV coinfection with baseline ↑ HBV DNA levels
    - However, despite this increased risk of hepatotoxicity in the setting of HCV or HBV coinfection, 80% to 90% of patients with HIV/HBV coinfection do not have ART-associated hepatotoxicity. Clinically significant hepatotoxicity (↑ direct bilirubin) is rare
  - Aminotransferases levels return to baseline in most cases even with continued administration of offending medication
- **Discontinuation of ART usually not necessary in the presence of hepatotoxicity. Exceptions:**
  - Hypersensitivity symptoms (fever, lymphadenopathy, rash)
  - Symptomatic hepatitis (nausea, vomiting, abdominal pain, or jaundice)
  - ↑Serum aminotransferase levels >10 X upper limit of normal
  - Development of jaundice is associated with severe morbidity/mortality

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Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Clinical challenges in managing ALT flares**
  - Drug induced (Which drug?) liver injury and HBV reactivation
  - IRIS
  - Emergence of HBV drug resistance
  - HBeAg seroconversion
- **Review:**
  - Medication History
  - ✓Test for serum HBV DNA, HBeAg, HIV RNA levels, and CD4 count
  - Liver histology can differentiate drug toxicity (↑ eosinophils) from viral hepatitis (portal hypertension)
  - Consult hepatologist for severe flare or if HBV drug resistance is suspected
- **Other causes of abnormal liver tests**
  - Use of drugs/alcohol, Hepatitis A,C,D,E, and nonalcoholic fatty liver disease

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Managing Treatment Failure

- **HBV Treatment failure on nucleos(t)ide analogues**
  - Primary non response after 12 weeks of therapy in adherent patients
  - Increase in HBV DNA levels > 1 $\log_{10}$ above nadir
  - Treatment failure generally due to
    - Drug resistant HBV if on Lamivudine/Emtricitabine monotherapy
    - Noncompliance
- **Treatment regimen should be modified when drug resistance occurs**
  - Obtain HBV-resistance testing
  - TDF has not been associated with clinical resistance, although slow response has been noted
  - Addition of Entecavir has led to suppression of HBV DNA in slow response pts

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Managing Treatment Failure

- **Lamivudine or Emtricitabine monotherapy should not be used**
  - Leads to emergence of drug-resistant HBV
  - Rate of development of Lamivudine resistance ~20%/year in HIV/HBV coinfection treated with lamivudine alone
  - If Lamivudine resistance suspected or documented, add TDF or TAF
  - Lamivudine-resistant HBV has cross resistance to Telbivudine, Emtricitabine
  - Lamivudine-resistant HBV has partial resistance to entecavir, should not be used
- **Entecavir treatment failure**
  - TDF or TAF with or without emtricitabine
- **Pegylated IFN-alfa**
  - Use nucleoside analogues, 2 agents for HBV and a fully suppressed ART regimen

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Managing Treatment Failure

- **TDF or TAF in the Lamivudine or Emtricitabine-experienced patient**
  - Begin Entecavir, especially if higher doses can be used
  - Documented in vivo resistance to tenofovir has not yet been reported
  - Typically see slow ↓ in HBV DNA especially with very high pre-therapy HBV DNA levels

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Managing Treatment Failure

- **Typically see quick drops in HBV DNA levels in patients receiving an HBV drug with high potency and a high genetic barrier to resistance**
  - i.e. Tenofovir
  - Patients may remain detectable for some years
  - In compliant pts with a partial virologic response to TDF/TAF continue therapy and monitor HBV DNA levels
  - Patients on low genetic barrier therapies such as Adefovir or L-nucleosides (Telbivudine/Emtricitabine/Lamivudine) should be switched to a more potent regimen such as Tenofovir (TDF or TAF) with emtricitabine or entecavir (if treatment naïve) because of the risk of development of drug resistance to the initial therapy.
- **End Stage Liver Disease**
  - In those with HIV/HBV coinfection, as it is in HIV-seronegative persons, should be referred to Hepatology

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Preventing Recurrence

- **Most patients should continue HBV therapy (exception: pegylated IFN) indefinitely to prevent relapses**
  - Especially with patients that have ↓ CD4 counts
  - Reports of hepatic flares have been documented

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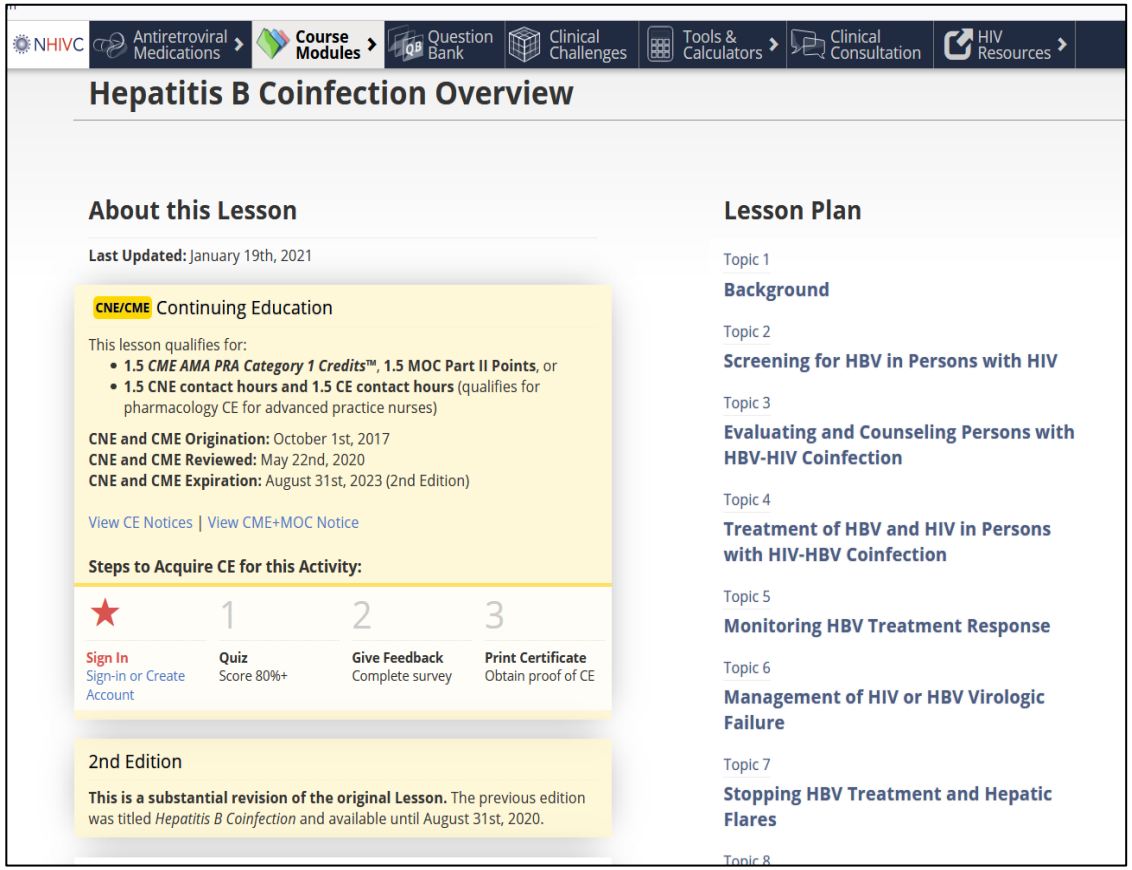
References

- CDC Hepatitis B Questions and Answers for the Public
  https://www.cdc.gov/hepatitis/hbv/bfaq.htm#bFAQc09
- CDC Viral Hepatitis
  https://www.cdc.gov/hepatitis/
- Centers for Disease Control and Prevention. (2008, September 19). Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *Morbidity and Mortality Weekly Reports.* Retrieved from https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5708a1.htm
- NIH Clinical Guidelines for HIV/AIDS
  https://clinicalinfo.hiv.gov/en
- NIH Clinical Guidelines for HIV/HBV Coinfection
  https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-opportunistic-infection/hepatitis-b-virus-infection?view=full

National Curriculum Modules

- Course Modules 4 (Co-Occurring Conditions) Lesson 5 - Hepatitis B Coinfection Overview
  https://www.hiv.uw.edu/custom/co-occurring-conditions/hepb-coinfection
- Course Module 2 Basic HIV Primary Care, Lesson 4 – Immunizations in Adults Overview, Topic 4
  https://www.hiv.uw.edu/custom/primary-care/immunizations/4



Questions?

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Questions answered within 24 – 48 hours

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