Hepatitis B and C Co-infection

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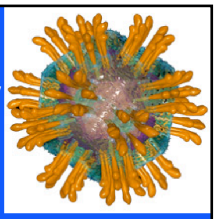
Objectives

- Review natural history of hepatitis co-infection
- Brief overview of treatment indications for co-infection
- Treatment options

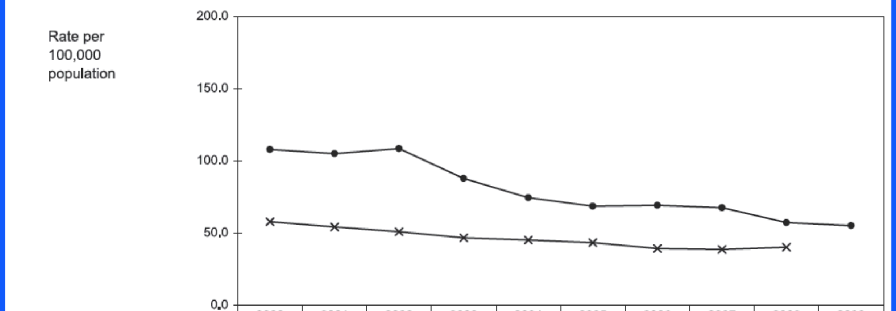
Hepatitis C overview



- HCV is an RNA virus
- Has a single strand of RNA which codes for a 3000 amino acid protein chain
- Molecular testing of virus has revealed 6 distinct genotypes:
  - In North America 1a and 1b predominate,
  - Genotypes 2 and 3 less common

• HCV – Hepatitis C
• The 6 distinct genotypes are particularly important when discussing HCV therapy, as treatment outcomes are genotype specific.

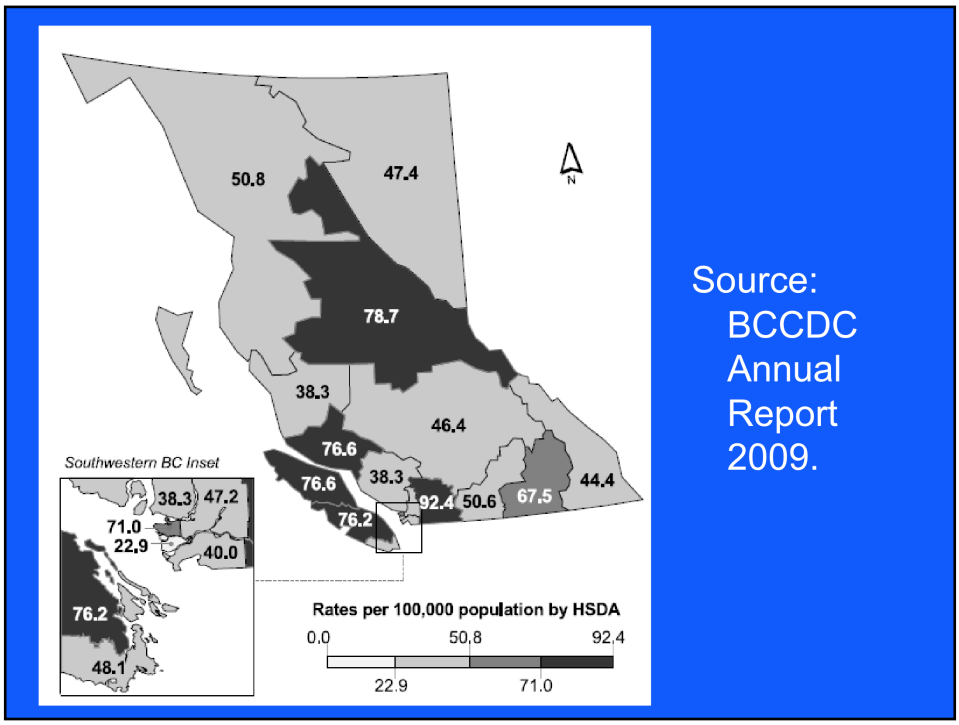
Hepatitis C Rates 2000-2009



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
BC Hepatitis C Reports	4353	4276	4436	3612	3086	2875	2932	2901	2500	2444
BC Hepatitis C Rate	107.8	104.9	108.2	87.6	74.3	68.5	69.1	67.3	57.1	54.9
Canadian Hepatitis C Rate*	57.8	54.1	50.8	46.6	45.0	43.2	39.2	38.5	40.0	

Source: BCCDC Annual Report 2009.

• The data displayed in this graph shows that that Hepatitis C rates in BC are significantly higher than the national Hepatitis C rates.



- Identifies HCV rates by Health Authority in BC.
- Fraser East HSDA (Health Service Delivery Area) had the highest rate at 92.4per 100,000
- Vancouver and Vancouver Island had rates of over 70 per 100,000

HIV/HCV Epidemiology

- An estimated 20% of HIV+ individuals are co-infected with HCV in Canada
- Transmission of HIV and Hepatitis C share common modes of transmission
  - 1. injection drug use:
    - IDU/former IDU accounted for 56% of Canadian HCV prevalent cases in 2002
    - Rates of co-infection amongst IDU may be as high as 95% Alter, MJ. J Hepatol 2006;44 (Suppl 1) S6-9.

• Vancouver's Downtown Eastside (DTES) is one example of a neighboorhood in which the IDU population have significant high rates of co-infection.

HIV/HCV Epidemiology

- 2. Sexual transmission
- Growing reports of possible sexual transmission of HCV amongst HIV+ MSM populations
  - 10 fold increased incidence in Amsterdam 2000-2003 Van der Laar, T. JID 2007; 196: 230.
  - Major risk factor among HIV+ patients with acute HCV in Australia 2004-2007 Matthews, G. AIDS 2007;21: 2112.

• Similar trends of sexual transmission among non-IDU MSM population is also being identified in Vancouver.

HIV and Hepatitis C Interactions

- **HIV has been demonstrated to have a significant impact on HCV infection:**
  - Decreased rates of spontaneous clearance
    - Only 5-10% will clear acute infection
  - Higher HCV viral loads
    - Impacts treatment response

HIV and Hepatitis C Interactions

- **HIV impact on HCV infection cont'd**
- more inflammatory activity

- More extensive fibrosis
  - 60% of co-infected patients with METAVIR fibrosis scores of 2-4 vs. 54% in mono-infected Benhamou, Y. Hepatology 1999;30:1054.

• HIV significantly impacts disease progression through the inflammatory process. As a result, fibrosis and inflammation eventually leads to the progression of cirrhosis.

HIV and Hepatitis C Interactions

- **HIV impact on HCV infection cont'd**
- Rapid progression to cirrhosis
  - Mean estimated interval to cirrhosis pre-HAART: 6.9 yrs vs. 23.2 yrs Soto, B. J Hepatol 1997;26:1.
- This translates into higher risk of decompensation
  - Meta-analysis of 8 studies found co-infection had RR of 6.14 (95% CI 2.86-13.20) for decompensated liver disease Graham, C. CID 2001; 33:562.

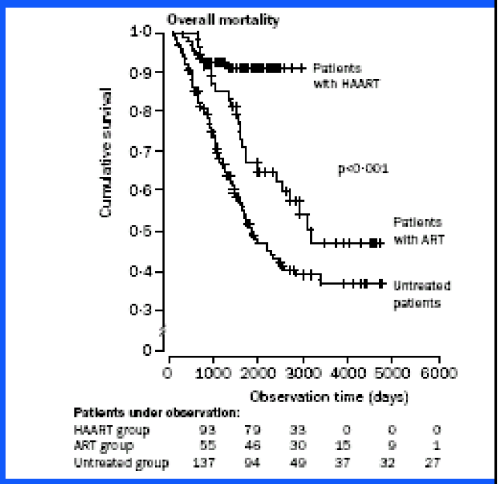
• Co-infected individuals with cirrhosis have a greater risk for decompensated liver disease including ascites, GI bleeds, hepatic encephalopathy etc.

HIV and Hepatitis C Interactions

- **Impact of Hepatitis C on HIV**
  - No clear direct effects on HIV disease progression
  - Increased risk of antiretroviral hepatotoxicity
    - Treatment of HCV has been shown to decrease risk
    - Study found 9.3% risk of ARV hepatoxicity in those with response to HCV treatment vs. 37.5% in patients without HCV response Labarga, P. JID 2007;196:670.

HIV and HCV Interactions

- **Impact of HAART**
- Control of HIV viremia may lead to slower rates of fibrosis Brau, N. J Hepatol;44:47.
- HAART associated with decreased rates of liver-related mortality in co-infected patients



Qurishi, N. Lancet 2003;362:1708

• In co-infected populations, HAART has been shown to slower the rates of fibrosis and decrease the rates of liver-related mortality.

• The use of HAART is essential in co-infected patients. As a result, guidelines have shifted, and co-infected individuals should be on antiretroviral therapy regardless of CD4 counts.

HIV and HCV Interactions

- However liver disease now responsible for 43% of deaths amongst co-infected patients in some cohorts
  - Factors associated with mortality included baseline fibrosis, lower CD4 cell count response and lack of HCV therapy (OR 11.32) Pineda,.J. J. Hepatology 2007;46:622.

• A cohort study in Spain investigated factors associated with mortality. The highest odds ratio in this study was related to the lack of HCV treatment. As a result, the need to evaluate HCV therapy in all patients is essential.

Baseline assessment

- All HIV+ patients should be screened for HCV
  - HCV Antibody
  - HCV RNA in pts with risk factors and abnormal liver enzymes and negative Ab
- HCV co-infected
  - confirm HCV RNA positive
  - Vaccinate for Hepatitis A,B if non-immune
  - Screen for signs of cirrhosis
    - Pts with cirrhosis need U/S q 6mo (+/- alpha-fetoprotein)
    - referral for gastroscopy for varices

• Annual HCV screening should be incorporated into practice in high risk populations.
• Patients with cirrhosis and co-infection require close follow-up for risks of hepatocellular carcinoma. Guidelines suggest ultrasound (U/S) every 6 months.

Evaluation for HCV treatment

- Confirm HCV RNA remains positive
- Identify HCV genotype
- Screen for other causes of chronic liver disease
  - Autoimmune hepatitis, Wilson's disease, hemochromatosis
- Role of liver biopsy:
  - Helpful to determine degree of inflammation, fibrosis and necrosis
  - Helps determine who can defer therapy vs. highlights urgency of treatment in cases of more advanced fibrosis

- Identify HCV genotype to determine length of therapy and treatment response.

Evaluation for HCV treatment

- **Which to treat first? A moving target…**
- HIV for CD4<500 cells/mm^3
- Ideally HCV if CD4>500cells/mm^3
  - No drug interactions, improves future ARV tolerance
  - However, new HIV guidelines recognize benefit of HAART in decreasing progression of HCV:
    - If patient not able to be considered for HCV therapy, offer HAART regardless of CD4 cell count!

• In patients with CD4 <500 cells/mm^3 it is best to initiate HIV treatment first
• In patients with CD4 >500cells/mm3, clinicians have more choices. It is known that completing HCV therapy first can improve future tolerance of HAART.

Evaluation for HCV treatment

- **Who should be treated?**
- Patients with ongoing chronic elevation in ALT: 1.5x ULN (BC guidelines)
  - 2 elevated levels in 6 months
- However, up to 20-25% of co-infected patients can have significant fibrosis despite normal liver enzymes –greater reason to biopsy Uberti-Foppa, C. JAIDS 2006;41:63.

• Co-infected patients with normal liver enzymes may require a liver biopsy to uncover the degree of fibrosis, which can then be used to indicate the need for treatment (covered by Pharmacare).

Evaluation for HCV treatment

Absolute Contra-indications	Relative Contra-indications
Pregnancy/refusal to use contraceptives	Major depression Major psychosis
Strong contra-indications	
Active autoimmune disease	Renal failure
Hepatic decompensation	Platelet count < 50,000
Coronary artery disease	Alcohol abuse

• In patients with a history of depression or major psychosis, treatment can be considered if they are stable and have the appropriate supports (i.e. physiatrist)

HCV Treatment

- Similar to mono-infection: pegylated interferon and ribavirin
  - Either Pegylated interferon a2a, or a2b may be used.
  - Peg-INF-alpha 2a 180mg Sc weekly + ribavirin 1000mg (wt <75kg) or 1200mg (wt>75kg) daily
  - Peg-INF-alpha 2b 1.5mg/kg Sc weekly + weight based ribavirin 800mg-1400mg daily

- Two forms of Pegylated Interferon:
  - Pegylated Interferon alpha-2a - Pegasys
  - Pegylated Interferon alpha-2b – Pegatron

2007 HIV-HCV International Guidelines

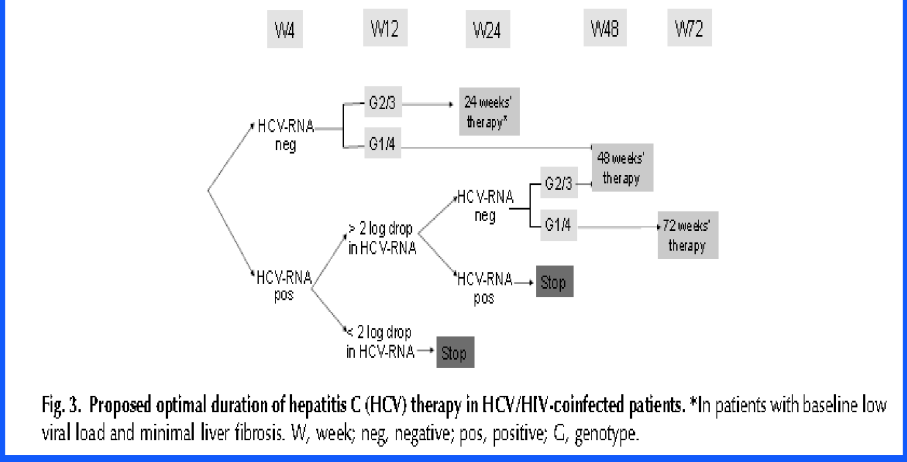


Fig. 3. **Proposed optimal duration of hepatitis C (HCV) therapy in HCV/HIV-coinfected patients.** *In patients with baseline low viral load and minimal liver fibrosis. W, week; neg, negative; pos, positive; G, genotype.

Source: Soriano, V. AIDS 2007;21:1073

- The above 2007 guidelines display a response-driven curve. If a rapid virological response is identified by week 4, patients can receive a similar length of treatment as mono-infected patients.
- For genotypes 2/3, if there is no response by week 2, the guidelines suggest to continue treatment for 48 weeks.
- In patients with genotype 1 who are mono-infected, the sustained virological response (SVR) at 48 weeks is approximately 50%. In patients with genotype 1 who are co-infected the SVR at 48 weeks is approximately 30-40%
- The same reductions in SVR are seen in genotypes 2/3.

Common Side Effects

- In clinical trials, 10-14% participants discontinued therapy due to adverse events.
- Common: influenza-like symptoms (>50%)
- Skin rashes
  - Exacerbation of psoriasis
- Hyperthyroidism/hypothyroidism
- Neuropsychiatric symptoms
  – 20-30% patients

- Side effects are the limiting factor in HCV treatment

Monitoring for laboratory side-effects

- Anemia
  - 25-30%, usually in first 8 weeks
  - Iron/B12/Folate supplementation may help
  - Consider EPO if Hgb drops >40g/L or if symptomatic (if pt has additional insurance)
    - Ultimately may need ribavirin dose reductions
- Neutropenia
  - 20% individuals
  - Not associated with increased infections in clinical trials
  - Canadian Guidelines: dose reduce interferon at 0.5×10^9 /L, halt if 0.3×10^9 /L
- Thrombocytopenia
  - Dose reductions necessary $< 30 \times 10^9$ /L, halt if $< 20 \times 10^9$ /L

HAART and HCV Therapy

- DDI contra-indicated due to increased toxicity due to ribavirin interactions
- D4T: increased risks of lactic acidosis while on ribavirin (avoid)
- AZT: increases risk of anemia (avoid)

Hepatitis B

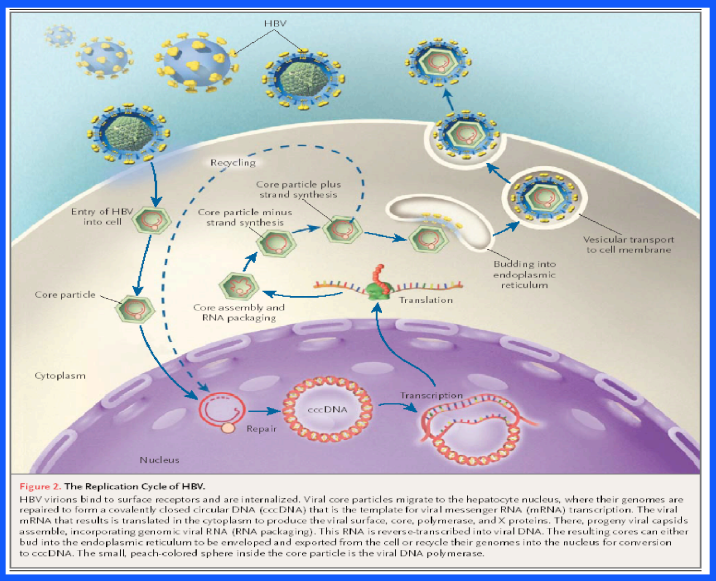
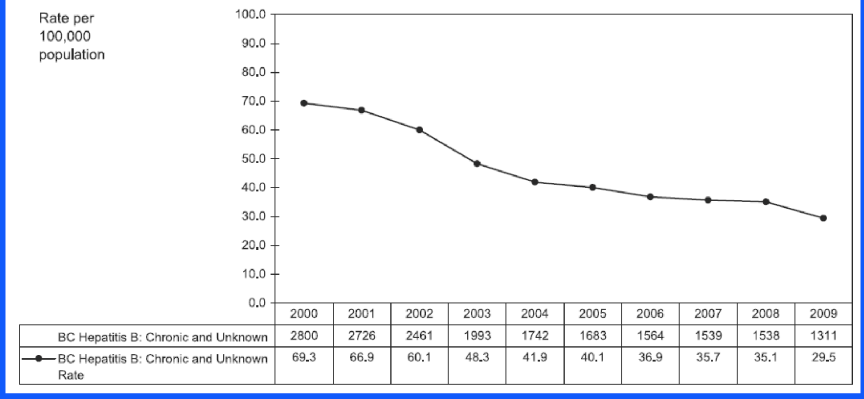


Figure 2. The Replication Cycle of HBV.
HBV virions bind to surface receptors and are internalized. Viral core particles migrate to the hepatocyte nucleus, where their genomes are repaired to form a covalently closed circular DNA (cccDNA) that is the template for viral messenger RNA (mRNA) transcription. The viral mRNA that results is translated in the cytoplasm to produce the viral surface, core, polymerase, and X proteins. There, progeny viral capsids assemble, incorporating genomic viral RNA (RNA packaging). This RNA is reverse-transcribed into viral DNA. The resulting cores can either bud into the endoplasmic reticulum to be enveloped and exported from the cell or recycle their genomes into the nucleus for conversion to cccDNA. The small, peach-colored sphere inside the core particle is the viral DNA polymerase.

Ganem, D. NEJM 2004;350:11 118.

• The Hepatitis B virus differs from the Hepatitis C virus in that it is a DNA virus with covalently closed circular DNA.

Chronic hepatitis B rates 2000-2009



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
BC Hepatitis B: Chronic and Unknown	2800	2726	2461	1993	1742	1683	1564	1539	1538	1311
BC Hepatitis B: Chronic and Unknown Rate	69.3	66.9	60.1	48.3	41.9	40.1	36.9	35.7	35.1	29.5

Source: BCCDC Annual Report 2009

- Hepatitis B rates are lower than Hepatitis C rates in BC
- Most cases arise in patients who come from endemic countries

HBV Natural History

- 90% of infants with vertical transmission become chronically infected
- In adult-acquired infections only 5- 10% of individuals do.
  - Likely higher if HIV+ = 25% risk
- 20% of chronically infected individuals will develop cirrhosis
- Chronic carriers also have an increased risk of hepatocellular carcinoma (HCC)

HBV Natural History

Patient populations in chronic hepatitis B

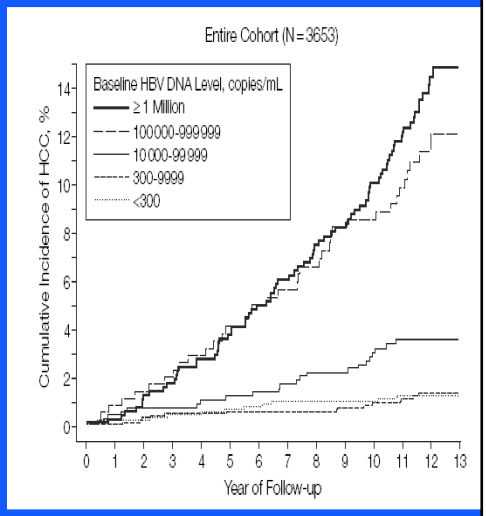
Marker	Immune tolerant (type 1)	Immune active (type 2)	Inactive HBsAg carrier (type 3)	HBeAg-negative CHB (precore/core promoter mutant) (type 4)
HBsAg	+	+	+	+
HBeAg	+	+	–	–
Anti-HBe	–	–	+	+
ALT	Normal	↑	Normal	↑
HBV DNA (IU/mL)	$>2 \times 10^4$	$>2 \times 10^4$	$<2 \times 10^2$	$>2 \times 10^3$
Inflammation on histology	Normal/mild	Active	Normal	Active

ALT, alanine aminotransferase; CHB, chronic hepatitis B; HBeAg, hepatitis B virus (HBV) envelope antigen; HBsAg, HBV surface antigen.

British HIV/HBV guidelines (BHIVA) 2010. Brook, G. HIV Medicine 2010;11:1-30

HBV Natural History

- Presence of HBV eAg+ correlates with increased risk of HCC
  - Relative risk of 9.6 in HBV sAg +/eAg-
  - RR of 60.2 in HBV sAg+/ eAg+ Yang, H. NEJM 2002;347:168
- Correlation between level of HBV DNA and
  - Risk of HCC Chen, CJ. JAMA 2006;295:65
  - Risk of cirrhosis Iloeje, U. Gastroenterol 2006;130:678



• Higher levels of HBV DNA correlate with increased risk of hepatocellular carcinoma and cirrhosis.

HIV-HBV co-infection

- 7- 10% of HIV+ are co-infected
  - 10x higher than rates in general population
- HIV leads to decreased clearance of HBV sAg and HBV eAg
  - higher viral replication and more frequent reactivations
- HIV leads to increased cirrhosis and higher mortality attributable to liver disease Nikopolous, G. CID 2009;48:1763.
- Higher risk of hepatotoxicity on HAART

Baseline Assessment

- All patients should be tested for HBV:
  - Initial screen of 3 markers: HBV sAb, HBV sAg, HBV cAb (core antibody).
  - Consider testing those with isolated core antibody with HBV DNA PCR - occult infection.
- For those with HBV sAg+ (chronic infection)
  - Test for presence of envelope Ag/Ab (HBV eAg, eAb)
  - HBV DNA PCR (HBV viral load)
  - Screen for Hepatitis Delta (HDV) antibody
  - Screen for HCC with Ultrasound q6mo if
    - **Cirrhosis**, age >40 with ALT elevation, High HBV DNA (>2000 copies/mL), low CD4 cell counts
  - Vaccinate for Hepatitis A
  - Alcohol cessation/safer sex counselling

• Initial screening for HBV will indentify if patients are immune, have chronic infection, or have been vaccinated.

Evaluation for HBV therapy

- Complex decision for mono-infected patients!
  - Based on ALT, HBV DNA level, eAg status
  - Fibrosis on biopsy
- Drugs active against HBV:
  - Pegylated Interferon
  - Lamivudine (3TC) – also active against HIV
  - Entecavir – weak activity against HIV (associated with HIV resistance if used as monotherapy)
  - Telbivudine
  - Adefovir
  - Tenofovir – also active against HIV

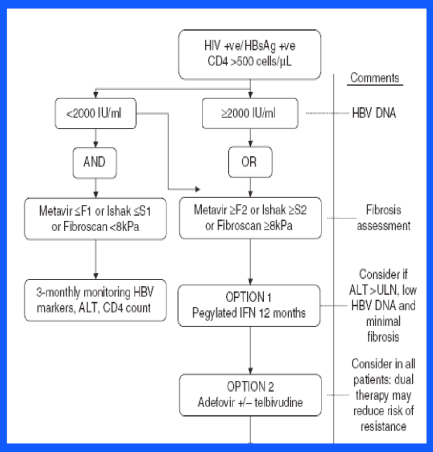
• HIV regimens that include Tenofovir and/or 3TC are also active against HBV. If patients have not been initiated on HAART, a Tenofovir + FTC/3TC regimen can provide treatment for both, HIV and HBV.

Evaluation for HBV therapy

- For co-infected patients decision easier:
  - For those with CD4 cell count <500 cells/mm^3
    - Begin ARVS with activity against HBV: 3TC/FTC + tenofovir
      - Monotherapy with 3TC(lamivudine) NOT recommended due to development of resistance
- For CD4 cell count>500 cells/mm^3 :
- Consider early initiation of HAART with agents active against HBV

Evaluation for HBV therapy

- For those who wish to defer HAART, can evaluate for HBV therapy
  - Based on HBV DNA, presence of fibrosis
  - Would use agents not thought to be active against HIV: Pegylated Interferon, adefovir



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Conclusions

- All patients should be screened for co-infection.
- Untreated co-infection associated with increased morbidity and mortality.
- Patients with co-infection should be considered for early initiation of HAART
  - Particularly if HBV
- Patients with HCV and preserved CD4 cell counts can be assessed for HCV therapy first.