Reactivation of Hepatitis B in Clinical Trials with Immunosuppressive Drugs

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HBV Reactivation (HBVr): Overview

• Clinical syndrome characterized by an increase in HBV DNA and ALT/AST with or without symptoms or jaundice
• Occurs in pts with active (HBsAg+) and resolved/occult (HBsAg-, anti-HBc+) HBV infection
• Wide clinical spectrum for HBVr
  – Ranges from silent to liver failure
• Can occur during treatment with many immunosuppressive agents, DAA, HIV, organ transplant
  – May also occur up to 12 months after event or treatment
• Preventable by antiviral prophylaxis

Definitions

- Virologic increase of 1 log IU/ml or de novo appearance of HBV DNA when previously non detectable
  
  Proposed: 2 log increase or de novo or reappearance of HBV DNA to a level of at least 100 IU/mL (AASLD Emerging Trends Conference on HBV Reactivation, March, 2013)

  In absence of HBV DNA measurements, reappearance of HBeAg or HBsAg is reasonable evidence

- Increase of 3 fold or greater in ALT levels if BSL levels normal or 2 fold or greater increase over BSL if initially abnormal.
Case: 55-Yr-Old Chinese Woman With Stage II Breast Cancer

- Treated with doxorubicin, paclitaxel, dexamethasone, and cyclophosphamide
HBV may reactivate in anyone who is Anti-HBc+

<table>
<thead>
<tr>
<th></th>
<th>HBsAg</th>
<th>Anti-HBc total</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBs</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Never exposed</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>Vaccinated</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>Exposure, Occult, Cleared disease</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>Acute HBV (rare during active/chronic disease)</td>
</tr>
<tr>
<td><strong>E</strong></td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Chronic HBV</td>
</tr>
<tr>
<td><strong>F</strong></td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>Exposure, Occult, Cleared disease “Isolated core”</td>
</tr>
</tbody>
</table>
The (non) role of anti-HBs

• Does the presence of anti-HBs in addition to anti-HBc in HBsAg-negative patients confer additional protection against HBVr?
  – Studies have shown pre-treatment anti-HBs titers to be an independent risk factor for reactivation only with rituximab (OR 0.003, 95%CI 0-0.3, p = 0.014)
  – No RCTs available that compare a monitoring strategy based on anti-HBs vs. antiviral prophylaxis to be non-inferior

• Recommendation:
  – The AGA suggests against using anti-HBs status to guide antiviral prophylaxis for all risk groups.

**GRADE:** Weak recommendation; Very low-quality evidence
Why Do Patients Reactivate HBV Despite Serological Evidence of Viral Clearance?

• HBV DNA persists within the liver even after resolution of infection
• cccDNA resides in nucleus of hepatocytes
• cccDNA can become transcriptionally active
• Viral replication is suppressed with intact immune function
• Loss of immune surveillance by IST results in active replication
**Pre-Chemo**
- HBsAg+
- HBV DNA +/-
- ALT Normal

**During-Chemo**
- HBsAg+
- HBV DNA +++
- ALT Abnormal

**Post-Chemo**
- HBsAg+
- HBV DNA +++
- ALT Flare

**HBV DNA In nucleus**
- cccDNA

**Loss of HBV-specific B & T cells**
- Control HBV replication
- Uncontrolled HBV replication

**Immune activation**
- HBV clearance
- Hepatocyte damage
HBcAg Staining Demonstrates Impact of Immunosuppression on HBV Activity

Immunohistochemistry from HBV patient

Increased HBcAg staining from HBV patient on immunosuppression
HBV Reactivation: Interaction of HBV Status and Immunosuppression

Risk of Reactivation

Degree of Immune Control

Degree of Risk for HBVr

HBsAg

Negative

Positive

Anti-HBc

Positive

HBV DNA

Negative

Low Level

High Level

Resolved Infection

Inactive HBsAg Carrier

Immuneactive Chronic HBV

(ex. Steroids < 5 days)

Low Risk

Immunosuppression

High Risk

Example: Rituximab

Adapted from Gonzalez and Perrillo, 2016
Natural History of HBV Reactivation During Chemotherapy

- Weeks after Exposure
- Recovery of neutropenia or steroid withdrawal
- Acute liver failure
- Death
- Liver Transplant
- Chronic hepatitis
- Cirrhosis
- Acute hepatitis
- IMMUNE change or SUPPRESSION
- IMMUNE REBOUND
- RECOVER

- HBV DNA
- ALT
- ChemoRx and/or Steroids Or HCV DAAs Or Liver SOT
Immunosuppressive Therapy (IST) Reported to Cause HBV Reactivation

**Anti-TNF**
(Infliximab, adalimumab, etanercept)

**Anti-Metabolite**
(Methotrexate)

**Purine Analogues**
(Azathioprine/6MP)

**Steroids**
(Prednisone, budesonide)

**Other**
(Rituximab, cyclosporine)
HBV lifecycle and targets for Immunosuppressive therapy

Loomba R, Liang JT Gastroenterology 2017:152;1297-09
## High risk for HBVr (>10%)

<table>
<thead>
<tr>
<th></th>
<th>HBsAg + core +</th>
<th>HBsAg - core +</th>
<th>Confidence in estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-cell depleting agents (rituximab, ofatumumab)</td>
<td>30 – 60%</td>
<td>17%</td>
<td>A</td>
</tr>
<tr>
<td>Anthracycline derivatives (e.g., doxorubin / epirubicin)</td>
<td>15 – 30%</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Corticosteroids for &gt; 4 wks (&gt; 10 mg prednisone)</td>
<td>&gt; 10%</td>
<td></td>
<td>B</td>
</tr>
</tbody>
</table>

**Categories of confidence in the estimate:**

(A) High confidence that the estimate lies within group risk boundaries
(B) Moderate confidence that the estimate lies within group risk boundaries
(C) Little or no confidence that the estimate lies within group risk boundaries
## Moderate risk (1% - 10%)

<table>
<thead>
<tr>
<th></th>
<th>HBsAg + core +</th>
<th>HBsAg - core +</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TNF-alpha inhibitors</strong></td>
<td>1 – 10% (B)</td>
<td>1% (C)</td>
</tr>
<tr>
<td>(etanercept, adalimumab, certolizimab, infliximab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other cytokine &amp; integrin inhib.</strong></td>
<td>1 – 10% (C)</td>
<td>1% (C)</td>
</tr>
<tr>
<td>(abatacept, ustekinimab, natalizumab, vedolizumab)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tyrosine kinase inhibitors</strong></td>
<td>1 – 10% (B)</td>
<td>1% (C)</td>
</tr>
<tr>
<td>(imatinib, nilotinib)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroids for &gt; 4 weeks</strong></td>
<td>1 – 10% (B)</td>
<td>1 – 10% (C)</td>
</tr>
<tr>
<td>(low dose: &lt;10 mg)</td>
<td></td>
<td>(&gt;10 mg)</td>
</tr>
<tr>
<td><strong>Anthracycline derivatives</strong></td>
<td></td>
<td>1% (C)</td>
</tr>
<tr>
<td>(e.g., doxorubicin / epirubicin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Low risk group (<1%)

<table>
<thead>
<tr>
<th></th>
<th>HBsAg + core +</th>
<th>HBsAg - core +</th>
</tr>
</thead>
</table>
| **Traditional immunsupp. agents**  
(azathioprine, 6-mercaptopurin, methotrexate alone) | <1% (A)        | <<1% (A)       |
| **Intra-articular corticosteroid**                     | <1% (A)        | <<1% (A)       |
| **Corticosteroids for ≤ 1 week**                       | <1% (B)        | <<1% (A)       |
| **Corticosteroids for > 4 weeks**                       | <1% (B)        |                 
  (low dose: <10 mg) |

**Categories of confidence in the estimate:**
(A) High confidence that the estimate lies within group risk boundaries
(B) Moderate confidence that the estimate lies within group risk boundaries
(C) Little or no confidence that the estimate lies within group risk boundaries
High Risk of Reactivation with Hematologic Malignancy

100 patients with NHL undergoing CHOP
27 HBsAg +ve

- HBV Reactivation: 48%
- Jaundice: 22%
- Non-Fatal Liver Failure: 4%
- Death: 4%

Lok et al, 1991
Rituximab in HBsAg- / Anti-HBc+ Patients with Lymphoma

Yeo et al, 2009

None due to HBV

All due to HBV

Yeo et al, 2009
HBV Reactivation With Rituximab in Pts With Hematologic Malignancies

- Single-center study of HBsAg-negative anti-HBc–positive pts receiving rituximab-containing chemotherapy (N = 62)
  - Baseline HBV DNA undetectable (< 10 IU/mL)
  - No previous HBV treatment
  - No chronic liver disease
- 24.2% of patients experienced HBV reactivation within 9 months
  - Reactivation occurred early (86.7% within 6 months)

Lower baseline anti-HBs levels associated with subsequent HBV reactivation ($P = .015$)

Rituximab-Associated HBV Reactivation in Lymphoproliferative Disorders

- Meta-analysis and review of FDA safety profiles
  - Case reports (n=27)
  - Case series reports (n=156)
- Onset post last rituximab dose
  - Median: 3 months (range: 0-12 months)
  - >6 months: 29%
- Reactivation in anti-HBc positive patients receiving rituximab versus no rituximab
  - Odds ratio: 5.73 (P=0.0009)

Anti-TNF Agents and HBV Reactivation

- TNF-α: proinflammatory cytokine that inhibits HBV replication
- Anti-TNF agents associated with HBV reactivation
  - Utilized in IBD, psoriasis, rheumatoid arthritis

<table>
<thead>
<tr>
<th>Disease Studied</th>
<th>No. Patients</th>
<th>HBsAg + HBcAb +</th>
<th>HBsAg – Anti-HBc +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple</td>
<td>257</td>
<td>39%</td>
<td>5%</td>
</tr>
<tr>
<td>IBD</td>
<td>88</td>
<td>9/25 (36%)</td>
<td>0%</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>122</td>
<td>12%</td>
<td>N/A</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>468</td>
<td>N/A</td>
<td>2%</td>
</tr>
</tbody>
</table>

- Antiviral prophylaxis warranted for all HBsAg+ on TNFi
- Low risk of HBVr in anti-HBc + only
  - Consider monitoring for HBVr
  - Higher risk may be associated with addition of other IST

Perez-Alvarez et al, 2011; Loras et al, 2010; Lee et al, 2013; Lee et al, 2013;
HBV Reactivation and Abatacept

- **Abatacept**: inhibitor of T-cell activation
  - Anecdotal data suggest it should be treated as a TNF inhibitor regarding HBV reactivation\[^1\]
  - Clinical studies have excluded pts who tested positive for hepatitis during screening\[^2\]

- **Package insert\[^2\]**
  - Pretreatment screening should be performed per guideline recommendations

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HBV Screening Prior to Immunosuppressive Therapy

• All pts should be screened

• Screening should include assessment of[1-6]:
  – HBsAg*
  – Anti-HBc #
  – Anti-HBs
  – *Additional: HBV DNA levels[2,3,5,6]
  – #isolated anti-HBc consider HBV DNA quant {7% are DNA+ if anti-HBc+ only}

HBV Prophylaxis for Pts Receiving Immunosuppressive Therapy

• Candidates
  – HBsAg+[1-6]
  – HBsAg-/anti-HBc+ if
    • Receiving therapy associated with high HBV reactivation risk (AGA,[5] ASCO[6]*)
    • Detectable HBV DNA (EASL,[2] APASL[3], AASLD[4])

• Timing of initiation[1-6]
  – At or before onset of immunosuppressive therapy

*ASCO states that these pts may alternatively be monitored and treated with on-demand therapy as needed.

HBV Prophylaxis for Pts Receiving Immunosuppressive Therapy

• Duration
  – Varies among guidelines
  – 6 mos post immunosuppressive therapy if HBV DNA < 2000 IU OR until treatment goals reached if > 2000 IU (AASLD)[1]
  – 6 mos post immunosuppressive therapy OR 12+ mos if B-cell–depleting agent (AGA, ASCO)[2,3]
  – 12 mos post immunosuppressive therapy (EASL, APASL)[4,5]

Randomized, Controlled Trials of HBV Prophylaxis

- **Control**
  - Lymphoma, HBsAg+ (N = 30)
  - HBsAg+ HBV DNA+ (N = 76)
  - Lymphoma, HBsAg+ (N = 52)
  - Breast Cancer, HBsAg+ Anti-HBc+ (N = 42)
  - Lymphoma, HBsAg-Anti-HBc+ (N = 80)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 30)
  - Lymphoma, HBsAg+ (N = 121)

- **Lamivudine**
  - Lymphoma, HBsAg+ (N = 30)
  - HBsAg+ HBV DNA+ (N = 76)
  - Lymphoma, HBsAg+ (N = 52)
  - Breast Cancer, HBsAg+ Anti-HBc+ (N = 42)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 80)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 30)
  - Lymphoma, HBsAg+ (N = 121)

- **Entecavir**
  - Lymphoma, HBsAg+ (N = 30)
  - HBsAg+ HBV DNA+ (N = 76)
  - Lymphoma, HBsAg+ (N = 52)
  - Breast Cancer, HBsAg+ Anti-HBc+ (N = 42)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 80)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 30)
  - Lymphoma, HBsAg+ (N = 121)

- **Tenofovir**
  - Lymphoma, HBsAg+ (N = 30)
  - HBsAg+ HBV DNA+ (N = 76)
  - Lymphoma, HBsAg+ (N = 52)
  - Breast Cancer, HBsAg+ Anti-HBc+ (N = 42)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 80)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 30)
  - Lymphoma, HBsAg+ (N = 121)

- **Combination of Lamivudine and Entecavir**
  - Lymphoma, HBsAg+ (N = 30)
  - HBsAg+ HBV DNA+ (N = 76)
  - Lymphoma, HBsAg+ (N = 52)
  - Breast Cancer, HBsAg+ Anti-HBc+ (N = 42)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 80)
  - Lymphoma, HBsAg- Anti-HBc+ (N = 30)
  - Lymphoma, HBsAg+ (N = 121)

Choosing an Antiviral for HBV Prophylaxis

- Drugs with high genetic barrier to resistance (tenofovir, entecavir) preferred[^1]
- Lamivudine associated with resistance[^1]
  - Entecavir prophylaxis associated with a significantly lower incidence of HBV reactivation vs lamivudine in randomized controlled trial[^2]
- Adefovir less potent than tenofovir for treating HBV[^3]
- Lamivudine plus adefovir may be an option[^4]

2015 ACR RA Treatment Guidelines: HBV Recommendations

• **Screening**
  – No specific recommendations\(^1\)
  – 2008 guidance\(^2\): screen pts receiving methotrexate or leflunomide if high risk for HBV infection exists

• **Prophylaxis/treatment\(^1\)**
  – Active HBV infection: immunosuppressive therapy can be administered with concomitant HBV treatment
  – HBsAg+: refer for HBV prophylaxis prior to immunosuppressive therapy
  – HBsAg-/anti-HBc+: monitor HBV DNA

# Risk Stratification for HBV Reactivation

<table>
<thead>
<tr>
<th></th>
<th>HBsAg +</th>
<th>HBsAg-/Anti-HBc +</th>
<th>Antiviral Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td>• Chemotherapy</td>
<td>• Chemotherapy for heme malignancy</td>
<td>Prophylaxis</td>
</tr>
<tr>
<td></td>
<td>• Anti-CD20 or CD52</td>
<td>• Anti-CD20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• IST for transplantation</td>
<td>• Anti CD52</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Steroids in combination with other IST</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td>• Anti-TNF agents</td>
<td>• Chemotherapy for solid tumors</td>
<td>Prophylaxis or On-Demand</td>
</tr>
<tr>
<td></td>
<td>• Maintenance low dose steroids</td>
<td>• IST for transplantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other IST w/o steroids</td>
<td>• Steroids w/IST</td>
<td></td>
</tr>
<tr>
<td><strong>Low risk</strong></td>
<td>Steroids only for a few days</td>
<td>• Anti-TNF agent</td>
<td>No prophylaxis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Low dose steroid maintenance</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Other IST</td>
<td></td>
</tr>
</tbody>
</table>

IST= Immunosuppressive therapy
Anti-CD20: Rituximab,
Anti-CD52: Alemtuzumab
Anti-TNF: Infliximab, Etanercept, Adalimumab, Golimumab

Adapted from Hwang and Lok 2014
AGA Institute Guidelines on Hepatitis B Reactivation (HBVr)

Clinical Decision Support Tool

High Risk (reactivation risk > 10%)

HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive

Patients taking B cell depleting agents (e.g., rituximab, ofatumumab)

Antiviral prophylaxis for at least 12 months after discontinuation of immunosuppressive therapy

GRADE – Strong Recommendation, moderate quality of evidence.

HBsAg-positive/anti-HBc-positive

Patients taking anthracycline derivatives (e.g., doxorubicin, epirubicin)

Antiviral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy

Patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks

AGA Institute Guidelines on Hepatitis B Reactivation (HBVr) Clinical Decision Support Tool

**Moderate Risk (reactivation risk 1-10%)**

- **HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive**
  - Patients taking TNF alpha inhibitors (e.g., etanercept, adalimumab, certolizumab, infliximab)
  - Patients taking other cytokine or integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, vedolizumab)

- **HBsAg-positive/anti-HBc-positive**
  - Patients taking other cytokine or integrin inhibitors (e.g., abatacept, ustekinumab, natalizumab, vedolizumab)
  - Patients taking tyrosine kinase inhibitors (e.g., imatinib, nilotinib)

- **HBsAg-negative/anti-HBc-positive**
  - Patients taking moderate dose (10-20 mg prednisone daily or equivalent) or high dose (> 20 mg prednisone daily or equivalent) corticosteroids daily for ≥4 weeks. Patients taking anthracycline derivatives (e.g., doxorubicin, epirubicin)

**Suggest antiviral prophylaxis for at least 6 months after discontinuation of immunosuppressive therapy**

**GRADE – Weak Recommendation, moderate quality of evidence**

*Patients who place a higher value on avoiding the long-term use of antiviral therapy and cost associated with its use and a lower value on avoiding the small risk of reactivation (particularly in those who are HBsAg-negative), may reasonably select no prophylaxis over antiviral prophylaxis*

AGA Institute Guidelines on Hepatitis B Reactivation (HBVr)
Clinical Decision Support Tool

Low Risk (reactivation risk <1%)

HBsAg-positive/anti-HBc-positive or HBsAg-negative/anti-HBc-positive

Patients taking traditional immunosuppressive agents (e.g., azathioprine, 6-mercaptopurine, methotrexate)

Patients taking intra-articular corticosteroids.
Patients taking any dose oral corticosteroids daily for duration of ≤ 1 week

Patients taking low dose (< 10 mg prednisone or equivalent) corticosteroids for ≥ 4 weeks

Suggest not to use routine antiviral prophylaxis in patients undergoing immunosuppressive drug therapy and are at low risk for HBVr

GRADE – Weak Recommendation
Moderate quality of evidence

FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C

Safety Announcement

[10-04-2016] The U.S. Food and Drug Administration (FDA) is warning about the risk of hepatitis B virus (HBV) becoming an active infection again in any patient who has a current or previous infection with HBV and is treated with certain direct-acting antiviral (DAA) medicines for hepatitis C virus. In a few cases, HBV reactivation in patients treated with DAA medicines resulted in serious liver problems or death.
HBV Reactivation in Pts Receiving DAAs: Postmarketing Cases Reported to FDA

- Case reports of HBV reactivation in pts receiving DAAs
  - Reactivation: increase in HBV DNA or seroconversion to HBsAg positive
- 29 confirmed cases in ~ 3 yrs (November 2013 to October 2016)
  - Pts from Japan (n = 19), US (n = 5), other (n = 5)
  - Usually occurred within 4-8 weeks (mean 52 days)
  - 2 deaths, 1 transplant, 6 hospitalizations, 10 DAA discontinuations

FDA Recommendations for Monitoring During DAA Therapy

• To decrease the risk of HBV reactivation in patients co-infected with HBV and HCV, health care professionals should:

• Screen all patients for evidence of current or prior HBV infection before initiating treatment with DAAs by measuring HBsAg and anti-HBc. In patients with serologic evidence of HBV infection, measure baseline HBV DNA prior to DAA treatment.

• Monitor patients who show evidence of current or prior HBV infection for clinical and laboratory signs (i.e., HBsAg, HBV DNA, serum aminotransferase levels, bilirubin) of hepatitis flare or HBV reactivation during DAA treatment and post-treatment follow-up.

• Consult a physician with expertise in managing hepatitis B regarding the monitoring and consideration for HBV antiviral treatment in HCV/HBV co-infected patients.
AASLD Guidance on HBV Reactivation in Pts Receiving HCV DAA Therapy

- HBV vaccination recommended for all susceptible individuals (eg, no previous immunization, no evidence of immunization response, anti-HBc (-))
- All pts starting HCV DAA therapy should be assessed for HBV infection (HBsAg, anti-HBs, and anti-HBc testing)
  - If HBsAg+, assess HBV DNA prior to, during, and immediately after HCV DAA therapy
    - For active HBV infection, initiate HBV therapy before or simultaneously with HCV DAA therapy
    - For low or undetectable HBV DNA, monitor for HBV reactivation during HCV DAA therapy
  - Insufficient data to provide recommendations for pts who are HBsAg- and anti-HBc+ or anti-HBs+/anti-HBc+

Reactivation of HBV is a concern in the context of immunosuppressive therapy; risk variable and dependent on the type of immunosuppressive therapy.

All patients should be screened for HBV (HBsAg and anti-HBc) prior to initiation of biologics and other immunosuppressive therapy.

Assess risk for reactivation based on HBV serologies and planned immunosuppressive therapy: Guidelines in place.

More information is needed regarding HBV reactivation associated with DAA therapy for HCV.
Acknowledgements

• Robert Perrillo MD
• Mike Fried MD
• Jordan Feld MD