



HBV Reactivation and Cancer Chemotherapy

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**AASLD and the Hepatitis B Special Interest Group
Thank the Following for Their Contribution in
Providing Peer
Review of This Slide Module:**

- **2010 AASLD Practice Guidelines Committee**

- **Andrew Artz, MD, MS:** Assistant Professor of Medicine, Hematology and Oncology, Pritzker School Of Medicine
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Disclosures

- Dr. Feld has served on the advisory board of Roche and Merck (Schering) Pharmaceuticals and has received a travel grant from Gilead Sciences.

Chemotherapy-induced HBV Reactivation

Definition:

- Loss of HBV immune control in a patient with inactive or resolved HBV infection
- Reappearance or increase in viral replication with liver damage occurring during and/or following immune reconstitution
- **Clinically:**
 - Range from subclinical to severe or even fatal hepatitis
 - Rise in HBV DNA +/- return of HBeAg
 - ALT increase (may be mild to very high)
 - May progress to liver failure and death

Pre Chemo

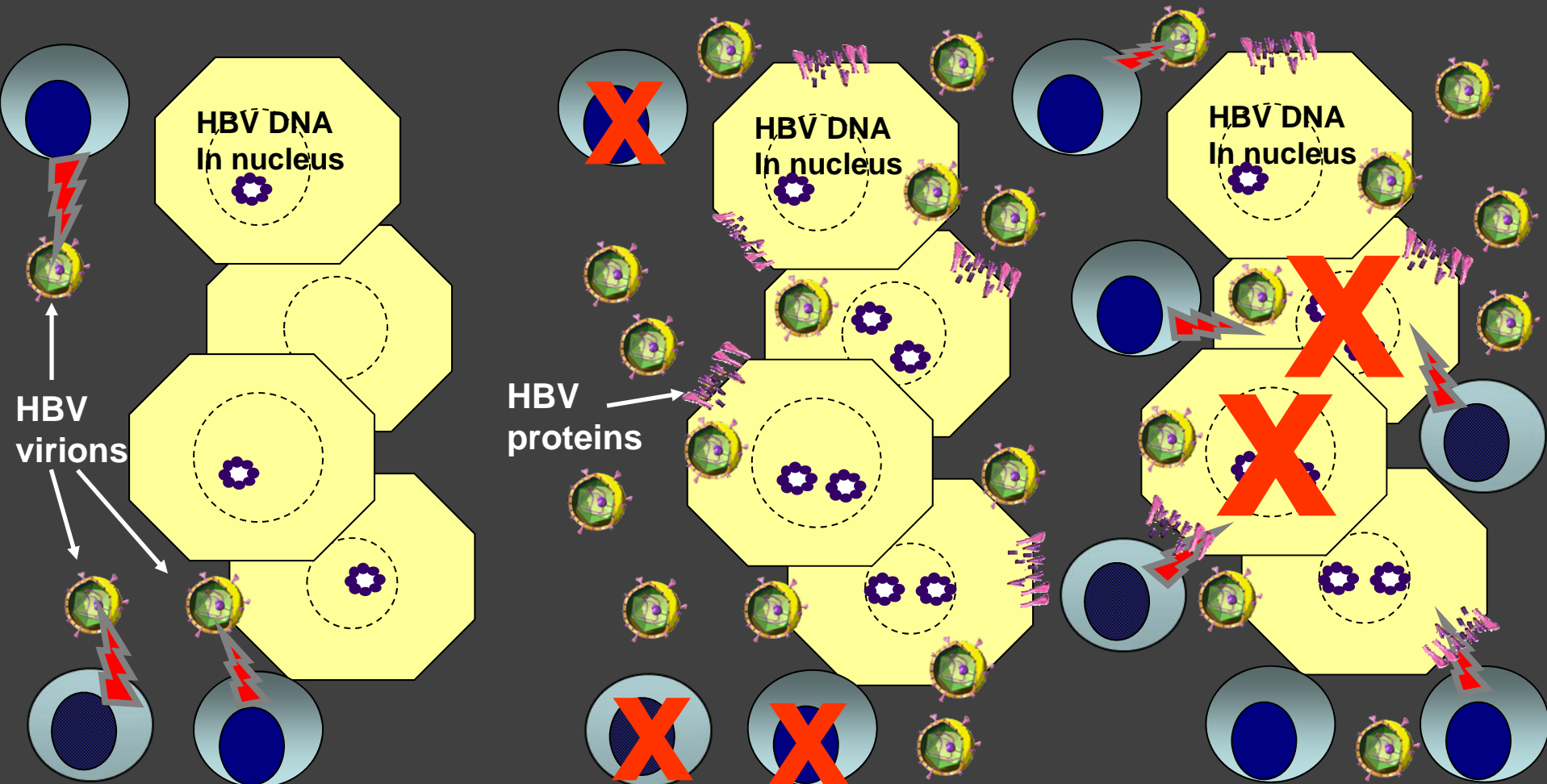
During Chemo

After Chemo

HBV DNA \pm
ALT NL

HBV DNA +++++
ALT NL or slightly abnl

HBV DNA \pm
ALT very elevated

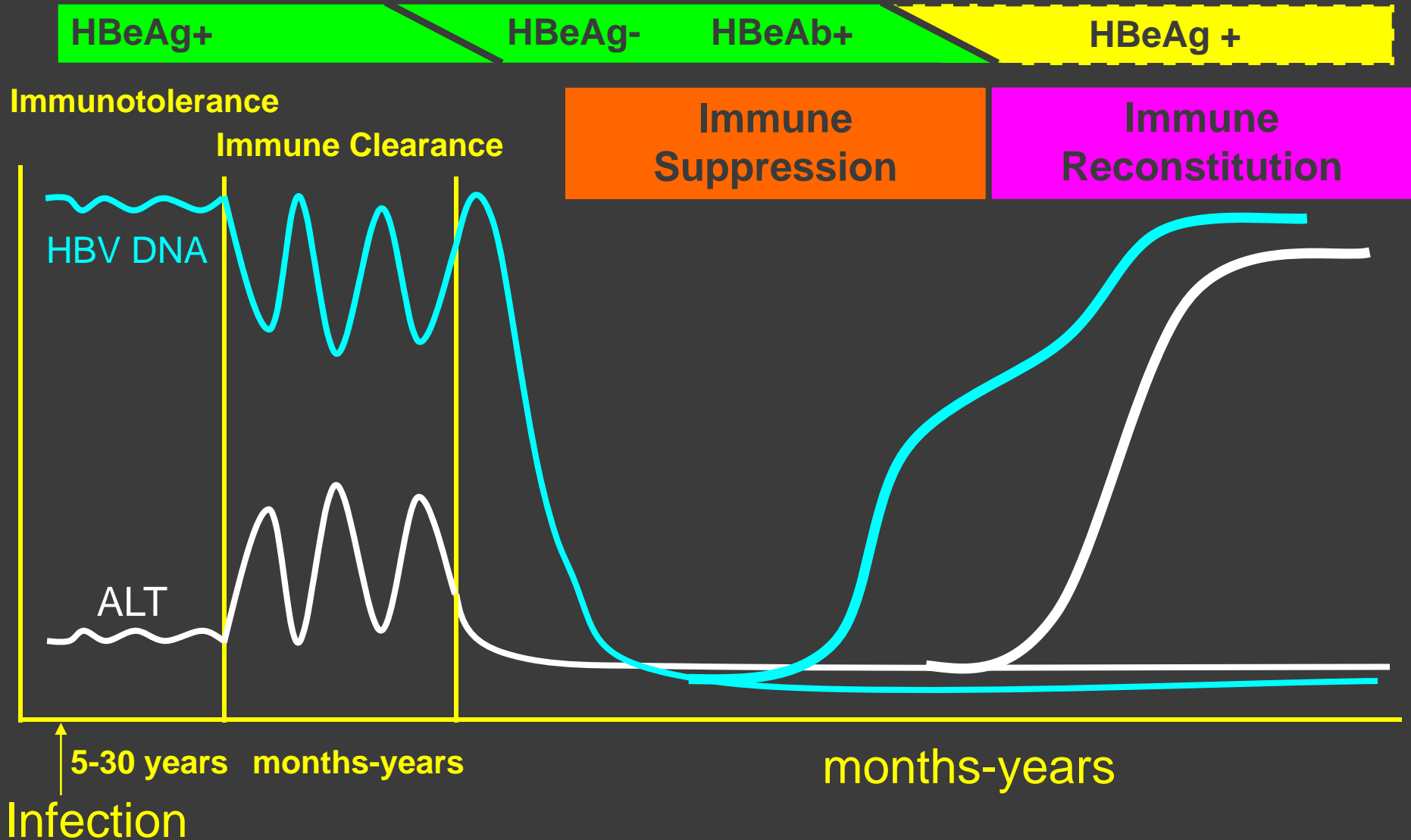


HBV-specific
B & T cells
Control HBV replication

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

Immune activation
HBV clearance
Hepatocyte damage

HBV Reactivation



Agents Reported to Cause HBV Reactivation

- Steroids 1975
(prednisone/dexamethasone)
- Anthracyclines 1975
(doxorubicin/epirubicin)
- Vincristine 1975
- Bleomycin 1982
- Busulfan 1984
- Etoposide 1985
- Methotrexate 1989
- 6-mercaptopurine 1990
- Actinomycin D 1990
- Azauridine 1991
- Chlorambucil 1992
- Cytosine arabinoside
1996
- Leucovorin 1996
- Cisplatin 2000
- Rituximab 2001
- Gemcitabine 2003



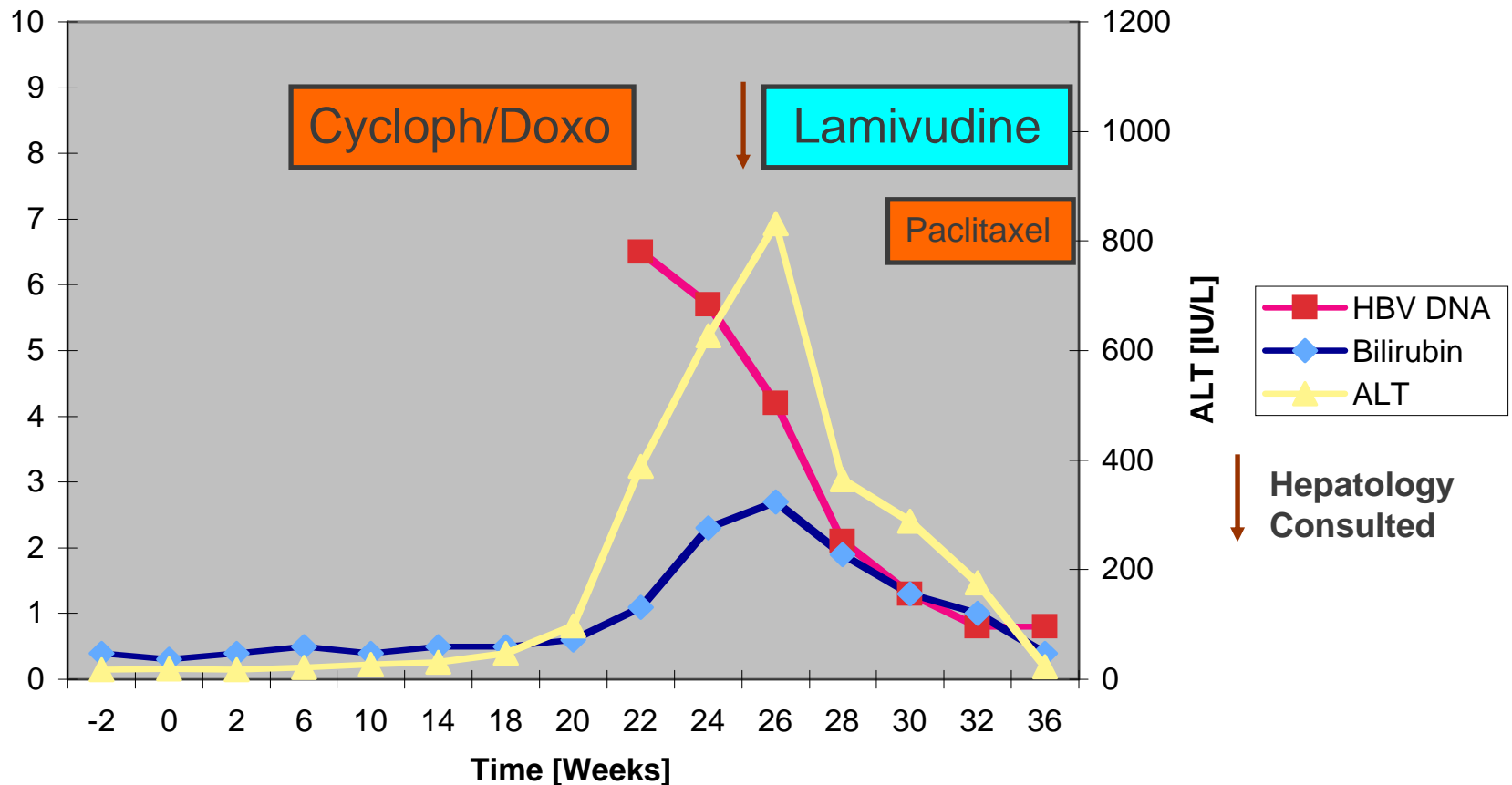
Management

Options:

- A) Start chemotherapy with routine monitoring of ALT, along with other labs.
- B) Test for HBsAg, anti-HBc & anti-HBs prior to chemotherapy. Follow ALT and HBV DNA, consult with liver specialist if *either* increasing.
- C) Test for HBsAg, anti-HBc & anti-HBs prior to chemotherapy and refer to liver specialist if HBsAg +ve.

Option A

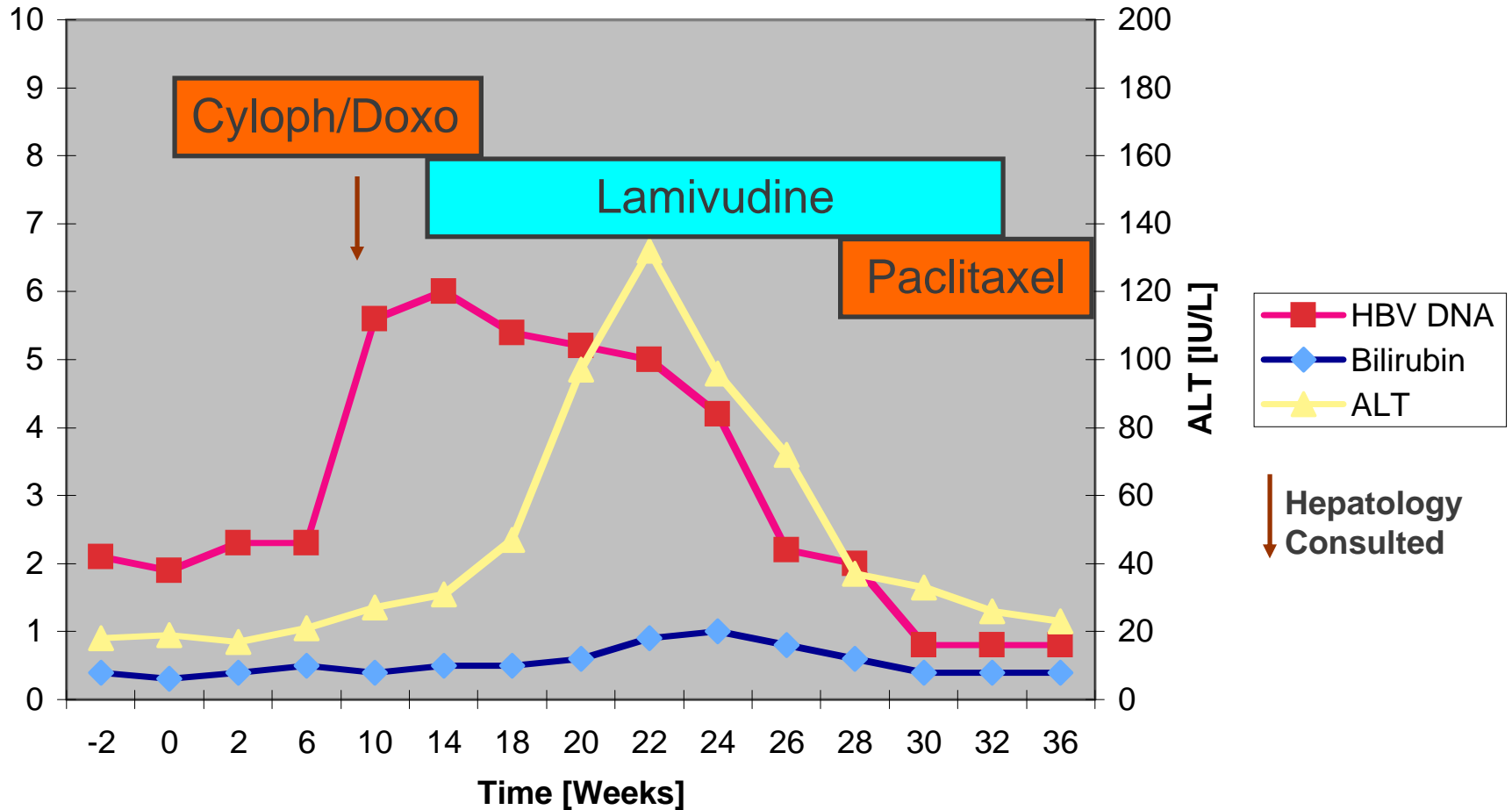
Patient HBsAg +ve with HBV DNA 2.1 log IU/mL at baseline



- Significant hepatitis flare (ALT peak 812) with mild rise in bilirubin
- Delay in starting paclitaxel

Option B

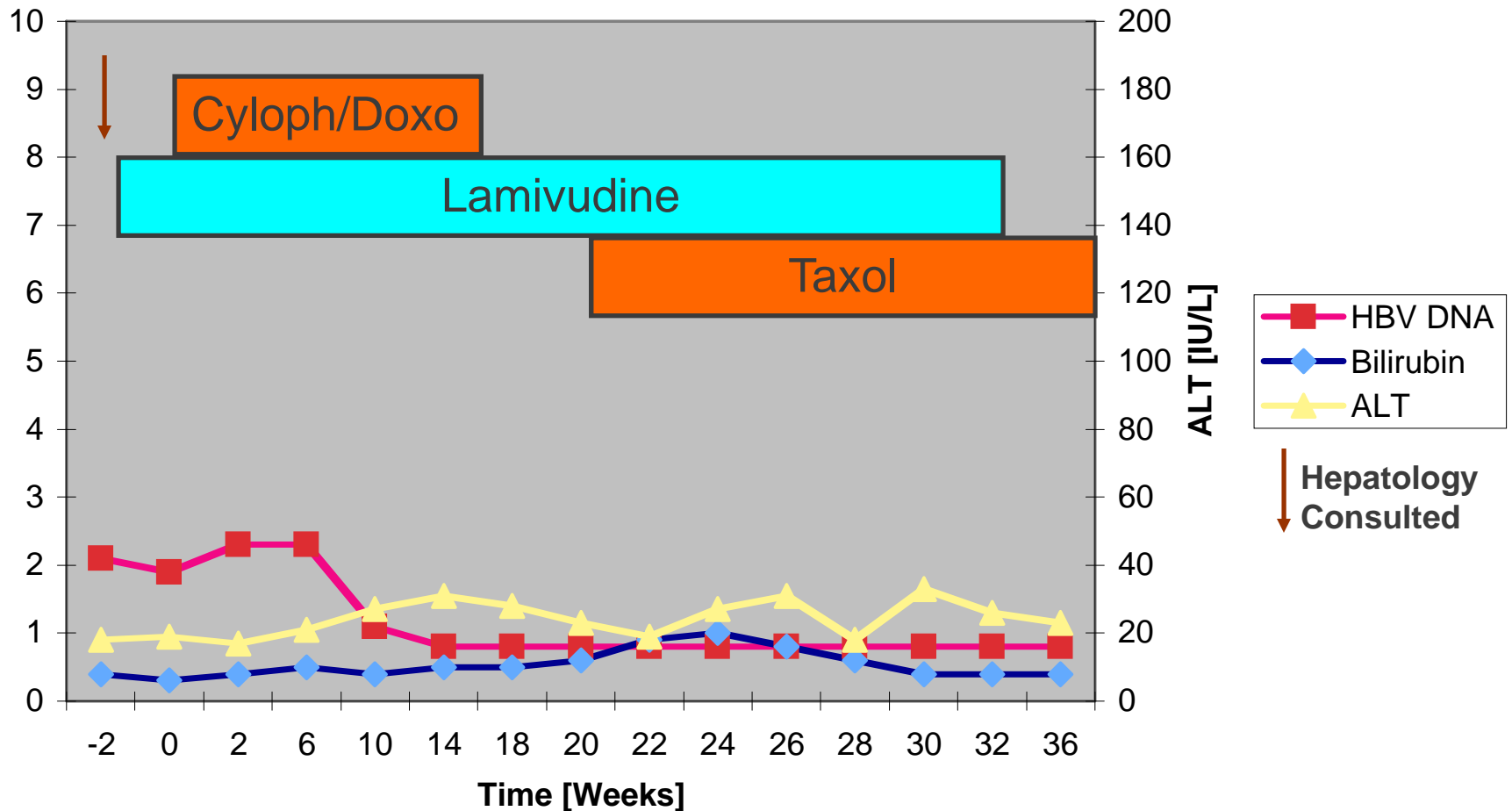
Patient HBsAg +ve with HBV DNA 2.1 log IU/mL at baseline



- Less severe hepatitis (ALT peak 132) with no bilirubin rise
- Delay in starting paclitaxel

Option C

Patient HBsAg +ve with HBV DNA 2.1 log IU/mL at baseline



■ Uninterrupted chemotherapy with no hepatitis flare

Consequences of Delayed Recognition/Treatment of Reactivated HBV

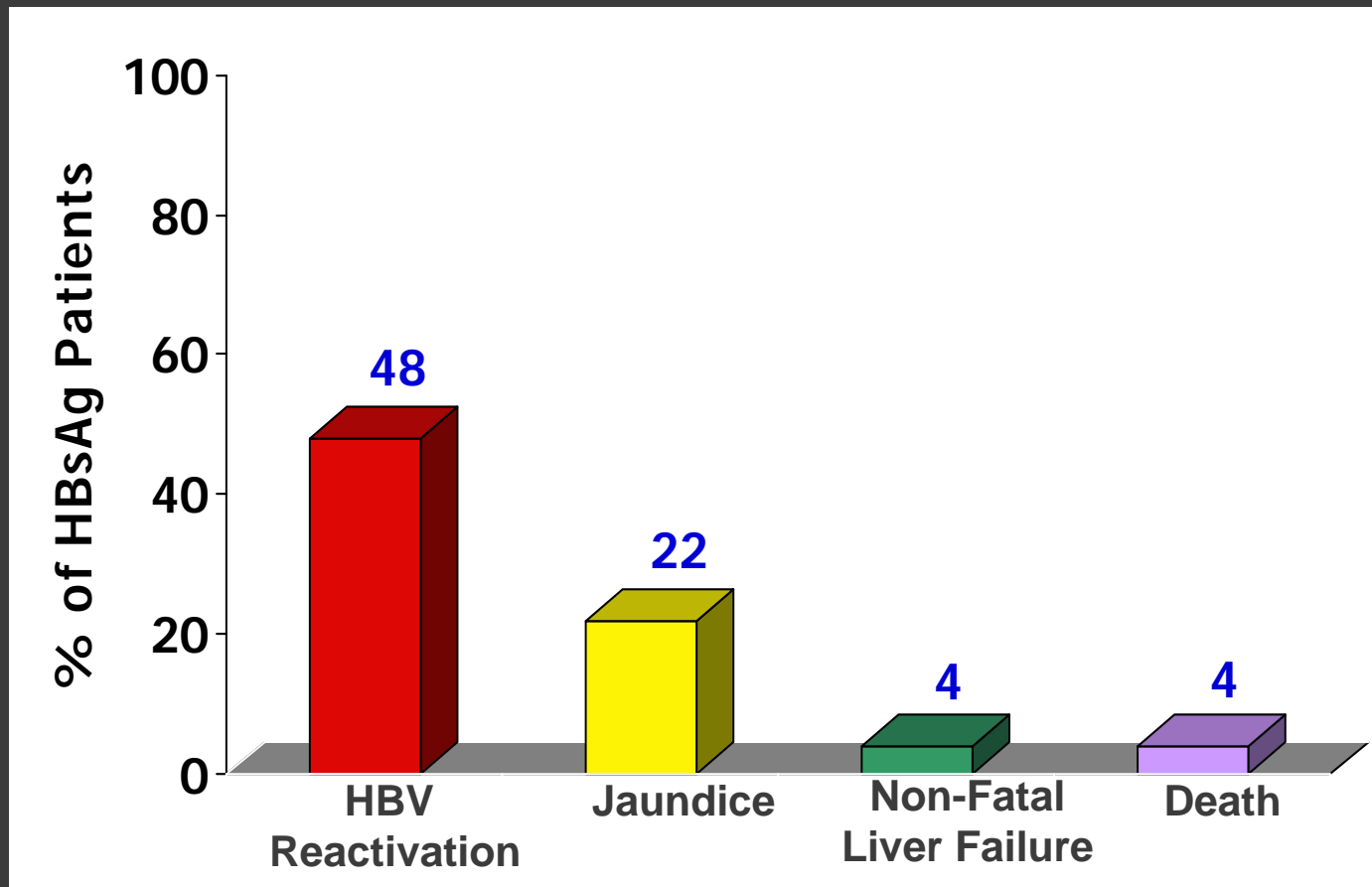
- **Hepatitis**
 - May be severe or even fulminant
 - Occasionally may miss HBV DNA spike if not followed routinely during treatment because HBV DNA falls when ALT rises
 - This may lead to misdiagnosis and unanticipated flares of hepatitis
- **Interruption of chemotherapy**
 - Potential for poorer cancer-related outcome

Rate of HBV Reactivation: Solid Tumors

- Rate of HBV-associated acute hepatitis 21% among HBsAg +ve breast cancer patients¹
 - With careful monitoring (ALT and HBV DNA), up to 41% with HBV reactivation²
 - HBV DNA may be undetectable by time of ALT peak
- Of those who flare, 78% need interruption and 14% have premature termination of chemotherapy³
- Risk Factors - male, HBeAg +ve, younger age³

Hematological Malignancy: The Bigger Risk

100 patients with NHL undergoing CHOP
27 HBsAg +ve



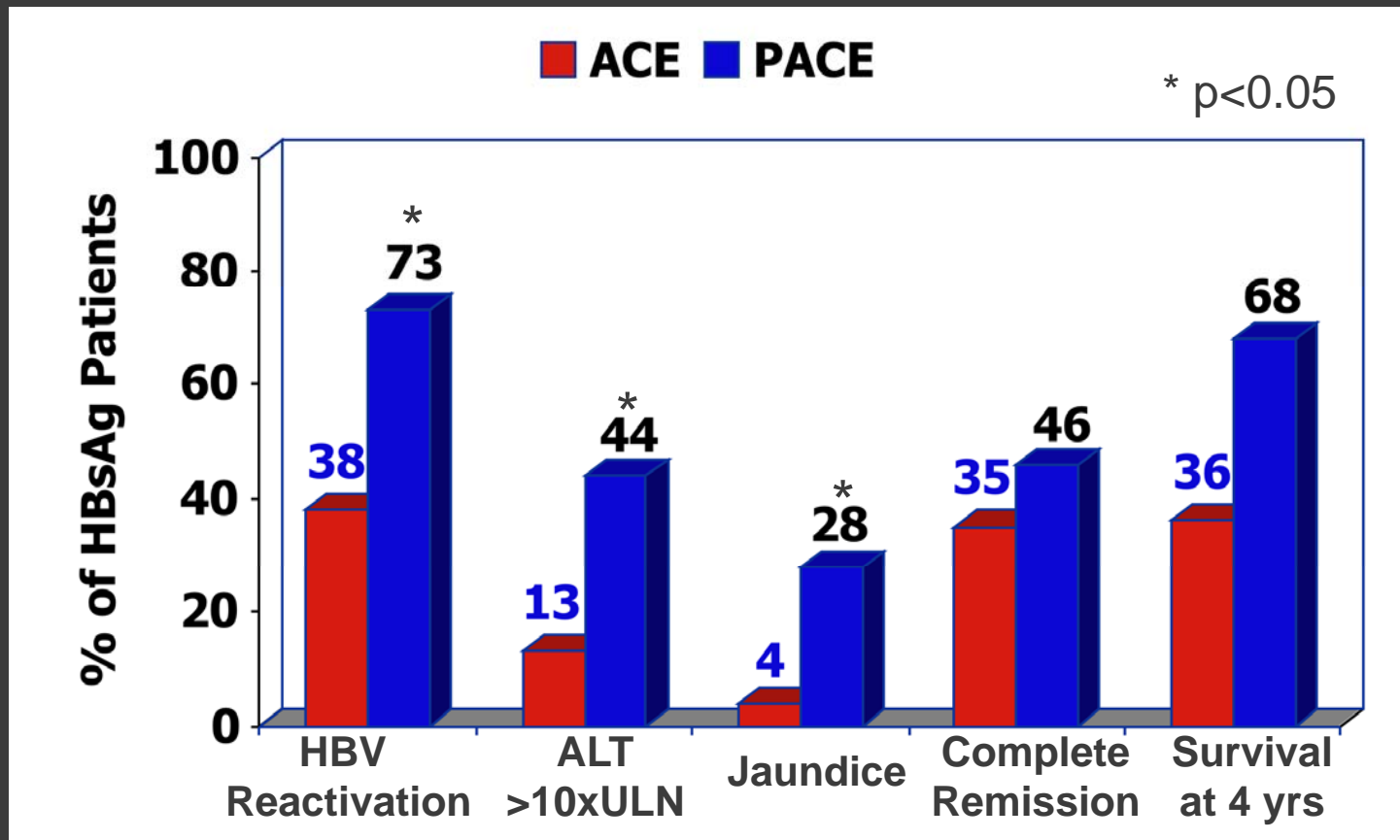
Risk Factors for Reactivation

- **Malignancy**
 - NHL 40-58% of HBsAg +ve
 - Breast cancer 20-41% of HBsAg +ve
- **Potency of Immunosuppression**
- **Serology**
 - If HBV DNA detectable, increased risk
 - If HBeAg +ve, increased risk
- **Demographics**
 - Men > women

Baseline liver tests - not relevant

Steroids Increase Risk

50 pts with NHL and HBsAg +ve randomized to Epirubicin, Cyclophosphamide & Etoposide (ACE) +/- Prednisone (P)



Prednisone increased risk and severity of HBV reactivation
But trend toward improved NHL outcome

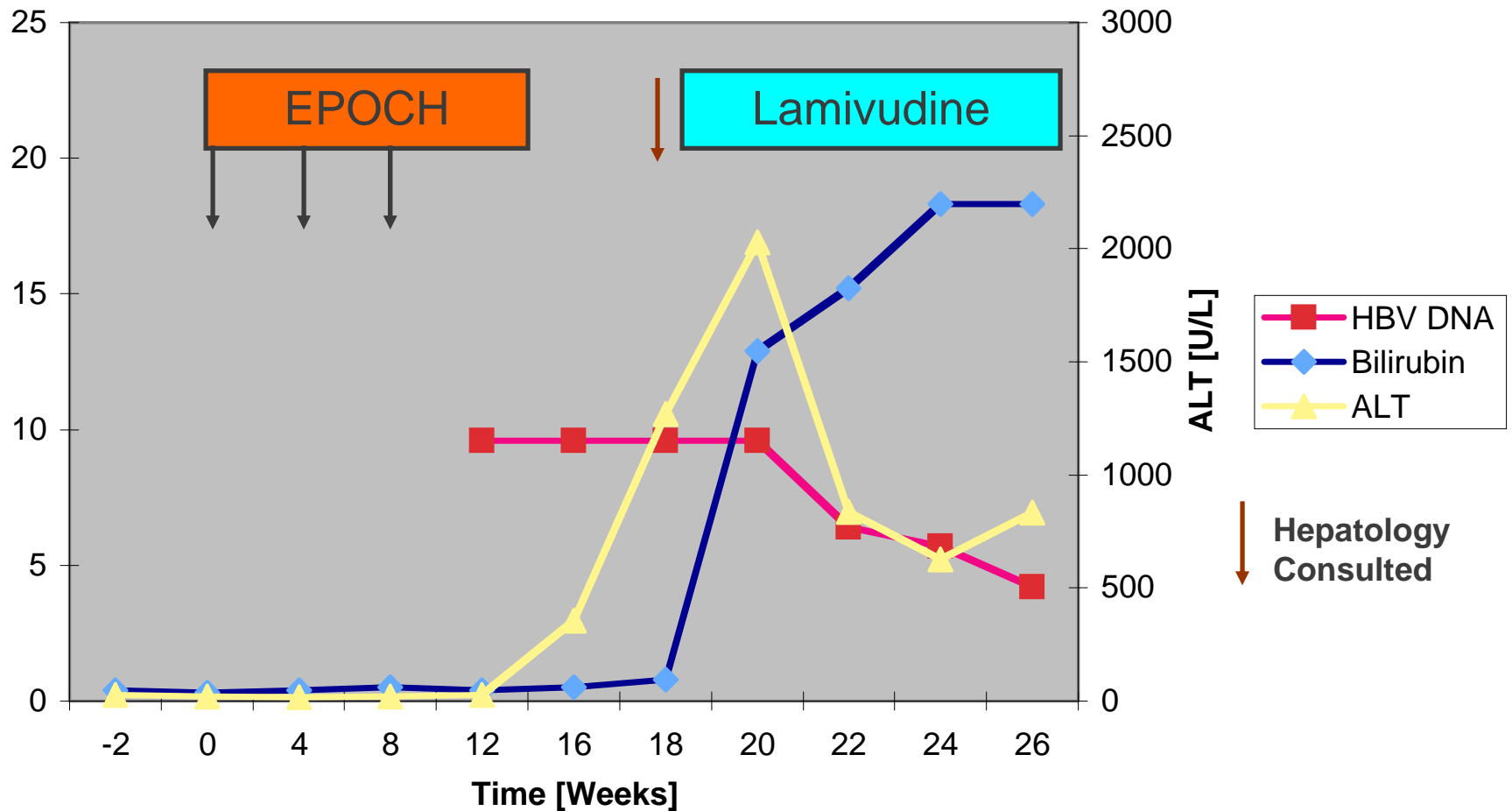
Options

- Work-up revealed HBsAg +ve, HBeAg -ve, anti-HBe +ve, HBV DNA 129 IU/mL

Do you:

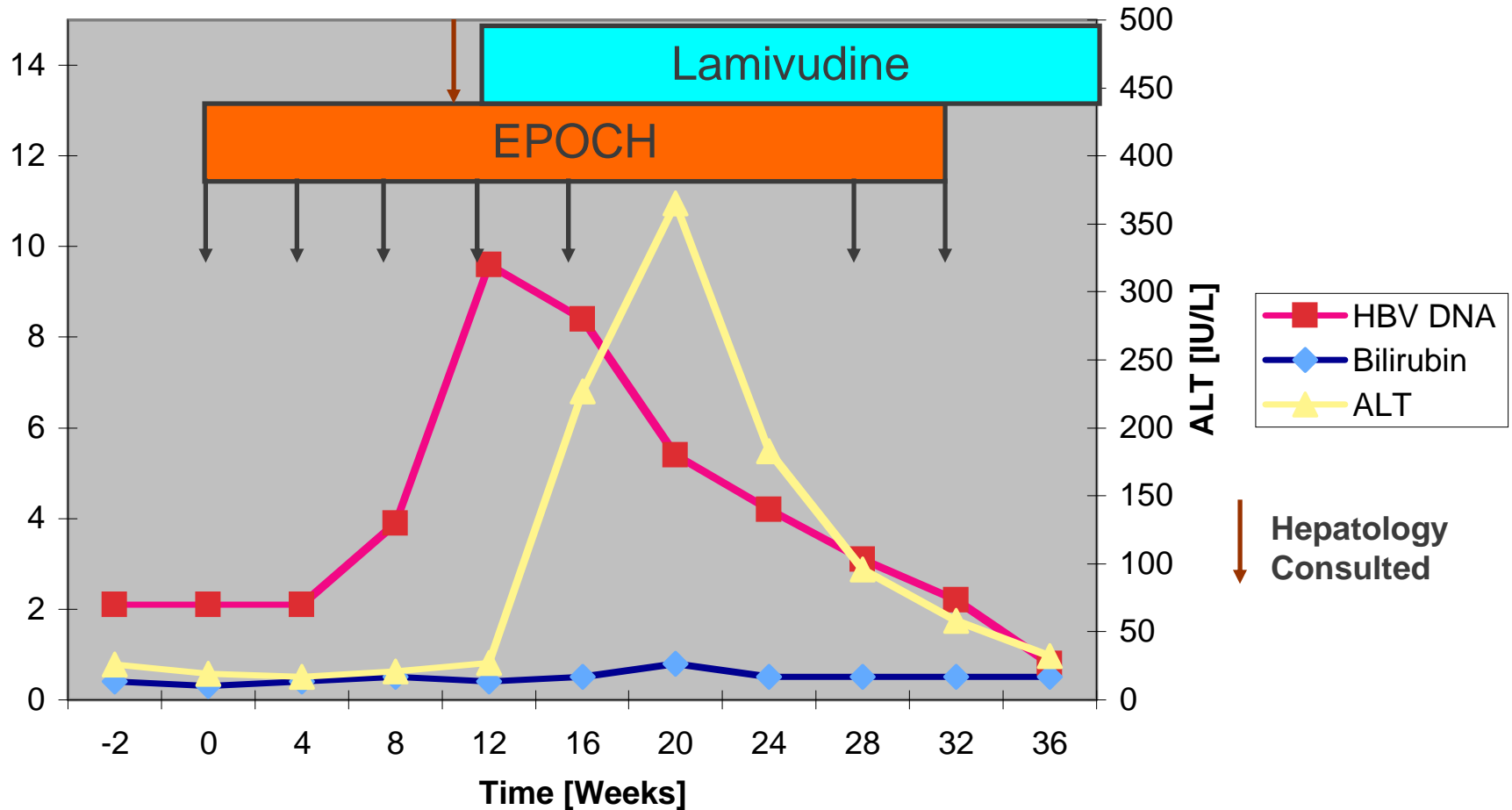
- A) Monitor ALT weekly to identify HBV reactivation
- B) Monitor HBV DNA and ALT monthly to identify HBV reactivation
- C) Consult liver specialist prior to chemotherapy and monitor ALT and HBV DNA during therapy

Option A



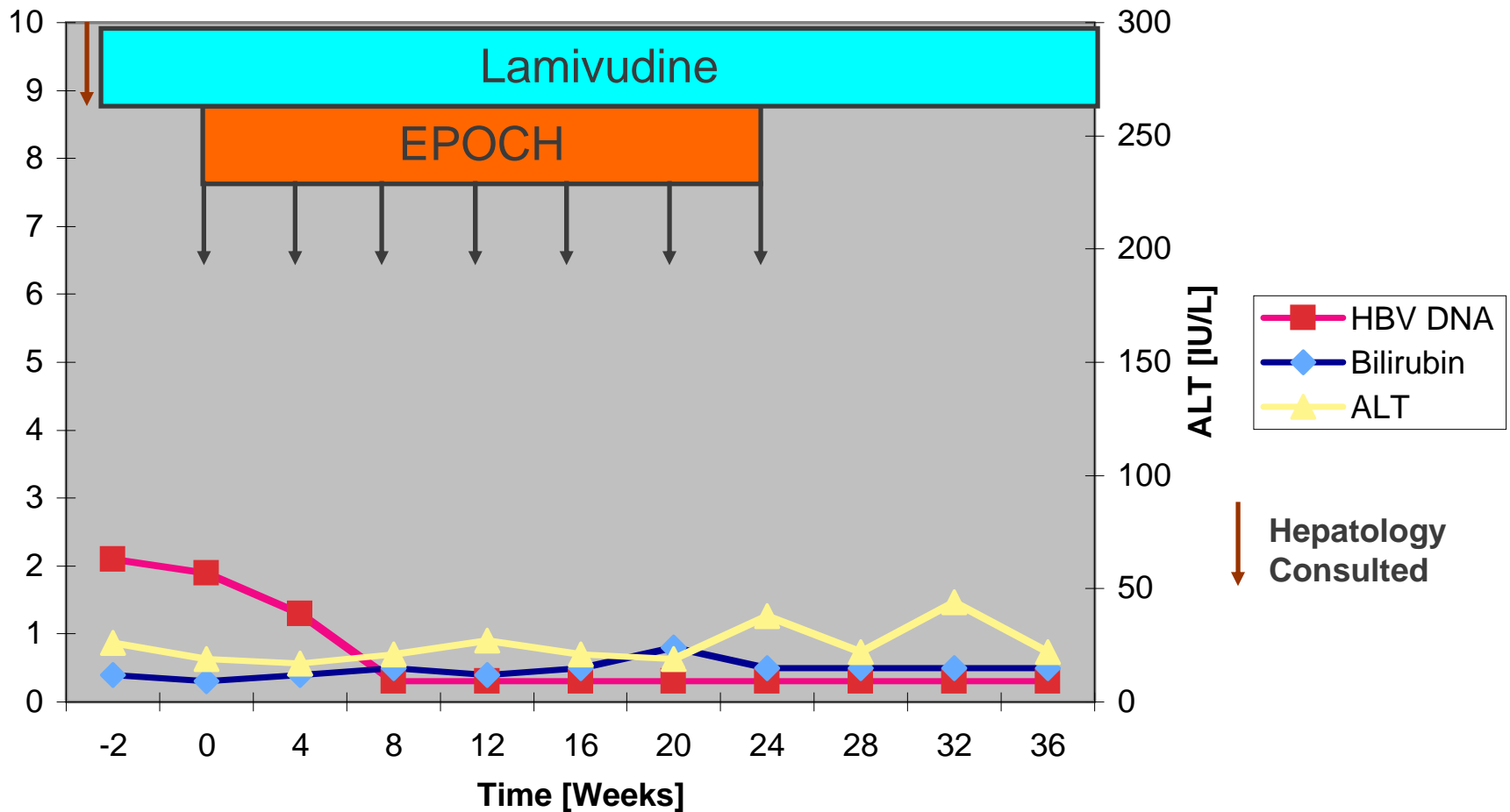
Despite lamivudine patient died of liver failure

Option B



Less severe flare resulting in chemotherapy interruption

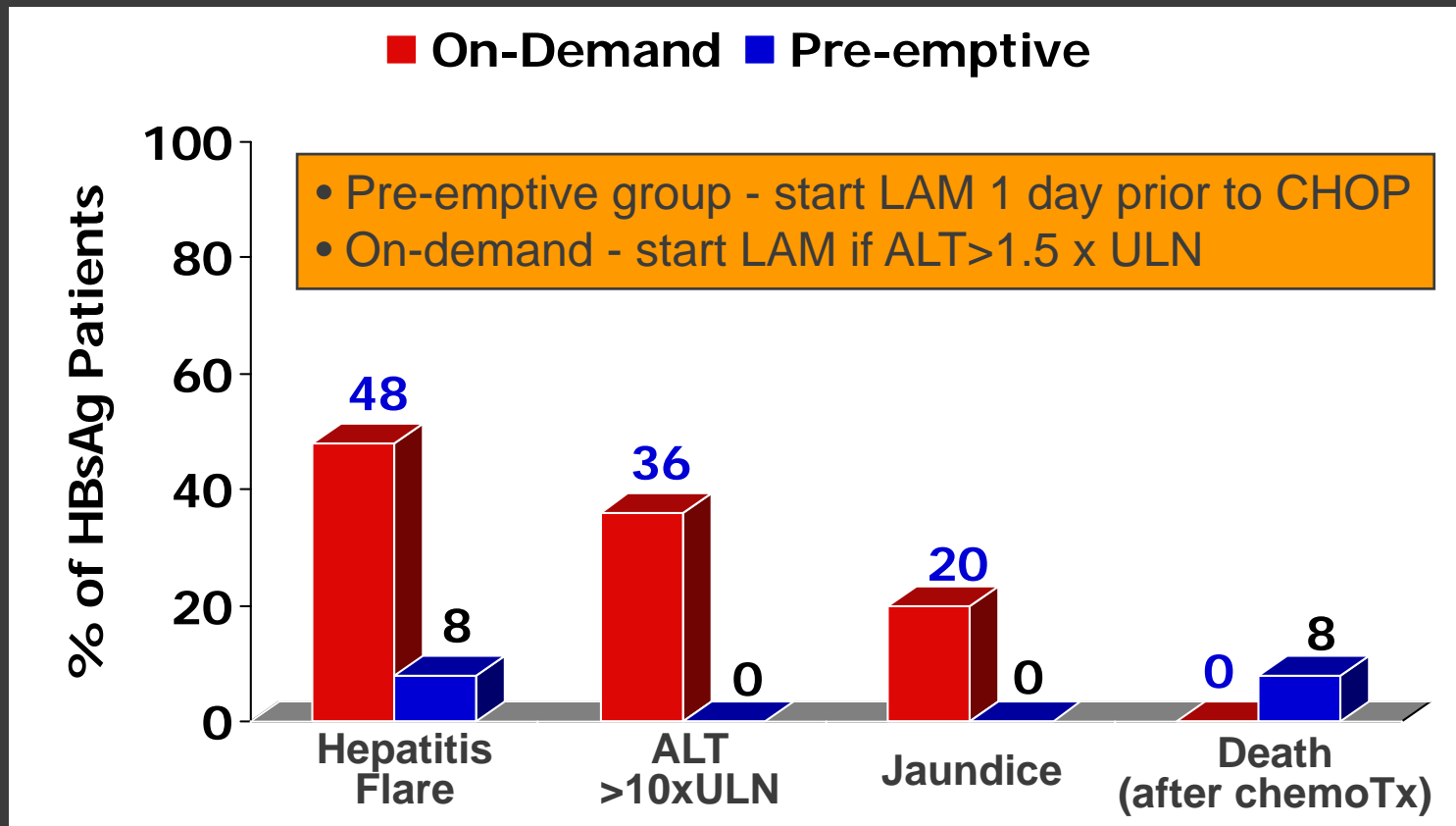
Option C



Uninterrupted successful chemotherapy

Value of Pre-Emptive Antivirals

HBsAg +ve pts with NHL treated with CHOP
Randomized 'Pre-emptive' vs 'On-Demand' Lamivudine



Pre-emptive antivirals decrease HBV reactivation

Who should be screened?

CDC recommends screening *ALL* patients prior to starting chemotherapy¹

Current ASCO Recommendations on Screening for HBV Before Chemotherapy



- Evidence insufficient to determine net benefits and harms of routine screening for chronic HBV infection....
- Physicians may consider screening groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy planned....
- Antiviral therapy before and during course of chemotherapy *may* be considered...

Screening Tests & Results

Test	Significance	Action
HBsAg	HBV infection	Prophylaxis indicated
Anti-HBs alone	Immunity to HBV	None
Anti-HBc +/- anti-HBs	Exposure to HBV	<ul style="list-style-type: none">- If HBsAg -ve, low risk for standard chemotherapy- If BMT or Rituximab consider prophylaxis



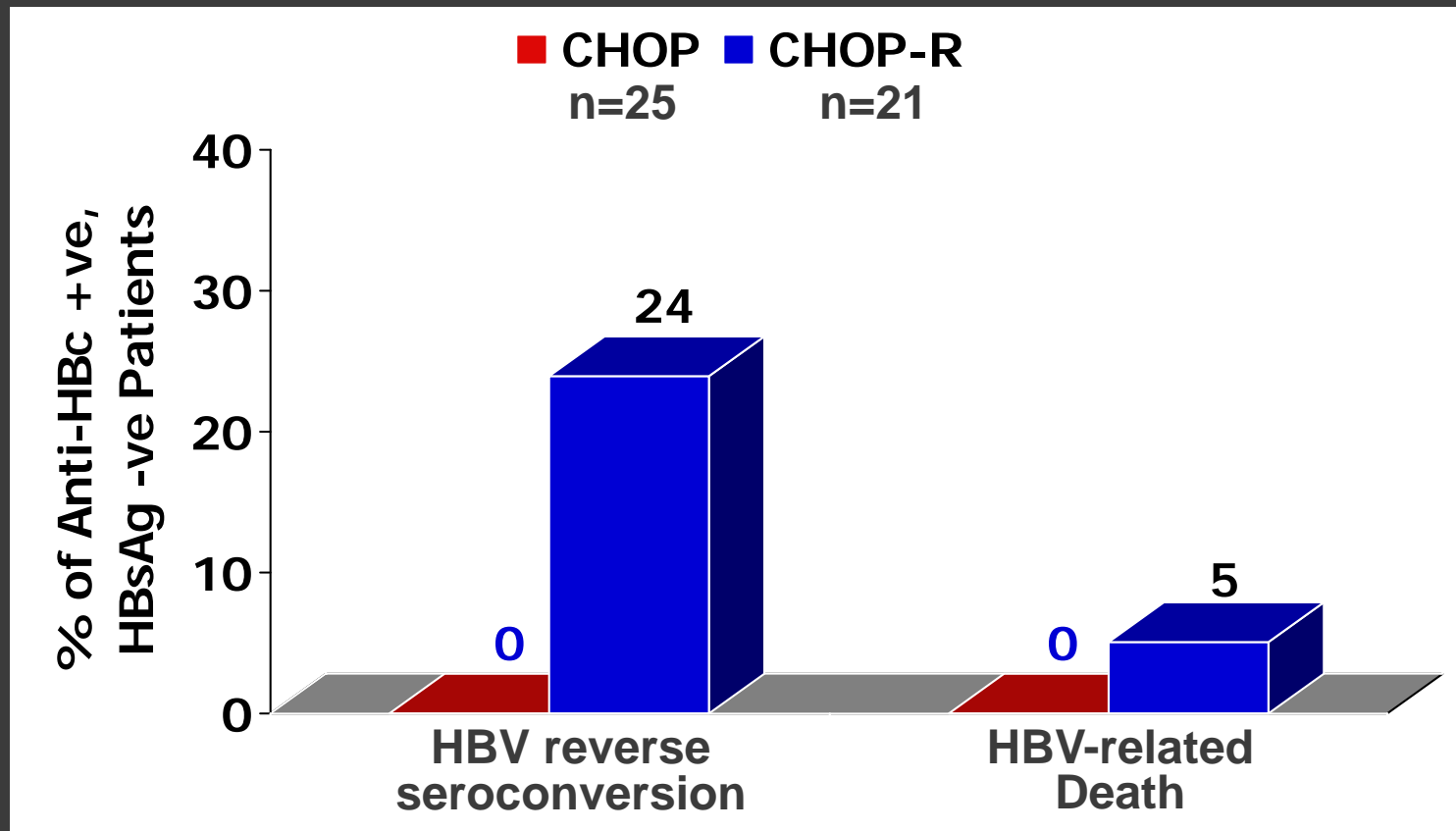
Rituximab: A Particular Problem

- Monoclonal antibody against CD20 - B cell marker
- Reduces B cell numbers and antibody levels
- Increasingly used as part of CHOP-R, EPOCH-R

- Increased risk of HBV reactivation, including HBsAg-negative patients
- Reverse Seroconversion: Reappearance of HBsAg in previously HBsAg-negative patient

Rituximab in HBsAg-Negative

46 pts Diffuse Large Cell B Lymphoma
HBsAg -ve, anti-HBc +ve
Treated CHOP or CHOP-R



Rituximab: Late and Severe

- Reverse seroconversion:
 - Median 98 days **AFTER** last cycle
 - Median peak ALT - 809 (362-3,499 U/L)
 - Median peak Bilirubin - 3.8 (1.1-14.6 g/dL)
- Risk Factors: Male, lack of anti-HBs
- 23 other cases reported in literature:
 - 6 to 23 months after rituximab
 - 15 liver failure, 13 liver-related death

Case 3

54 yo Asian man stage 4 Diffuse Large Cell B Lymphoma

Anti-HBc +
HBsAg -

+

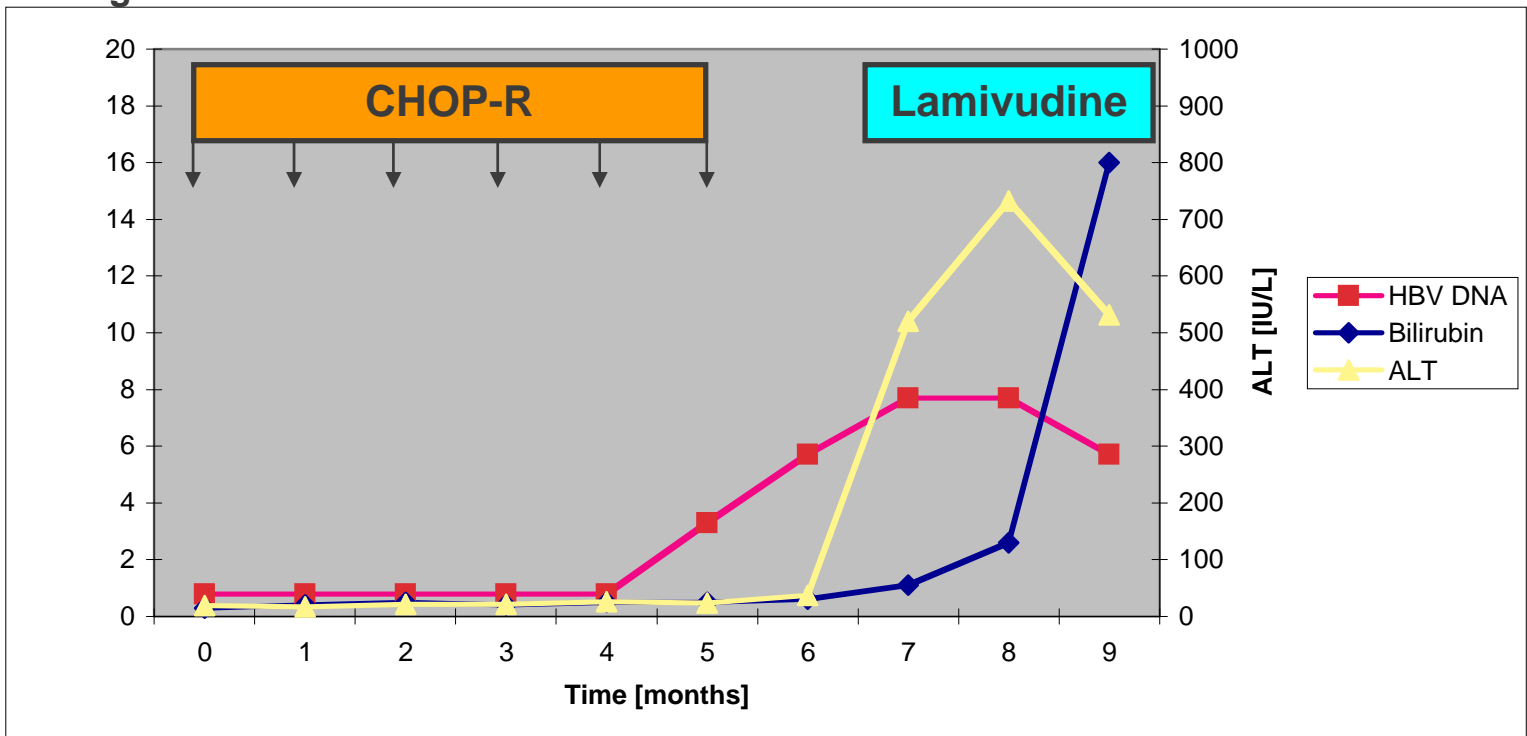
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Patient died of liver failure despite lamivudine

Bone Marrow Transplantation: Increased Risk of Reactivation

- **Markedly increased rate of reactivation (HBsAg +ve)**
 - Up to 75%¹
 - Long-term complications: cirrhosis 10%²
- **Reverse seroconversion common if anti-HBc +ve**
 - Up to 50% become HBsAg +ve³
 - May occur very late
- **HBV status of donor important**
 - Natural immunity (anti-HBs, anti-HBc) – recipient may clear HBsAg²
 - Vaccinated (anti-HBs) - possibly some protection



Case 4 - Thinking Long-term

- 54 yo Jamaican woman with multiple myeloma
- Allo stem cell transplant from her sister
- Pre-transplant:

	Patient	Sister
HBsAg	-ve	-ve
anti-HBc	+ve	-ve
anti-HBs	-ve	-ve

- ALT 17 U/L, Bili 0.4 g/dL

Options

- 18 months post-transplant presents with GI and skin GVHD
 - ALT found to be 162 IU/L
-
- A) Treat GVHD with steroids & tacrolimus
 - B) Extensive work-up for causes of ALT elevation
 - C) Assume ALT is due to drug toxicity and change to alternative immunosuppressive therapy

Option A or C

- Skin and GI GVHD ultimately responded well to immunosuppressive therapy with improvement in ALT
- Repeated similar bouts - treated identically with apparent good clinical response

Case 4: Long-Term Results

- 4 years post-transplant:
Presents with edema/ascites
ALT 70 U/L, Bilirubin 1.7 g/dL, Albumin 2.9 g/L,
INR 1.4
Work-up revealed HBsAg +ve, HBeAg +ve
HBV DNA 2.2×10^8 IU/mL
- Liver biopsy - established cirrhosis with active HBV hepatitis
- Treated with entecavir by hepatologist
- Died 6 months later of variceal hemorrhage with no recurrence of myeloma



Option B

- Work-up revealed HBsAg +ve, HBeAg +ve
HBV DNA 1.5×10^6 IU/mL
- HCV, CMV, EBV all negative
- Liver biopsy - active HBV hepatitis with minimal fibrosis
- Treated with entecavir by hepatologist with good response
- No recurrence of myeloma 6 years later



Optimal Prophylaxis

- Considerations:
 - **Timing**
 - Pre-emptive (1 wk prior to chemo) superior to as needed
 - Also reduces costs of frequent monitoring
 - **Antiviral potency**
 - Important if treating reactivation with high viral load
 - Not as important for pre-emptive therapy
 - **Resistance profile**
 - Depends on baseline viral load + duration of therapy
 - **Duration of therapy**
 - Depends on duration of immunosuppression

Summary

- HBV reactivation not uncommon in HBsAg +ve individuals with standard chemotherapy
- HBV may reactivate even in those with apparently resolved infection (anti-HBc +ve, HBsAg -ve)
- Risk highest with rituximab and stem-cell/BM transplantation
- HBV reactivation can be effectively prevented with pre-emptive antiviral therapy
- Pre-emptive therapy requires pre-emptive screening - screening recommended by CDC, AASLD and IOM
 - All patients to receive standard chemotherapy: Screen HBsAg
 - All patients to receive rituximab/BMT: Screen HBsAg, anti-HBc, anti-HBs