HBV Reactivation: A Preventable Menace

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Disclosures

- Research Grant Support
  - Gilead
  - BMS

Case Presentation

- 38F HBsAg+ with newly dx'd breast CA
  - poorly differentiated infiltrating ductal CA
- Recommendation made for immediate chemotherapy followed by surgery
- HBsAg+ known since age 24
- SH: emigrated from Shanghai, married with 3 yo child, works as chemist
- Labs: LFTs WNL, CBC, INR normal, HBsAg(+), eAg(-), HBV DNA < 60 IU/mL

Case Presentation

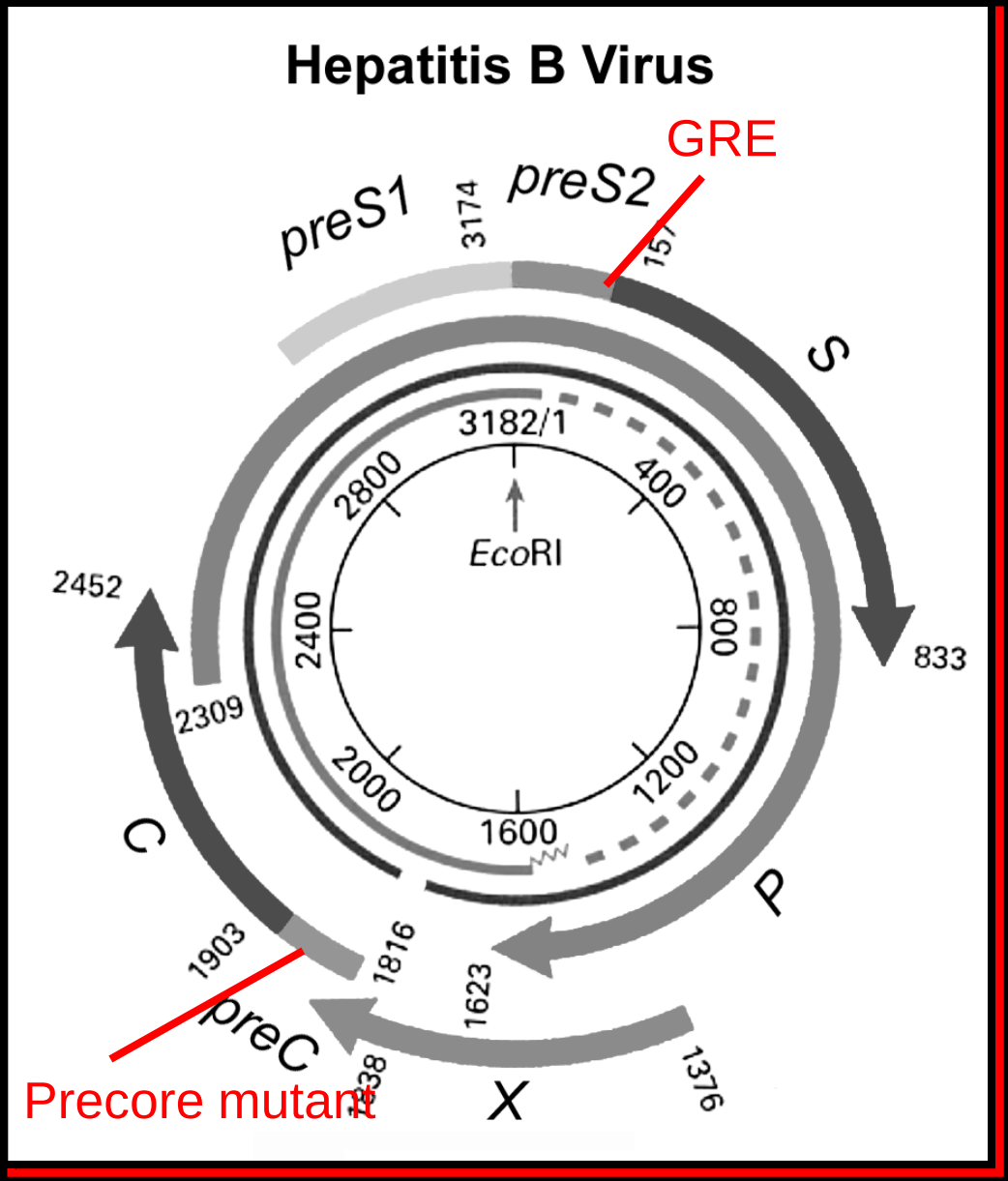
- Begun on preoperative Doxorubicin/Cyclo
  - LFTs normal pre-treatment and after first 3 cycles
- After 4th cycle: AST 3800, ALT 900, LDH 1800, TB 1.7, admitted to OSH
- 3 days later (6.23.07): TB 20/DB 13.5, AST 298, ALT 312, INR 5.2, NH_3 47 → 122, transferred to MGH
- ETV 1 mg/d begun, HBV DNA $4.0x10^{10}$ IU/mL
- ALT, AST improved, but INR rose to 15, HE worsened, NH_3 to 160
- Listed status I for OLT 7.3.07 → OLT 7.7.07
- 2017: has done well on ETV since, NED

HBV Reactivation

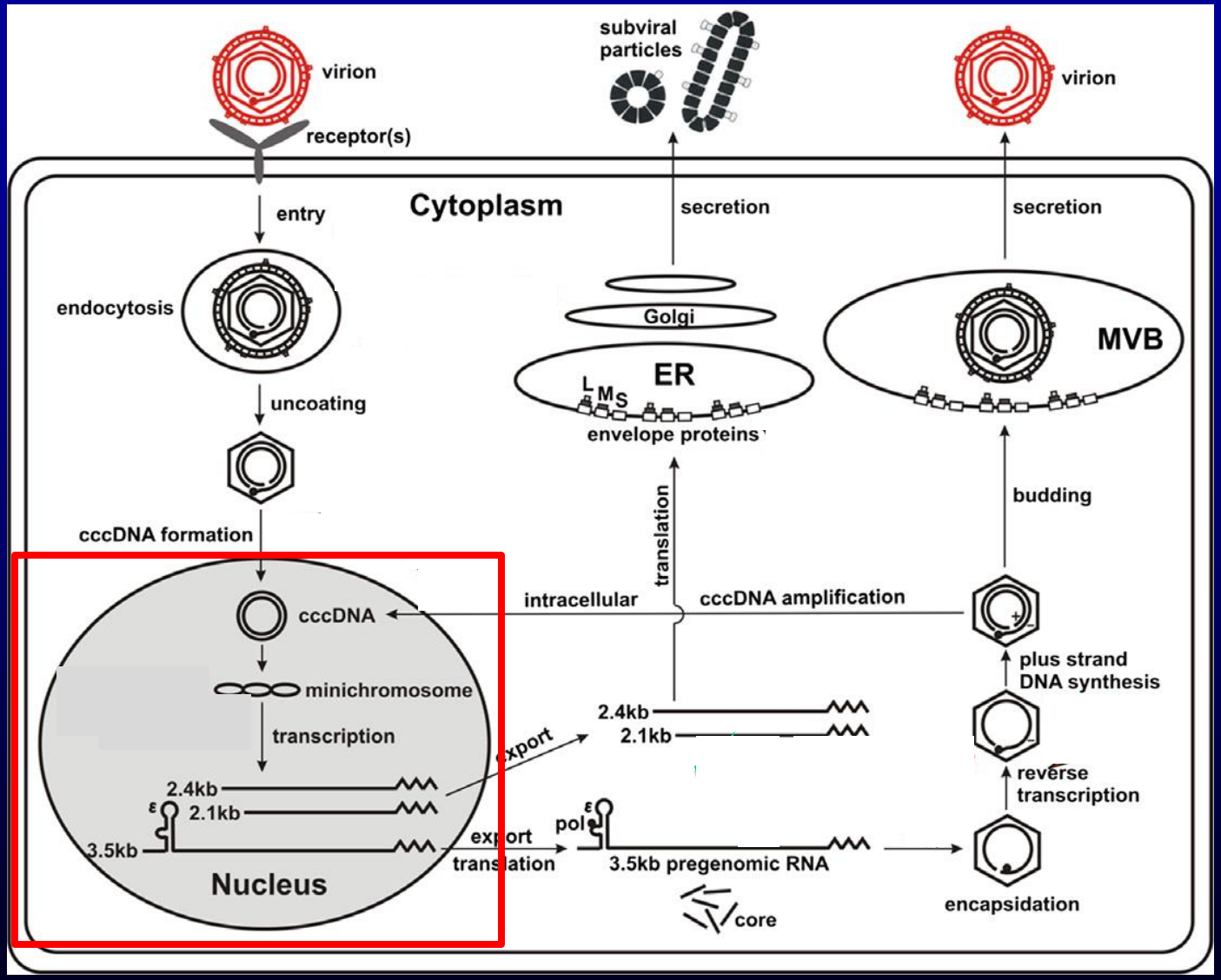
- A significant and underappreciated problem
- Completely preventable with appropriate preparation
- Clinical scenarios:
  - Chemotherapy
  - Immunosuppression
  - Biologics
  - Cure of HCV with DAAs

Hepatitis B Virus

- Small partially double-stranded DNA virus
- Prototype of the *hepadnavirus* family
- 4 major gene products
- glucocorticoid responsive element



The HBV lifecycle

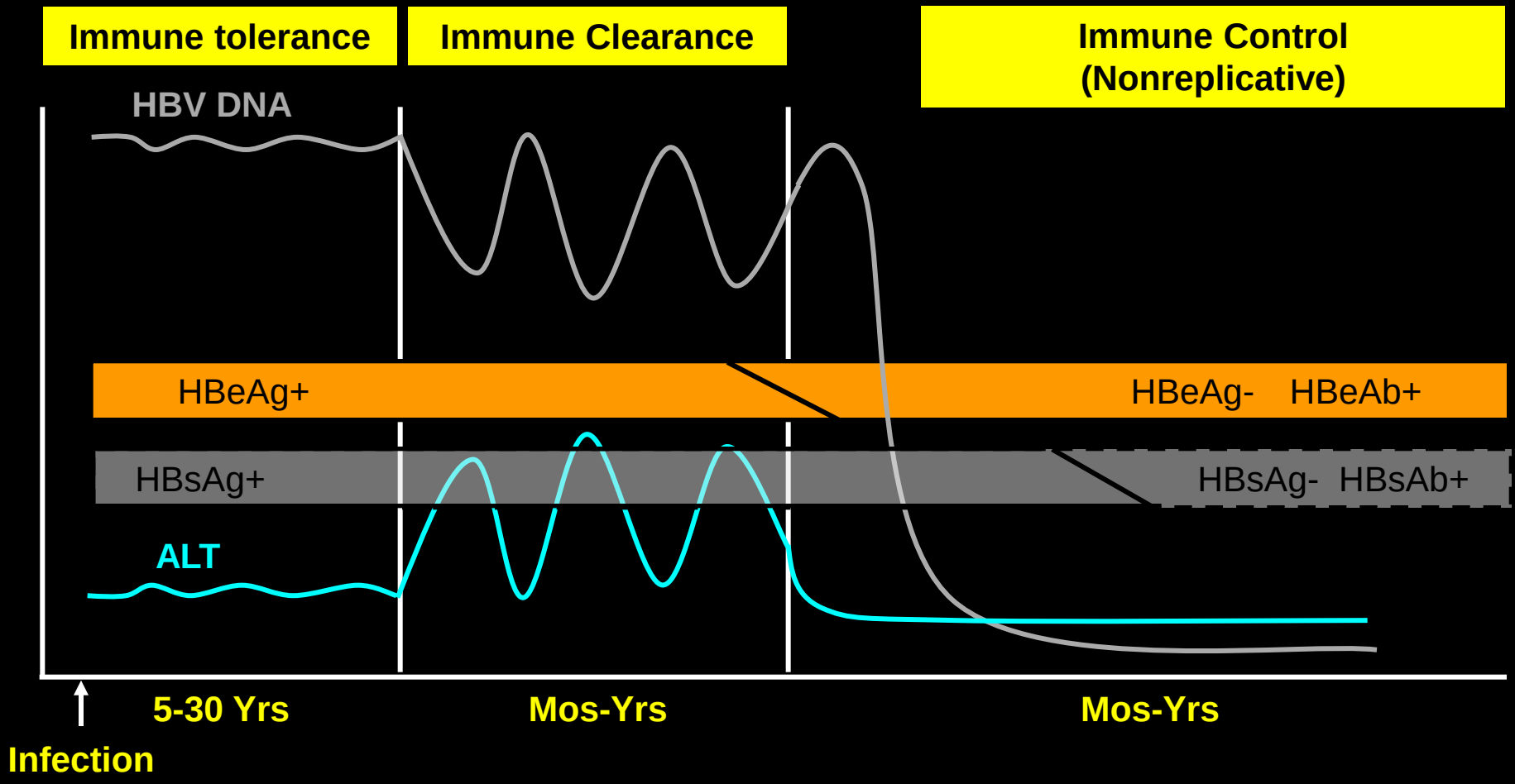


Block et al, *Antiviral Res* 2013 98:27

Typical Interpretation of Serologic Test Results for HBV Infection

Serologic Marker Results				
HBs Ag	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
-	-	-	-	Never infected and no evidence of immunization
+	+	+	-	Acute infection
+	+	-	-	Chronic infection
-	+	-	-	Exposure, false positive or chronic infection
-	+	-	+	Exposure and clearance of HBV infection
-	-	-	+	Immune (immunization)

Natural History of Chronic HBV Infection



Yim HJ, et al. Hepatology. 2006;43:S173-S181.

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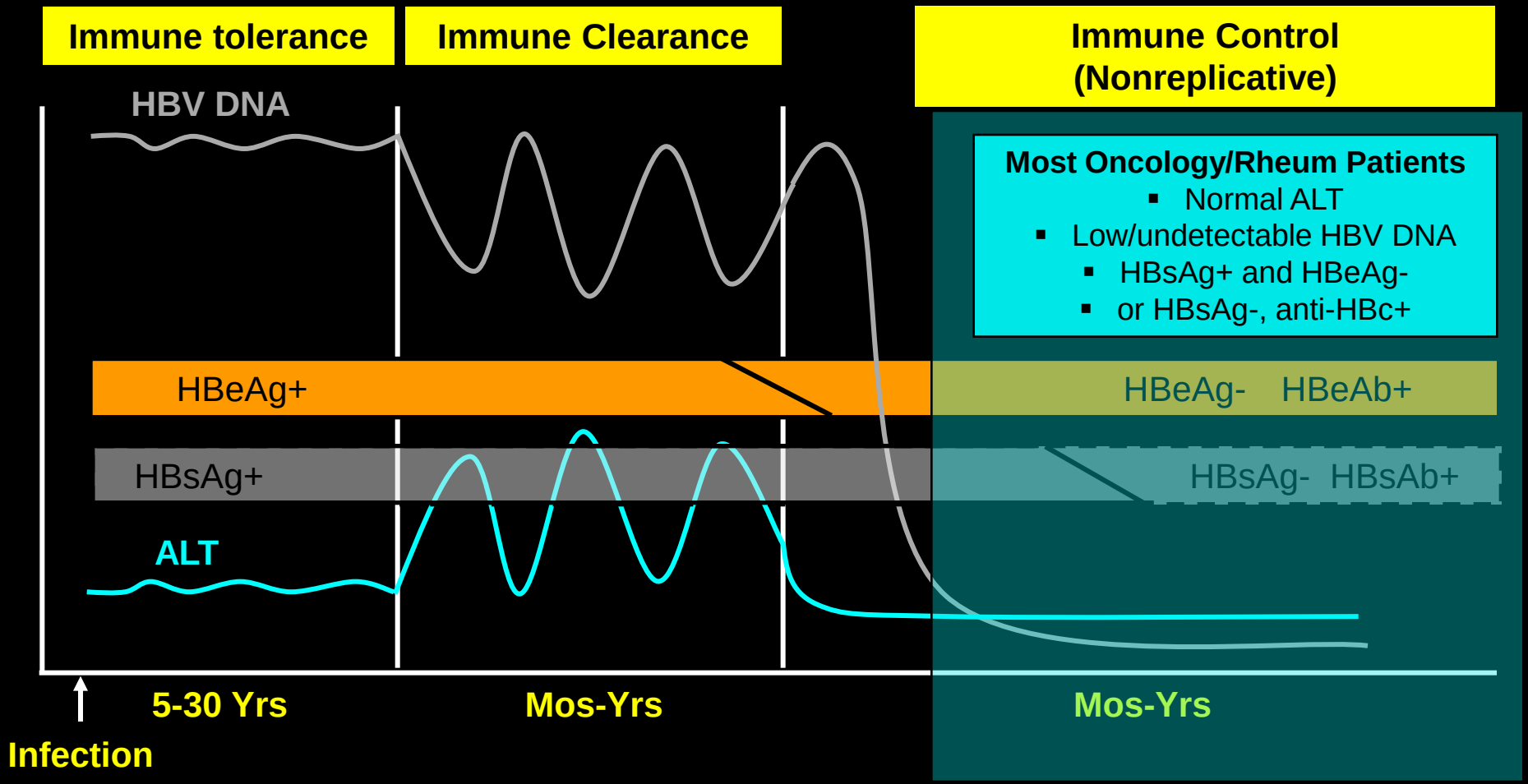

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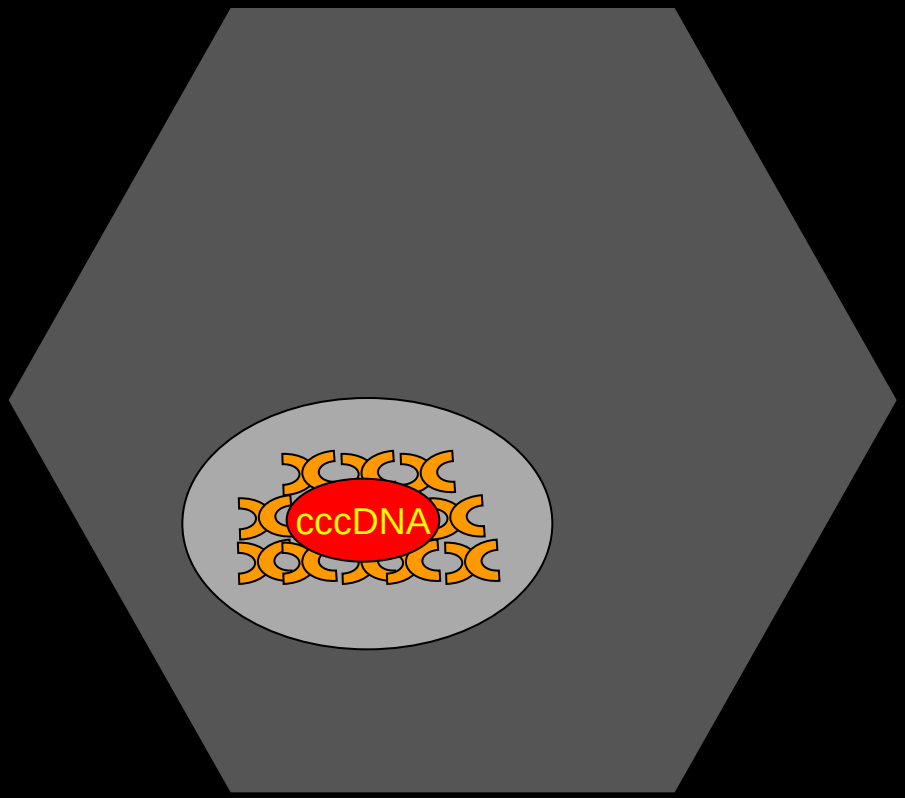
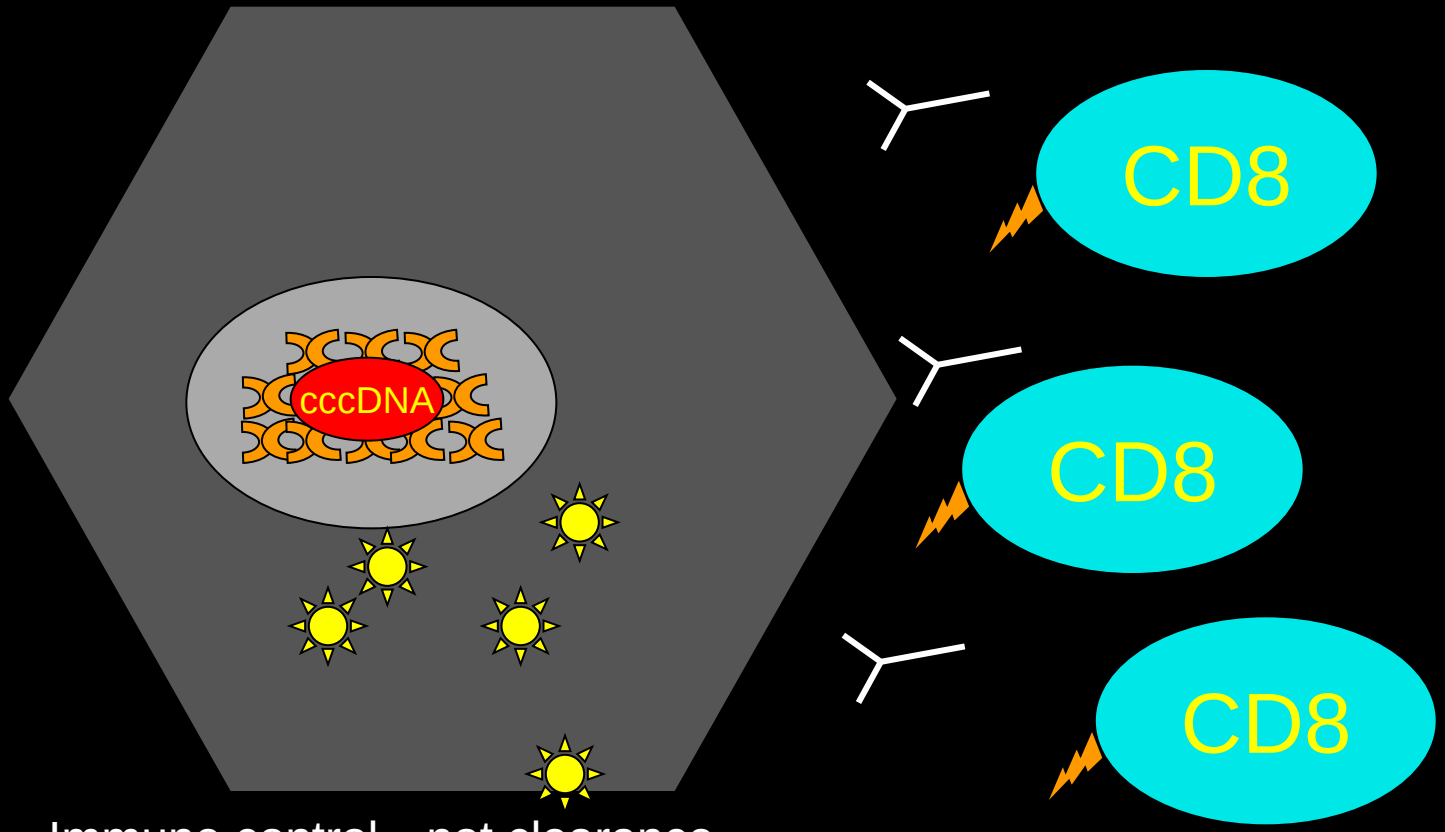
HBV has a latent reservoir



- Immune control—not clearance
- “Resolved HBV” a misnomer—still HBV DNA in liver
- cccDNA—episomal replicative intermediate responsible for persistent infection of hepatocytes

Werle-Lapostolle B, et al. Gastroenterology. 2004;126:1750-1758.

Inactive HBV is controlled by the host immune response



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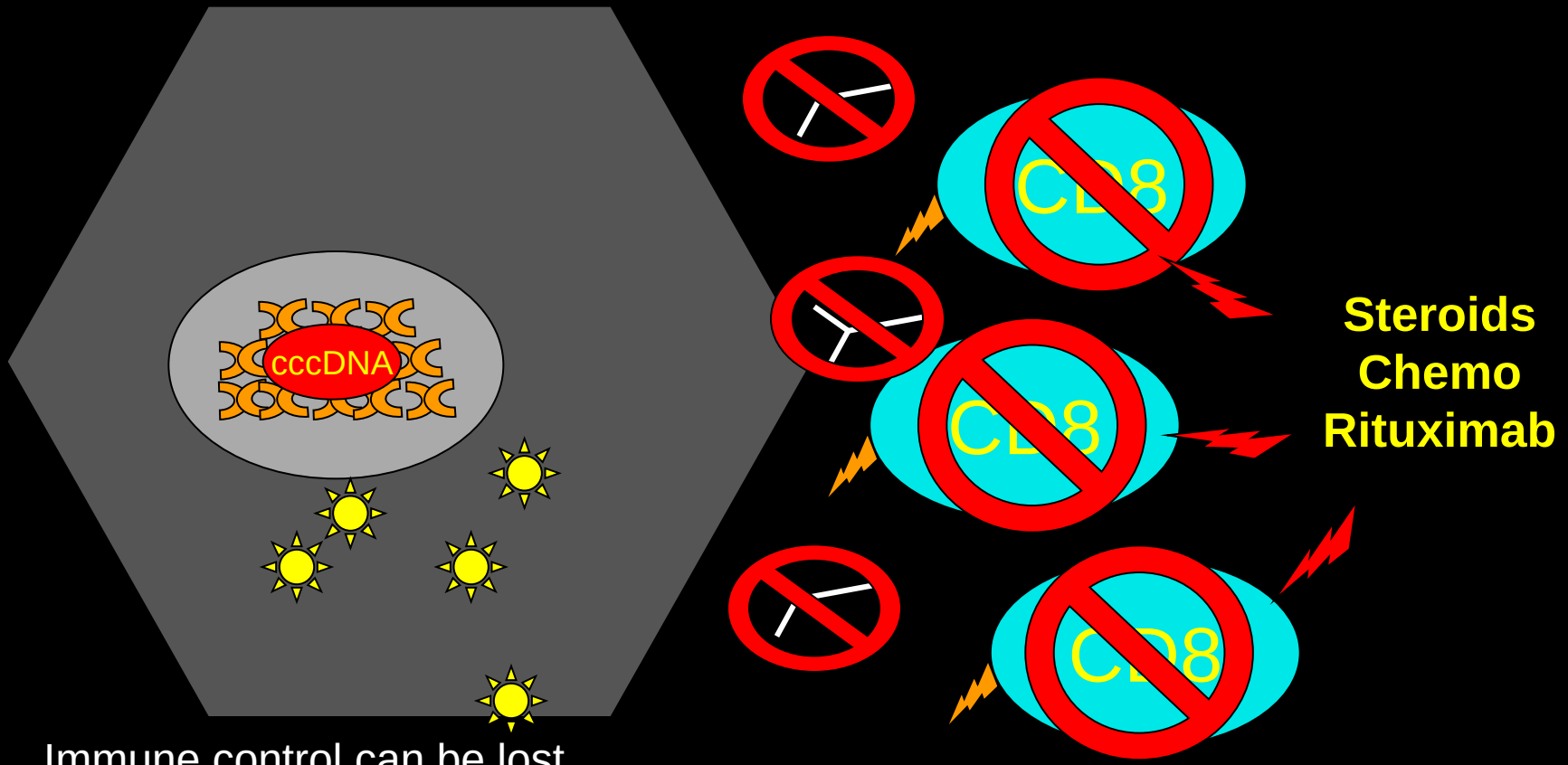
Immune Suppression



- Immune control can be lost
- Immune-mediated liver damage with immune reconstitution

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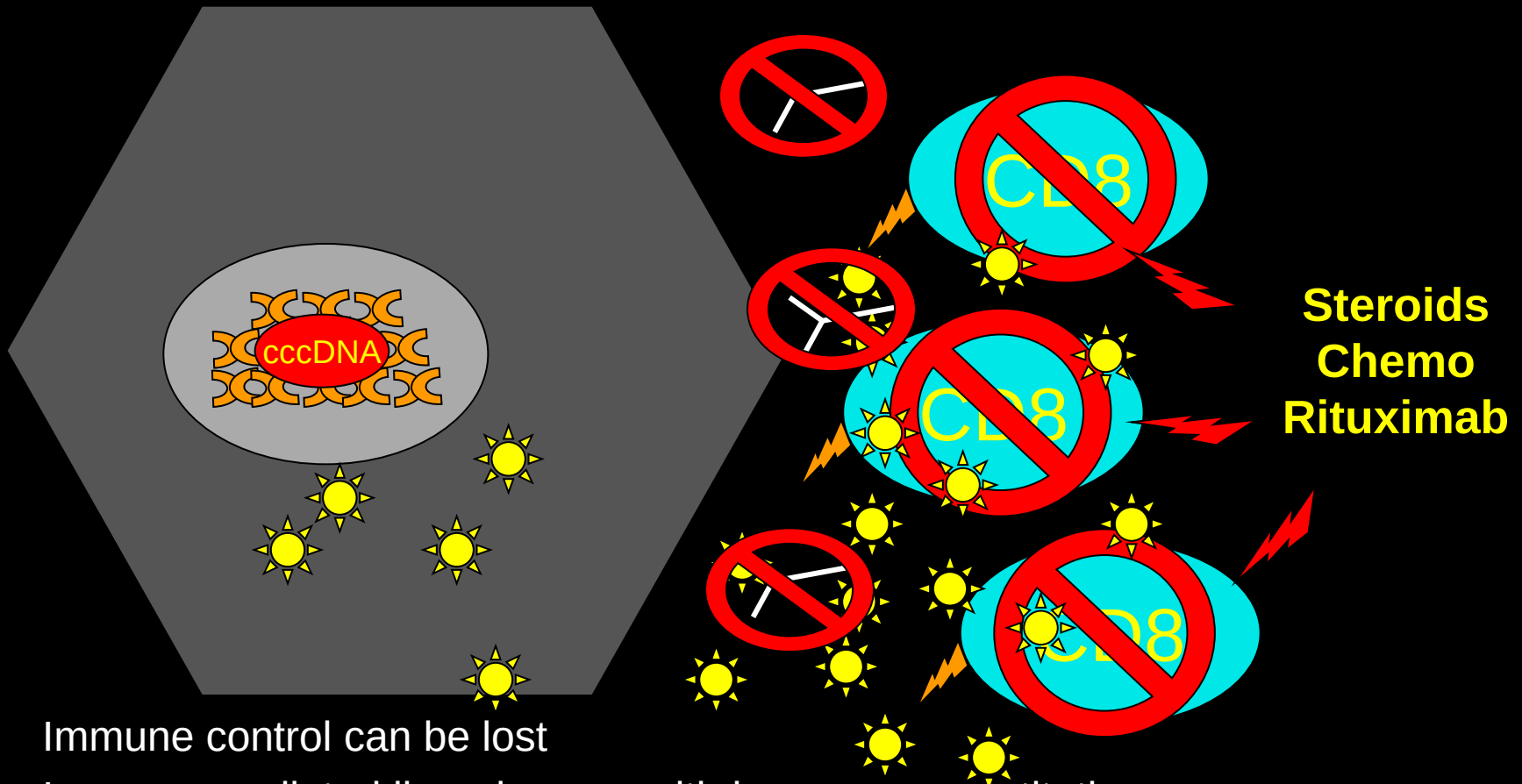
HBV Replication Promoted



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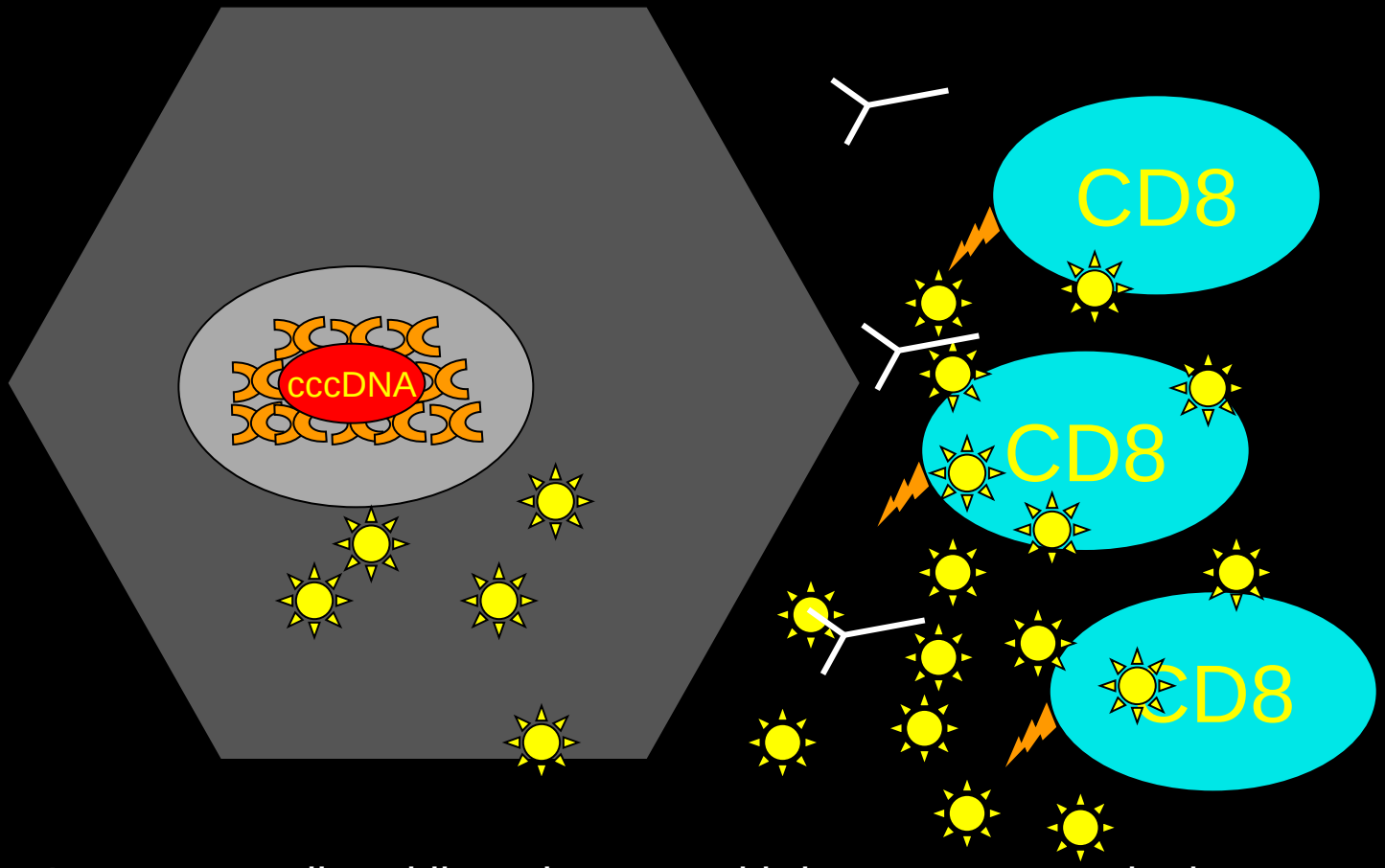
Immune reconstitution



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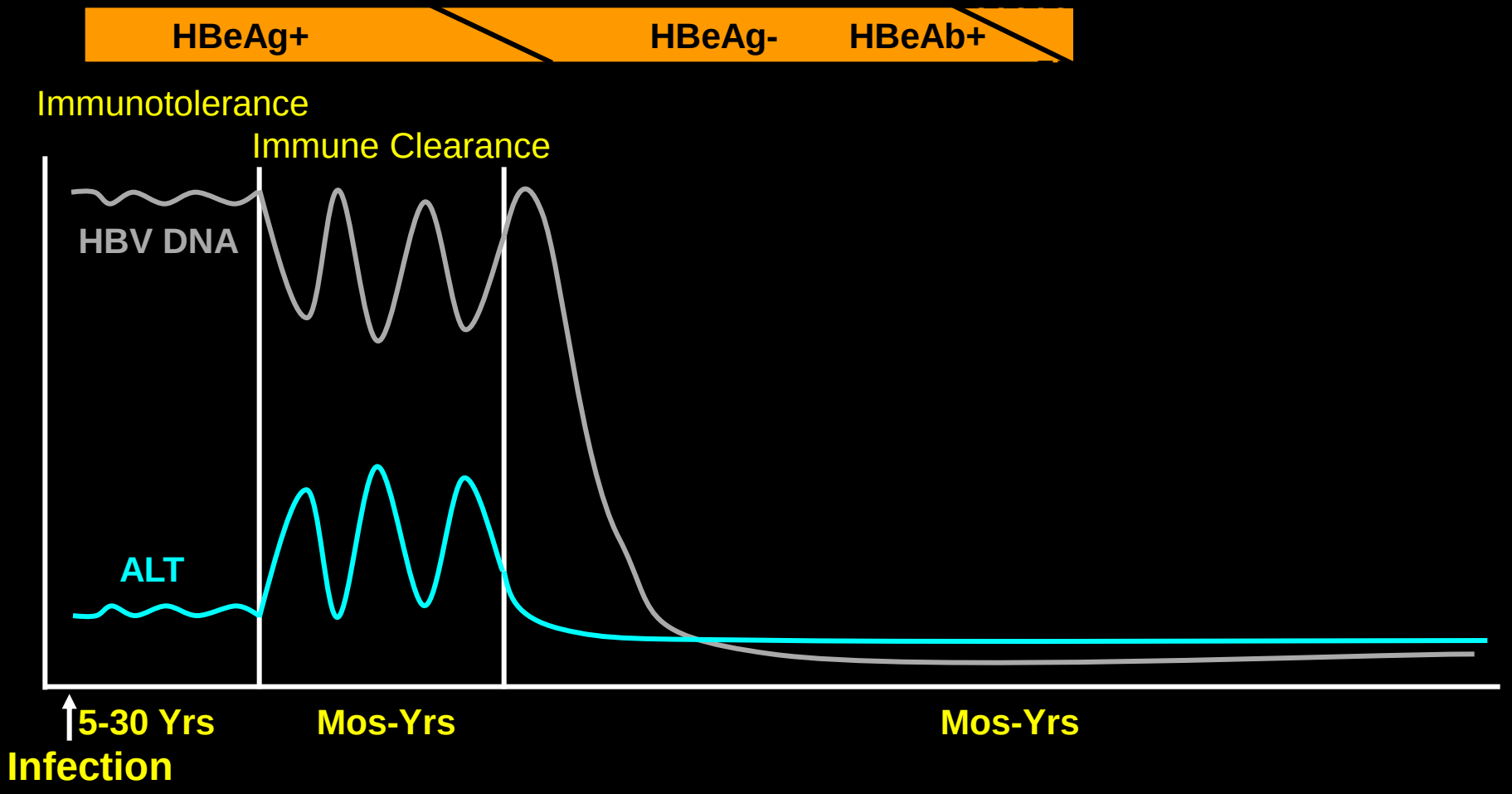
HBV Reactivation



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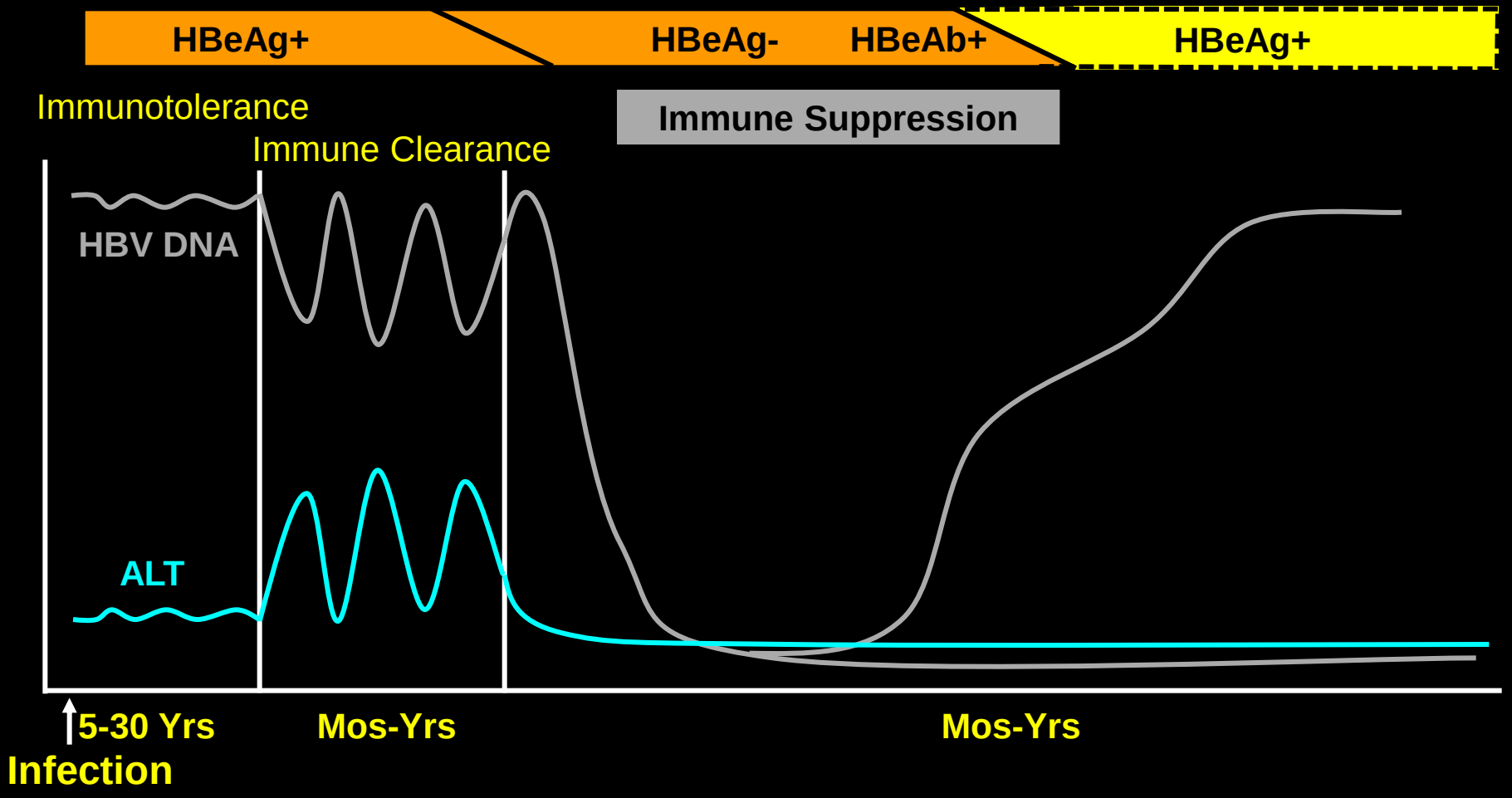

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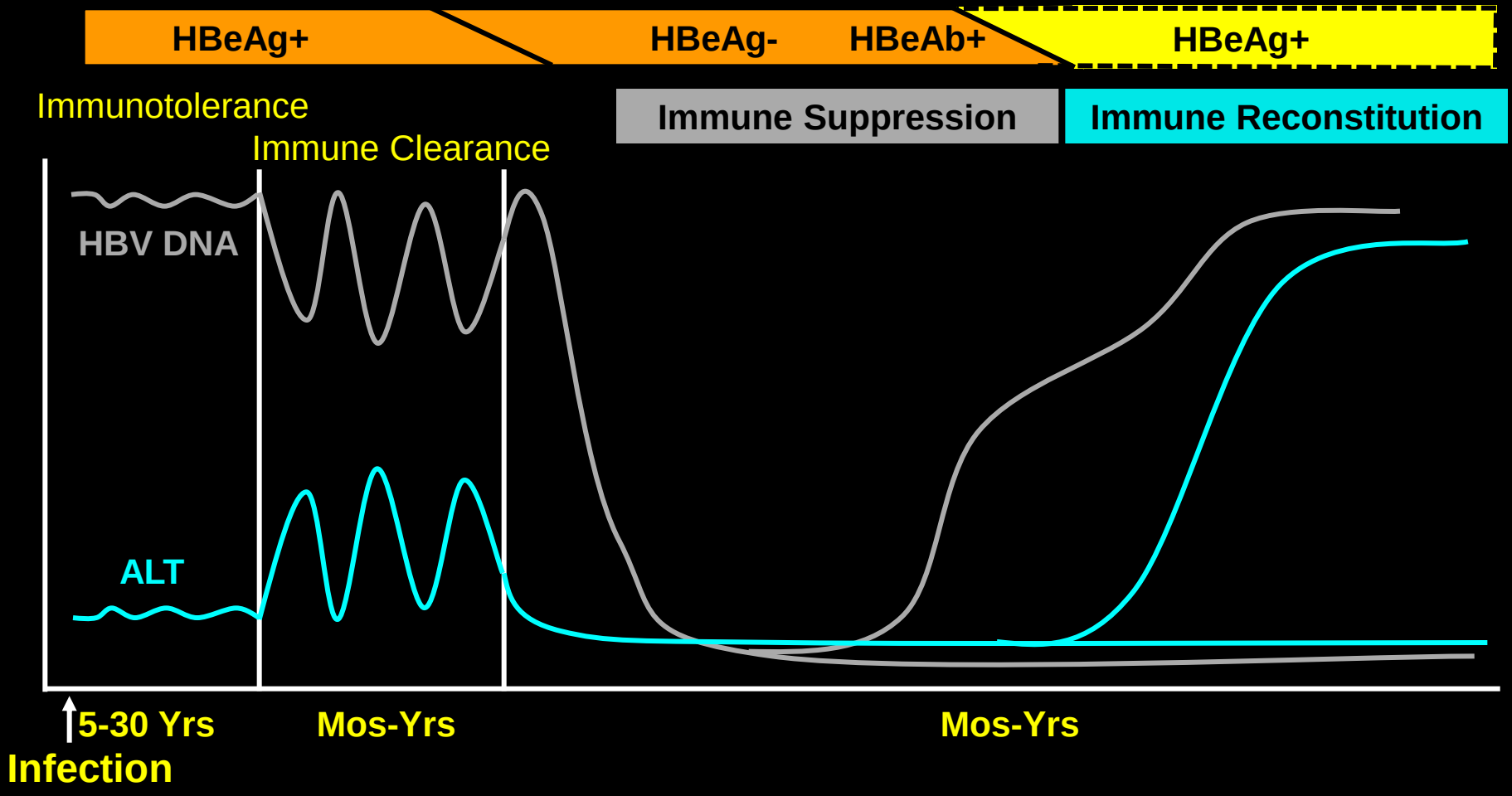
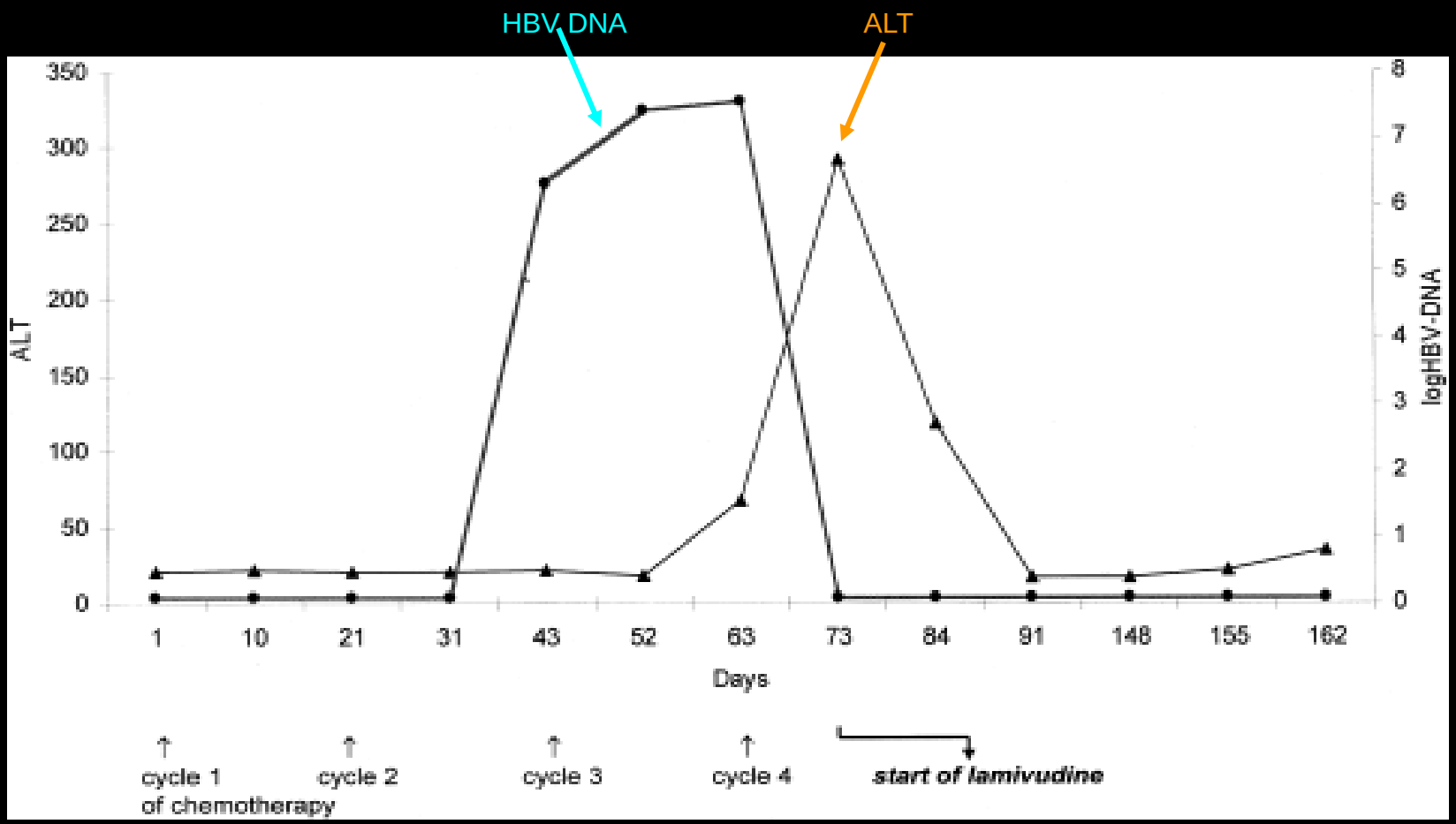


Kinetics of reactivation



Yeo W et al, Hepatology 2006;43:209

HBV Reactivation

Definition

- Loss of HBV immune control in a patient with inactive or "resolved" HBV infection
- Abrupt reappearance or increase in viral replication (>1log) with liver damage occurring during and/or following immune reconstitution

Clinical

- Range from subclinical to severe/fatal hepatitis
- Rise in HBV DNA ± return of HBeAg
  - may miss HBV DNA spike because HBV DNA may fall with ALT rise
- ALT increase (mild to severe)
- May progress to liver failure/death despite antiviral therapy

Agents Reported to be Associated with HBV Reactivation

Class	Agents
Corticosteroids	High dose dexamethasone, methylprednisolone, prednisolone (very high)
Antitumor antibiotics	Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C (high)
Plant alkaloids	Vinblastine, vincristine (high)
Alkylating agents	Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ifosfamide (high)
Antimetabolites	Azauridine, cytarabine, fluouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine (lower)
Biologics	Alemtuzumab, rituximab (very high) Etanercept, infliximab, adalimumab (high)
Others	L-asparaginase, docetaxel, etoposide, fludarabine, folinic acid, procarbazine (high)

Yeo W, et al. Hepatology. 2006;43:209-220.

Oncologic Consequences of Delayed Recognition of HBV Reactivation

Interruption of chemotherapy

- 35% premature termination
- 35% chemo interruption
- Potential for poorer cancer-related outcome

Yeo W, et al. Hepatology. 2006;43:209-220.

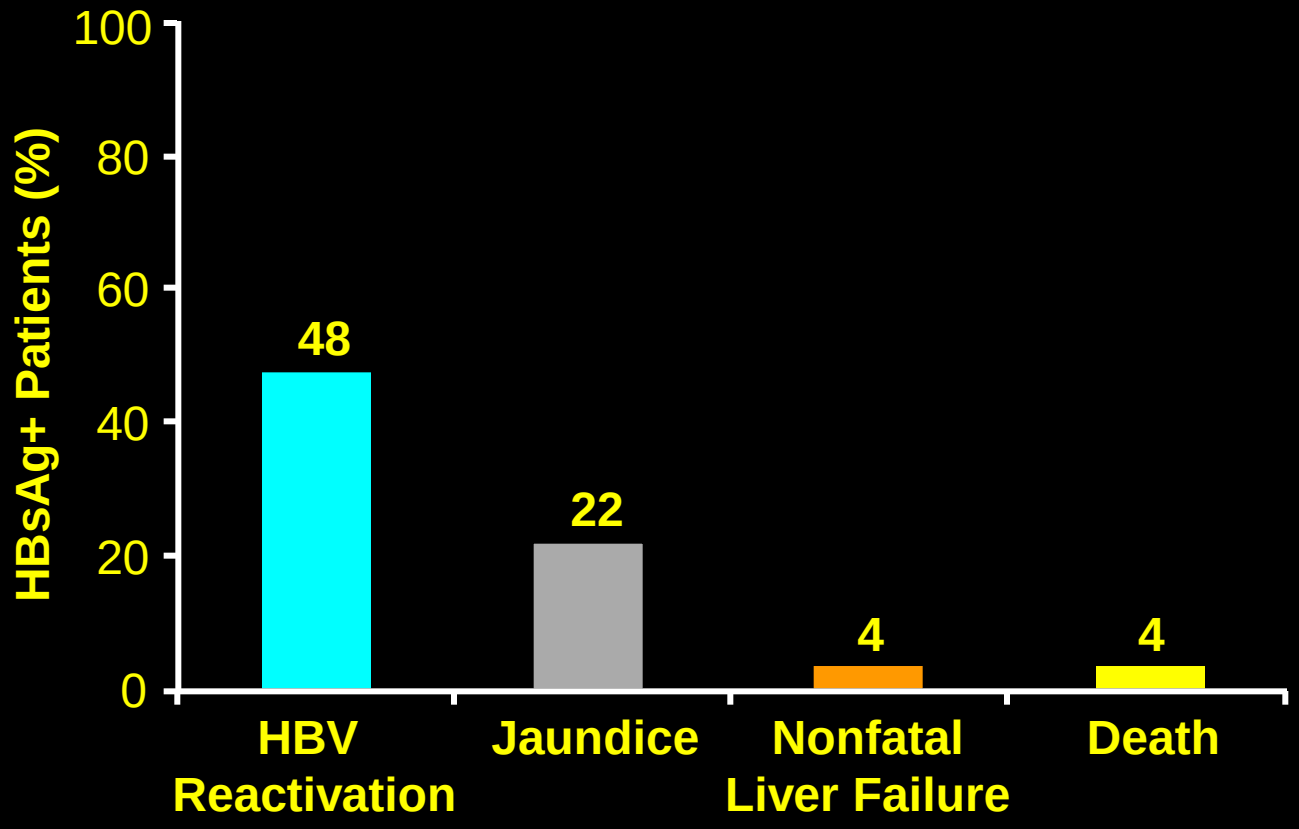
Rate of HBV Reactivation: Solid Tumors

- HBsAg-positive breast cancer patients receiving chemotherapy
  - Rate of HBV-associated acute hepatitis: 21%[1]
  - With careful HBV DNA monitoring, up to 41% with HBV reactivation[2]
  - Limited data on other solid tumors

1. Kim MK, et al. Korean J Intern Med. 2007;22:237-243.
2. Yeo W, et al. J Med Virol. 2003;70:553-561.

Hematologic Malignancy: The Bigger Threat

100 patients with NHL undergoing CHOP; 27 HBsAg positive



Lok AS, et al. Gastroenterology. 1991;100:182-188.

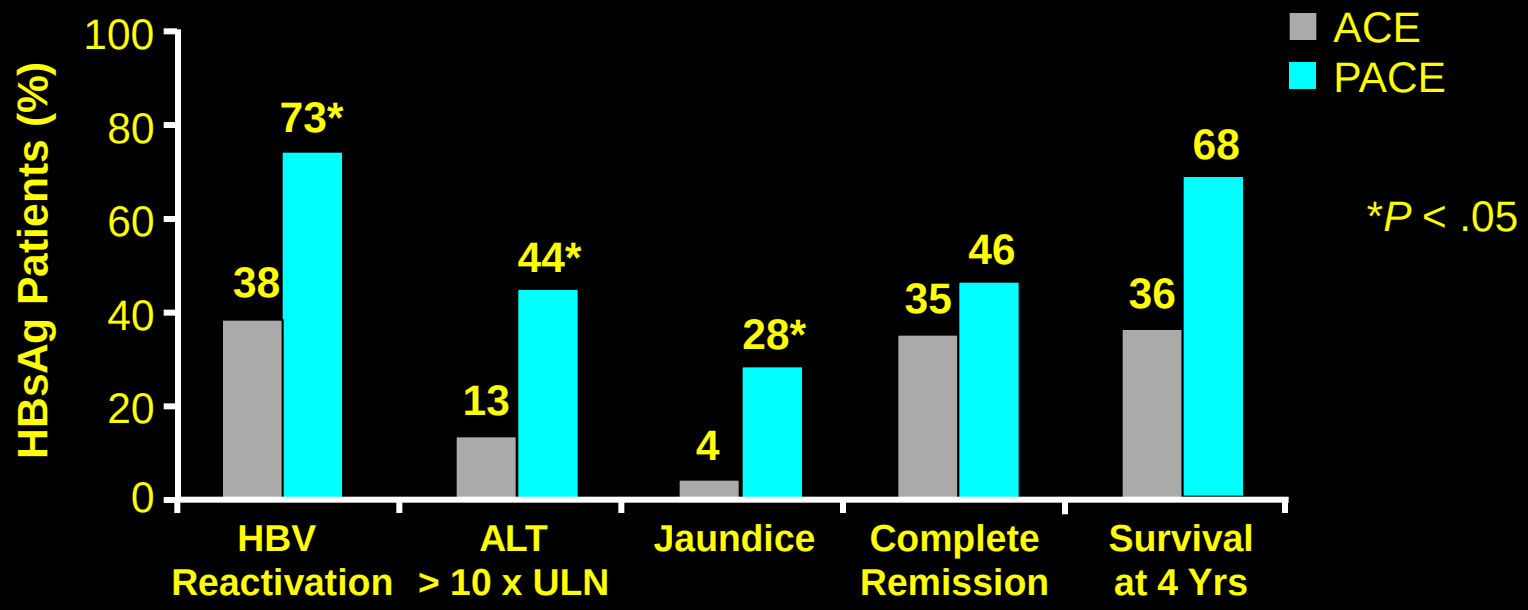
Risk Factors for HBV Reactivation

- Malignancy
  - NHL: 40% to 58% of HBsAg+
  - Breast cancer: up to 41% of HBsAg+
- Chemotherapy
  - Prednisone, anthracyclines, rituximab
  - “Potency of immunosuppression”
- HBV DNA
  - HBV DNA > 3×10^5 copies/mL
  - Elevated if HBeAg positive
- Demographics
  - Men > women

Yeo W, et al. Hepatology. 2006;43:209-220.

Steroids Increase Risk of HBV Reactivation

- 50 patients with NHL who were HBsAg+ randomized to epirubicin, cyclophosphamide and etoposide (ACE) ± prednisolone (P)



Cheng AL, et al. Hepatology. 2003;37:1320-1328.

Who Should Be Screened?

- AASLD recommends screening high-risk individuals
  - Immigrants from endemic areas
    - Asia, Africa, Pacific Islands, Middle East, Eastern Europe, South/Central America, Caribbean, Aboriginal
  - Children of immigrants
  - Men who have sex with men
  - HIV or HCV positive
  - History of IDU, incarceration
  - Hemodialysis

Lok AS, et al. Hepatology. 2009;50:661-662.

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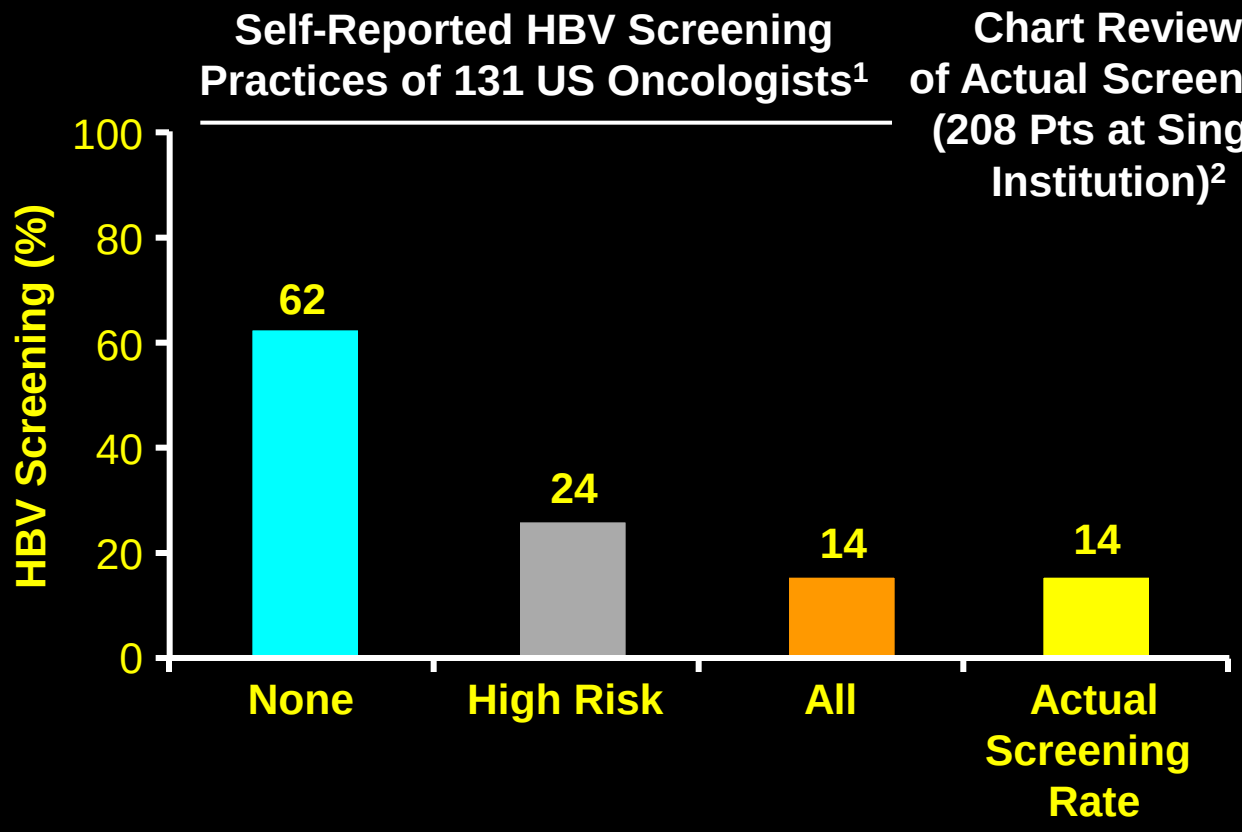
- CDC, EASL recommend screening of all patients pre-chemo[2-4]

1. Lok AS, et al. Hepatology. 2009;50:661-662. 2. Weinbaum CM, et al. MMWR Recomm Rep. 2008:57 (RR-8):1-20. 3. Weinbaum CM, et al. Hepatology. 2009:49(suppl 5):S35-S44. 4. EASL. J Hepatol. 2012; 57:167-185.

Few oncologists routinely screen patients initiating chemotherapy for HBV



1. Khokhar OS, et al. Chemotherapy. 2009;55:69-75. 2. Lee R, et al. Curr Oncol. 2010;17:32-38.

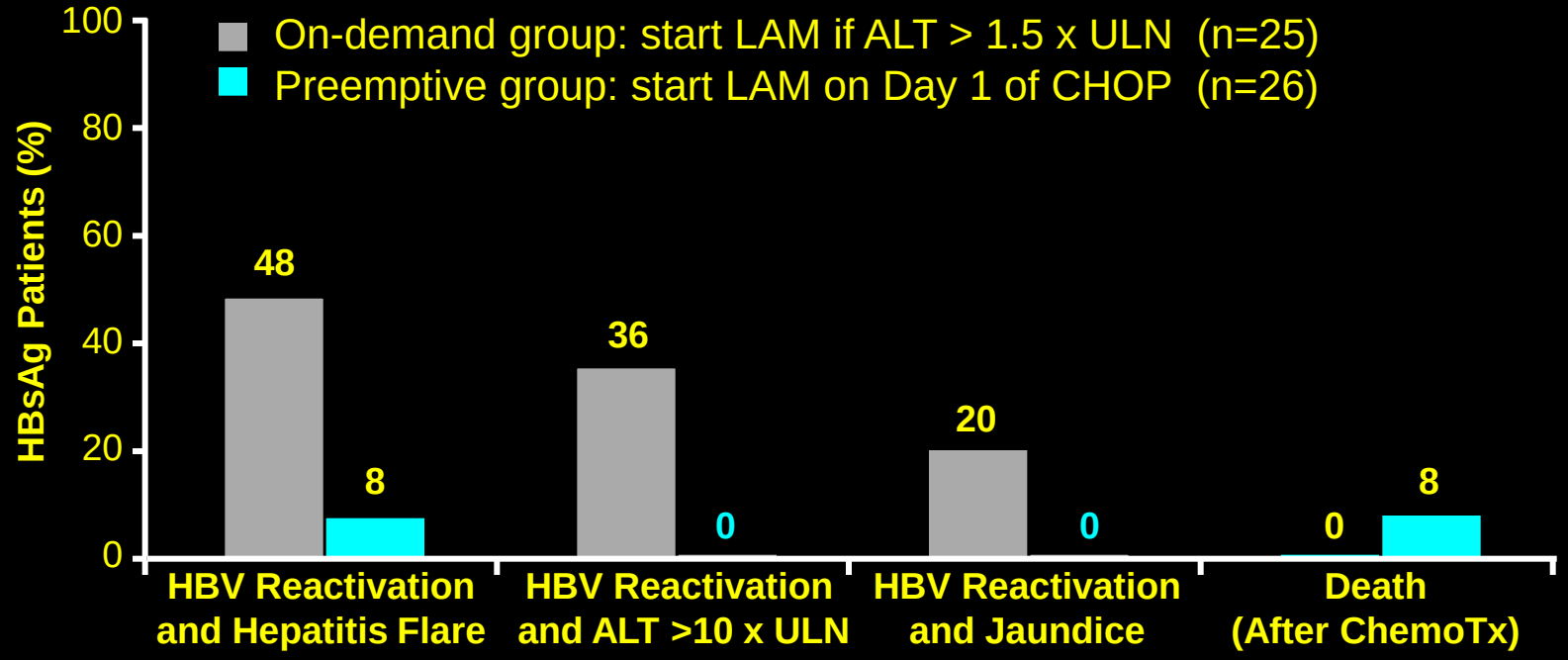
What Is the Optimal Screening Strategy?

- Screening all patients is most cost-effective and easiest to implement
- HBsAg should be tested in all individuals, with follow-up HBV DNA in HBsAg+ patients
- Role of anti-HBc testing less clear; recommendations from various societies mixed
  - EASL: HBsAg and anti-HBc[1]
  - AASLD: HBsAg and anti-HBc[2]
  - CDC: HBsAg, anti-HBc and anti-HBs[3]
  - ASCO: Consider HBsAg alone → HBsAg, anti-HBc

1. EASL. J Hepatol. 2012;57:167-185. 2. Lok AS, et al. Hepatology. 2009;50:661-662. 3. Weinbaum CM, et al. Hepatology. 2009:49(suppl 5):S35-S44. 4. Artz AS, et al. J Clin Oncol. 2010;28:3199-320 5. Hwang J, J Clin Oncol 2015;33:2212

Preemptive Antivirals Markedly Diminish HBV Reactivation

- HBsAg-positive patients with NHL treated with CHOP randomized to "preemptive" vs "on-demand" lamivudine



Hsu C, et al. Hepatology. 2008;47:844-853.

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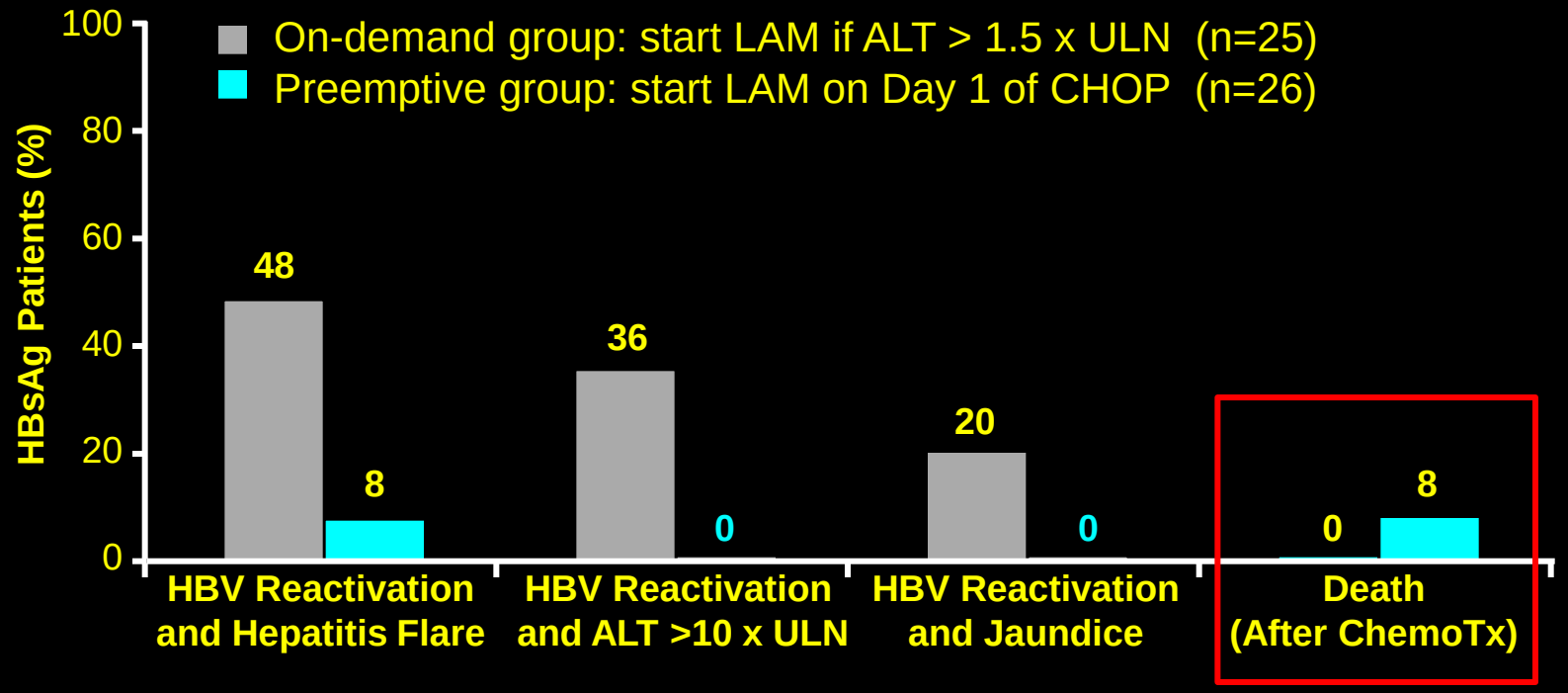


Hsu C, et al. Hepatology. 2008;47:844-853.

Choice of Antiviral Therapy and Monitoring

- High barrier compounds recommended
  - ETV or TDF (?TAF)
  - May consider LAM for undetectable or low HBV DNA (<2000 IU/mL), short course chemo
- RTX-based lymphoma therapy: RCT showed ETV superior to LAM (0 vs 13%)
- HBV DNA and ALT should be monitored every 1-3 mos

EASL. J Hepatol. 2012;57:167-185. Huang H et al. JAMA 2014 ;312:2521-30.
Lok AS, et al. Hepatology. 2009;50:661-662.

Timing of Antiviral Therapy

- When to start
  - Ideally before or together with chemotherapy
  - Do not delay start of chemotherapy
- When to stop
  - If baseline HBV DNA > 2000 IU/mL: high risk of withdrawal flare
    - Continue therapy as for chronic HBV infection
  - If baseline HBV DNA < 2000 IU/mL
    - 6-12 mos after end of chemotherapy
    - RTX: 12 mos after last dose
- Monitor for withdrawal flares with monthly HBV DNA and ALT

EASL. J Hepatol. 2012;57:167-185. Lok AS, et al. Hepatology. 2009;50:661-662.

Significance of Isolated Anti-HBc Positivity

- Indicates exposure to HBV
- Usually persists lifelong
- May be false positive if no HBV risk factors
- No guidelines for management
- Risk for reactivation
  - Low risk for most standard solid tumor regimens
  - Consider preemptive HBV therapy if cirrhosis is present
  - Consider preemptive HBV therapy for
    - Rituximab
    - Bone marrow/stem cell transplantation

Manzano-Alonso ML, et al. World J Gastroenterol. 2011;17:1531-1537.

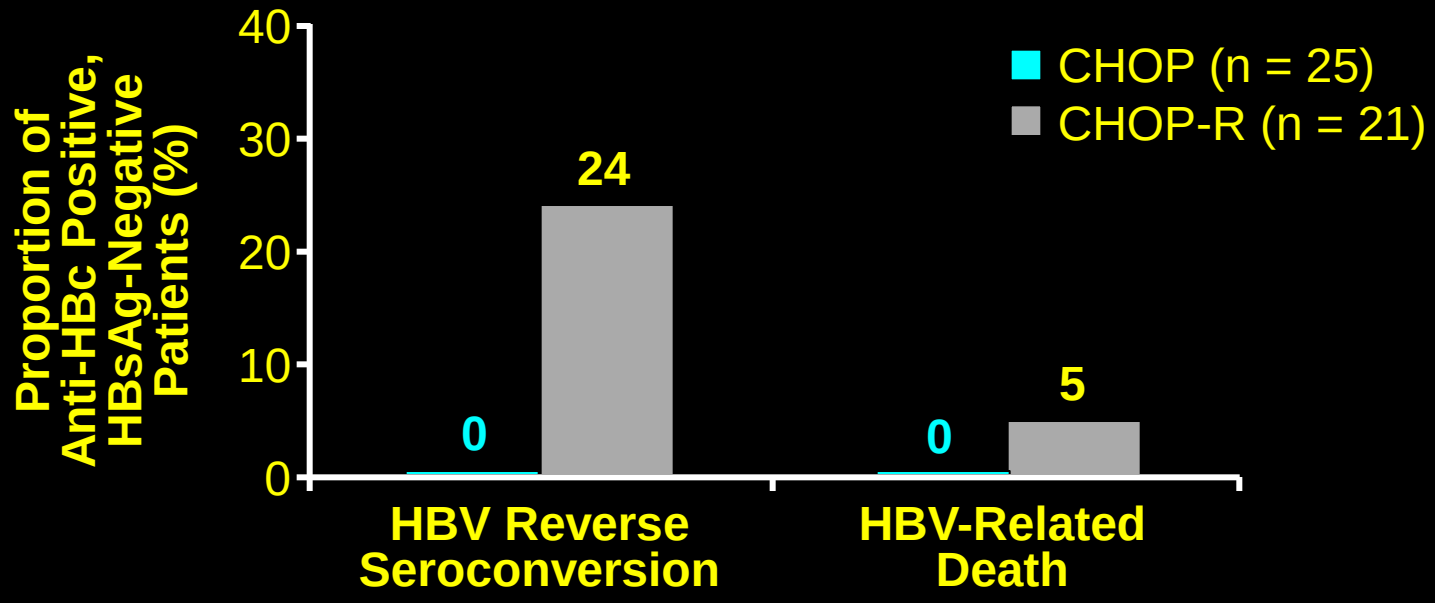
Rituximab: A Thorny Problem

- Monoclonal antibody against CD20 (B-cell marker)
- Reduces B-cell numbers and neutralizing Ab levels
- Increasingly used as part of CHOP-R, EPOCH-R
- Increased risk of HBV reactivation, including HBsAg-negative (anti-HBc+ +/- anti-HBs) patients
  - High FHF, fatality rates
- Seroreversion: reappearance of HBsAg in previously HBsAg-negative patient due to loss of immune control

Yeo W, et al. Hepatology. 2006;43:209-220.
Papamichalis P, et al. Clin Res Hepatol Gastroenterol. 2012;36:84-93.

HBV Reactivation With Rituximab in HBsAg-Negative Individuals

- Patients with diffuse large B-cell lymphoma
  - HBsAg-negative, anti-HBc–positive individuals treated with CHOP or CHOP-R



Yeo W, et al. J Clin Oncol. 2009;27:605-611.

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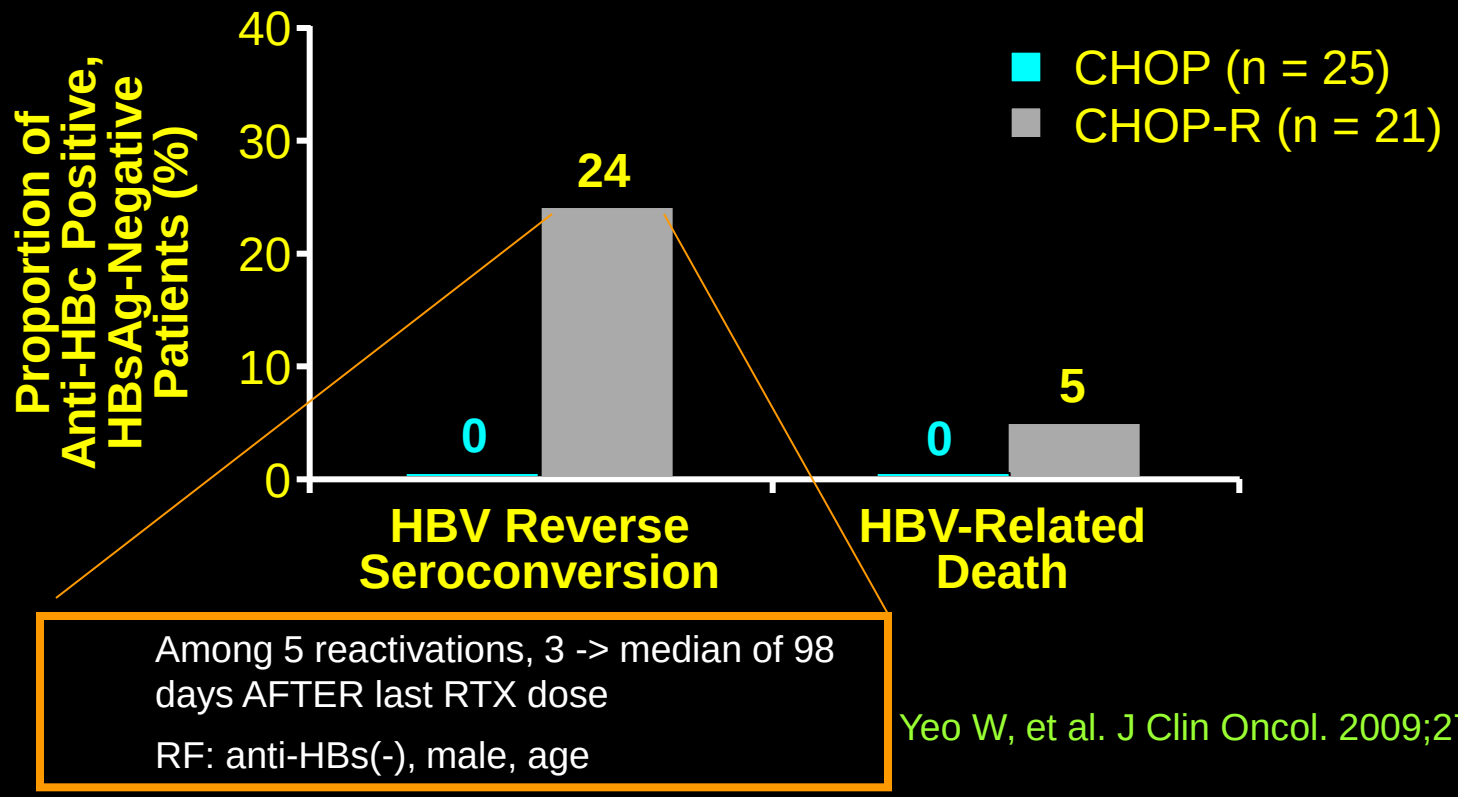

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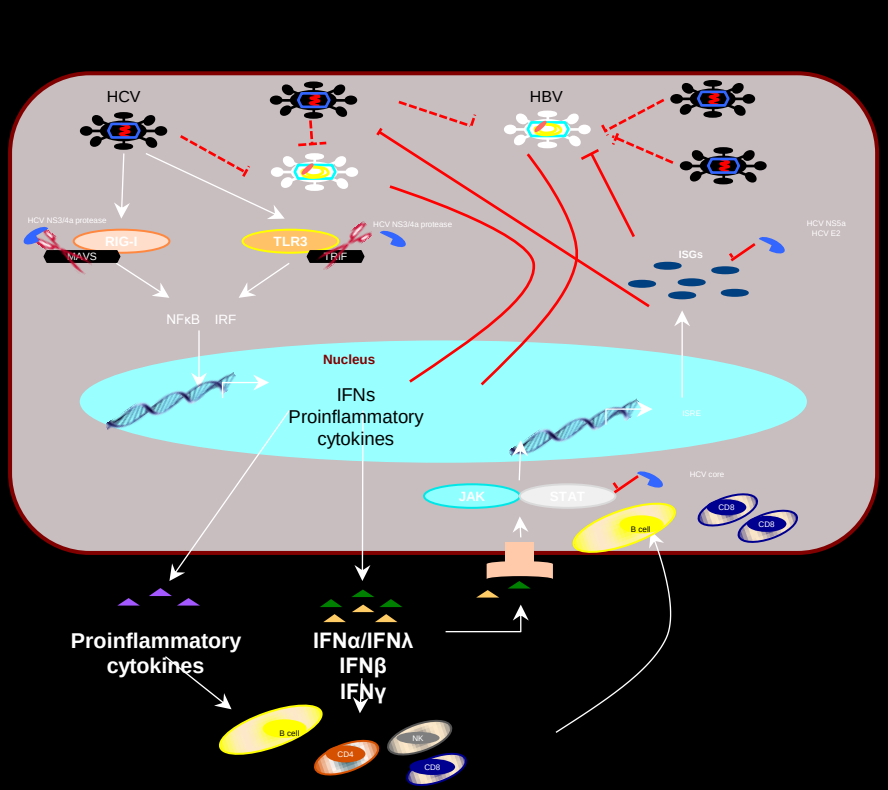
Recommendations for the anti-HBc+ (+/- anti-HBs+) patient

- Test for HBV DNA
  - those with detectable HBV DNA should be treated as HBsAg+ patients
  - those with undetectable HBV DNA who receive chemotherapy and/or IS should be followed carefully by ALT and HBV DNA testing q1-3 months and treated upon HBV reactivation before ALT elevation (if f/u unreliable -> ppx)
  - preemptive NA therapy in all who receive rituximab and/or combined regimens for hematological malignancies, bone marrow and stem cell transplants

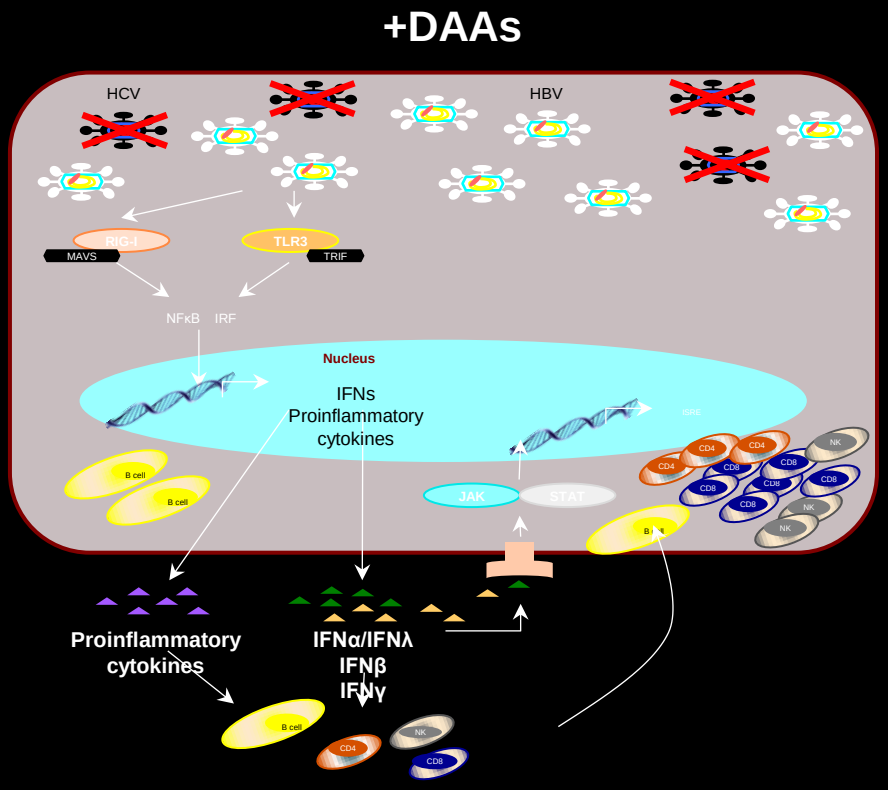
HBV reactivation and DAAs for HCV

- FDA reported 24 cases of HBV reactivation in context of SVR with DAAs
- 22/24 cases HBsAg+ at baseline
- 3 cases FHF → 2 deaths (1 isolated anti-HBc+), 1 LTx
- Occurred during week 4-12 of DAAs
- Precise frequency of reactivation unknown
- ?Competitive relationship between viruses, altered immune milieu after DAAs

HCV/HBV-coinfected hepatocyte



+DAAs



FDA recommendations

- HBV status should be assessed in all pts (HBsAg, anti-HBc)
- Pts with serologic evidence of HBV infection should be followed actively during and after DAA therapy
- Antiviral therapy for HBV should be initiated for HBV as warranted

FDA Update Feb 14, 2017.

Recommendations

- Screening of all patients undergoing chemotherapy or IS should be performed
- Screening is recommended by CDC, EASL, AASLD, and IOM
  - Patients receiving standard chemotherapy, IS
    - Screen HBsAg +/- anti-HBc
  - Patients receiving complex chemotherapy (e.g., rituximab/ BMT)
    - Screen HBsAg, anti-HBc, anti-HBs
- Screen all patients receiving DAAs for HCV
- HBV reactivation is preventable!!

HIV Management
Hepatitis Management

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