HBV REACTIVATION

PLAYING WITH FIRE

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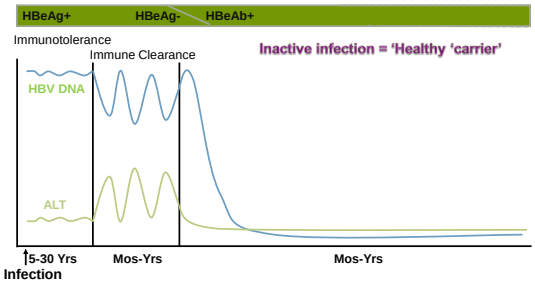
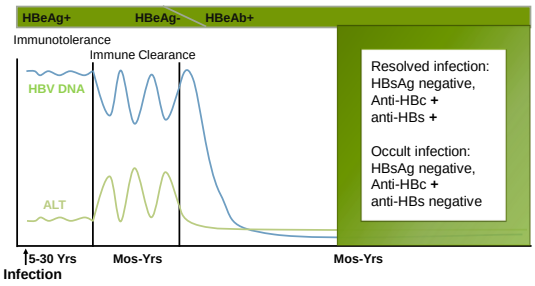
Chronic HBV Infection

(n = >370 million world-wide
n = 218,000 in Australia)

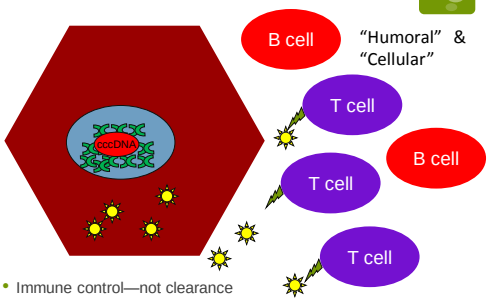


HBV Infection

(up to 2 billion people world-wide,
up to 2 million in Australia)

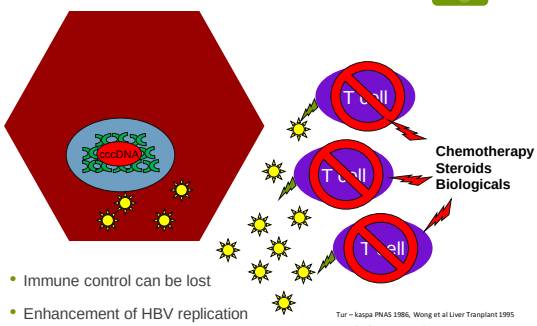


Do You Ever Really Get Rid of HBV?



- Immune control—not clearance
- "Resolved" HBV a misnomer—still HBV cccDNA in liver

Add Immunosuppression !



- Immune control can be lost
- Enhancement of HBV replication

Tur – kaspa PNAS 1986, Wong et al Liver Tranplant 1995
McMillan & Locarni Hepatology 1995

HBV Reactivation:

Immunosuppression

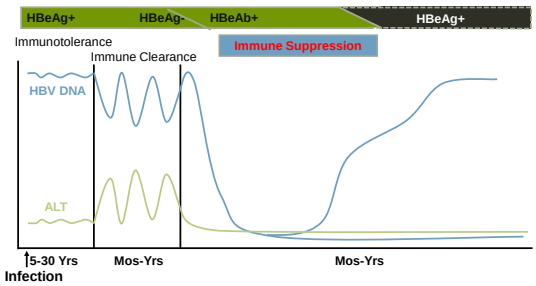
- Common reasons for immune deficiency in chronic HBV [or occult/resolved HBV] include:
  - haematology [eg patients treated for lymphoma]
  - oncology [eg patients on chemotherapy with steroids]
  - internal medicine [rheumatology & gastroenterology, anti-TNF]
  - transplantation
  - HIV infection
- A large number of patients undergoing immuno or chemotherapy are not screened for HBV markers prior to initiation of treatment.

HBV in Immunosuppressed Subjects: Background

- HBV reactivation occurred in 48% of HBsAg+ patients and in 4% anti-HBc+ patients with occult HBV receiving chemotherapy, particularly in haemopoietic disorders but also solid tumours
- 11% developed hepatic failure, one (4%) of whom died.
- Clinical reactivation frequently occurred following withdrawal of chemotherapy and emergence of immune recovery. (Median onset 16w [range:4-36w])
- There is no reliable way to predict severity of HBV reactivation during and after chemotherapy

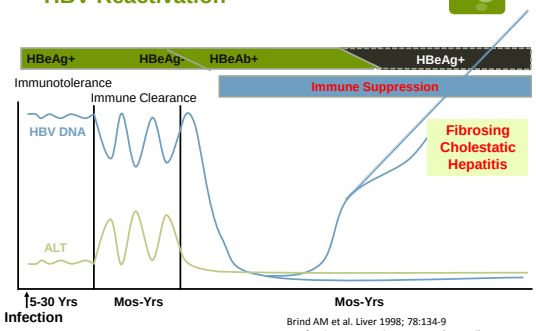
*Ref: Lok A et al Gastroenterology **1991**:100;182*

HBV Reactivation



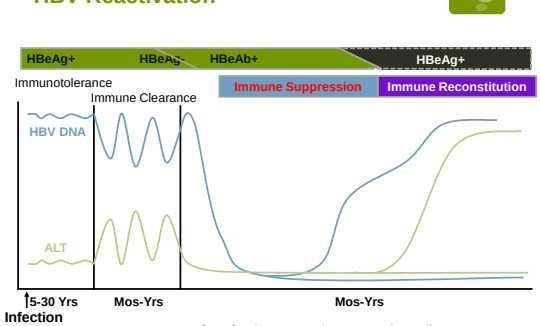
Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

HBV Reactivation



Brind AM et al. Liver 1998; 78:134-9
Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

HBV Reactivation



Ref: Hoofnagle JH. Hepatology. 2009;49(5 suppl):S156-S165.

HBV and immune suppression

Does the type of immunosuppression matter?

Chemotherapy induced HBV reactivation

Comparison Between Classic and No Steroid Protocols

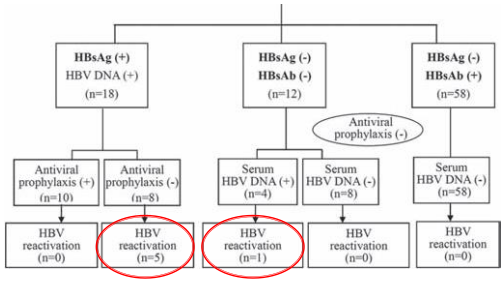
Total # Patients	Steroid-Treated Patients		Steroid-Free Patients	
	HBV reactivations/ total	HBV-related death	HBV reactivations/ total	HBV-related deaths
70	42/63	18	2/7	0
50	18/38	3	1/12	0
45	17/50	7	0/0	0
9	5/6	3	1/3	0

Yeo W et al, Hepatology 2006:43;209
Cheng AL Hepatology 2003:37;1320

HBV reactivation is rare in rheumatoid diseases treated with "non biological" immunosuppressants

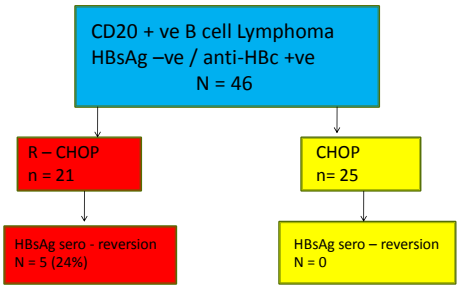
Author	Age/sex	Immunosupr.	Time to Flare	Outcome
Hagiyama et al (Clin Exp Rheumatol 2004)	72/F	MTX 4mg/wk	60 days	Died
Ito et al (Arthritis &Rheum 2001)	75/F	MTX 7.5mg/wk Prednis 5mg	15 days	Died
Narvaez et al (J Rheumatol 1998)	67/M	MTX 7.5mg/wk Prednis 5mg	21 days	Died
Flowers 90 (Ann Intern Med 1990)	57/F	MTX 7.5-10mg/wk	41 days	Liver Tx

Anti-TNF treatment for Rheumatoid Disease in anti-HBc +ve patients [n=88]



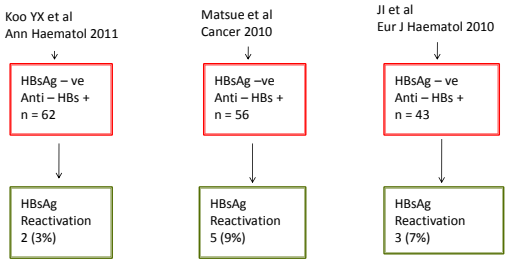
Lan J et al, Annals Rheumat Dis 2011

High risk of HBV reactivation with Rituximab



Yeo et al, J Clin Oncol 2009

Risk for HBV reactivation in resolved HBV patients receiving Rituximab



HBV and immune suppression

1. Does the type of immunosuppression matter? **YES**
2. Should there be universal screening of all patients for HBV serological markers prior to commencing immunosuppression?

Screening: What do the Liver Guidelines Say ?

- 2008 National Institutes of Health Consensus
- 2009 AASLD practice guidelines
- 2012 EASL clinical practice guidelines

All recommend screening for HBV before beginning Immunosuppressive therapy.

Weinbaum et al MMWR Recomm Rep 2008;57(RR-8):1-20
Lok AS et al Hepatology 2009;50:661
Sorrell MF et al Ann Intern Med 2009;150:104

American Society of Oncology Guidance 2010

- The **evidence is insufficient** to determine the net benefits and harms of routine screening for chronic HBV infection in individuals with cancer who are about to receive cytotoxic or immunosuppressive therapy or who are already receiving therapy
- Individuals with cancer who undergo certain cytotoxic or immunosuppressive therapies and have HBV infection or prior exposure to HBV may be at elevated risk of liver failure from HBV reactivation. **As such, HBV screening requires clinical judgment.** Physicians may consider screening patients belonging to groups at heightened risk for chronic HBV infection or if highly immunosuppressive therapy is planned

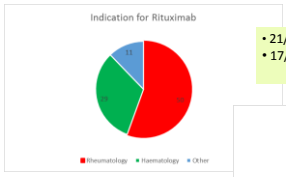
Artz AS et al, J Clin Oncol 2010

Oncology HBV screening practices

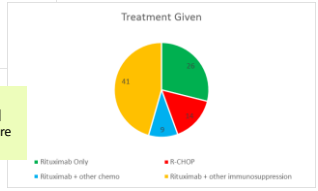
- 20% to 47% oncologists do not routinely screen for HBV prior to treatment
- 20% never screen
- 38 to 65% screen selected sub-groups if there are risk factors, mainly "ethnicity"
- Oncologists who did not screen quoted "inadequate evidence" for benefit of screening

Day et al, J Oncol Pract 2011;7:141
Tran T et al, Aliment Pharmacol & Ther 2010;31:240

Audit of HBV screening in adults receiving Rituximab (Freeman Hospital, Sept to Dec 2012, n= 90)



- 21/90 (23%) screened fro HBsAg - All - ve
- 17/90 (19%) also tested for anti-HBc - 2 + ve



- None received prophylactic Rx
- 1 HBcAb +ve alone [occult infection] developed HBV reactivation with severe cholestasis, treated with Tenofovir

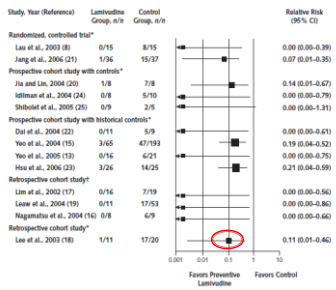
McPherson S, Hudson M et al.

HBV and immune suppression

1. Does the type of immunosuppression matter? **YES**
2. Should there be universal screening of all patients for HBV serological markers prior to commencing immunosuppression? **YES**
3. Should there be routine prophylaxis [= prevention] or containment in
   1. Inactive chronic HBV = HBsAg positive
   2. Occult/resolved HBV infection = HBsAg negative ?

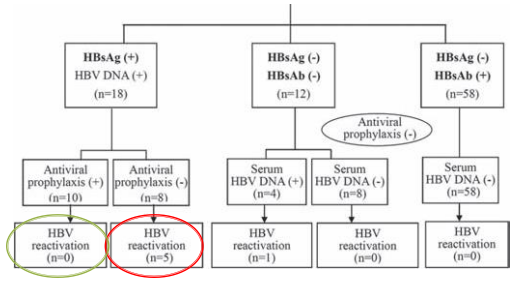
Is Prophylaxis with anti-viral therapy effective in HBsAg+ve patients?

Lamivudine vs No Therapy



Ref: Loomba et al, Ann Intern Med 2008

Anti-TNF treatment for Rheumatoid Disease in anti-HBc +ve patients [n=88]



Lan J et al, Annals Rheumat Dis 2011

NICE recommendations – Prophylactic treatment during immunosuppressive therapy

HBsAg +ve and HBV DNA > 2000 IU/mL

- Offer prophylaxis with Entecavir or Tenofovir
- Start before immunosuppression
- Continue for a minimum of 6 months after HBeAg seroconversion and HBV DNA is undetectable

HBsAg +ve and HBV DNA < 2000 IU /mL

- Offer prophylaxis - consider Entecavir or Tenofovir if immunosuppression Rx expected > 6 months (If < 6 months consider Lamivudine)
- Monitor HBV DNA monthly in patients Rx with Lamivudine and change to Tenofovir if HBVDNA remains detectable > 3 months
- Start prophylaxis before immunosuppression and continue for minimum 6 months after stopping

NICE CG 165 June 2013

Clinical Practice Guidelines

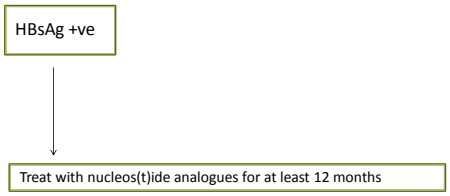
EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

J Hepatol 2012:57;167 - 185

Management of patients receiving immunosuppression: **EASL Clinical Practice Guidelines 2012**



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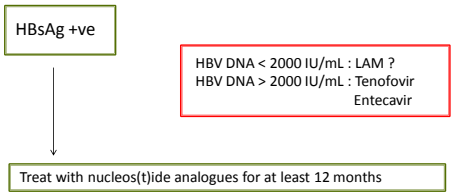

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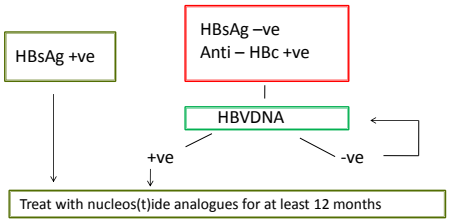

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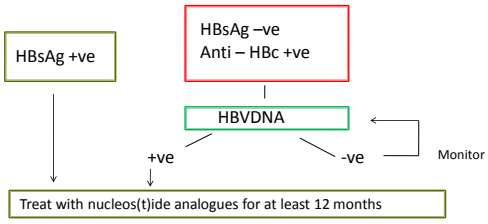

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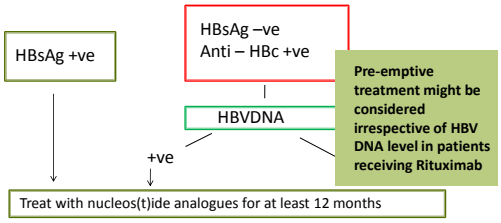

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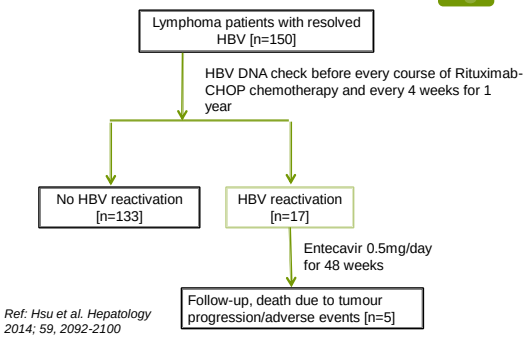
Chemotherapy-induced HBV reactivation in Lymphoma patients with occult/resolved HBV

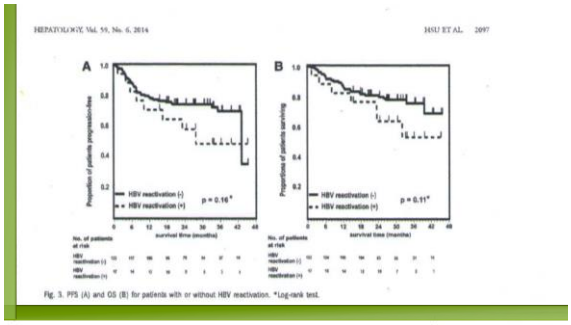


Ref: Hsu et al. Hepatology 2014; 59, 2092-2100

Chemotherapy-induced HBV reactivation in Lymphoma patients with resolved HBV Infection

- There was no baseline clinical feature predictive of HBV reactivation, but patients with HBV reactivation were less likely to test positive for anti-HBs at baseline. HBV reactivation occurred in 8% of anti-HBs+ve patients
- Median time from start of chemotherapy to HBV reactivation was 21 weeks (range 3.0-57.0)
- HBsAg became positive in 12/17 & HBeAg became positive in 7/17
- Hepatitis occurred in 26 patients, 10 of which were HBV-related flares. 4/10 HBV-related flares were severe, **despite Entecavir treatment.**

Ref: Hsu et al. Hepatology 2014; 59, 2092-2100



- Patients with HBV reactivation (----line) were associated with poorer progression-free survival (PFS) and overall survival (OS).
- In univariate analysis the hazard ratio was 1.72 for PFS and 1.93 for OS.

HBV and immune suppression

1. Does the type of immunosuppression matter? **YES**
2. Should there be universal screening of all patients for HBV serological markers prior to commencing immunosuppression? **YES**
3. Should there be routine prophylaxis [= prevention] or containment in
   1. Inactive chronic HBV
   2. Occult/resolved HBV infection ?

ROUTINE PROPHYLAXIS

Hepatitis B Virus: Playing with Fire

- Reactivation of HBV during chemotherapy is a potentially lethal situation.
- We have safe, potent drugs to block HBV replication and avoid this situation.
- If, within the tightly controlled situation of a prospective trial, 40% of patients with reactivation had severe hepatitis despite Entecavir therapy, in daily practice the risk is undoubtedly higher.
- **It begs the question, why play with fire?**

J-F Dufour, Hepatology Highlights
Hepatology 2014, 59; 2059

HBV reactivation

"Knowing is not enough; we must apply. Willing is not enough; we must do."
—Goethe

Ask what is happening in your own hospital?
Talk to the physicians prescribing Rituximab & anti-TNF etc
Develop local (and national) guidelines.

THANK YOU

Acknowledgements:
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