

# HBV reactivation in patients receiving chemotherapy or immune suppressive therapy

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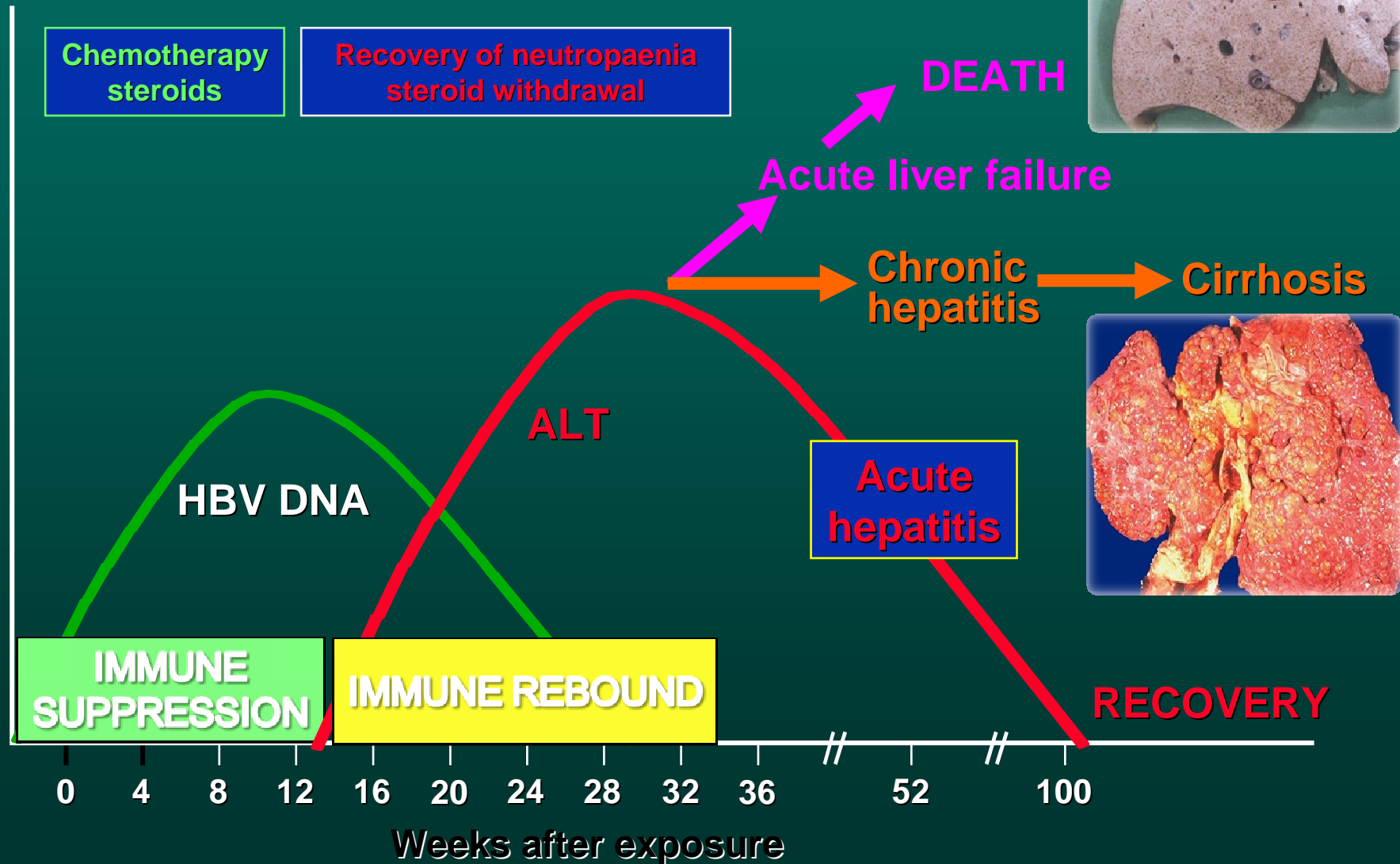
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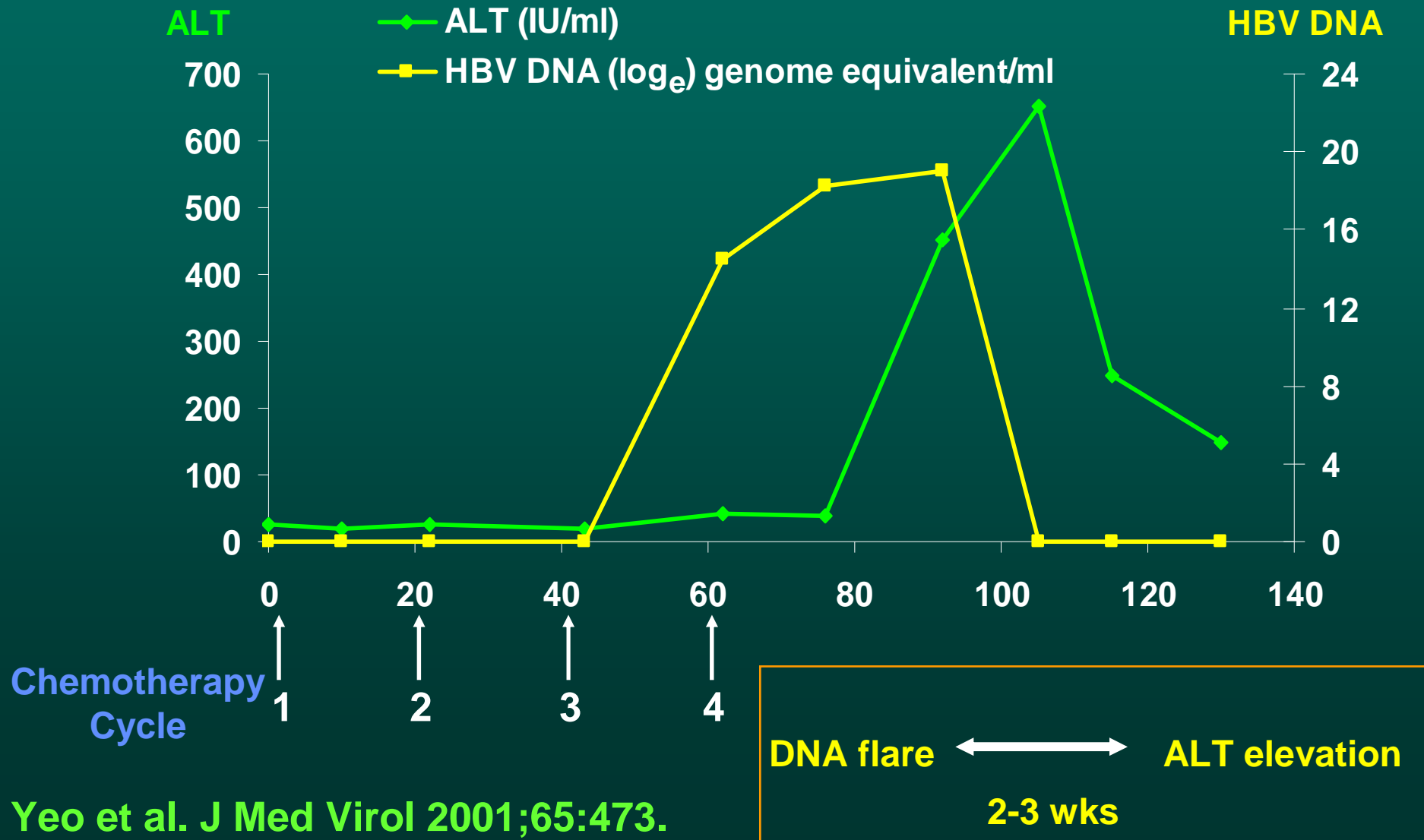
# Outline

- **Introduction**
- **Natural course and risk factors** of HBV reactivation during C/T or immune suppressive therapy
- **Screen for HBV** patients undergoing C/T or immune suppressive therapy
- **Prevention and management** of HBV reactivation during C/T or immune suppressive therapy
- **Conclusion & Future**

# Natural history of HBV reactivation during C/T or immune suppressive therapy



# HBV reactivation during chemotherapy - enhanced replication precedes hepatitis



# Definition and Diagnosis of HBV reactivation during C/T

- Rising HBV DNA followed by rising ALT
- HBV DNA **increase > 10-fold** or absolute increase that exceeds  $9 \log_{10}$  copies/ml.
- **ALT > 100 U/L or ALT > 3 baseline level**

Lalazar G. Br J Haematol 2007;136:699-712

Yeo W. Hepatology 2006;43:209-20



# Predictors of HBV reactivation

- **HBV status**
  - HBsAg status
  - HBV DNA level
  - liver function tests
- **Level of immunosuppression**
  - corticosteroids
  - cytotoxic chemotherapy
  - rituximab
- **Immune reconstitution**
  - steroid withdrawal
  - recovery of neutropaenia

## Terminology Used for Different Phases and Activity States of Chronic HBV infection

	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc	Typical HBV DNA level by PCR (copies/mL)
Resolved infection	-	+	-	+	+	Undetectable
Inactive carrier state	+	-	-	+	+	$<10^4$
Replicative phase (HBeAg + chronic hepatitis)	+	-	+	-	+	$>10^5$
Replicative phase (HBeAg - chronic hepatitis)	+	-	-	+	+	$>10^4$

# HBV reactivation

- **Reactivation of HBV**

(for inactive carrier)

→ HBsAg (+)

- **De novo HBV reactivation**

(for infection resolved patient or occult HBV)

→ HBsAg (-), Anti-HBs Ab (+), Anti-HBc Ab (+)

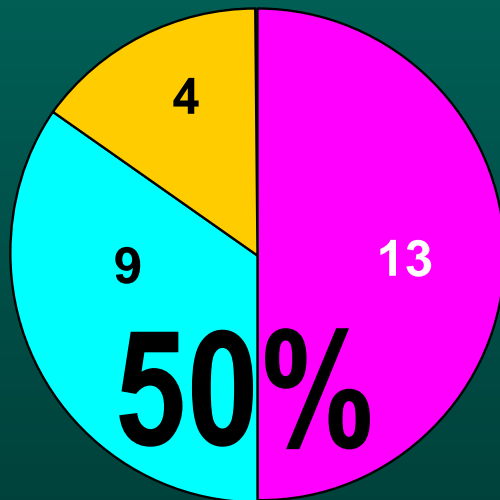
→ HBsAg (-), Anti-HBsAb (-), Anti-HBcAb(+)

# Predictors of HBV reactivation

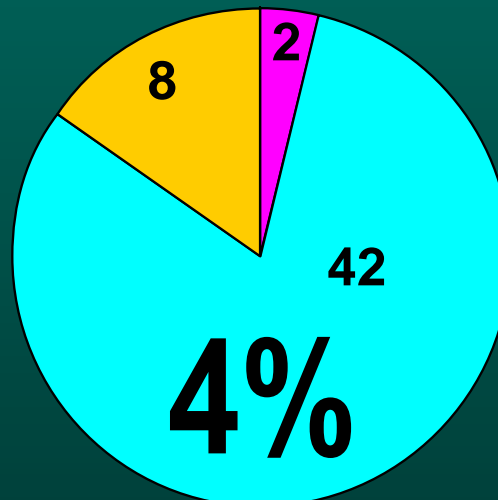
## (1) HBV status

100 patients with NHL at Queen Mary Hospital, HK

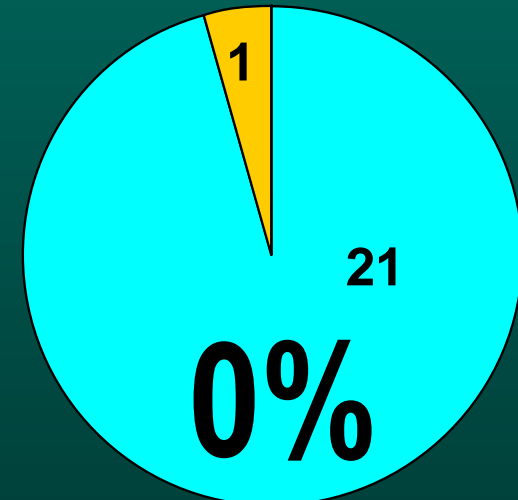
■ HBV reactivation ■ No hepatitis ■ Other causes of hepatitis



26 HBsAg+ve  
Chronic HBV



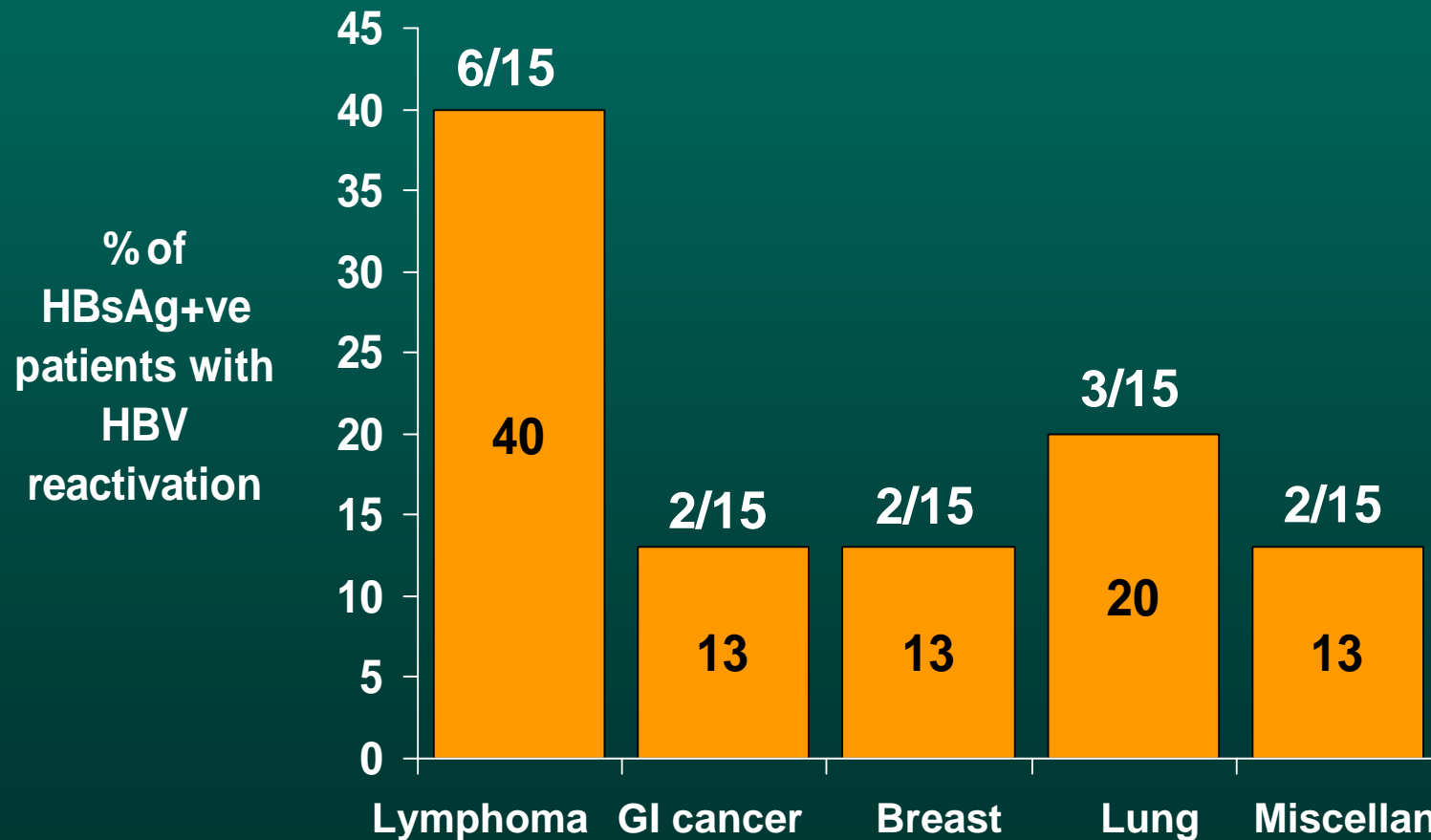
52 anti-HBs+ve  
Previous exposure



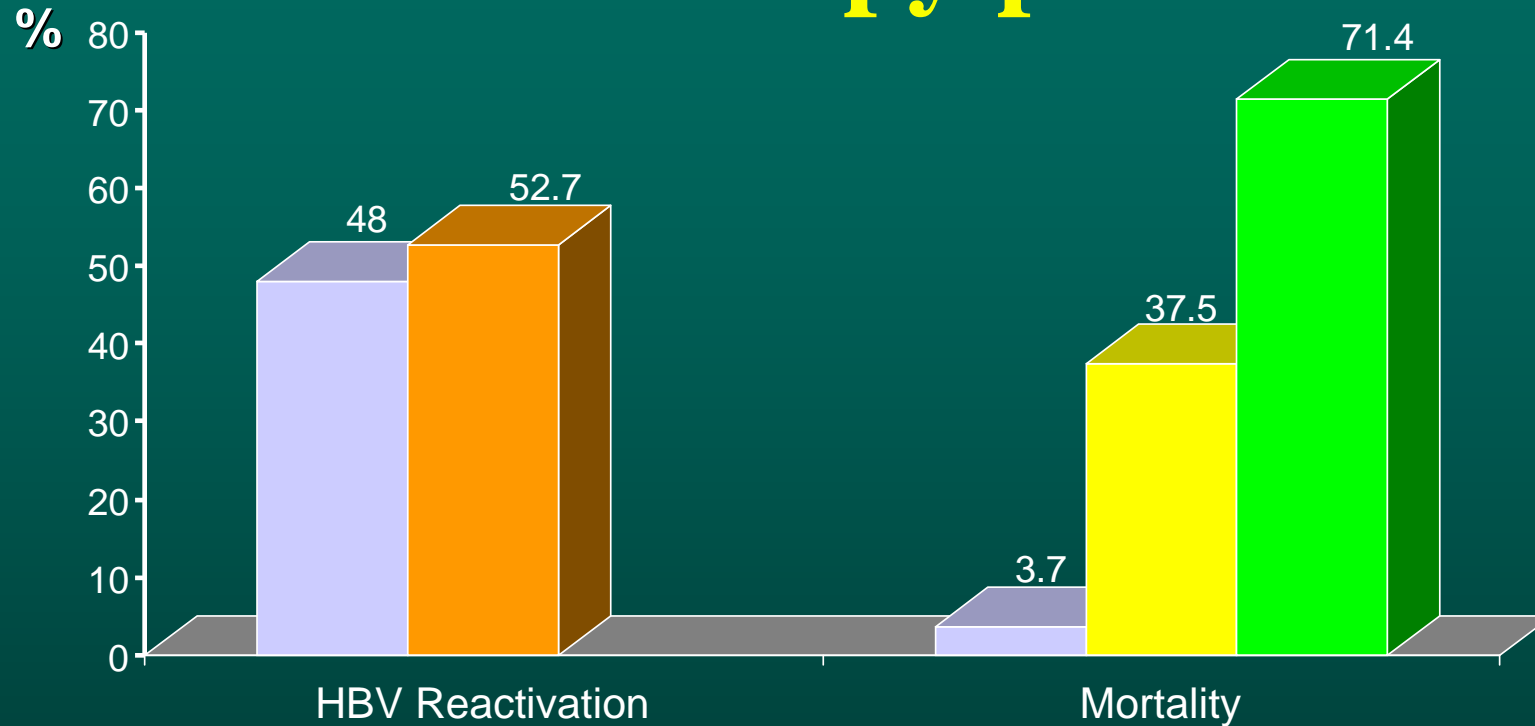
22 HBsAg-ve / anti-  
HBs-ve  
HBV naive

# Predictors of HBV reactivation: type of malignancy

Reactivation =  $\uparrow$ HBV DNA  $>10^6$  c/mL and  $\uparrow$ ALT



# Hepatitis B reactivation in chemotherapy patients



■ Lok ASF et al. *Gastroenterology* 1991; 100: 182-8.

■ Nakamura et al. *Cancer* 1996; 78: 2210-5.

■ Markovic S et al. *Hepato Gastroenterol* 1999; 46: 2925-30.

■ Lim LL et al. *Aliment Pharmacol Ther* 2002; 16: 1-6.

# HBV reactivation

## -(3) Type of chemotherapy-

193 patients chemotherapy at Prince of Wales Hospital, HK

	HBV – Hepatitis		P-value
	YES	NO	
<b>Steroids</b>	26%	13%	0.01
<b>Vinca-alkaloid</b>	39%	15%	0.001
<b>Anthracycline</b>	30%	12%	0.0001

**N.S.:Cyclophosphamide, 5-fluorouracil, Folinic acid, Etoposide,  
Platinum, Gemcitabine, Taxanes**

*Yeo et al. Br J Cancer 2004; 90: 1306*  
*Yeo et al. J Med Virol 2000; 62: 299*

# Clinical picture of HBV reactivation during C/T

- Onset: during or after C/T (4-36 weeks)
- HBV DNA flare followed by ALT elevation: 1-11 weeks; median 2-3 weeks.
- HBsAg + : 48-78 %
- HBsAg-/ Anti-HBc +: 4%
- Premature termination of C/T:  
70% v.s. 30% in breast cancer patients
- Fatal rate: 5-40%

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Yeo W. Hepatology 2006;43:209-20



# 健保給付修訂為：

慢性B型肝炎病毒帶原者HBsAg(+)

(1)接受非肝臟之器官移植後,B型肝炎發作者可長期使用

(2)接受癌症化學療法中,B型肝炎發作者經照會消化系專科醫師同意後,可長期使用

(3)接受肝臟移植者可預防性使用

(4)接受癌症化學療法,經照會消化系專科醫師同意後,可於化學療法前一週開始給付使用,直至化學療法結束後6個月,以預防B型肝炎發作。



# Screen for HBV patients undergoing chemotherapy

# Screen for HBV patients undergoing chemotherapy

- All patients should screen for HBV:  
HBs Ag, Anti-HBs Ab, Anti-HBc Ab
- HBs Ag (+) : HBV DNA, HBe Ag, Anti-HBe Ab.
- HBs Ag(-), Anti-HBc (+): HBV DNA if needed.



**HBs Ag (+)**

**HBV DNA**

**Start anti-viral therapy regardless of  
HBV DNA status**

**Follow ALT, HBV DNA**

**Consider discontinuation of anti-  
viral agent at 6-12 months after  
cessation of chemotherapy**

**HBs Ag (-)**

**Anti- HBc (-)**

**Anti-HBs (-)**

**Vaccination  
against HBV  
(3 doses)**



**HBs Ag (-) Anti- HBc (+)  
Anti-HBs (-)**

**HBV vaccine (1st dose)**

**Check Anti-HBs within 2-4 weeks**

**Anti-HBs (+)**

**No Anti-  
viral Tx**

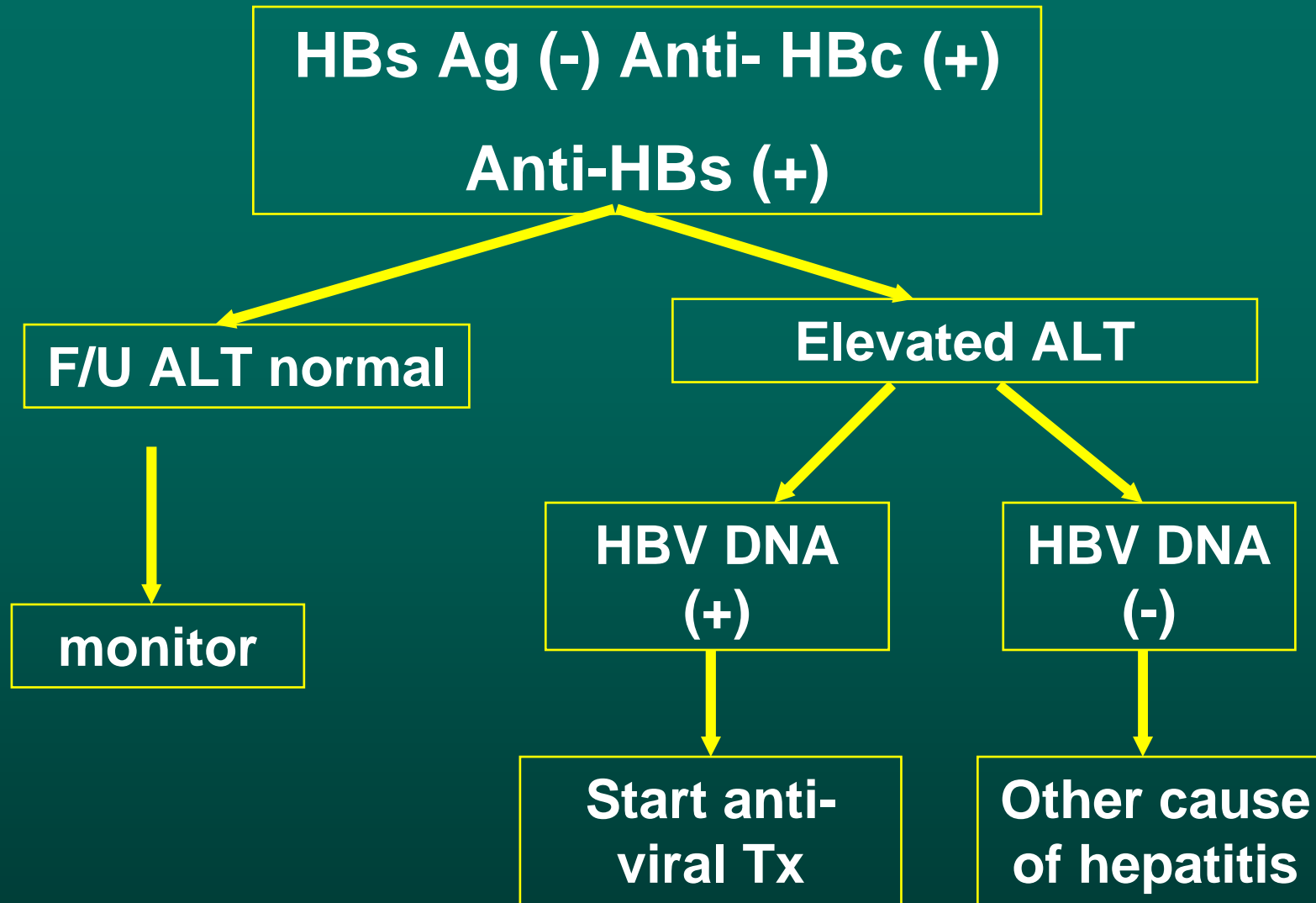
**Anti-HBs (-)**

**HBV  
DNA (+)**

**Start anti-  
viral Tx**

**HBV  
DNA (-)**

**Complete  
vaccination (2  
more doses)**



# Prevention and management of HBV reactivation during chemotherapy or immune suppressive therapy

# Prevention and management of HBV reactivation during immune suppressive therapy

- Steroid-free agents (X)
- Interferon (X)
- Oral anti-viral therapy

Deferred therapy

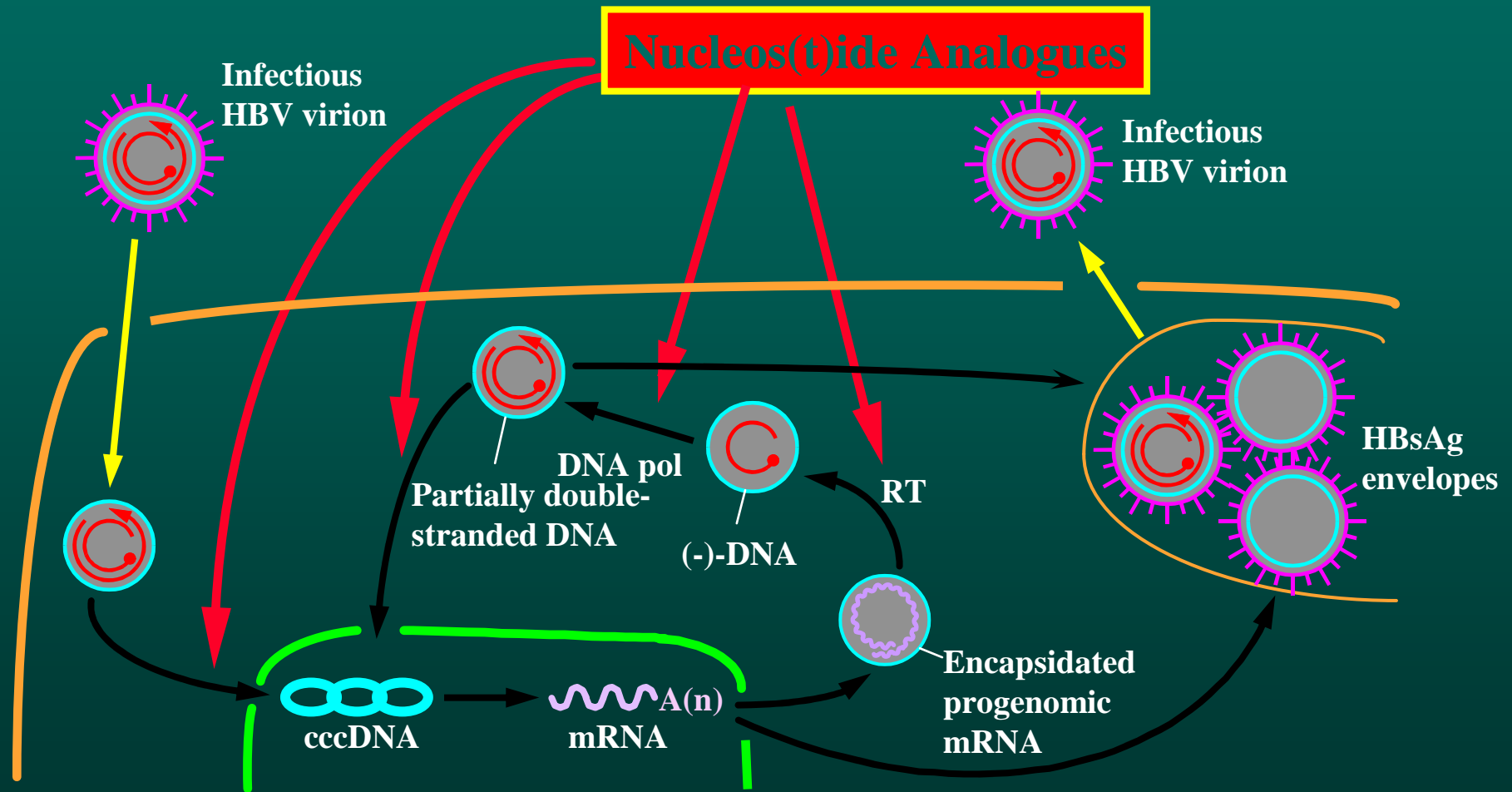
Pre-emptive therapy

Prophylactic therapy

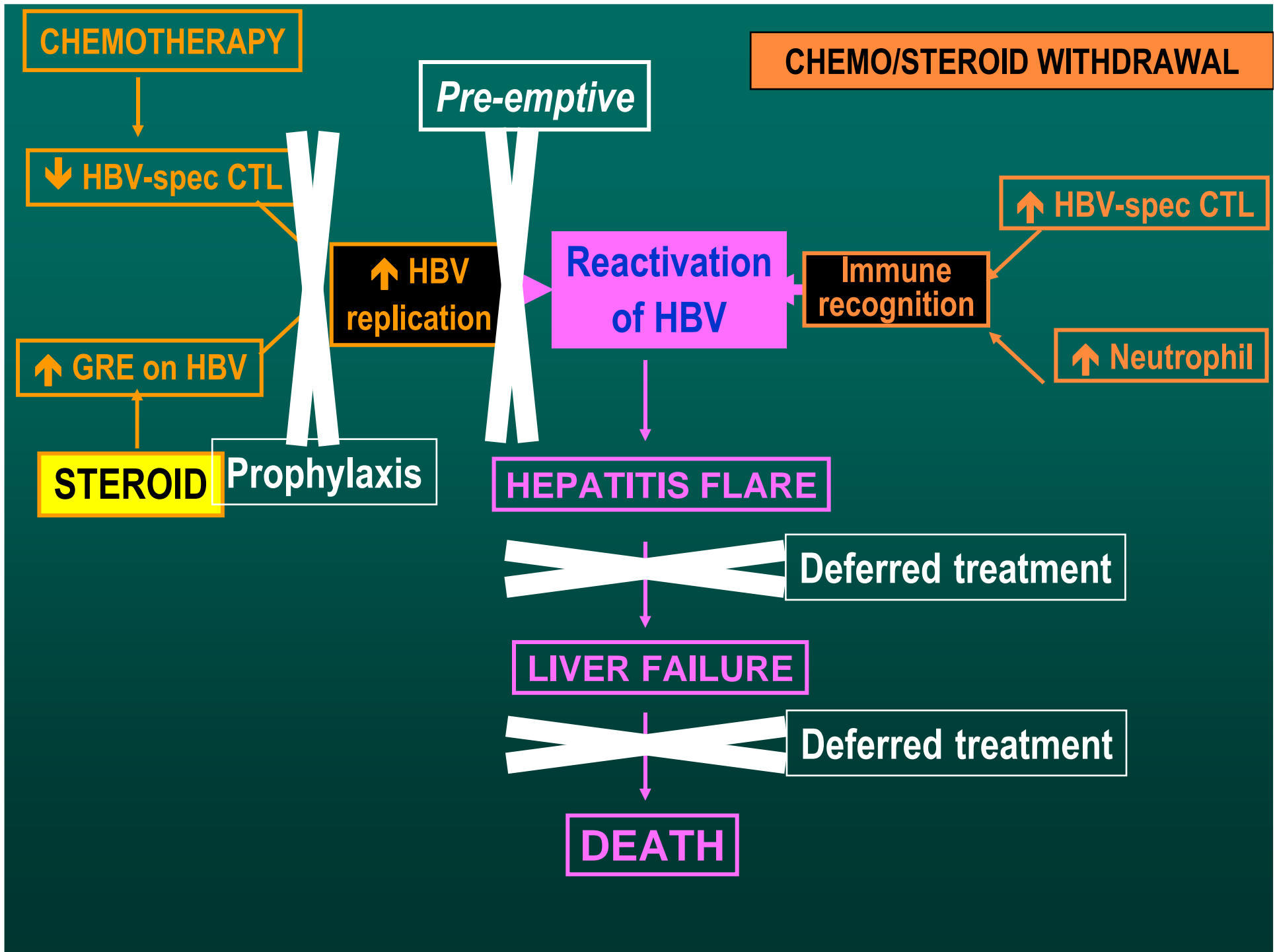


# HBV Replication

## - Inhibition by Nucleos(t)ide Analogues -

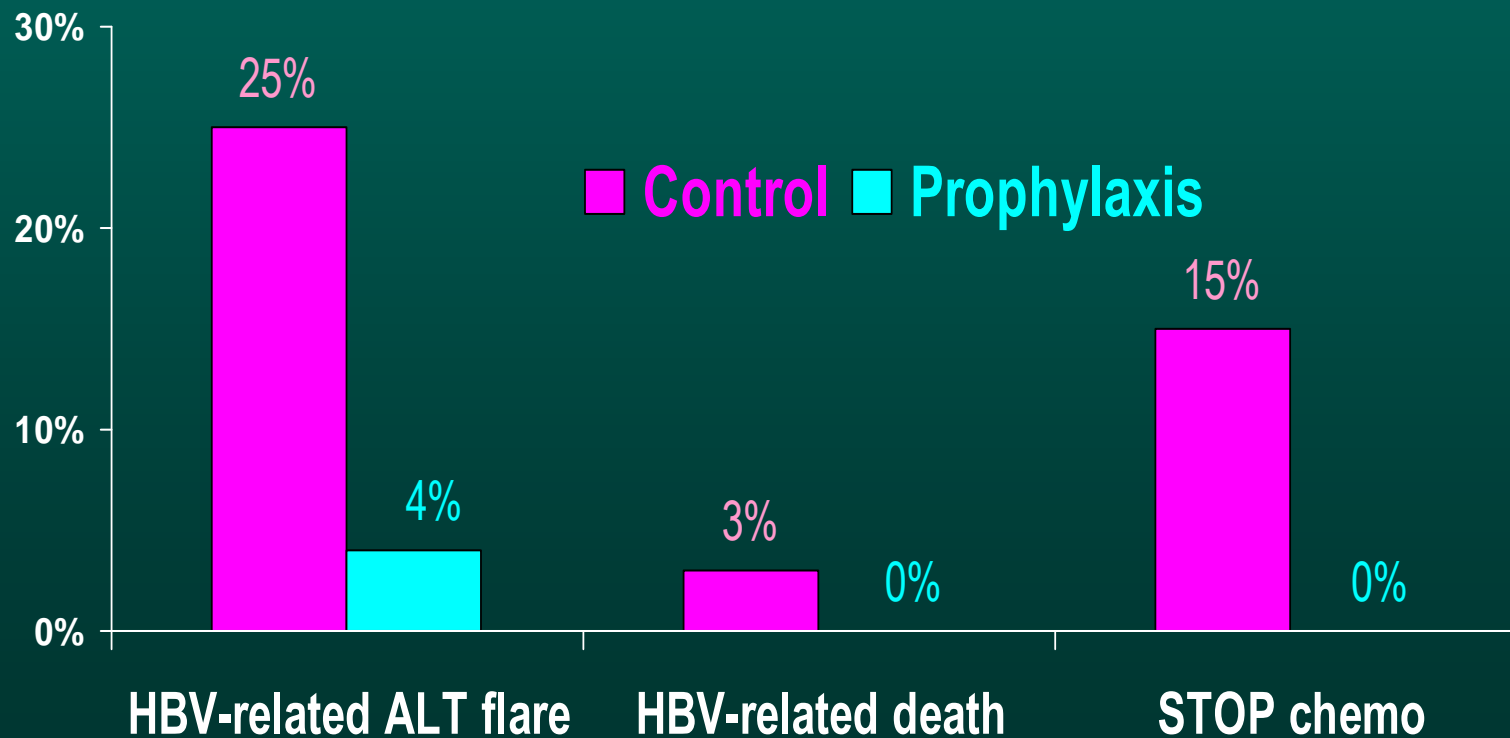


Lai et al., J Med Virol 2000

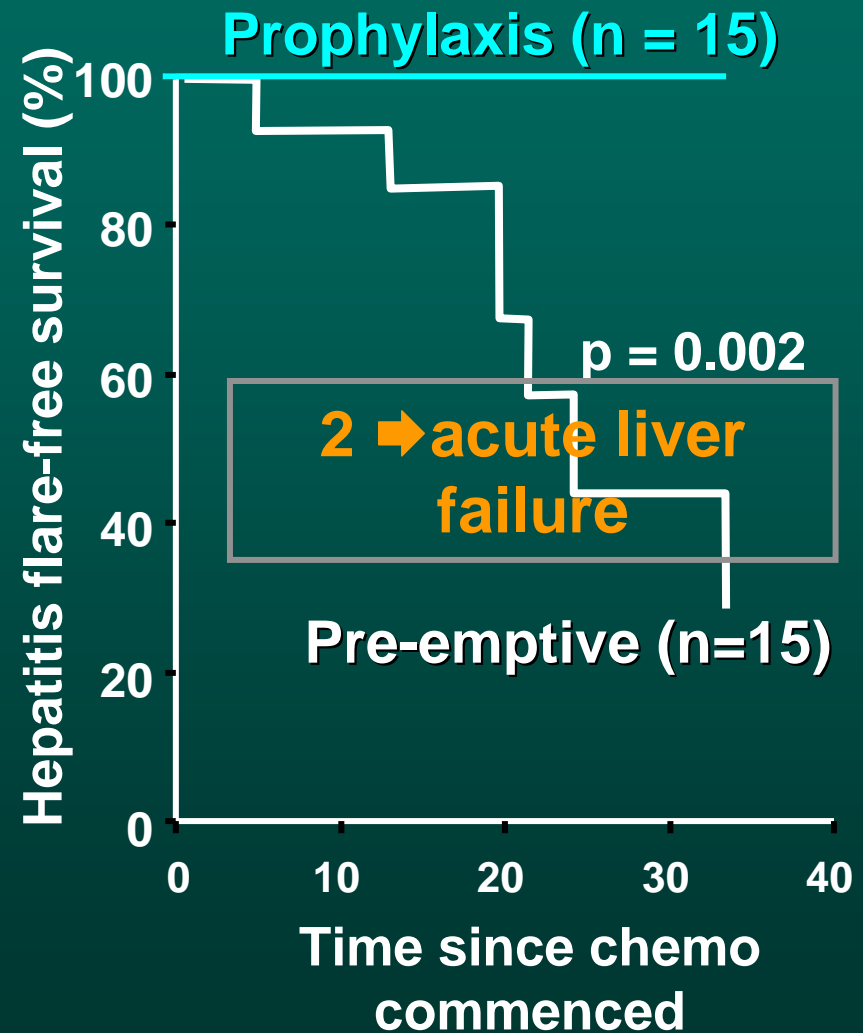
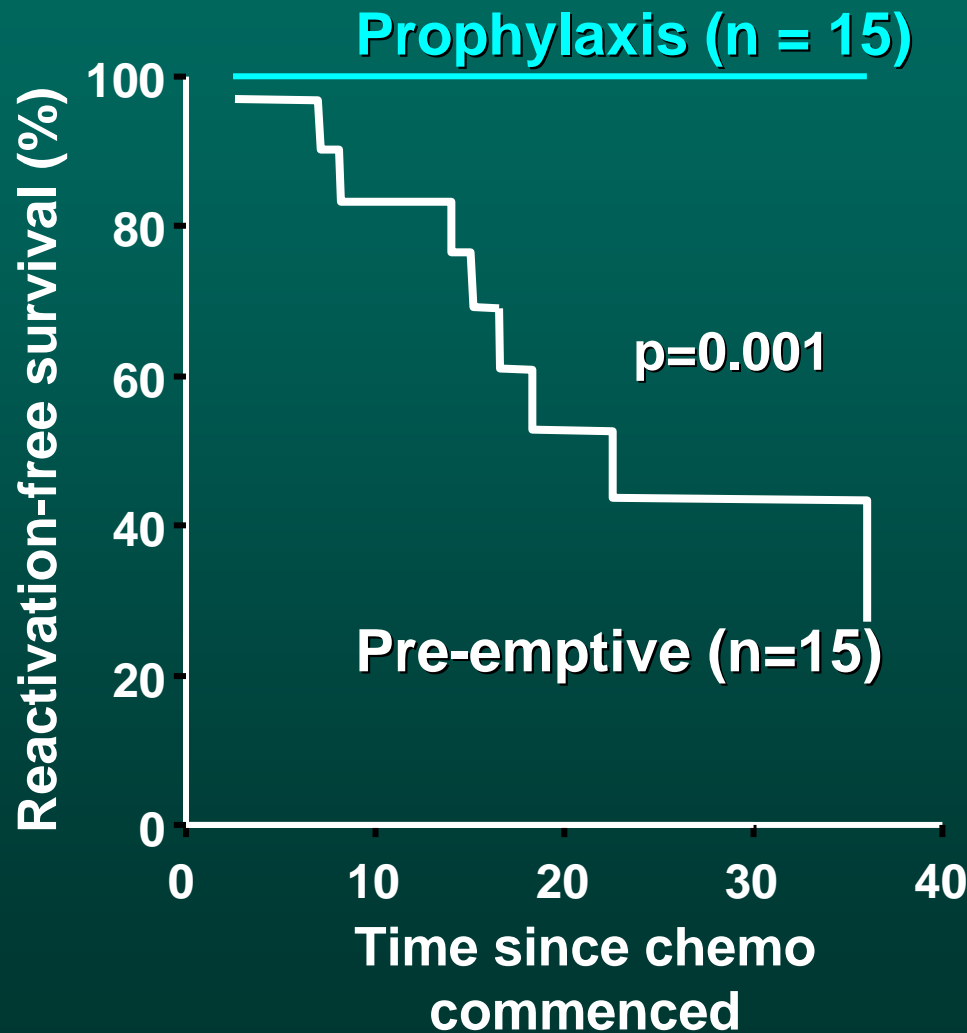


# HBV reactivation during chemotherapy: prophylaxis versus deferred treatment

- 258 HBsAg +ve patients on chemotherapy at the Prince of Wales Hospital, Hong Kong
  - NHL 45; breast 81; colonic 67; gynaecological 25; lung 13
  - 65 received lamivudine prophylaxis, 193 controls



# *Prophylaxis versus pre-emptive treatment*



***Brief Summary: lamivudine on HBV reactivation during chemotherapy***

- Prophylaxis > pre-emptive > deferred Tx
- HBV reactivation :

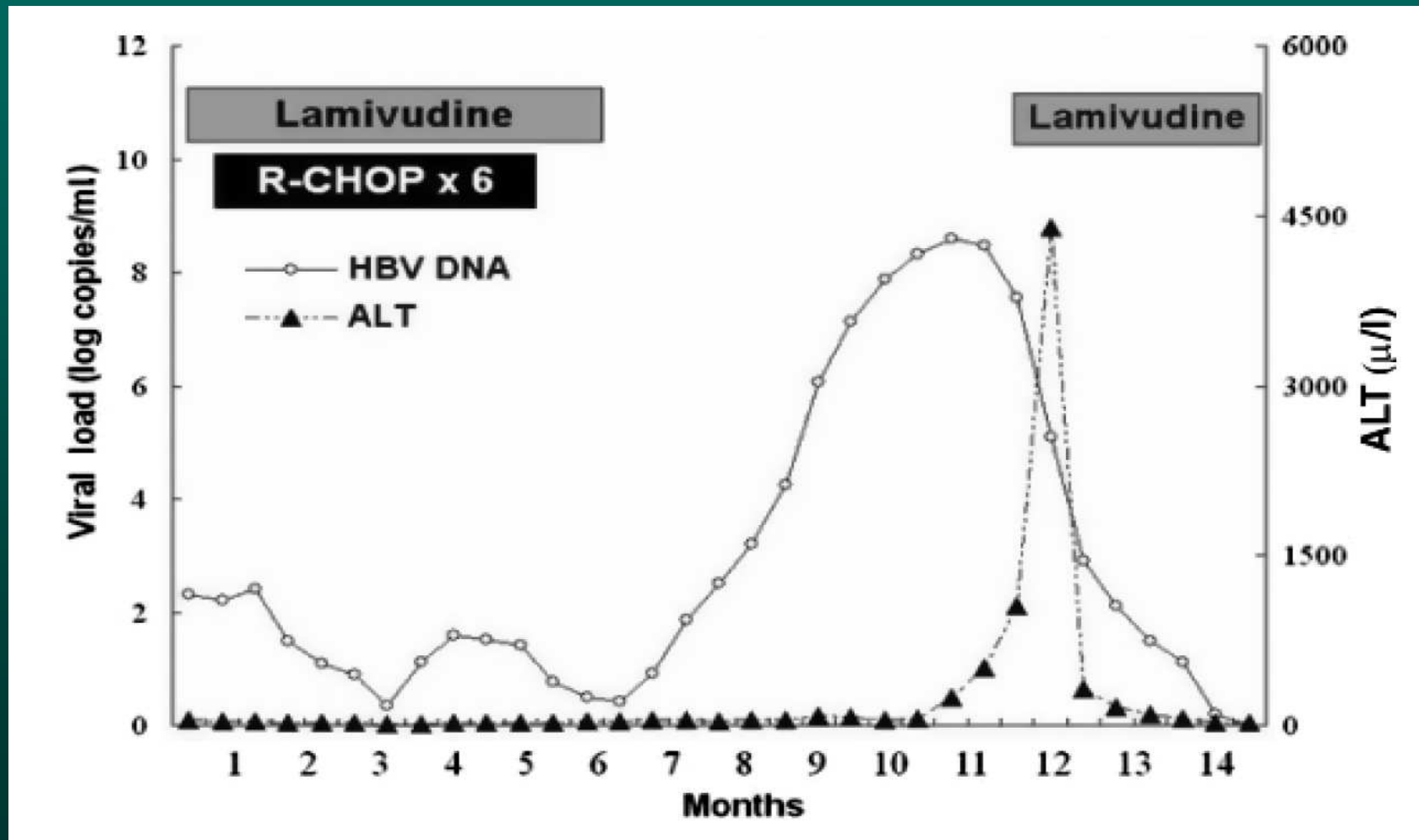
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<b>Prevent LAM</b>	v.s.	<b>Deferred LAM</b>
<b>0-9%</b>	v.s.	<b>25-85%</b>

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- Start LAM 2-3 weeks prior to C/T ;  
**no later than the first day of C/T.**
- Premature termination of LAM may lead delayed HBV reactivation.

# 早期停藥可能導致 HBV reactivation 併 hepatitis flare (in chemotherapy pt's with preemptive antiviral agent)



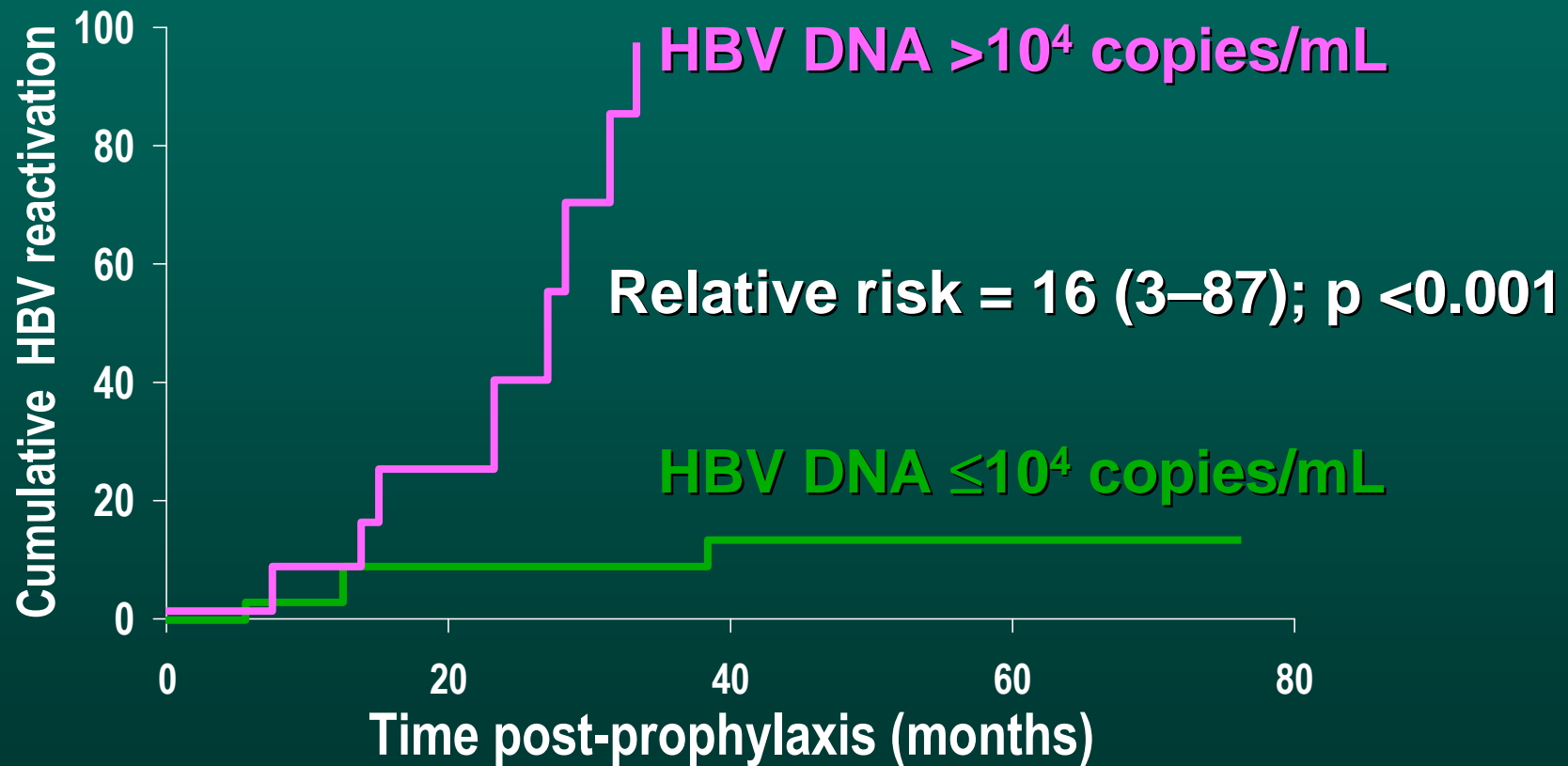
## ***Delayed HBV reactivation after lamivudine prophylaxis***

- 46 HBsAg+ patients at Queen Mary Hospital, Hong Kong
  - NHL in 33; other haematological malignancy 13
    - LAM prophylaxis until 12 weeks after chemo
  - Monitor for reactivation
    - ALT, DNA every 2 weeks for 12 weeks, then every 4 weeks
    - Duration of f/u: 26 months (6–76)

### **» Risk of reactivation**

- ▬ 0/46 during prophylaxis
- ▬ **11/46 after prophylaxis**

# Risk of delayed HBV reactivation after lamivudine prophylaxis



# Duration of preventive anti-viral therapy

- Still unconcluded.
- AASLD: > 6 months after discontinue C/T.
- Elevated ALT and high HBV DNA ( $> 10^4$  copies/ml) before C/T →

Suggest long-term anti-viral therapy.

- Close monitor ALT (1-2 monthly) and HBV DNA (3-6 monthly) after stopping anti-viral agents.



# 健保給付修訂為：

慢性B型肝炎病毒帶原者HBsAg(+)

(1)接受非肝臟之器官移植後,B型肝炎發作者可長期使用

(2)接受癌症化學療法中,B型肝炎發作者經照會消化系專科醫師同意後,可長期使用

(3)接受肝臟移植者可預防性使用

(4)接受癌症化學療法,經照會消化系專科醫師同意後,可於化學療法前一週開始給付使用,直至化學療法結束後6個月,以預防B型肝炎發作。

# Conclusion

- All patients for immune suppressive therapy should be screen for HBV.
- HBV reactivation is high in HBsAg (+) P't.
- Early, prophylactic oral anti-viral therapy is prefer for HBs Ag (+) patients undergoing immune suppressive therapy .
- Start anti-viral therapy 2-3 weeks prior to Tx or not later than the day of Tx.
- Keep treatment for > 6-12 months after Tx.
- Long-term therapy should be considered if elevated ALT and HBV DNA >  $10^4$  copies/ml before Tx.

# 建議臨床處理方式

- 若過去不曾檢查過，請於化療前檢驗：**HBsAg**，**Anti-HBcAb**，**Anti-HBsAb**，**Anti-HCV Ab**。
- 若**HBsAg(+)** 或 **Anti-HCV Ab (+)**，請通知助理林儷如小姐；亦可指定會診胃腸科余憲忠醫師。我們會協助進一步檢查及必要時申請預防性用藥。
- 因預防性給藥最好在化療前一週，最好待結果出來後再化療，若時間上有困難不能等待，可與我們聯繫先給藥，日後不是再停掉。

# 建議臨床追蹤監測方式

## \* 針對B、C型帶原患者-----

- 住院化療或免疫抑制治療至少每週監測 **ALT** 及 **Bilirubin**。
- 門診化療或免疫抑制治療至少每月監測 **ALT** 及 **Bilirubin**。
- 化療或免疫抑制治療終止後，前3個月應每月檢測 **ALT** 及 **Bilirubin**，之後每3個月檢測一次迄滿一年為止。
- 門診之追蹤會以胃腸科特約門診方式辦理，助理林儷如小姐會安排。

謝謝聆聽

請多指教