Can we stop chronic hepatitis B treatment?

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Case Presentation

- 26 y-o/F
- HBsAg positive during family screening
  - Her mother and two sisters: HBsAg (+)
- ALT 112 U/L

- HBeAg (+)
- Anti-HCV and anti-delta (-)
- HBV-DNA >110 million U/mL
- US: normal

- Liver Bx: HAI:2, F:2 (Ishak's)
- Tenofovir was initiated

- HBV-DNA became undetectable 72 weeks after tenofovir

- 5th year of tenofovir …
  - HBV-DNA still undetectable
  - ALT normal
  - HBeAg (+)
- She planned pregnancy; came to discuss with her husband

- They were informed.....
- Tenofovir was discontinued

- 4th month of pregnancy
  - ALT 850 U/L
  - AST 730 U/L
- Tenofovir was re-initiated

- ALT regressed significantly in one month
- Pregnancy was uneventful; HBIG was administered and vaccination was initiated
- She decided breast feeding under tenofovir

- 2 years later
- Development of the kid is normal
- ALT normal
- HBV-DNA undetectable
- HBeAg-positive

- She decided to be pregnant
- Tenofovir was discontinued

- 3 months later ALT 250 IU/L
  - After one week 1100 IU/L
- Tenofovir was re-initiated
  - She called yesterday (28 Feb); ALT 23 U/L

Can we stop the therapy?

- HBeAg (+)
  - HBeAg seroconverted or not
- HBeAg (-)
- Advanced fibrosis/cirrhosis

Drugs

- IFN
- Nucloes(t)ides

Parameters

- HBsAg
- HBV-DNA
- HBeAg
- HBsAg quantity
- cccDNA

Importance of HBsAg Loss

- The goal of HBV therapy is to achieve seroclearence of HBsAg
- HBsAg seroclearence: the closest event to a cure of CHB.

The biochemical, virologic, histologic, and prolonged prognoses of 231 Japanese patients with HBsAg seroclearance (median follow-up, 6.5 years).

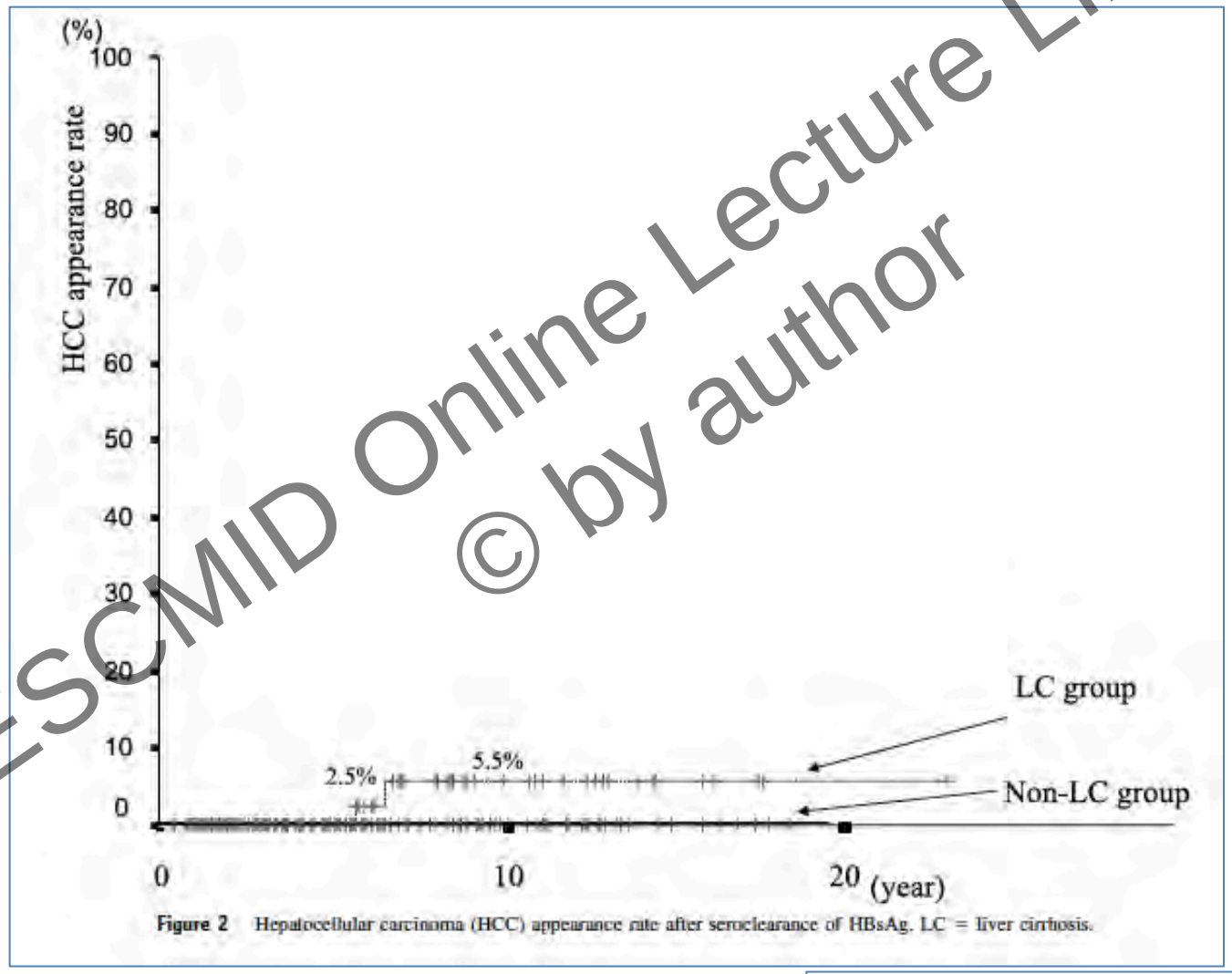

Figure 2 Hepatocellular carcinoma (HCC) appearance rate after seroclearance of HBsAg. LC = liver cirrhosis.

Am J Med 2006; 119, 71.e9-71.e16

Table 4 Recent studies on the outcomes following HBsAg clearance

Source	Status at clearance	No of cases	No of HBV alone	Follow-up, mo	Mean age, y	Outcomes	
						Decompensated LC	HCC
Fattovich et al[14]	LC	32	30*	55	44	6	1§
Huo et al[15]	Non-LC	55	32*	23	54	6	1§
Chen et al[16]	Non-LC	189	146*	65.4	43	0	2§
	LC	29	17*	50.8	54	4†	1§
Yuen et al[10]	LC or non-LC	92	92	51.1	42.6		5
Present	Non-LC	167	167	61.1	51	0	0
	LC	67	67	74.1	52.5	0	2

LC = liver cirrhosis; HCC = hepatocellular carcinoma.
*Remaining patients had concurrent virus of hepatitis C virus and/or HDV.
†Two of 4 patients had concurrent virus.
§These patients had concurrent virus.

Am J Med 2006; 119, 71.e9-71.e16

HBsAg seroclearence;

- HBsAg loss on two analyses at least 6 months apart
- It is rare during natural course
  - 0.12-2.38%/year in Asian cohorts
  - 0.54-1.98%/year in Western cohorts

Antivir Ther 2010;15:133-43
Gastroenterologie Clin Biol 2010;34(Suppl2):S119-25.

- HBV therapy can be discontinued after HBsAg loss
- In cirrhotics
  - Liver functions can improve or remain stable
  - Hepatic decompensation is rare
  - Although at a very low rate, HCC can still develop
    - When cirrhosis is established before HBsAg loss
      - When HBsAg loss occurs at an older age

Antivir Ther 2010;15:133-43
Gastroenterologie Clin Biol 2010;34(Suppl2):S119-25.
Hepatol Int 2012;6:531

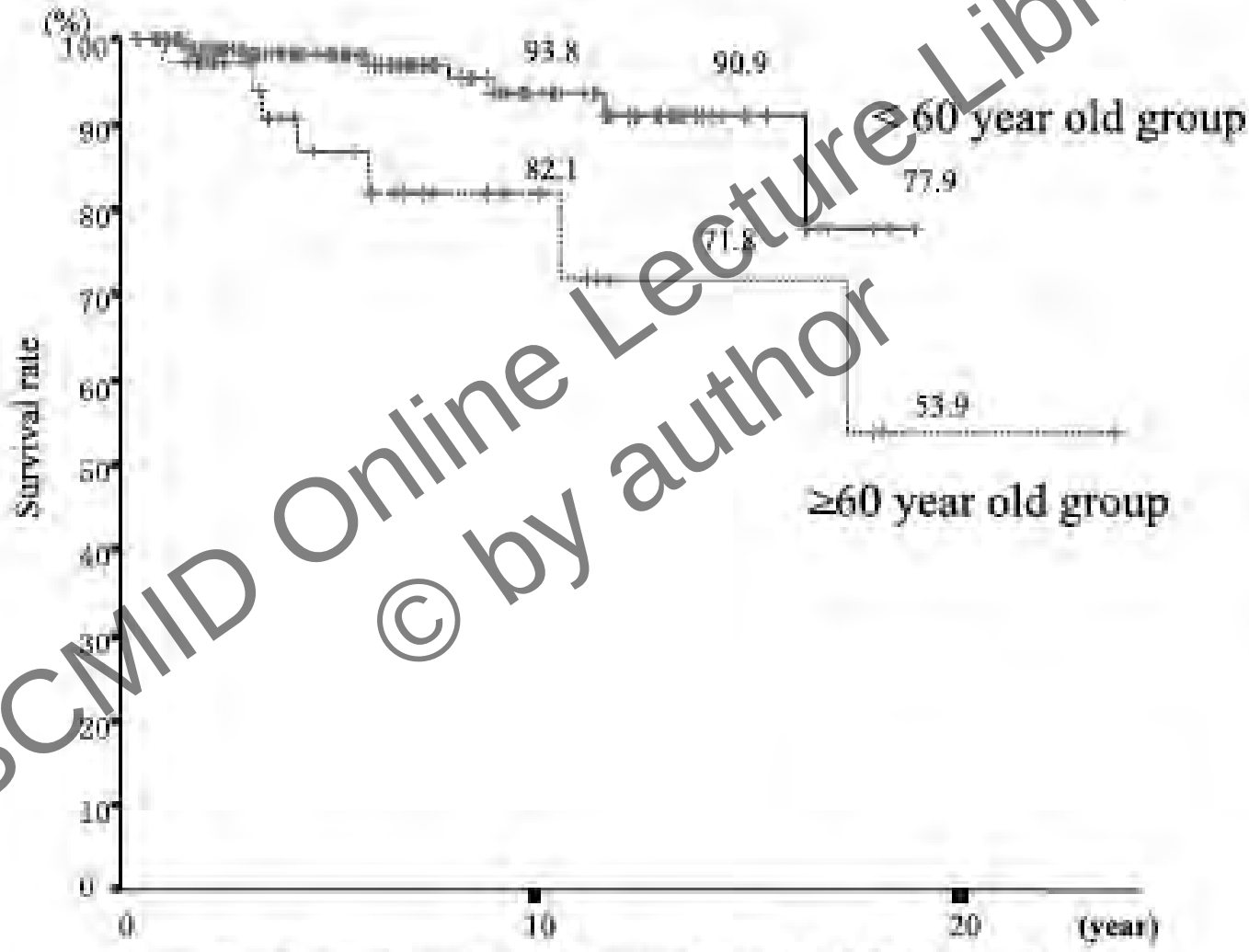

Figure 3 Survival based on difference of age after HBsAg seroclearance.

cccDNA

- Transcriptional template of HBV
- It exists in the cell nucleus as a viral minichromose
- Serves as the intrahepatic reservoir for HBV

cccDNA

- Its clearence; the main challenge of antiviral therapy in HBV
- Difficult to obtain, not practical
- Serum HBsAg level is used as a partial surrogate marker

HBV-DNA

- Its negativity is required to discontinue NUCs

HBeAg

- In HBeAg-positive patients, before HBsAg loss, HBeAg loss is expected
- Spontaneous HBeAg seroconversion occurs in 2-15% per year
  - Depends on age, ALT level, genotype
- HBeAg seroconversion leads to an “inactive carrier state”
  - Low or undetectable HBV-DNA
  - Normal ALT
  - Favorable outcomes

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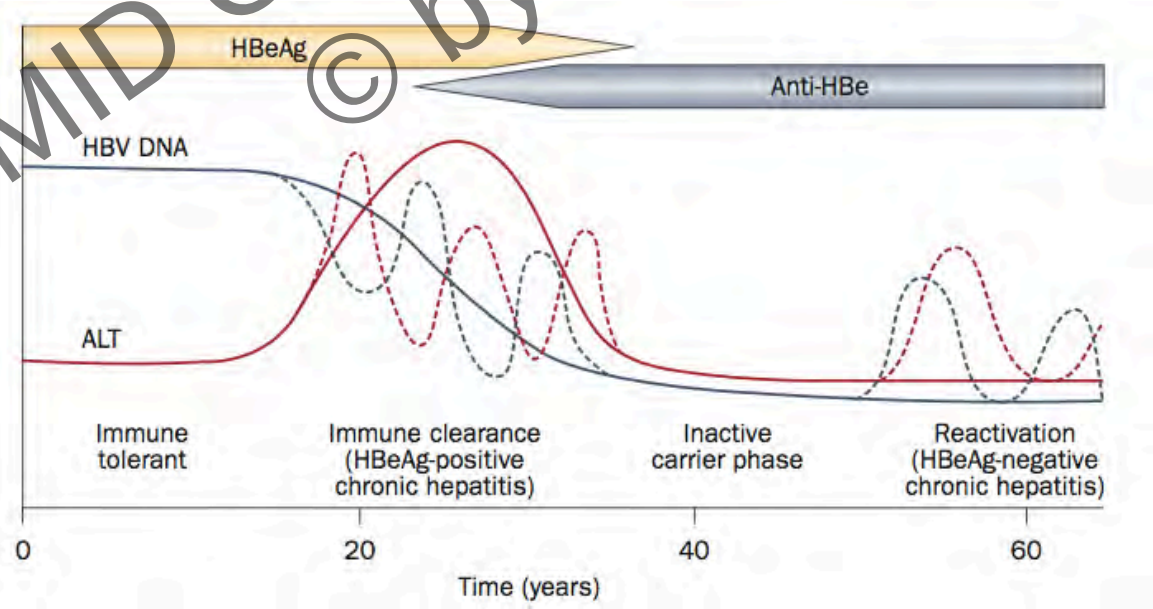
HBeAg seroconversion

- Is not enough to discontinue the therapy
  - Relapse 2-3% per year
  - Fluctuating HBV-DNA and ALT levels in HBeAg-negative chronic hepatitis B



HBsAg Quantitation

HBeAg-positive:

- <1500 IU/mL at w12 of Peg-IFN: 18% HBsAg loss at 6 months post-treatment

  J Hepatol 2011;54:S31

- Any decline at w12 of Peg-IFN: a good predictor of response; a NPV of 97%

  Hepatology 2010;52:1251

HBsAg Quantitation

HBeAg-negative:

- <10 IU/ml at w48 of Peg-IFN and on-treatment >1 log IU/mL decline: significantly associate HBsAg loss 3 years after treatment

Hepatology 2009;49:1141

Interferon

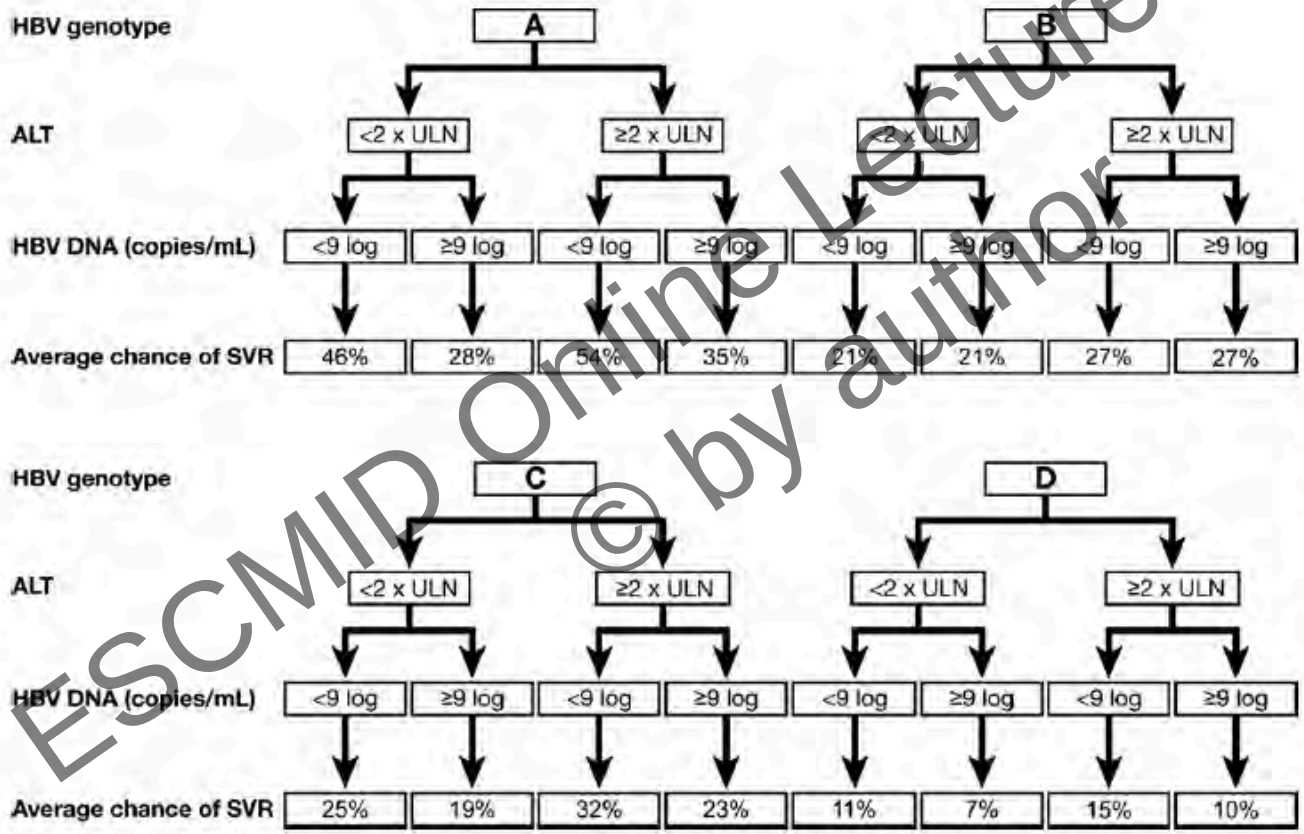


Figure 3. Flowcharts to easily obtain average predicted probabilities of sustained response in patients infected with HBV genotypes A–D. These flowcharts show the average predicted probability of sustained response depending on HBV genotype, ALT level (> or <2 × ULN), and HBV-DNA level (> or <9 $\log_{10}$ copies/mL). For a precise estimate of the probability of sustained response in an individual patient, the nomograms in Figure 2 can be used.

Gastroenterology 2009;137:2002–2009

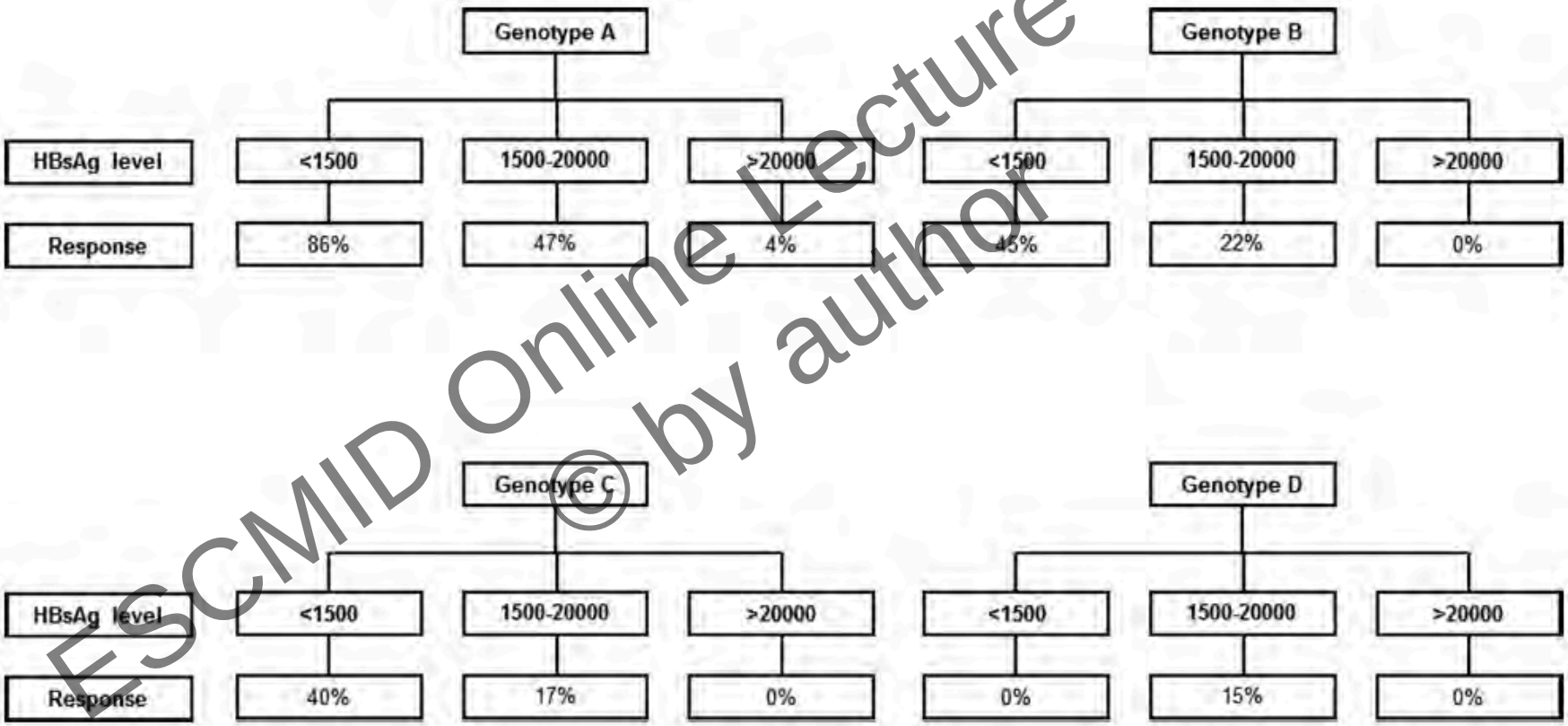
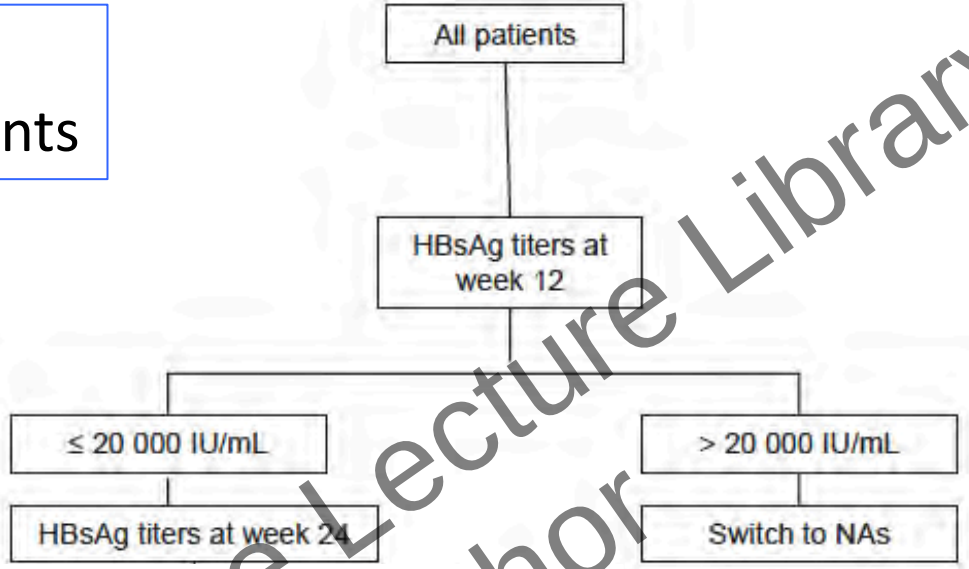
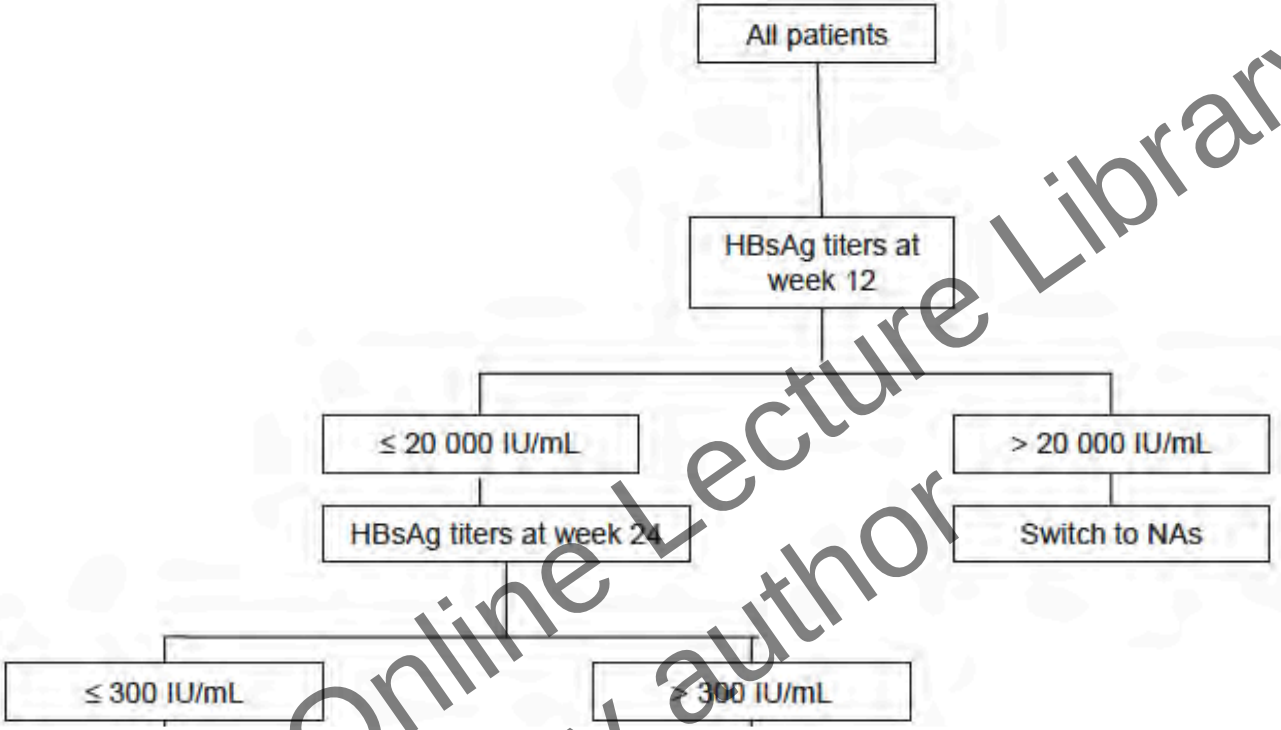


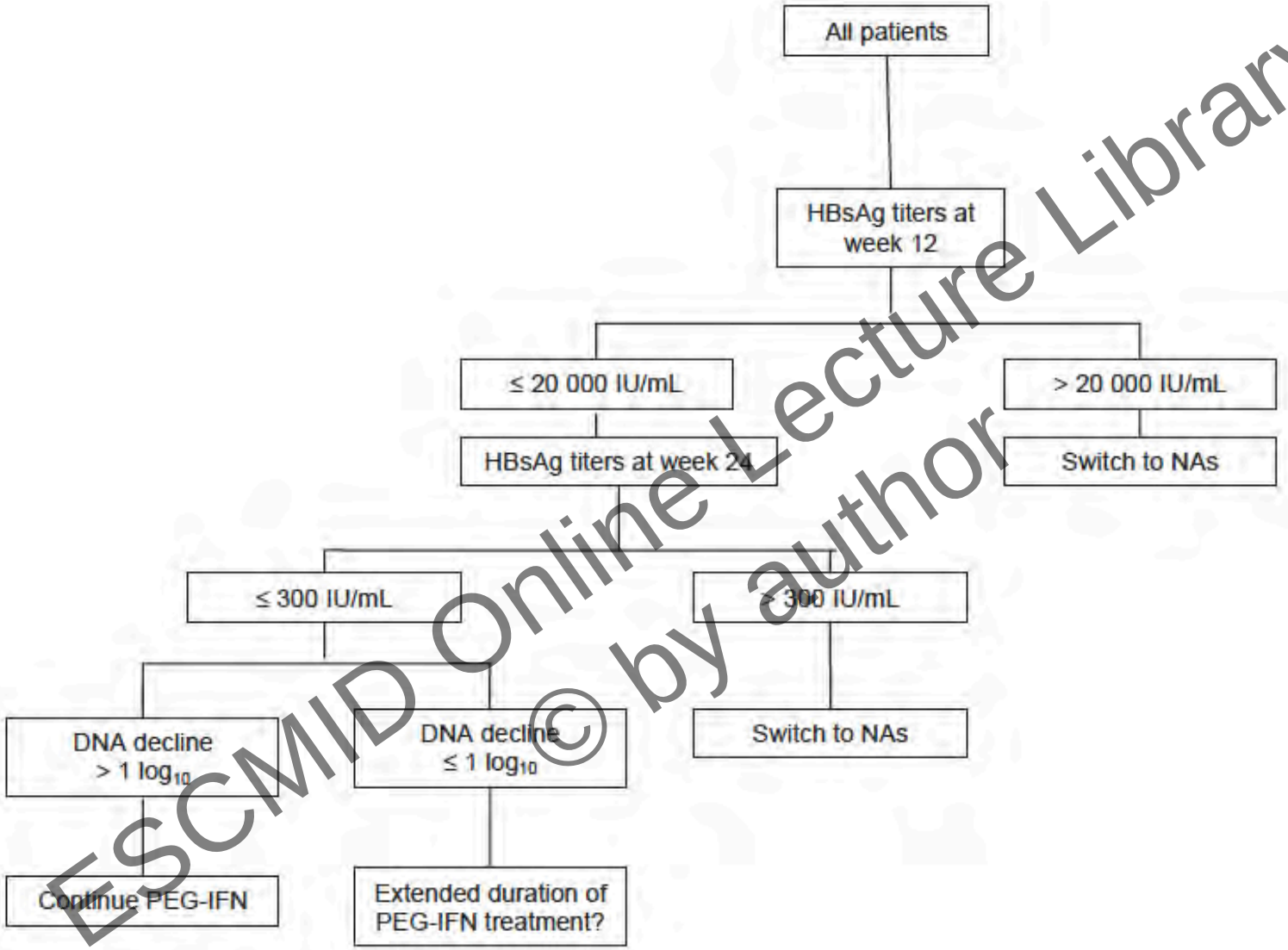
Fig. 4. Relationship between HBsAg level (in IU/mL) at week 24 of treatment and response (HBeAg loss with HBV DNA <2,000 IU/mL) 6 months off-treatment.

Hepatology 2013;58:872-880

An Algorithm for HBeAg-positive Patients







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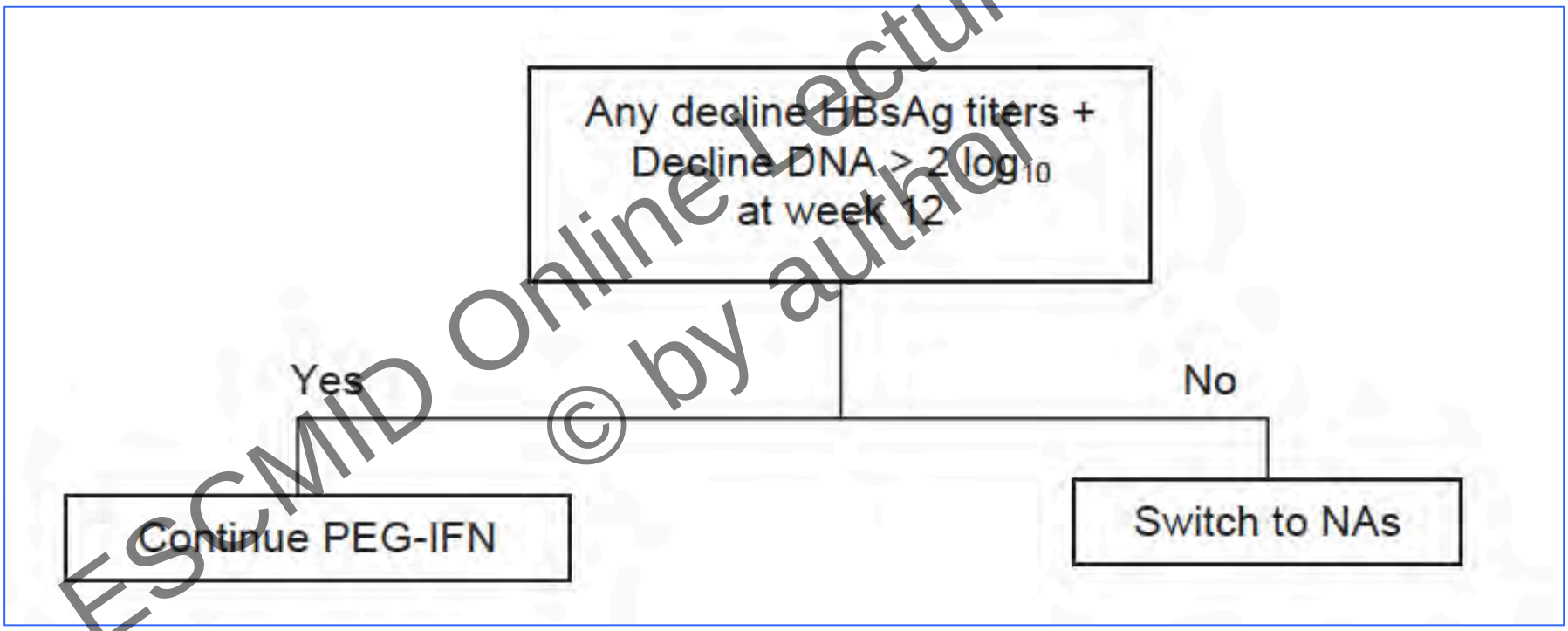
An Algorithm for HBeAg-negative Patients



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NUCs

- Tenofovir and entecavir
  - High potency
  - Minimal or null drug resistance
  - Rapid reduction of HBV-DNA
  - Normalization of ALT

NUCs

- Little effect on cccDNA
- HBsAg loss is uncommon

- Treatment should be long-term
- Virological relapse after discontinuation of therapy is frequent (even after HBeAg loss has been achieved)

Table 2. HBsAg loss with first-line NAs at 1, 3 and 5 years of treatment in HBeAg-positive and -negative patients

		Treatment (%)		
Antiviral treatment	HBeAg	1 year	2–3 years	5 years
Tenofovir	Positive	3	8	10
	Negative	0	0	0
Entecavir	Positive	2	5	1.4
	Negative	0	0	0

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Continue till HBsAg loss: is it really needed?

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Long-Term Therapy with Adefovir Dipivoxil for HBeAg-Negative Chronic Hepatitis B

Stephanos J. Hadziyannis, M.D., Nicolaos C. Tassopoulos, M.D., E. Jenny Heathcote, M.D., Ting-Tsung Chang, M.D., George Kitis, M.D., Mario Rizzetto, M.D., Patrick Marcellin, M.D., Seng Gee Lim, M.D., Zachary Goodman, M.D., Jia Ma, M.S., Sarah Arterburn, M.S., Shelly Xiong, Ph.D., Graeme Currie, Ph.D., and Carol L. Brosgart, M.D., for the Adefovir Dipivoxil 438 Study Group*

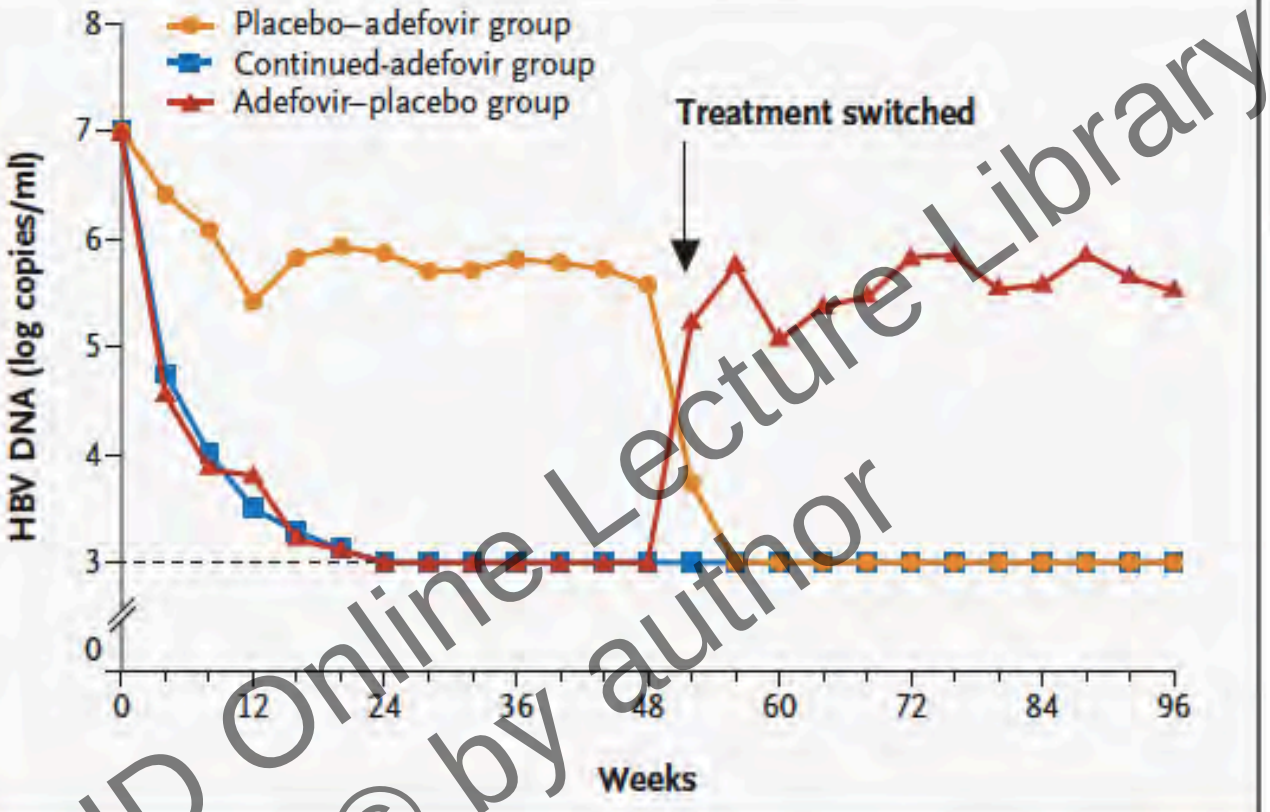

Figure 1. Median Serum HBV DNA Levels through Week 96.

The dashed line indicates 3 log copies per milliliter, which was the lower limit of detection for the assay.

CONCLUSIONS

In patients with HBeAg-negative chronic hepatitis B, the benefits achieved from 48 weeks of adefovir dipivoxil were lost when treatment was discontinued. In patients treated for 144 weeks, benefits were maintained, with infrequent emergence of viral resistance.

GASTROENTEROLOGY 2012;143:629–636

Sustained Responses and Loss of HBsAg in HBeAg-Negative Patients With Chronic Hepatitis B Who Stop Long-Term Treatment With Adefovir

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- A cohort observational study, following 33 HBeAg-negative patients with CHB, undetectable serum HBV DNA, and normal levels of aminotransferases after long-term (4 or 5 years) treatment with adefovir

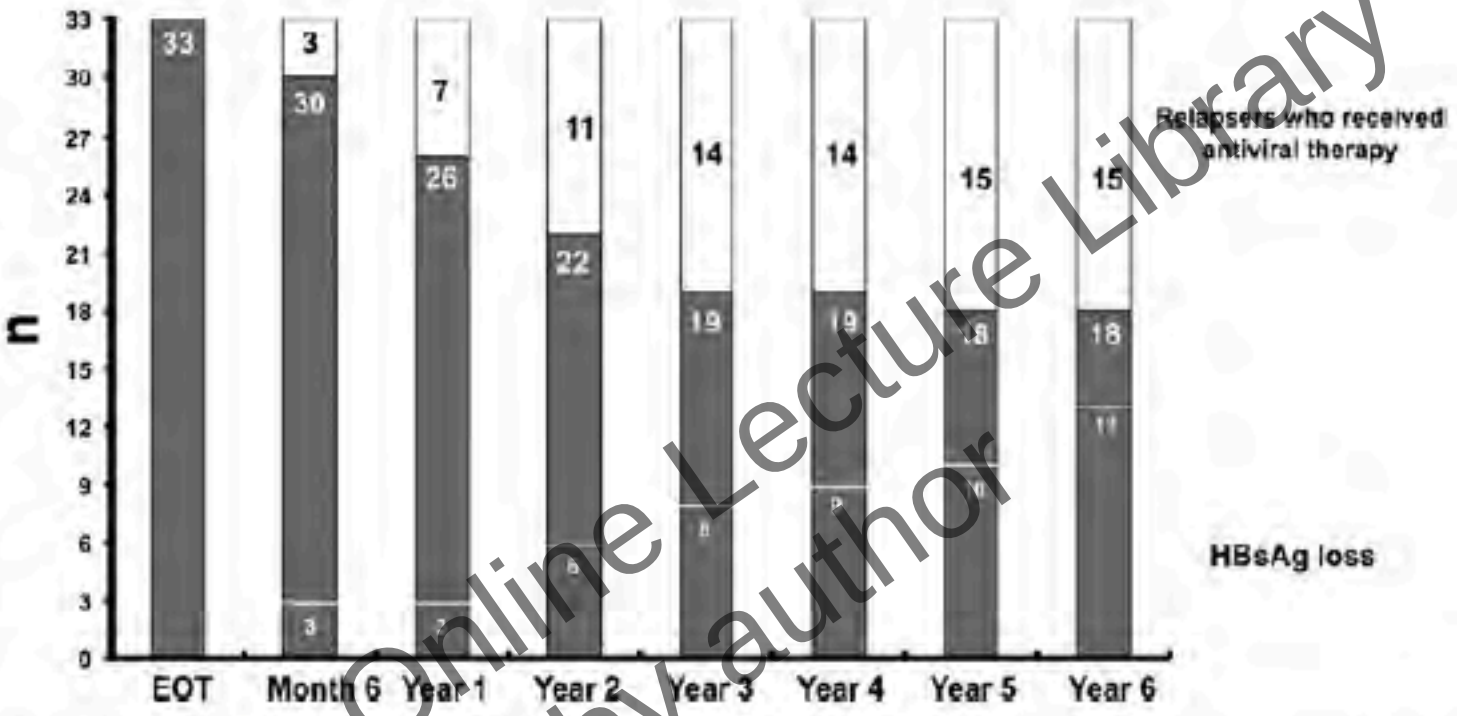

Figure 2. The number of patients who experienced a relapse and received antiviral therapy (relapsers) or lost HBsAg among the remaining patients during follow-up.

- In HBeAg-negative patients with CHB, it is safe and effective to discontinue ADV therapy after 4 or 5 years; 55% of patients have sustained responses, and 39% of patients lose HBsAg.

Can we stop HBV therapy?

- Is the diagnosis of CHB correct?
  - Inactive carrier
  - Immunotolerant

Can we stop HBV therapy?

- HBeAg-negative
  - Mild-moderate fibrosis
    - HBsAg-negative: YES
    - HBsAg-positive (in low titers), DNA undetectable for years: probably YES
    - HBsAg-positive (in high titers), DNA recently undetectable: probably NO

Can we stop HBV therapy?

- HBeAg-negative
  - Mild-moderate fibrosis
    - HBsAg-negative: YES
    - HBsAg-positive (in low titers), DNA undetectable for years: probably YES
    - HBsAg-positive (in high titers), DNA recently undetectable: probably NO
  - Advanced fibrosis/cirrhosis
    - HBsAg-negative: probably YES
    - HBsAg-positive: NO
  - Decompensated cirrhosis
    - NO

- HBeAg-positive
  - Mild-moderate fibrosis
    - HBeAg-negative, HBsAg-negative: YES
    - HBeAg-negative, HBsAg-positive (in low titers), DNA undetectable for years: probably YES
    - HBeAg-positive: probably NO

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  - Mild-moderate fibrosis
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    - HBeAg-negative, HBsAg negative: probably YES
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  - Decompensated cirrhosis
    - NO