HBV treatment in the light of current international guidelines

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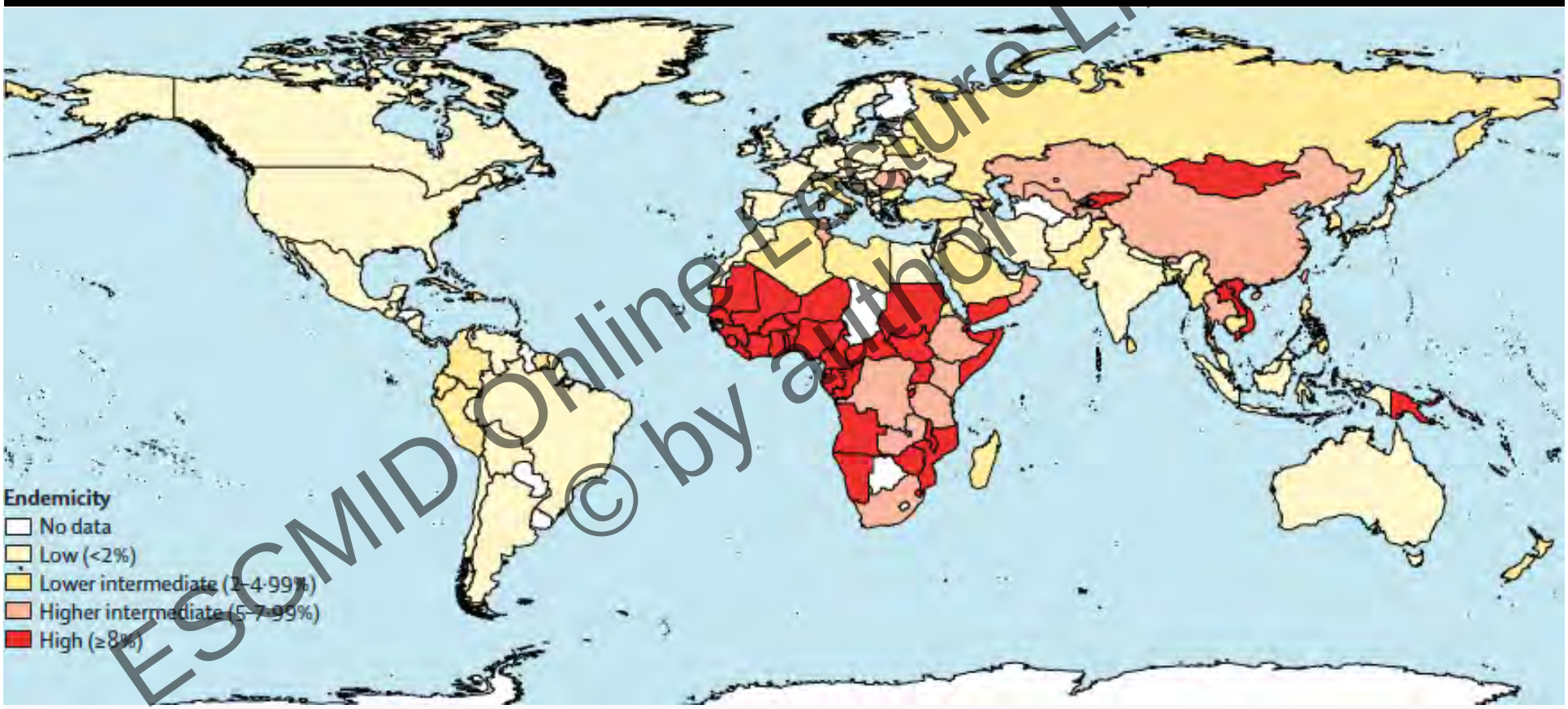
Disclosures

- Workshop or meeting invitation: Gilead, Bristol-Myers Squibb, Schering-Plough / MSD, Roche, Janssen, Mayoly-Spindler
- Board: Gilead, Bristol-Myers Squibb

Global HBV Epidemiology



Global HBsAg endemicity (1957-2013)

Schweitzer A et al. Lancet 2015

HBV across Europe

Differences in the availability of diagnostics and treatment modalities for chronic hepatitis B across Europe

R. Ozaras[1], G. Corti[2], S. Ruta[3], K. Lacombe[4], M. U. Mondelli[5], W. L. Irwing[6], M. Puoti[7], A. Khalighi[8], M. L. Santos[9], A. Harxhi[10], I. Lazarevic[11], V. Soriano[12], J. Gervain[13], H. Leblebicioglu[14], D. Salmon[15] and J. E. Arends[16], on behalf of the ESCMID Study Group for Viral Hepatitis

Prof. Dr. Resat Ozaras
Istanbul University
Istanbul, Turkey

Ozaras R et al. Clin Microbiol Infect 2015

HBV International Guidelines

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Journal of Hepatology **2012** vol. 57 | 167–185

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

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AASLD

PRACTICE GUIDELINE

HEPATOLOGY, Vol. 63, No. 1, 2016

AASLD Guidelines for Treatment of Chronic Hepatitis B

Norah A. Terrault,[1] Natalie H. Bzowej,[2] Kyong-Mi Chang,[3] Jessica P. Hwang,[4] Maureen M. Jonas,[5] and M. Hassan Murad[6]

GUIDELINES

Hepatol Int (2016) 10:1–98
DOI 10.1007/s12072-015-9675-4

Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update

2 questions

- When to treat ?
- How to treat ?

When to treat chronic HBsAg positive patients?

General indications for treatment

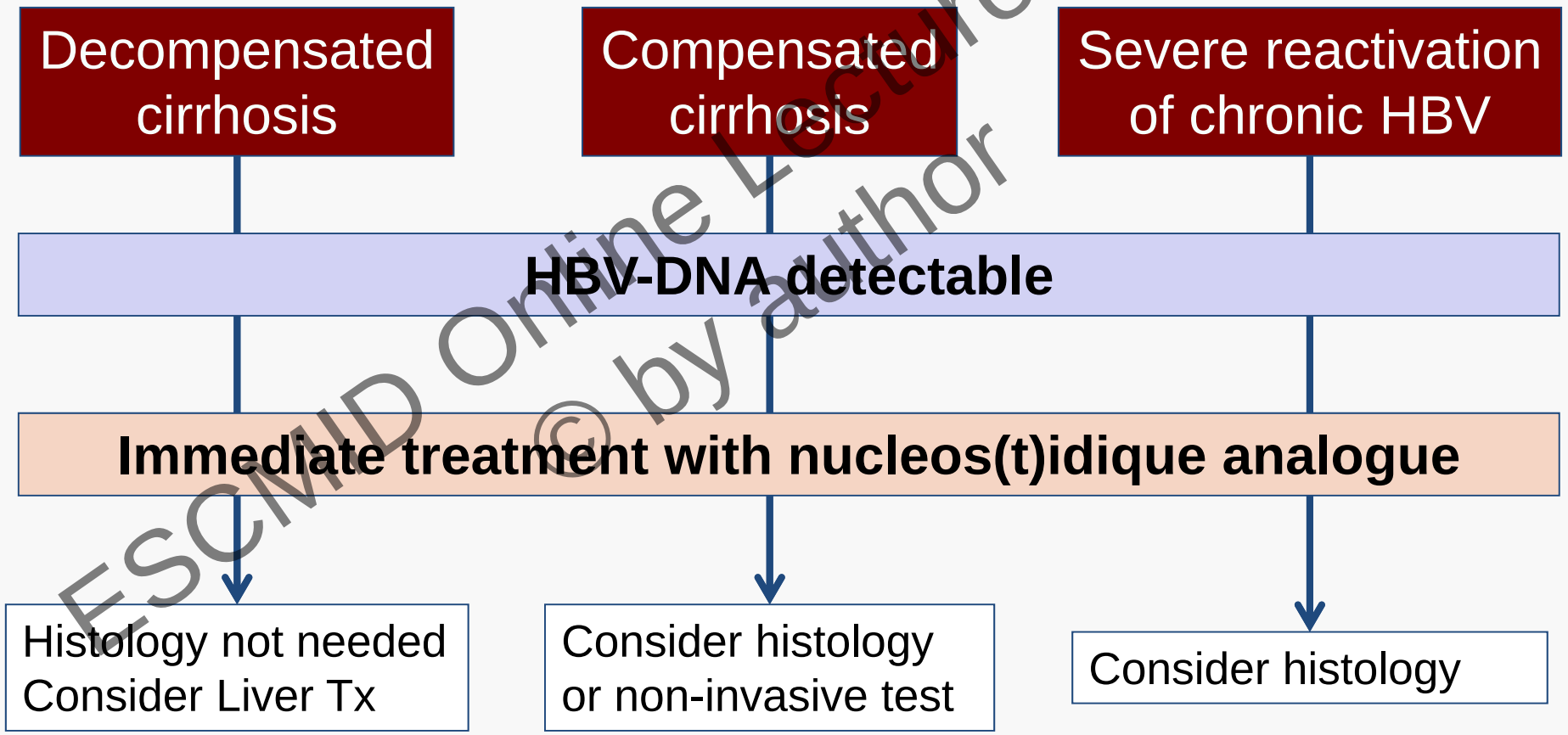
The indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB. This is based mainly on the combination of three criteria:

- Serum HBV DNA levels.
- Serum ALT levels.
- Severity of liver disease.

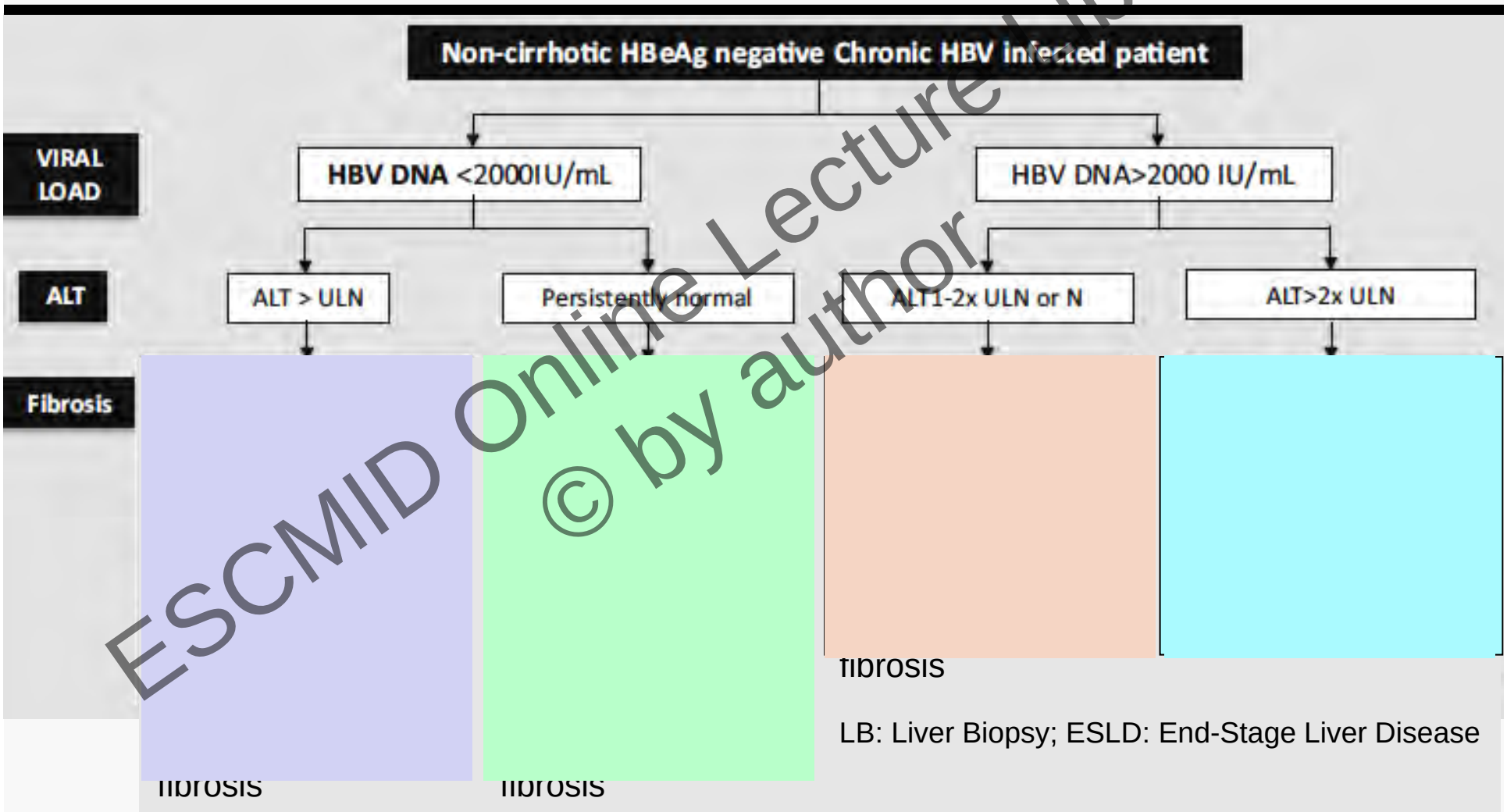
Follow-up for HBV-DNA and ALT levels (i.e. every 3 months during 1 year)

EASL Clinical Practice Guidelines 2012

Who treat immediately?



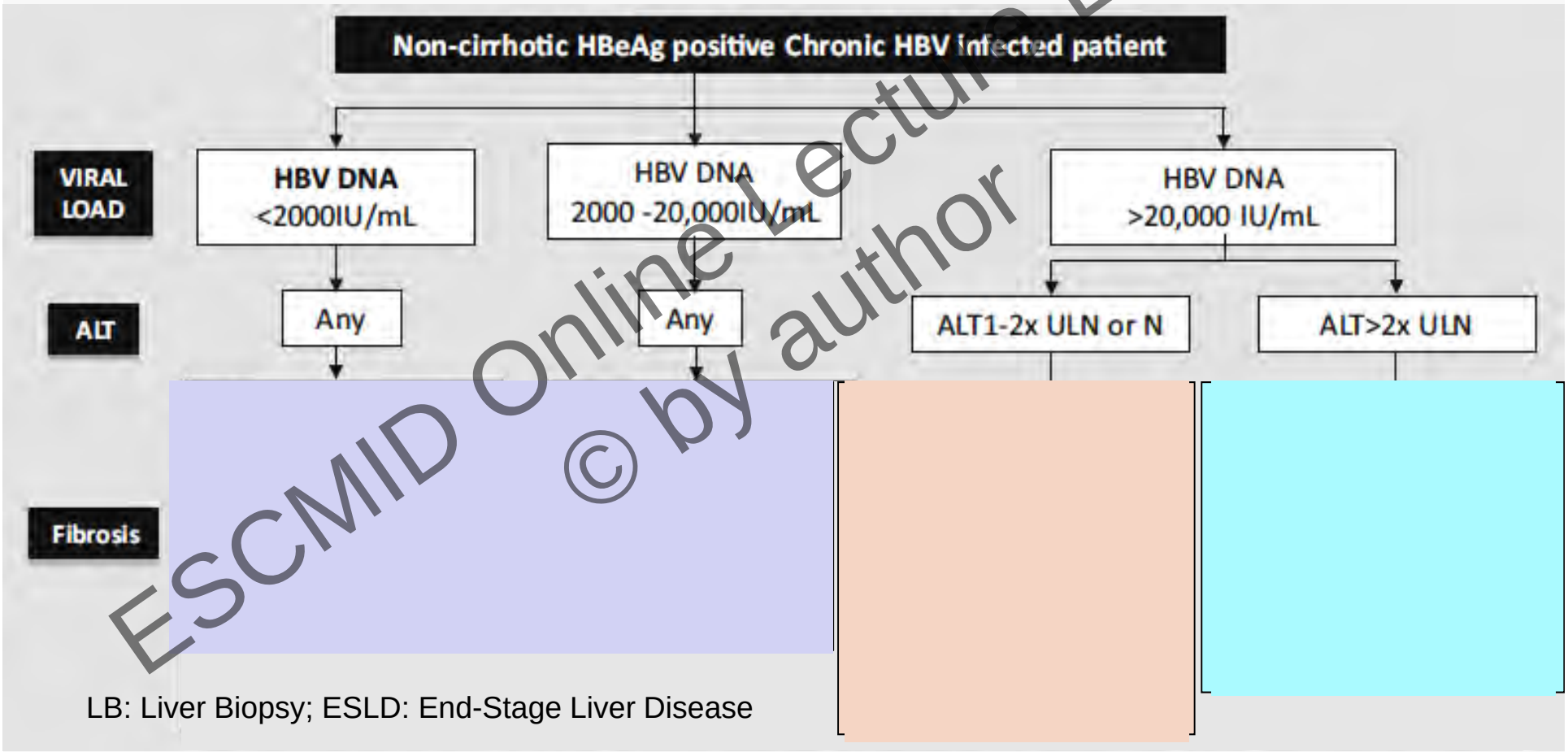
Non-cirrhotic HBeAg negative patients



LB: Liver Biopsy; ESLD: End-Stage Liver Disease

Adapted from APASL Guidelines 2016

Non-cirrhotic HBeAg positive patients



LB: Liver Biopsy; ESLD: End-Stage Liver Disease

Adapted from APASL Guidelines 2016

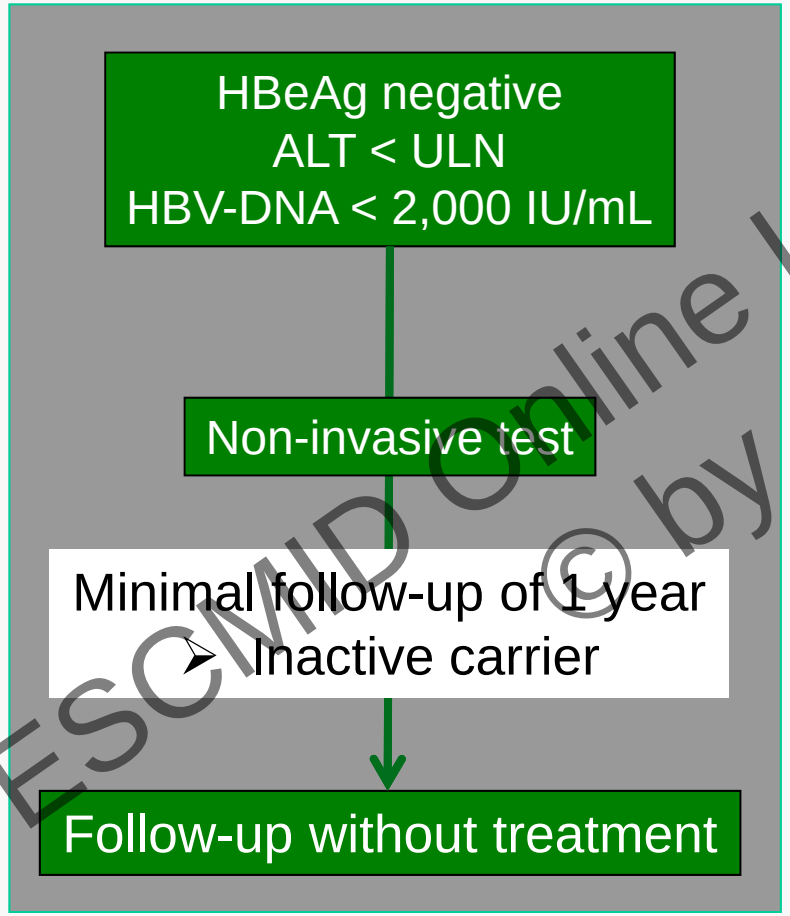
Immuno-tolerant patients

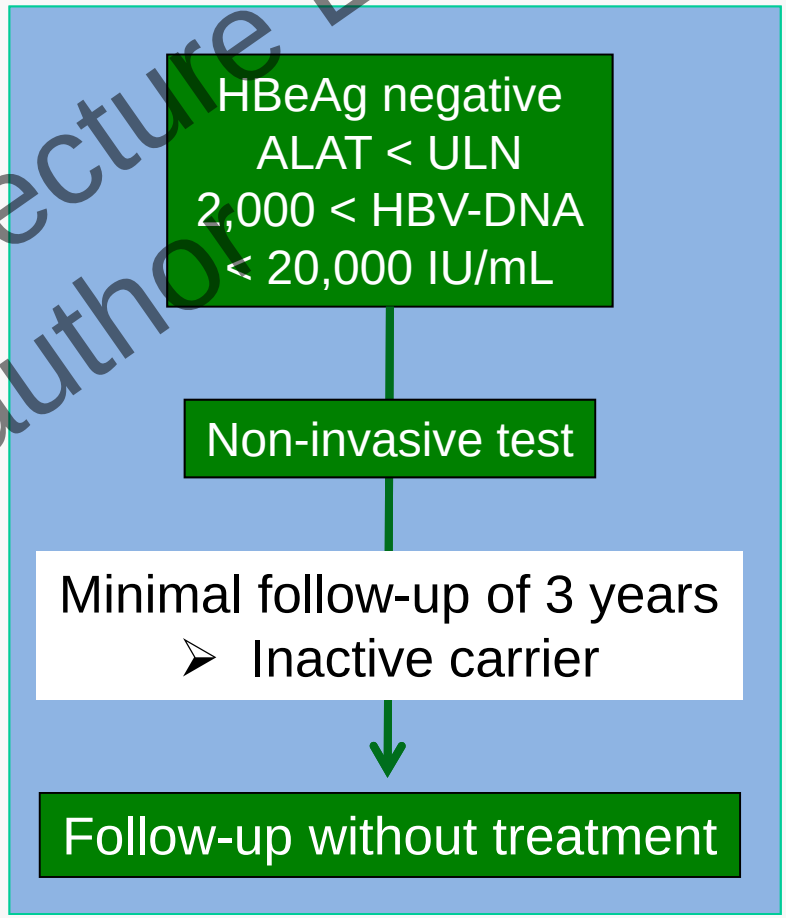
2A. The AASLD recommends against antiviral therapy for adults with immune-tolerant CHB.

Quality/Certainly of Evidence: Moderate
Strength of Recommendation: Strong

Definition
- Young (< 35 y.o.)
- Usually Asian
- HBeAg positive
- ALT normal
- HBV-DNA > 6 log IU/mL

HBV inactive carriers





EASL Clinical Practice Guidelines 2012

Other indications for treatment

	Aim	Indication
Préemptive	Prevent reactivation in case of immunosuppression	HBsAg positive and immunosuppression
Health professional	Prevent carer/patient transmission	Health professional with significant viral load
Mother-to-child transmission	Prevent MTCT	Mother with high viral load (associated with serovaccination)
Prevention of HCC	Prevent HCC	Family history Age > 50 years High viral load
Prevention of post-LT recurrence	Prevent graft-reinfection	Post LT (analogue + antiHBs Ig)
Extra-hepatic manifestations	Better prognosis	Periarthritis nodosa Glomerulonephritis Neurologic manifestations

Patients HBsAg + at risk for HCC

- Patients with cirrhosis → Screen and treat if HBV-DNA +
- Other patients
  - Persons with a family history of HCC (1st relative)
  - Asian men over 40 years / Asian women over 50 years
  - Africans over 20 years
  - Any carrier over 40 years with persistent or intermittent ALT elevation and/or high HBV-DNA

↓

Screen? and treat if HBV-DNA +?

AASLD 2009 / Bruix et al. Hepatology 2011

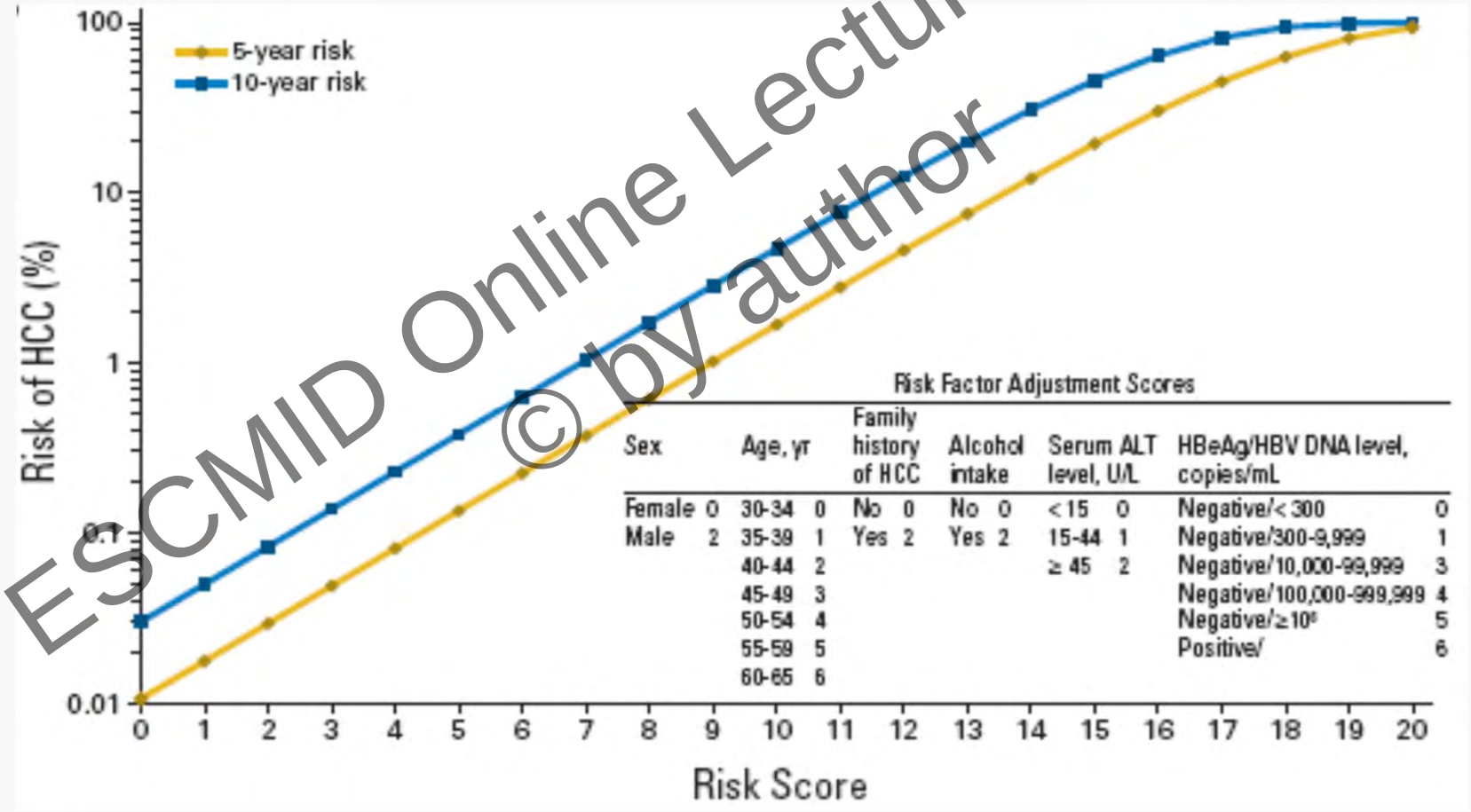
Family risk of HCC

Odds Ratio	Hepatocellular Carcinoma	Cirrhosis
Mother	2.6	2.9
Father	ns	ns
Brother	3.7	4.7
Sister	4.6	6.8
All relatives	2.6	2.3

Yu et al. JNCI 2000

Evaluation of a risk-score for HCC (1)

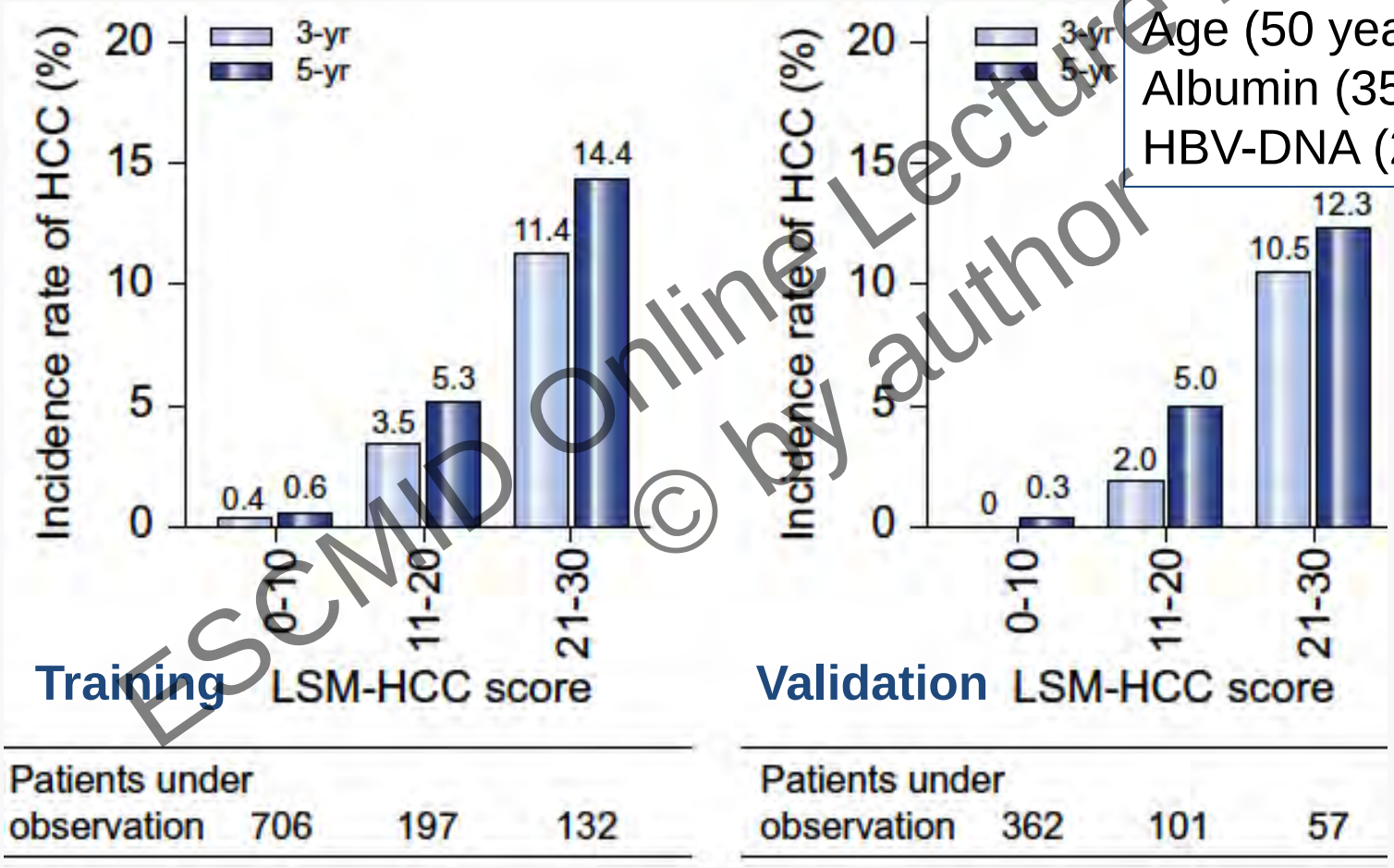
REVEAL cohort – Taiwan (training 2,435 / validation 1,218)



Yang et al. JCO 2010

Evaluation of a risk-score for HCC (2)

LSM (12 kPa)
Age (50 years)
Albumin (35 g/L)
HBV-DNA (200.000 IU/mL)



Wong et al. J Hepatol 2014

No ideal risk-score for HCC at this time

- **Efficacy: Sensitivity & Specificity (PPV & NPV)**

- Easy to perform and to repeat
- Validation in non-Asian populations
- Including non-invasive evaluation of fibrosis
- Including family history of HCC
- Including HBV-DNA level
- HBeAg positive / HBeAg negative

How to treat chronic HBsAg positive patients?

1st line treatment

1B. The AASLD recommends Peg-IFN, entecavir, or tenofovir as preferred initial therapy for adults with immune-active CHB.

Quality/Certainly of Evidence: Low
Strength of Recommendation: Strong

Treatment with analogue only:
- Decompensated cirrhosis
- Severe reactivation
- Preemptive treatment

PEG-IFN vs. Nucleos(t)ide Analogues

	(PEG-)IFN	NAs
Advantages	• Finite duration • Absence of resistance • Higher rates of anti-HBe and anti-HBs seroconversion with 12 mo of therapy	• Potent antiviral effect • Good tolerance • Oral administration
Disadvantages	• Moderate antiviral effect • Inferior tolerability • Risk of adverse events • Subcutaneous injections	• Indefinite duration • Risk of resistance • Unknown long-term safety

EASL Clinical Practice Guidelines 2012

PEG-IFN

Pre-treatment factors associated with response

- Low viral load
- High ALT (ALT 2-5 ULN)
- High activity score on liver histology
- Genotypes A & B (vs. genotypes C & D)
- Initial qHBsAg ?
- HBeAg positive (vs. HBeAg negative)?

Factors during treatment associated with response

- ↘ qHBsAg at S12
  - ↘ qHBsAg ≥ 0.5 log IU/mL[1]
  - ↘ qHBsAg[2]
  - ↘ qHBsAg < 1,500 IU/mL[3,4]

[1]Moucari R et al. Hepatology 2009
[2]Sonneveld MJ et al. Hepatology 2010
[3]Gane E et al. EASL 2011
[4]Piratvisuth T et al. Hepatol Int 2010

2nd generation nucleos(t)ide analogue

Main goal: complete and prolonged virosuppression (HBV-DNA undetectable)

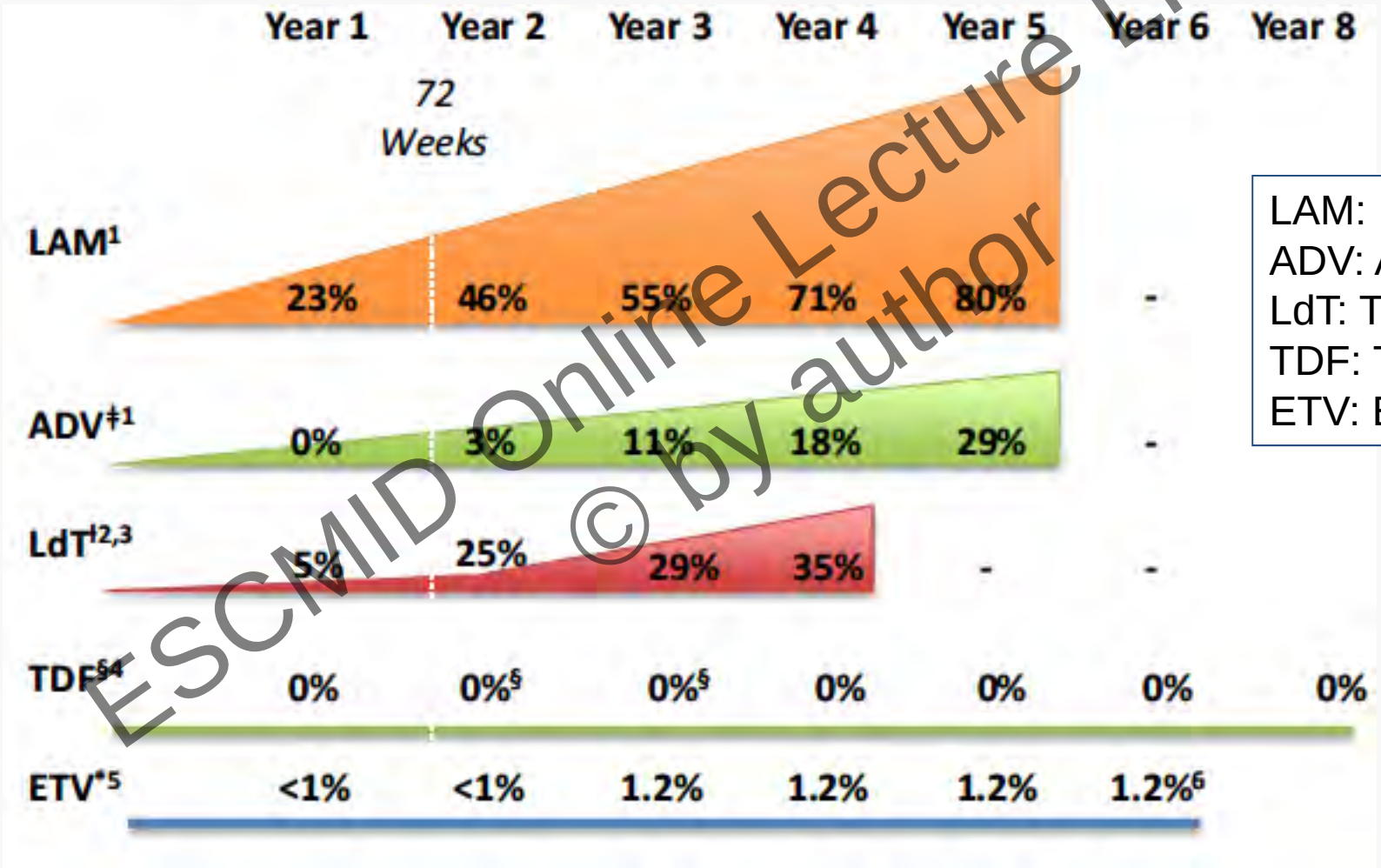
Factors during treatment associated with response

- Observance
- Resistance

Potential side effects

- Renal fonction
- Bone density
- Lactic acidosis in decompensated cirrhosis

Incidence of antiviral resistance with NA therapy (1st line treatment)



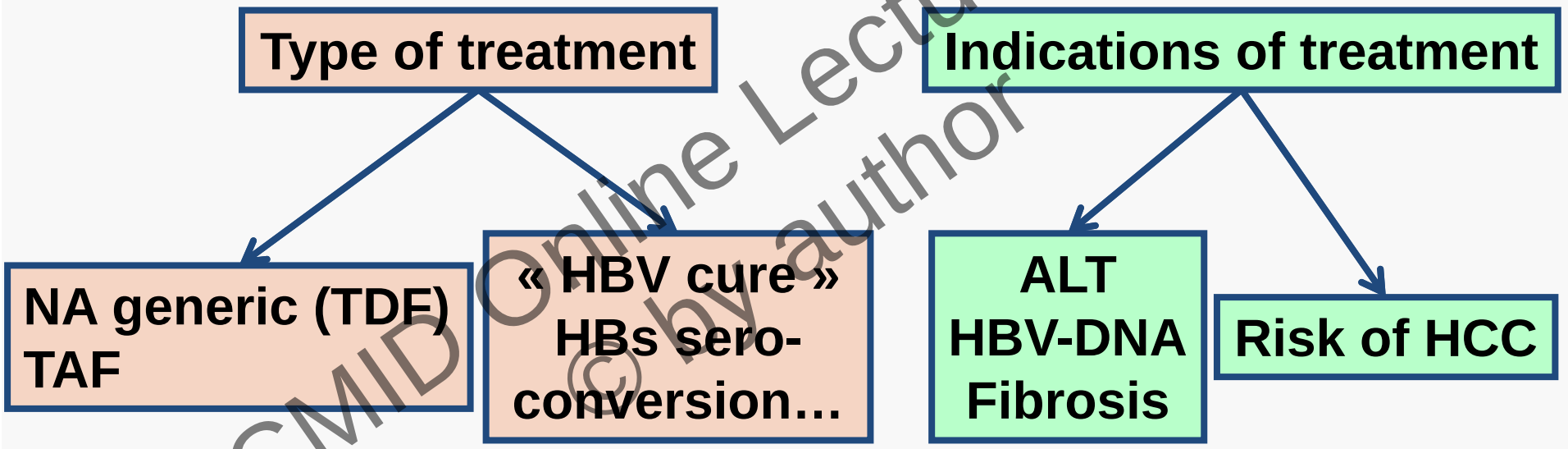
LAM: Lamivudine
ADV: Adefovir
LdT: Telbivudine
TDF: Tenofovir DF
ETV: Entecavir

Conclusion

- Indication of treatment in chronic HBsAg positive patients based on ALT, HBV-DNA and severity of liver disease
- Immediate indication for patients with HBV cirrhosis or severe HBV reactivation
- No indication for immuno-tolerant patients and inactive carriers
- 1st line of treatment : PEG-IFN, entecavir or tenofovir
- Limited indication for (PEG)-IFN
- Around 100% virosuppression with 2nd generation NA (entecavir or tenofovir) in 1st line treatment ➔ adherence
- No indication in practice for combined treatment

  (i.e. PEG-IFN + NA / NA + NA)

Future directions



Screening / vaccination