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Why do I treat my HBeAg negative patients with NUC ?

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Outline

- Efficacy and safety of ETV and TDF
- Naïve and experienced patients
- Histology data
- Long-term outcome (decompensation, portal hypertension, HCC)
- Survival

Relevance of HBeAg-negative CHB

- Prevalence increasing worldwide
- Progressive liver disease in most patients
- Difficult to diagnose, i.e. active vs inactive carriers
- Limited sustained response to peg-IFN (genotype D)
- Long-term NUC therapy needed

EASL 2012 Clinical Practice Guidelines: What is long-term treatment success in CHB and how do we achieve it?

"...to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death"

"This goal can be achieved if HBV replication can be suppressed in a sustained manner. Then, the accompanying reduction in histological activity of CHB lessens the risk of cirrhosis and decreases the risk of HCC, particularly in non-cirrhotic patients"

Clinical Practice Guidelines

EASL JOURNAL OF HEPATOLOGY

Clinical Practice Guidelines

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

European Association for the Study of the Liver*

Introduction

Our understanding of the natural history of hepatitis B virus (HBV) infection and the potential for therapy of the resultant disease is continuously improving. New data have become available since the previous EASL Clinical Practice Guidelines (CPGs) prepared in 2008 and published in early 2009 [1]. The objective of this manuscript is to update the recommendations for the optimal management of chronic HBV infection. The CPGs do not fully address prevention including vaccination. In addition, despite the increasing knowledge, areas of uncertainty still exist and therefore clinicians, patients, and public health authorities must continue to make choices on the basis of the evolving evidence.

Context

Epidemiology and public health burden

Approximately one third of the world's population has serological evidence of past or present infection with HBV and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers. The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) [2–4]. HBV-related end stage liver disease or HCC are responsible for over 0.5–1 million deaths per year and currently represent 5–10% of cases of liver transplantation [5–8]. Host and viral factors, as well as coinfection with other viruses, in particular hepatitis C virus (HCV), hepatitis D virus (HDV), or human immunodeficiency virus (HIV) together with other co-morbidities including alcohol abuse and obesity, can affect the natural course of HBV infection as well as efficacy of antiviral strategies [2–8]. CHB may present either as hepatitis B e antigen (HBeAg)-positive or HBeAg-negative CHB. The prevalence of the HBeAg-negative form of the disease has been increasing over the last decade as a result of aging of the HBV-infected population and predominance of specific HBV genotypes and represents the majority of cases in many areas, including Europe [4,9,10]. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or hepatocellular carcinoma (HCC). Longitudinal studies of untreated patients with CHB indicate that, after diagnosis, the 5-year cumulative incidence of developing cirrhosis ranges from 8% to 20%. The 5-year cumulative incidence of hepatic decompensation is approximately 20% for untreated patients with compensated cirrhosis [2–4,11–13]. Untreated patients with decompensated cirrhosis have a poor prognosis with a 14–35% probability of survival at 5 years [2–4,12]. The worldwide incidence of HCC has increased, mostly due to persistent HBV and/or HCV infections; presently it constitutes the fifth most common cancer, representing around 5% of all cancers. The annual incidence of HBV-related HCC in patients with CHB is high, ranging from 2% to 5% when cirrhosis is established [13]. However, the incidence of HBV related HCC appears to vary geographically and correlates with the underlying stage of liver disease and possibly exposure to environmental carcinogens such as aflatoxin. Population movements and migration are currently changing the prevalence and incidence of the disease in several low endemic countries in Europe and elsewhere. Substantial healthcare resources will be required for control of the worldwide burden of disease.

Natural history

Chronic HBV infection is a dynamic process. The natural history of chronic HBV infection can be schematically divided into five phases, which are not necessarily sequential.

(1) The "immune tolerant" phase is characterised by HBeAg positivity, high levels of HBV replication (reflected by high levels of serum HBV DNA), normal or low levels of aminotransferases, mild or no liver necroinflammation and no or slow progression of fibrosis [2,3,6,8]. During this phase, the rate of spontaneous HBeAg loss is very low. This first phase is more frequent and more prolonged in subjects infected perinatally or in the first years of life. Because of high levels of viremia, these patients are highly contagious.

(2) The "immune reactive HBeAg-positive phase" is characterised by HBeAg positivity, relatively lower level of replication compared to the immune tolerant phase (as reflected by lower serum HBV DNA levels), increased or

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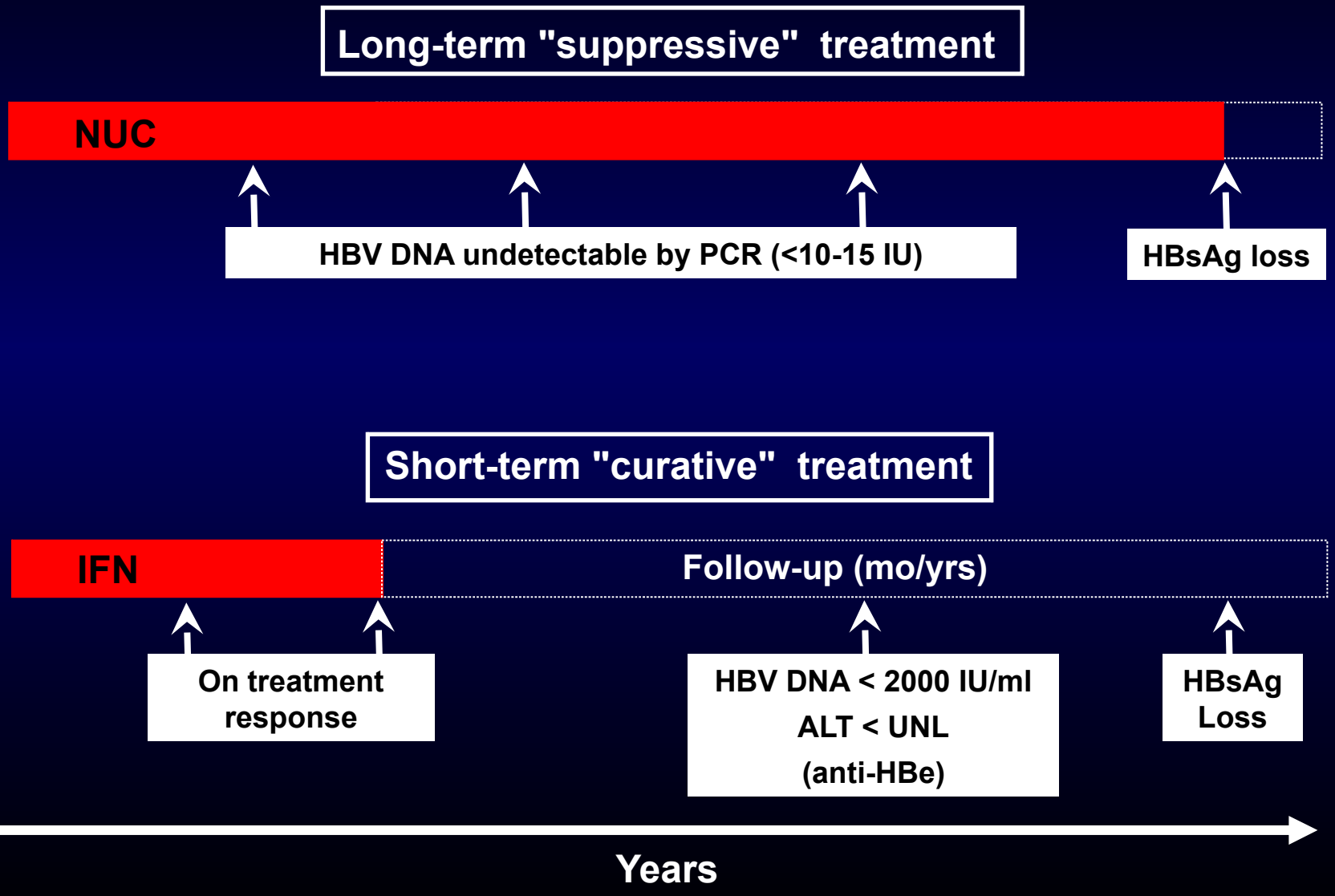
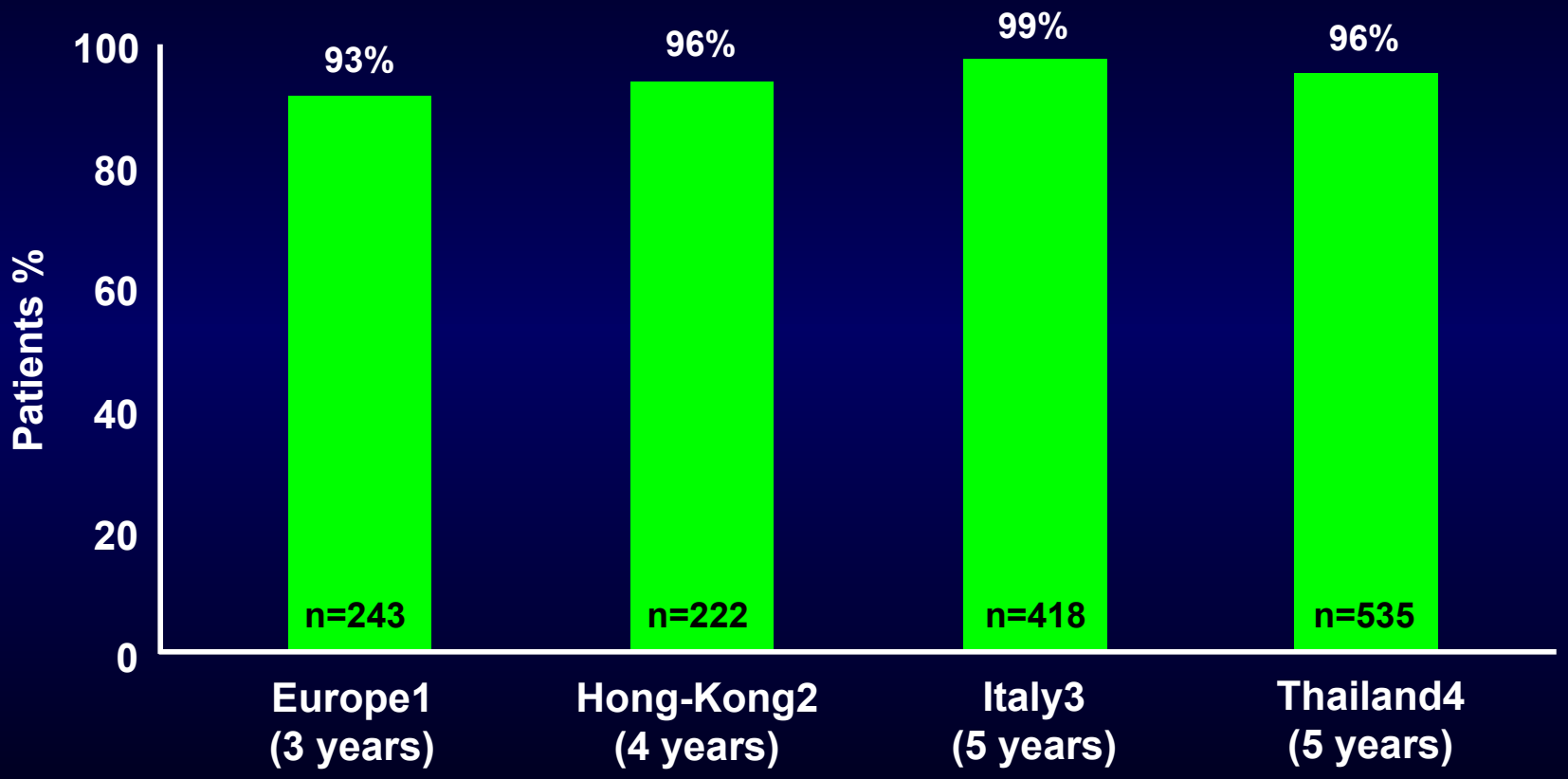
Therapeutic strategies for HBeAg neg CHB

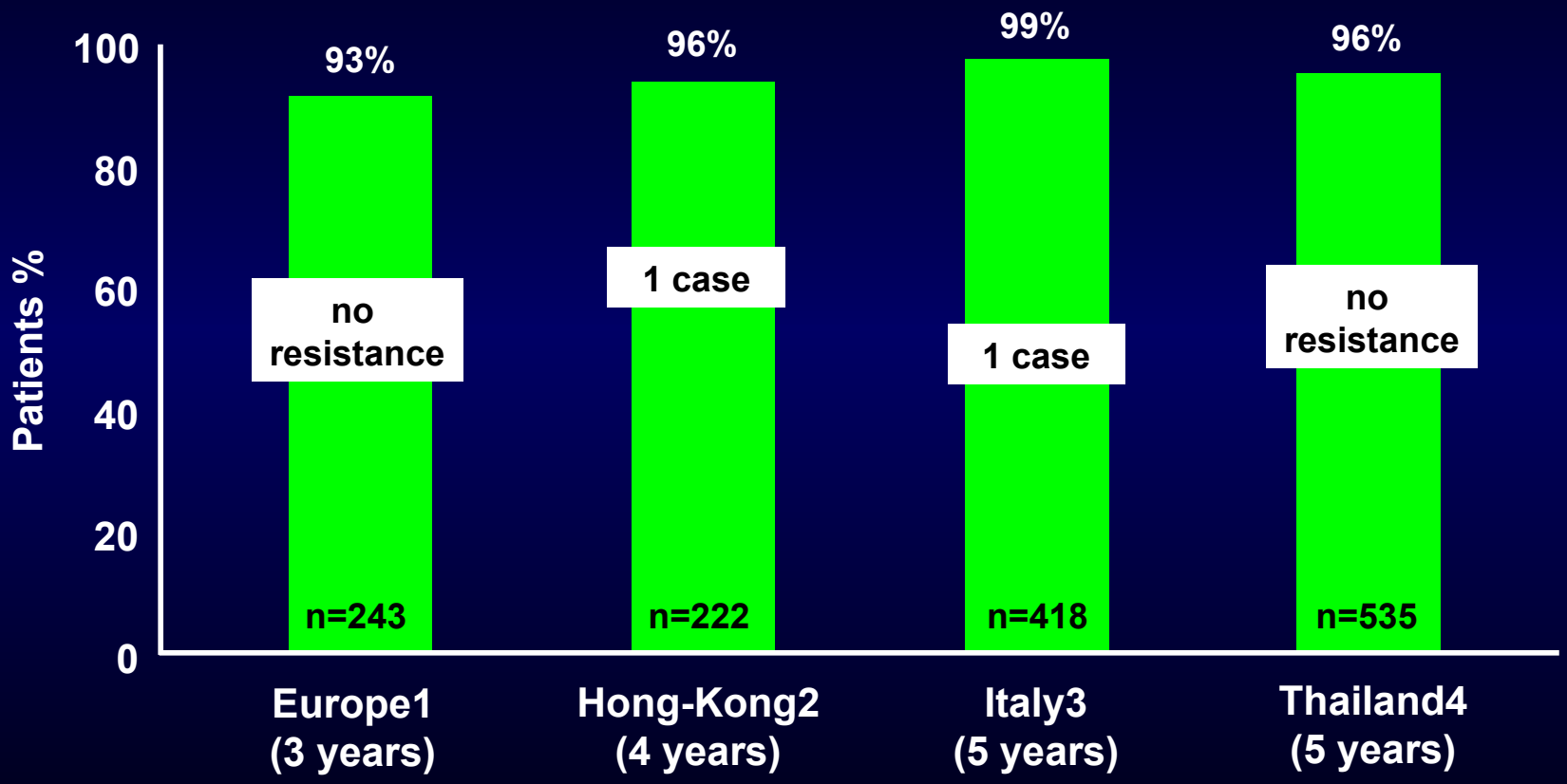


3-5 years ETV for real life, naive CHB patients
Virological summary



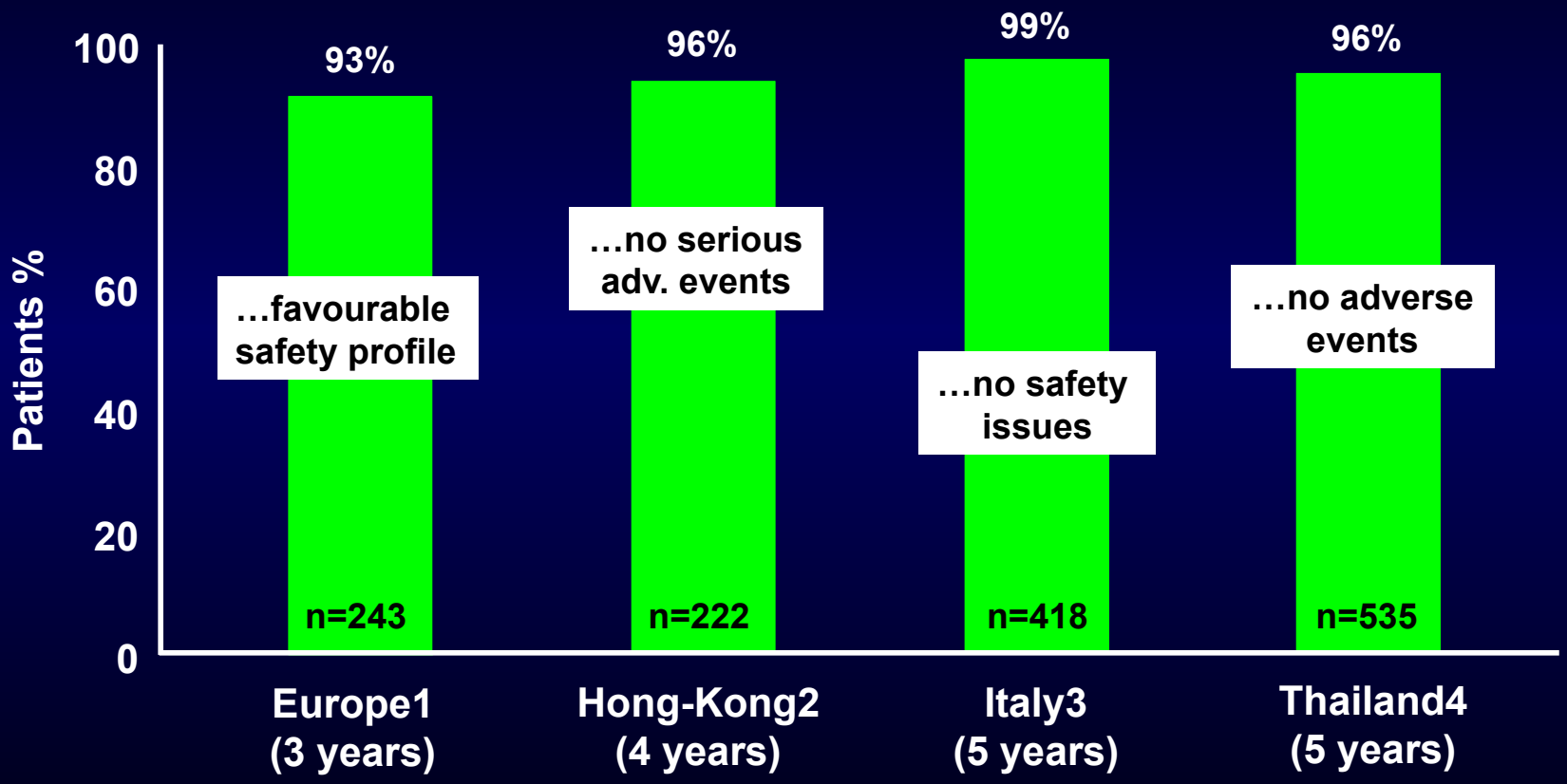
1) Zoutendijk R et al, Hepatology 2011; 2) Seto WK et al, EASL 2011; 3) Lampertico P et al, EASL 2013;
4) Tanwandee T et al, AASLD 2013

3-5 years ETV for real life, naive CHB patients
Resistance summary



1) Zoutendijk R et al, Hepatology 2011; 2) Seto WK et al, EASL 2011; 3) Lampertico P et al, EASL 2013; 4) Tanwandee T et al, AASLD 2013

3-5 years ETV for real life, naive CHB patients
Safety summary



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Seven years TDF for naïve CHB patients Efficacy summary ‡

Response	HBeAg- Patients (Study 102)		HBeAg+ Patients (Study 103)	
	Year 6	Year 7	Year 6	Year 7
HBV DNA < 400 copies/mL Intent-to-treat*, (n/N)	81.4% (281/345)	77.3% (269/348)	62.5% (157/251)	60.3% (149/247)
HBV DNA < 400 copies/mL On-treatment†, (n/N)	99.6% (283/284)	99.3% (271/273)	96.8% (167/169)	99.4% (159/160)

*** LTE-TDF (missing = failure; addition of FTC = failure)**
† Observed (missing = excluded/addition of FTC = included)

- No case of TDF resistance
- HBeAg loss/seroconversion rates of 55% and 40%, respectively
- 12% of HBeAg+ patients had confirmed HBsAg loss (10% with seroconversion)

Neither Truvada (TVD = TDF + FTC) or emtricitabine (FTC) are licensed for use to treat CHB

Marcellin P, et al. AASLD 2013. Washington, DC. #926

Seven years TDF for naïve CHB patients ‡
Safety summary

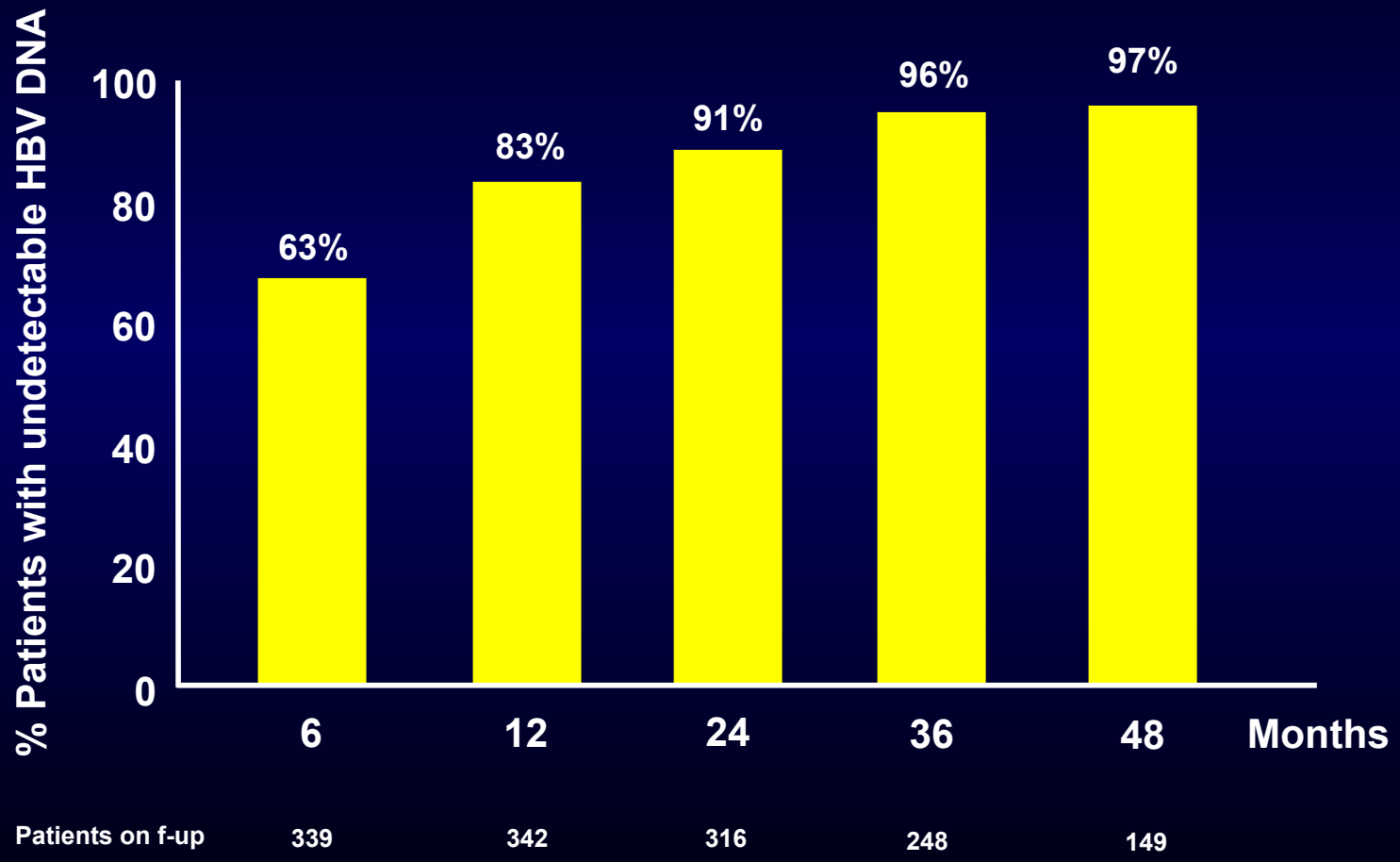
	By Initial Treatment Assignment		Total (N=585)
	TDF-TDF (n=389)	ADV-TDF (n=196)	
AEs leading to drug discontinuation, n (%)	11 (2.8)	2 (1.0)	13 (2.2)
Deaths, n (%)	9 (2.3)	3 (1.5)	12 (2.1)
Serious AEs*, n (%)	5 (1.3)	2 (1.0)	7 (1.2)
Grade 3 or 4 AEs*, n (%)	3 (0.8)	3 (1.5)	6 (1.0)
sCr 0.5 mg/dL above baseline†, n (%)	6 (1.5)	4 (2.0)	10 (1.7)
PO4 < 2 mg/dL†, n (%)	5 (1.3)	4 (2.0)	9 (1.5)
CrCl < 50 mL/min†, n (%)	3 (0.8)	3 (1.5)	6 (1.0)

*Study drug related †Confirmed upon retest

Marcellin P, et al. AASLD 2013. Washington, DC. #926

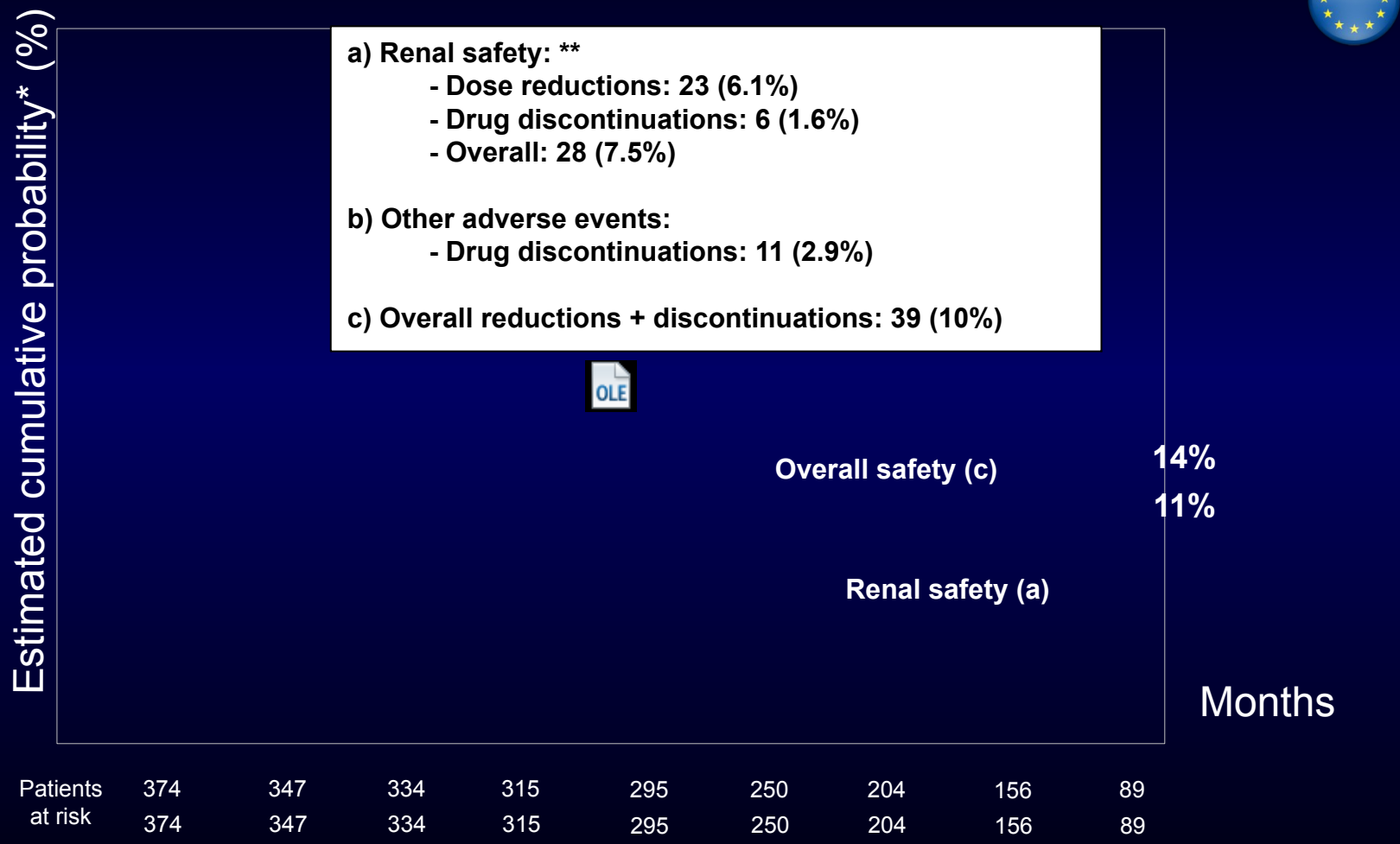
Four years TDF for NUC naive CHB patients
Virological response

(n=374)



Lampertico et al, AASLD 2013

Four years TDF for NUC naive CHB patients
Dose reductions/discontinuations



*Kaplan-Meier estimates

** 24 patients for low eGFR, 4 for low phosphate (overall n=28)

Lampertico et al, AASLD 2013

Management of HBV Resistance (Early rescue)

LAM resistance	Switch to TDF (or add ADV)
LDT resistance	Switch to TDF* (or add ADV)
ETV resistance	Switch to TDF* (or add ADV)
ADV resistance	Switch to ETV or TDF (LAM naive) Switch to ETV (LAM naive + HVL) Switch to TDF and add a nucleoside (LAM resist.)
TDF resistance**	Switch to ETV (LAM naive) Add ETV (LAM resistant)*

*the long-term safety of these combinations is unknown
**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

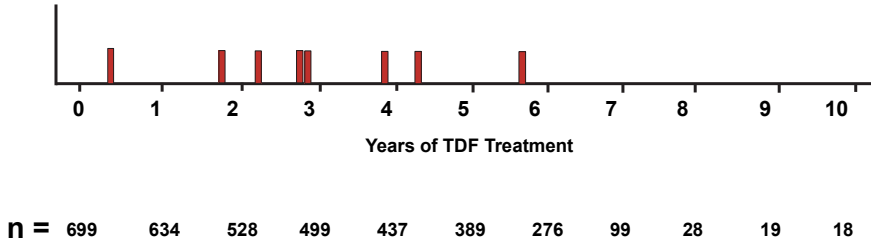
adapted from EASL HBV guidelines, J Hepatol 2012

Four years TDF monotherapy in NUC-exp patients

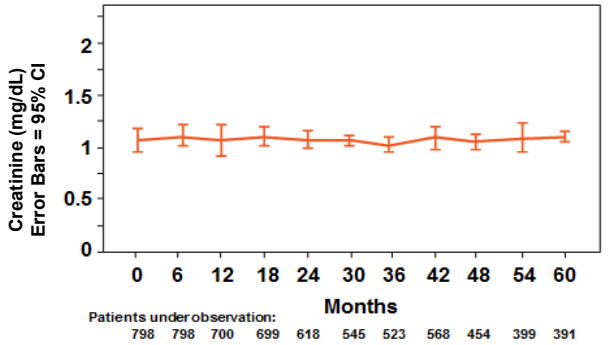
Efficacy, safety, influence of prior treatments, and incidence of HCC in a European real-life cohort of 798 patients treated with TDF monotherapy for > 6 months

- 798 patients with ≥ 6 months TDF treatment (mean 54 ± SD 24 [range 6–141])
- Treatment history: 404 (51%) LAM-experienced, 308 (39%) ADV-experienced, 13 (1.6%) ETV-experienced
- 44 (5.5%) were cirrhotic at Baseline
- GFR declined from normal values in 3 patients
- No additional decrease in GFR in patients with pre-existing kidney dysfunction
- HCC detected in 8 patients (1%) after a mean treatment period of 32 ± SD 31 (range 3–68) months

Incidences and Timepoints of Newly Diagnosed HCC



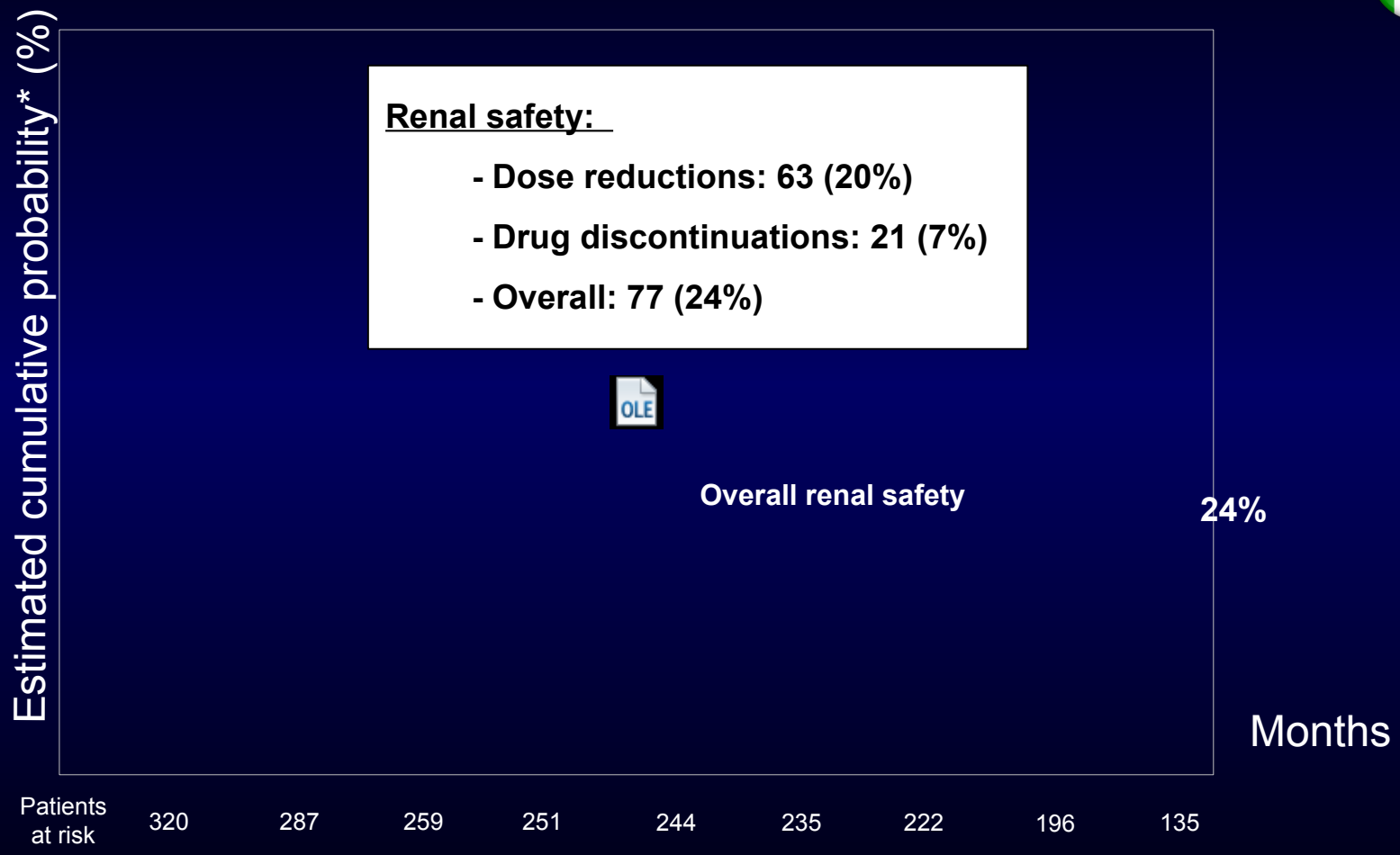
Mean Serum Creatinine Levels Remained Unchanged



Long term second- and third-line monotherapy with TDF was as comparably safe and effective as in treatment-naïve patients

van Boemmel F, et al. AASLD 2013. Washington, DC. #941

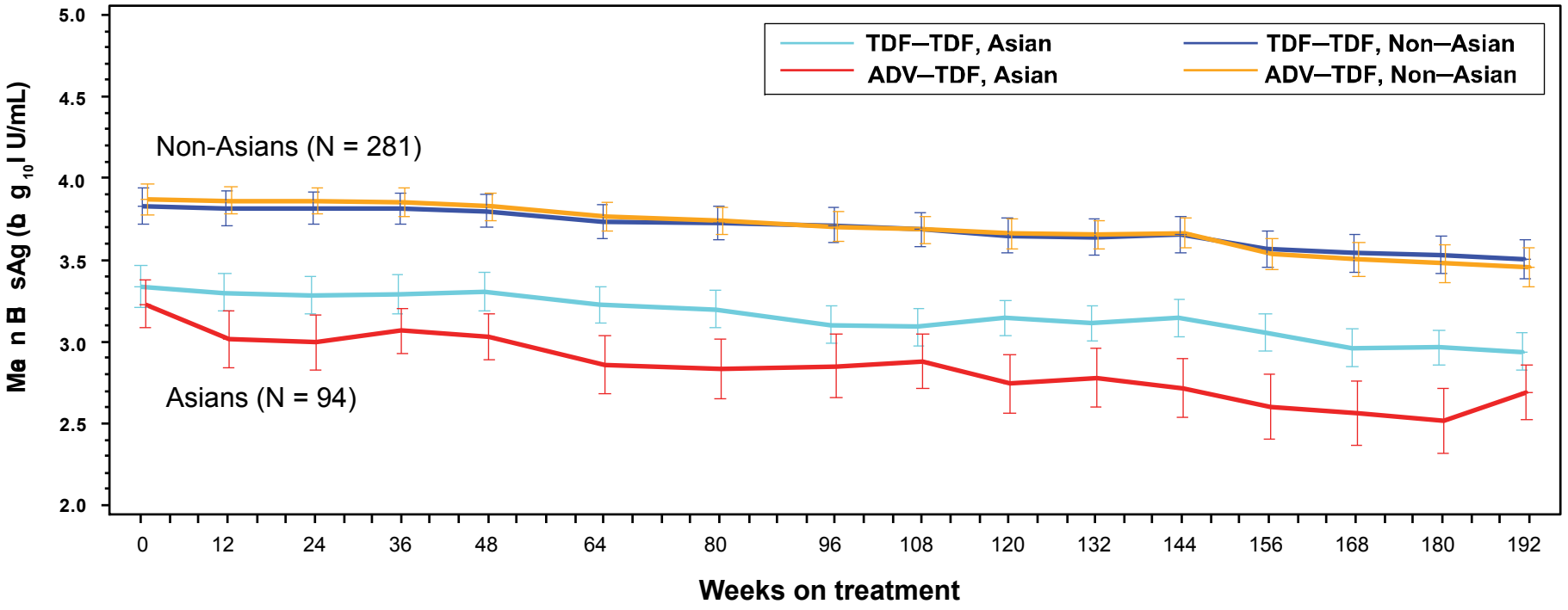
4 years TDF for LAM-ADV-exp CHB patients
Dose reduction/discontinuations



* Kaplan-Meier estimates

Lampertico et al, AASLD 2013

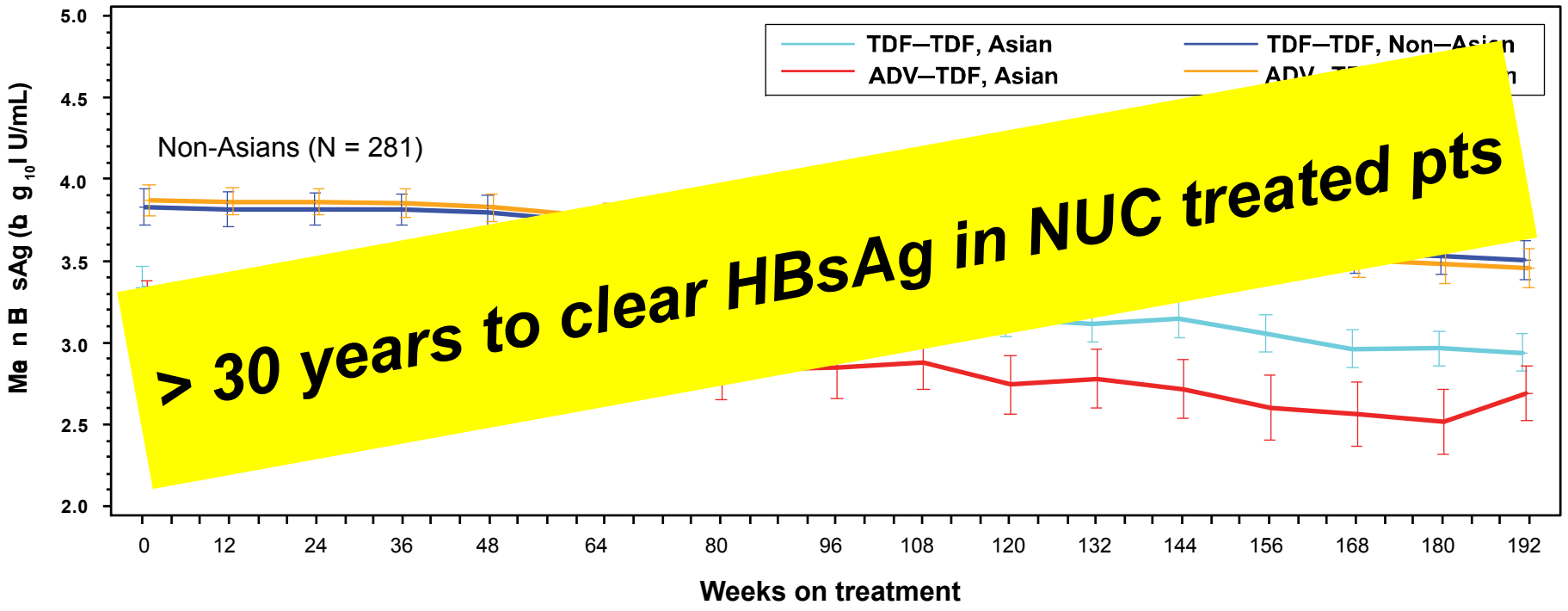
HBsAg kinetics in HBeAg-negative patients treated with TDF for 4 years



- Asians have lower baseline levels of HBsAg than non-Asians
- In both groups, the overall 192 week declines were modest

Fung S, *et al*. APASL 2012; Poster #PP09-043.

HBsAg kinetics in HBeAg-negative patients treated with TDF for 4 years



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When to stop NUC therapy ?

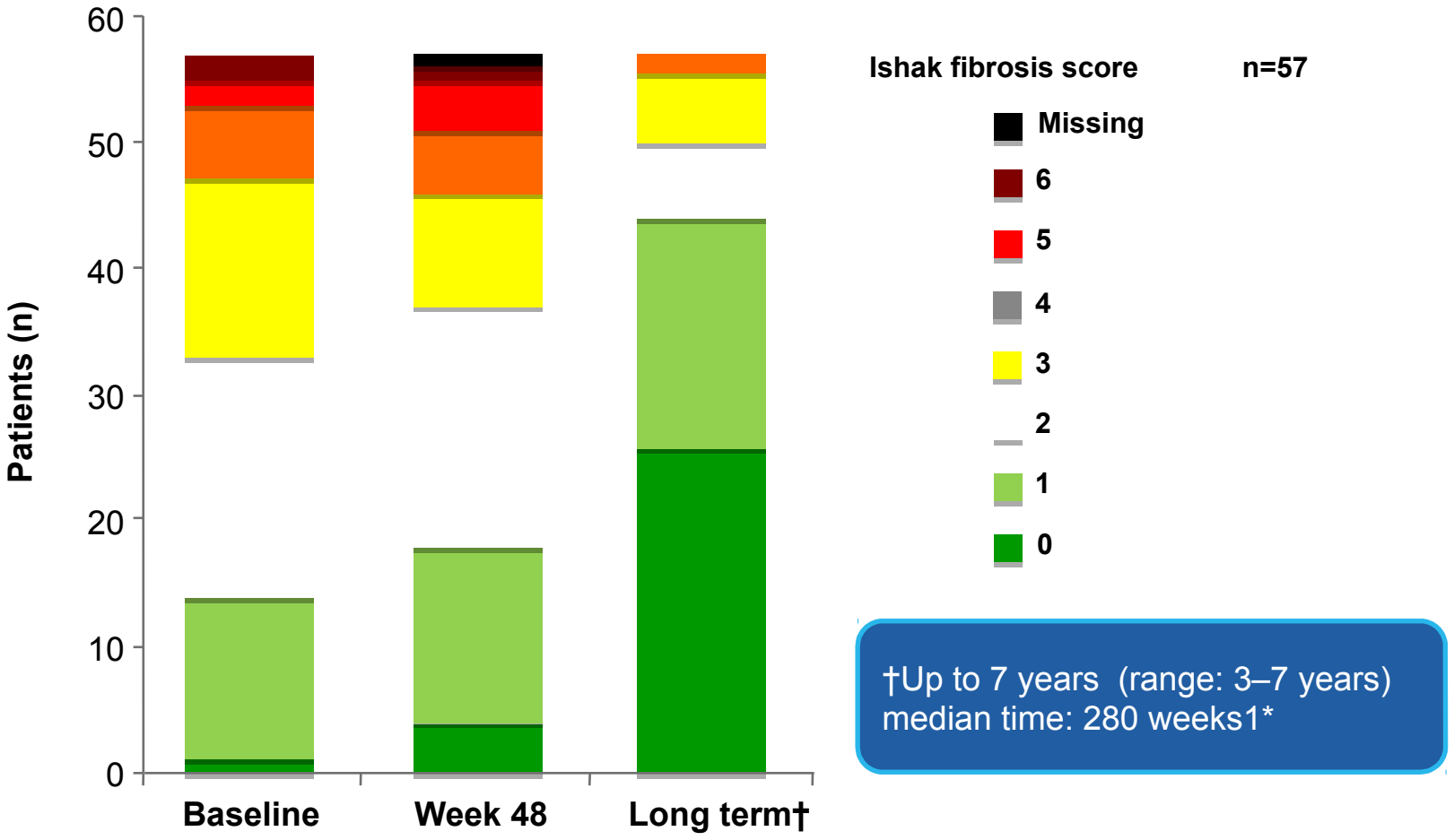
CHB Treatment Guidelines	EASL 2012 guidelines
HBeAg positive	A) confirmed anti-HBe seroconversion (and undectable HBV DNA) after at least 12 months of consolidation* B) confirmed HBsAg loss and anti-HBs seroconversion
HBeAg negative	confirmed HBsAg loss and anti-HBs seroconversion
Cirrhotics	confirmed HBsAg loss and anti-HBs seroconversion

*A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response

adapted from EASL HBV Guidelines, J Hepatol 2012

Histology

Improvement in Ishak fibrosis score with long-term ETV



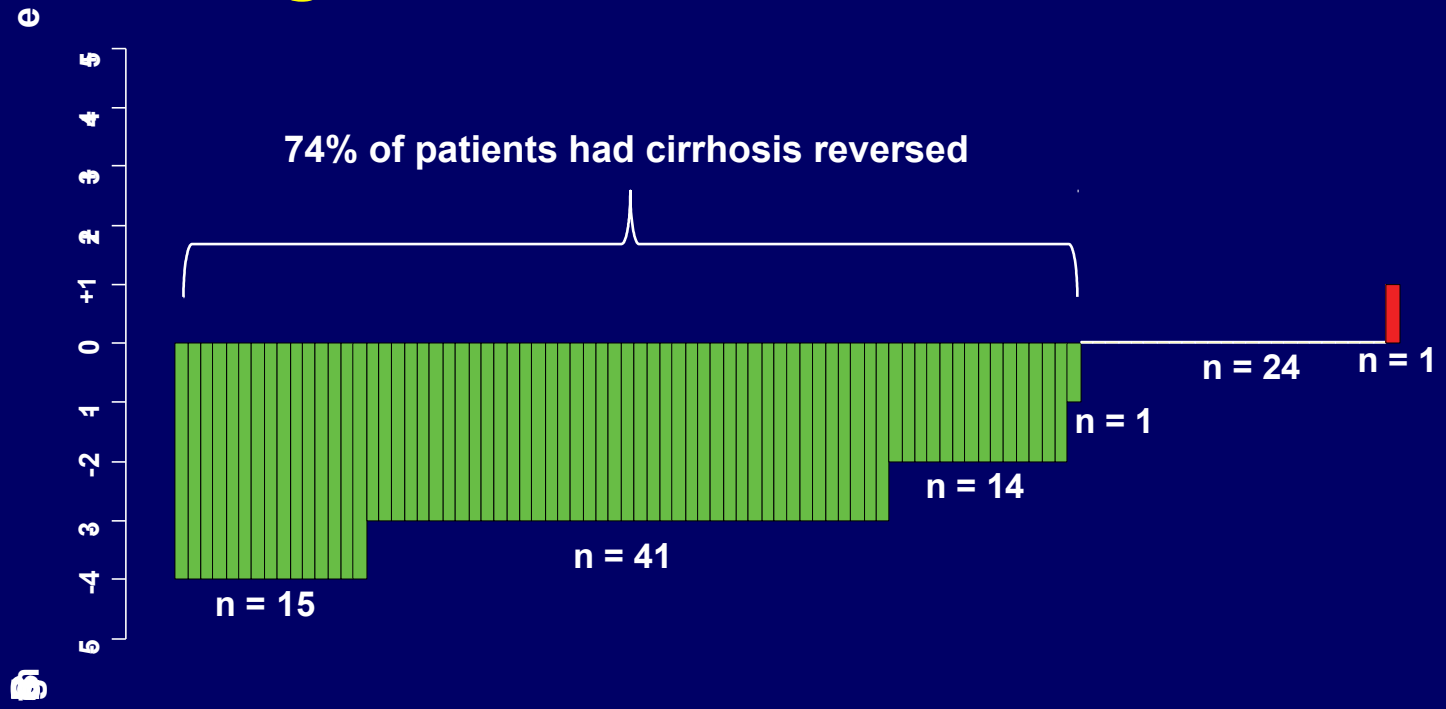
†Up to 7 years (range: 3–7 years) median time: 280 weeks1*

*In the randomised, controlled studies, patients received 0.5 mg ETV. In the 901 rollover study, patients received 1 mg ETV. Please refer to the SmPC for further information on the treatment regimen.2

1. Adapted from Chang T-T, et al. *Hepatology* 2010;52:886–93; 2. Baraclude® (entecavir) SmPC May 2011.

5-year TDF treatment in patients with CHB

Changes of fibrosis in cirrhotics

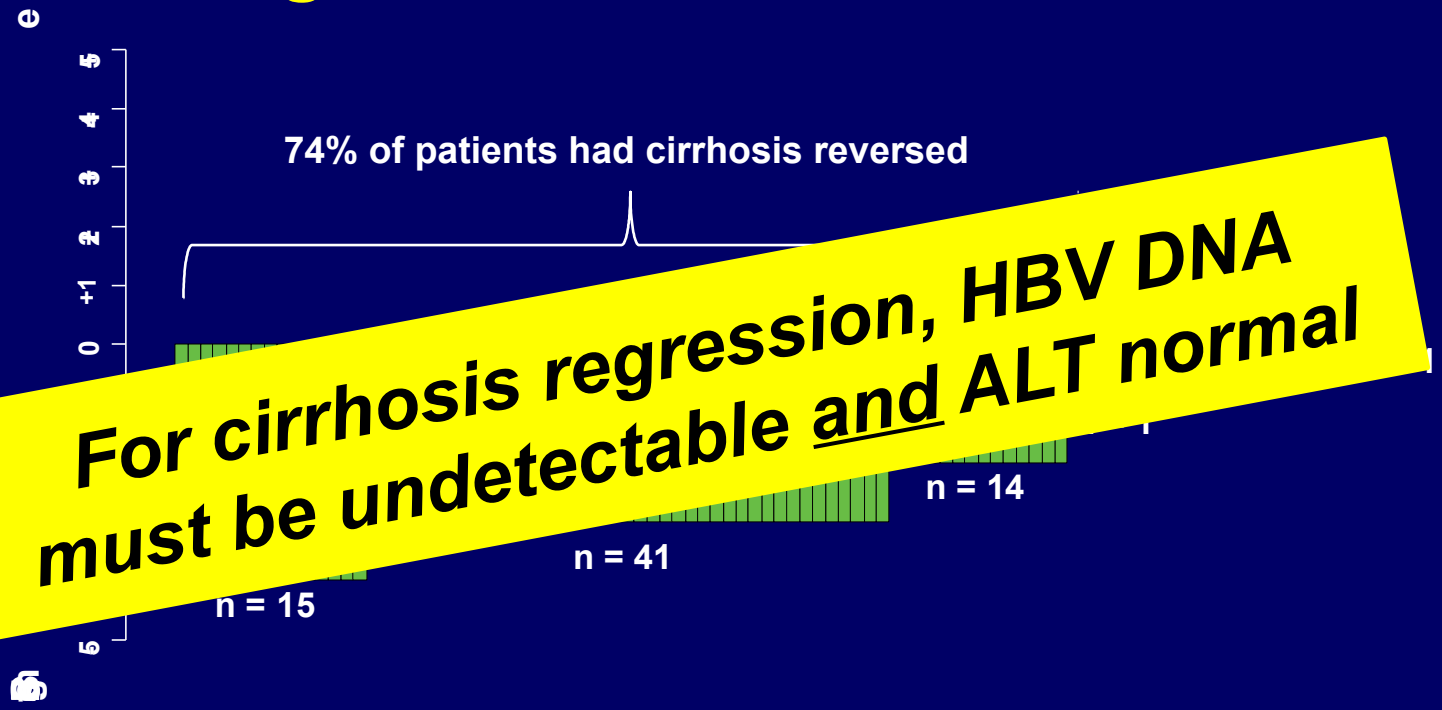


- 96 patients with cirrhosis (Ishak fibrosis score ≥5) had paired BL and Year 5 biopsies
- 74% (n=71) of patients had cirrhosis reversed (Ishak fibrosis score <5) at Year 5, and 73% (n= 70) had decreases of ≥2 points at Year 5; 25% (n=24) did not change
  - Of 94 patients who did not add FTC, 73% had cirrhosis reversed; 26% showed no change

Marcellin P et al, Lancet 2013

5-year TDF treatment in patients with CHB

Changes of fibrosis in cirrhotics



For cirrhosis regression, HBV DNA must be undetectable and ALT normal

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Marcellin P et al, Lancet 2013

Decompensation and portal hypertension

Does long-term NUC therapy reduce decompensation ?

- ETV: 3-5 years real life cohort studies in Europe and Asia (1-3)
- TDF: 3-4 years real life cohort studies in Europe (4-5)

1. Wong GL, et al, Hepatology 2013; 2. Zoutendijk R, et al, GUT 2013; 3. Lampertico P, et al, EASL 2013; 4. Lampertico P, et al, AASLD 2013; 5. Papatheodoridis G et al, AASLD 2013

Does long-term NUC therapy reduce decompensation ?

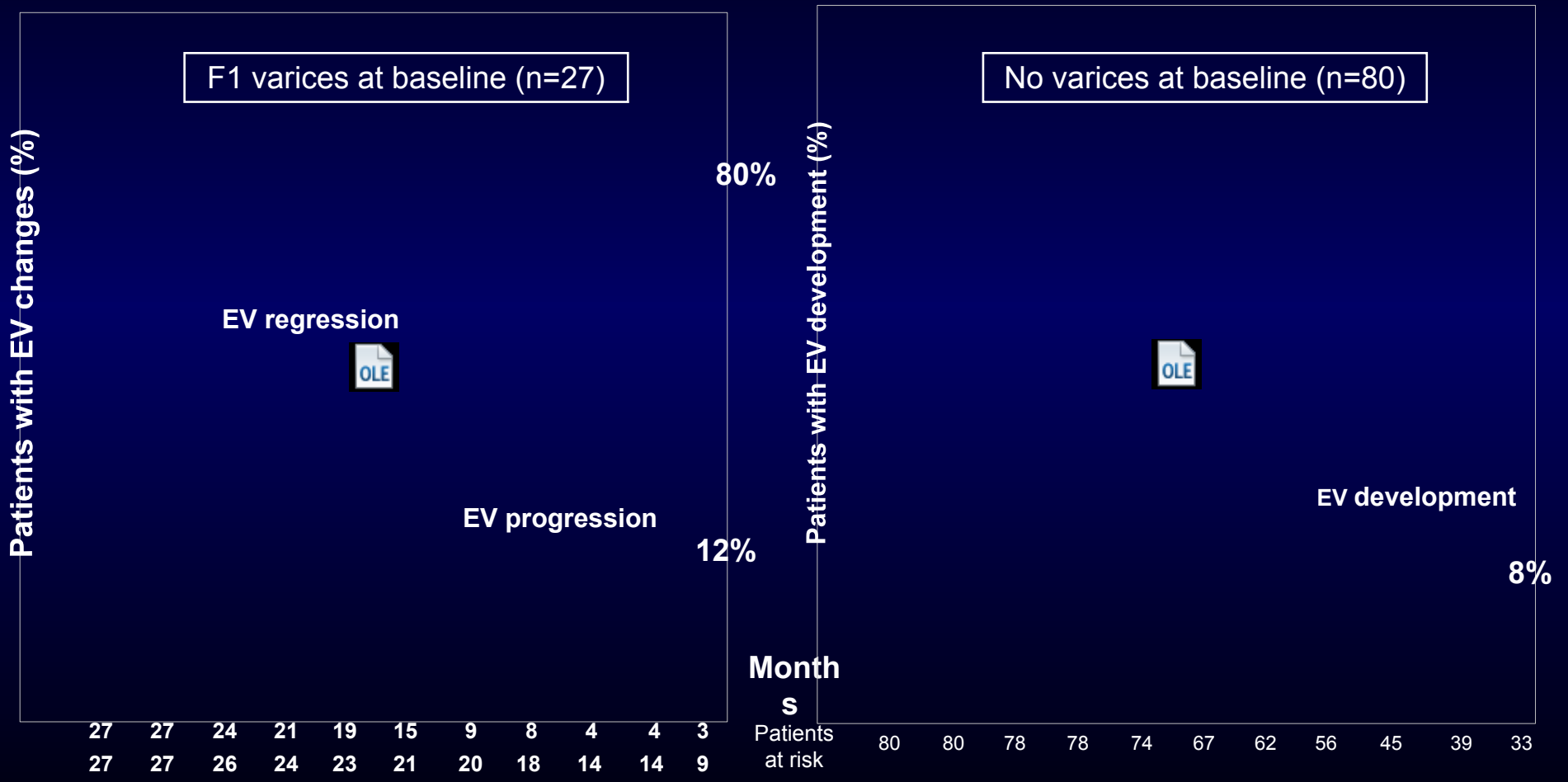
- ETV: 3-5 years real life cohort studies i[illegible]nd Asia (1-3)
- [illegible] in Europe (4-5)

Decompensation is prevented in ETV or TDF treated compensated cirrhotics

1. Wong GL, et al, Hepatology 2013; 2. Zoutendijk R, et al, GUT 2013; 3. Lampertico P, et al, EASL 2013; 4. Lampertico P, et al, AASLD 2013; 5. Papatheodoridis G et al, AASLD 2013

Changes of esophageal varices (EV) in compensated cirrhotics treated with LAM±TDF for 10 years

Overall, EV worsening rate per year: 0.9%*



* 6 of 7 progressors (86%) had either LMV-R and/or HCC

Lampertico et al, data on file 2013

Does long-term effective NUC therapy prevent or reduce HCC ?

Other indications for NUC therapy

- Decompensated cirrhosis and OLT
- Patients with HCC
- Acute on chronic liver disease
- Acute or fulminant hepatitis
- Prophylaxis or therapy in immunocompromised host
- HBV in Pregnancy
- Extrahepatic manifestations of HBV
- ……

NUC for HBeAg negative CHB
Summary and Conclusion

- Third generation NUCs (ETV or TDF) as monotherapy
- Easy: one pill/day
- Simple: no baseline selection, no on-therapy adaptation
- Safe: no major safety issues
- Effective: >95% viral suppression, >85% normal ALT; independent of disease severity or resistance
- Long-term outcome guaranteed:
  - Fibrosis/cirrhosis regression
  - Decompensation/portal hypertension prevented
  - HCC is the only complication in treated cirrhotics

The most popular antiviral therapy (>90%)