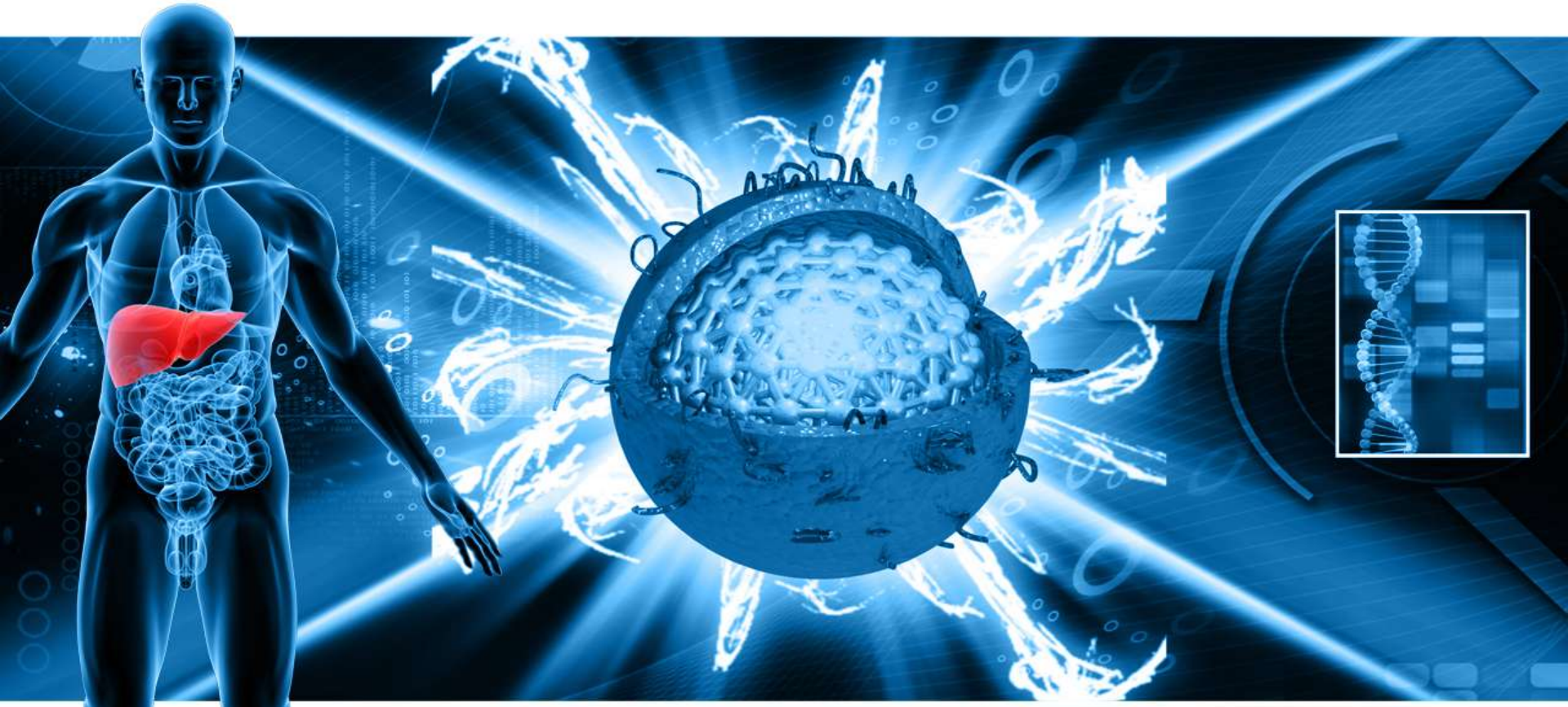

KNOWING THE SCORE

Can We Prevent HCC in CHB Infection?

12:00–13:30, 7 June 2013

Hall 1, Suntec Singapore International Convention & Exhibition Centre, Singapore

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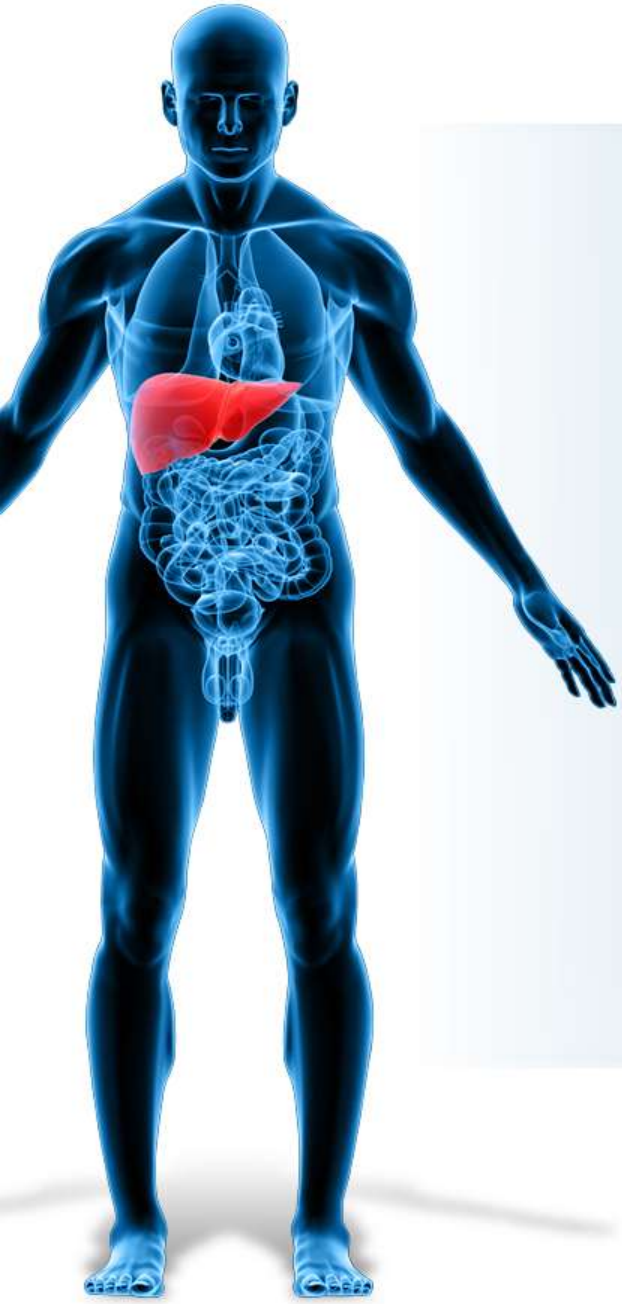

Real-world Outcomes with Long-term CHB Management

Diana A. Payawal, MD

Bristol-Myers Squibb

Differences between randomised clinical trials and real-world studies

RCTs systematically exclude special populations:

- Concurrent diseases
- Concurrent drug use
- Age extremes
- Risk of non-compliance

US Food and Drug Administration. 2009. Available at: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180547. (Feb 2012).

Differences between randomised clinical trials and real-world studies

RCTs systematically exclude special populations:

- Concurrent diseases
- Concurrent drug use
- Age extremes
- Risk of non-compliance

Real-world studies give valuable additional insights in heterogeneous populations

US Food and Drug Administration. 2009. Available at: http://www.fda.gov/Safety/SafetyofSpecificProducts/ucm180547. (Feb 2012).

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Real-world outcomes with long-term CHB management: Asian patients

- Long-term real life studies will help us to make informed choices about optimal first-line antiviral therapy and long-term management in Asian CHB patients
  - The REALM China Sub-study (4 years, Hou *et al*.)
  - The Hong Kong Cohort (5 years, Seto *et al*.)
  - Real-world China Study (5 years, Luo *et al.*)
  - Real-world Asian American Study (48 weeks, Chan *et al.*)

REALM China sub-study: 4 years of ETV

- Phase IV prospective, observational, open-label study
- China sub-study involving patients enrolled in the 50 centres in China
- Aim of this analysis: To study the long-term efficacy and safety of ETV versus other standard of care (oSOC) in NUC-naive patients in a real-world setting in China

Baseline characteristics	ETV n = 1724	Other Standard of Care n = 1720
Age, mean (range), years	36 (16–70)	35 (16–69)
Male, n (%)	1373 (80)	1396 (79)
HBV DNA, mean (range), log_{10} IU/mL	6.74 (1.04–9.69)	6.78 (1.04–9.72)
HBeAg status, n (%) HBeAg (+) HBeAg (–) Unknown	 1114 (64) 582 (34) 28 (2)	 1108 (64) 571 (33) 41 (2)
Median time on original study therapy, weeks (range) ETV *LVD (n = 69)* *ADV (n = 1612)* *LdT (n = 39)*	 231.1 (1.3–276.9)	 234.4 (12.1–271.0) 227.0 (0.3–282.0) 204.5 (1 47.4–218.1)

ADV, adefovir; ETV, entecavir, LVD, lamivudine; LdT, telbivudine

Hou JL, *et al.* APASL 2013. Abstract 456.

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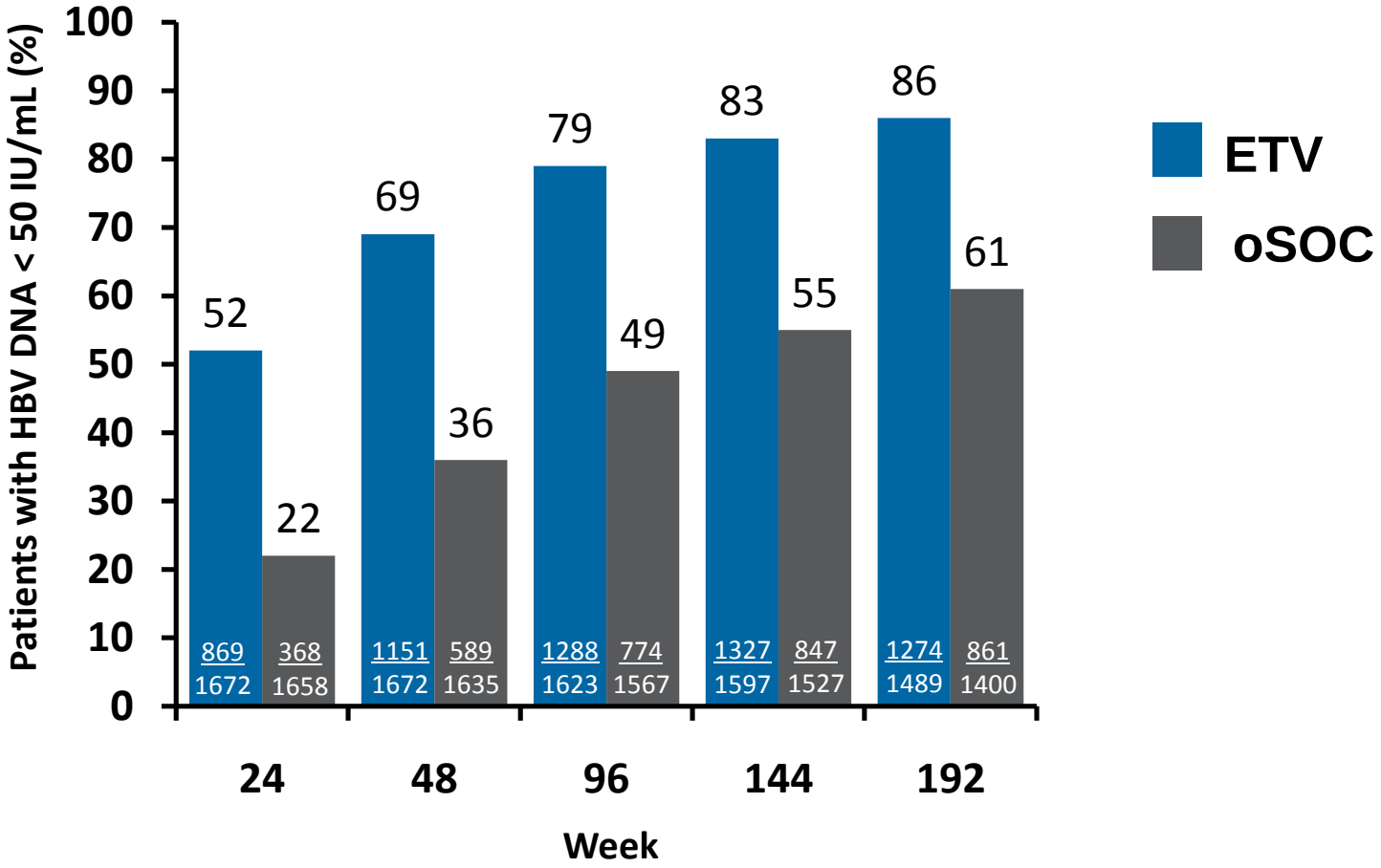
REALM China: virological efficacy ETV versus other standard of care



oSOC, other standard of care.
Non-completer = missing analysis

Hou JL, *et al.* APASL 2013. Abstract 456.

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REALM China: safety through Week 192

	ETV (n = 1766)	oSOC (n = 1760)
Serious AEs related to study therapy*		
Any	3 (< 1)	1 (< 1)
Complications of chronic hepatitis	1 (< 1)	0
ALT increased	1 (< 1)	0
Blood bilirubin increased	1 (< 1)	0
Blood creatine phosphokinase increased	0	1 (< 1)
Discontinuations from originally prescribed study therapy due to AEs†	1 (< 1)	2 (< 1)
Deaths†	31 (2)‡	37 (2)**

All data presented as n (%).
* Among treated patients;
† Among randomised patients.
‡ Causes: HCC (14), liver-related, non-HCC (5), malignancy, non-HCC (1), other (6), unknown (5).
** Causes: HCC (25), liver-related, non-HCC (3), malignancy, non-HCC (1), other (2), unknown (6).

AE, adverse event; ALT, alanine aminotransferase, HCC; hepatocellular carcinoma

Hou JL, *et al.* APASL 2013. Abstract 456.

The Hong Kong cohort: 5 years of ETV

- Prospective cohort study in a single centre in Hong Kong
- Aim: To study the serological, biochemical, virological responses and resistance profile of continuous 0.5 mg ETV in treatment-naive CHB patients up to 5 years

Baseline characteristics (N = 222)	
Male	157 (70.7%)
Median age, years	47 (21–77)
HBeAg(+)	90 (40.5%)
HBV DNA (range), log IU/mL	6.40 (3.32– > 8.10)
HBsAg (range), log IU/mL	3.41 (0.96–5.88)
Number of patients with HBsAg ≥ 3 log IU/mL	173 (77.9%)
Albumin, g/L	42 (22–50)
Bilirubin, µmol/L	13 (2–216)
ALT (range), U/L	92 (17–2168)
Number of patients with elevated ALT level	181 (81.5%)
LVD resistance (rtM204I)	2 (0.9%)
ETV resistance	0

Seto WK, *et al.* EASL 2013. Poster 772.

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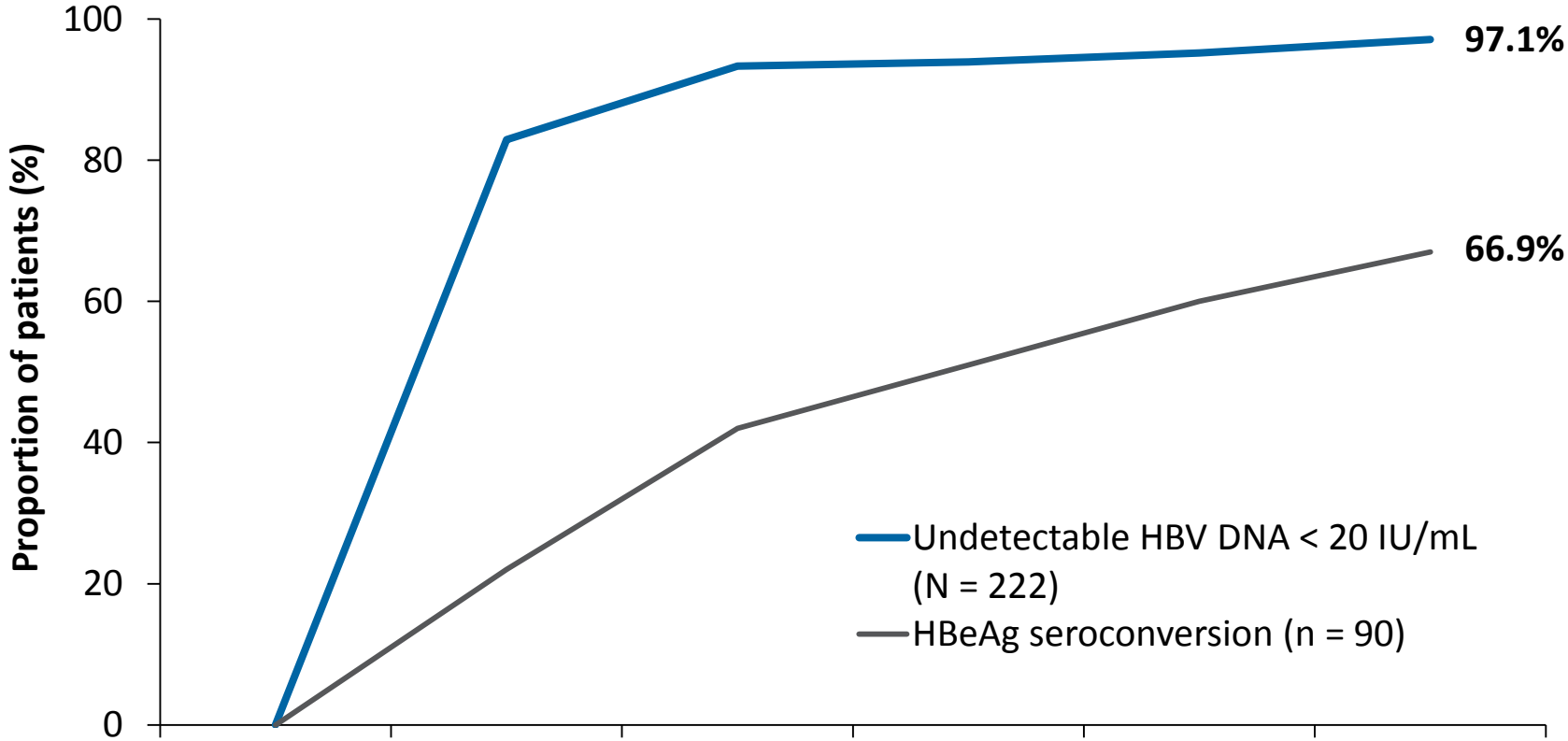
The Hong Kong cohort: cumulative* outcomes with ETV through Year 5



Patients on follow-up (n):	Baseline	Year 1	Year 2	Year 3	Year 4	Year 5
	222	222	188	173	170	156

* Cumulative rates estimated by Kaplan-Meier method.
ALT upper limit of normal: 58 U/L for men, 36 U/L for women.

Seto WK, *et al.* EASL 2013. Poster 772.

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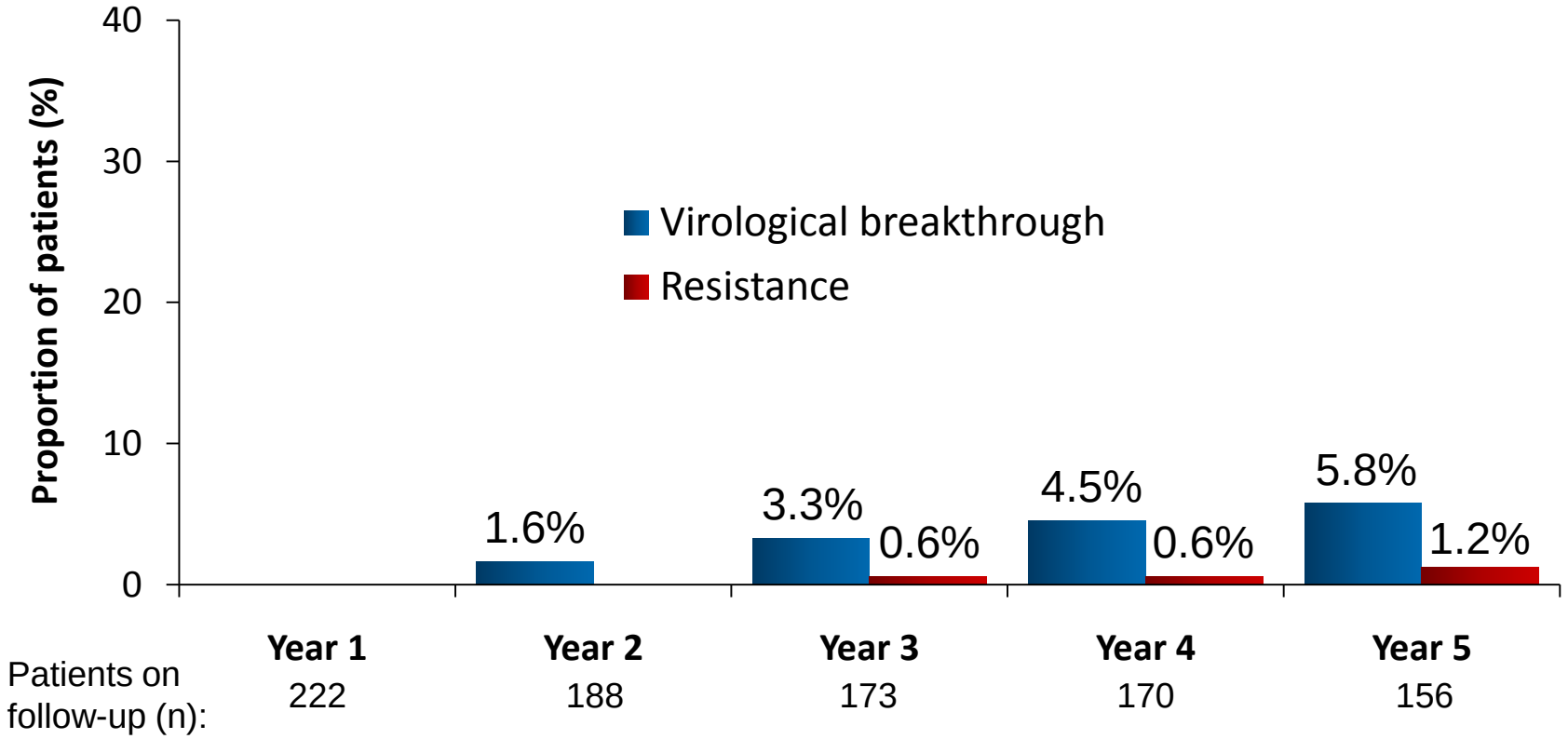
The Hong Kong cohort: cumulative* outcomes with ETV through Year 5



The majority of virological breakthrough was attributed to non-compliance.

* Cumulative rates estimated by Kaplan-Meier method.
ALT upper limit of normal: 58 U/L for men, 36 U/L for women.

Seto WK, *et al.* EASL 2013. Poster 772.

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Real-world study in Asian Americans: 48 weeks of TDF

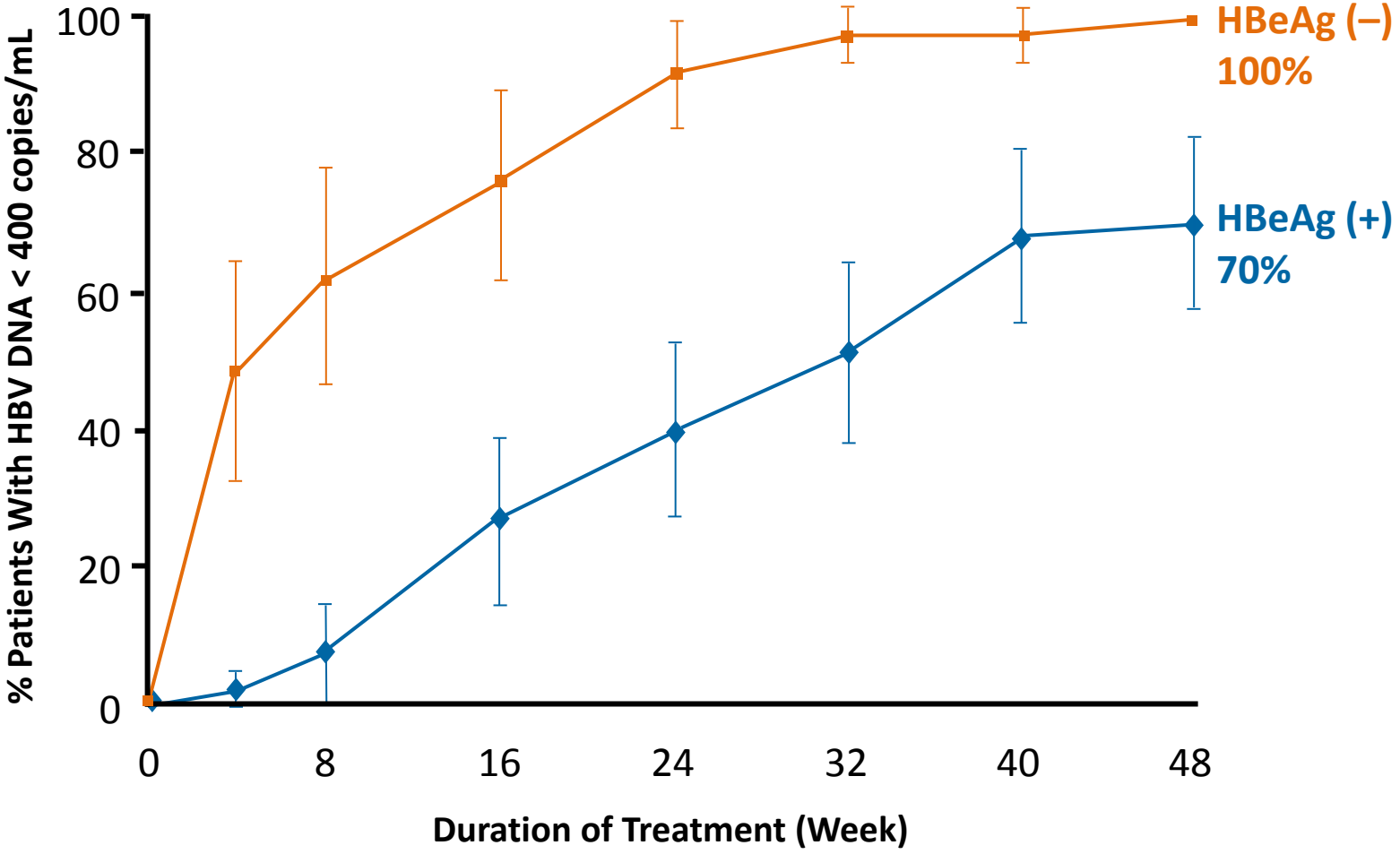
- Open-label single arm study of 48 weeks TDF 300 mg once daily
- 19 study sites, 16 community-based practices in the US

Baseline characteristics	N = 90
Age (years)*	36 (18–62)
Male/Female	47/43
HBV DNA $\log_{10}$ copies/mL	7.5 ± 1.8
HBeAg-positive	52 (58)
Prior Treatment History	
Lamivudine	3 (3%)
Adefovir dipivoxil	6 (7%)
Interferons	5 (6%)
Genotypes	
B	43 (48%)
C	45 (52%)
Ethnicity	
Chinese	58 (64%)
Vietnamese	19 (21%)
Korean	12 (13%)
Cambodian	1 (1%)

* Median (range); † Mean ± SD; TDF, Tenofovir.

Chan S. *et al*. APASL, 2011; Poster PP05-101.

Real-world study in Asian Americans: virological response at Week 48* of TDF



* Analysis included all enrolled subjects who received at least one dose of study drug.

Chan S. *et al*. APASL 2011; Poster PP05–101.

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Real-world outcomes with long-term CHB management: Asian patients

- In real-world studies in Asian patients long-term ETV or TDF therapy resulted in durable suppression of HBV DNA replication, improved liver histology and/or low emergence of resistance through Year 5[1–4]

- The efficacy and safety data for ETV and TDF in real-world studies are consistent with results from global and Asian clinical long-term studies with ETV and TDF, respectively[5–9]

1. Hou JL, *et al.* APASL 2013. Abstract 456; 2. Seto WK, *et al.* EASL 2013. Poster 772; 3. Luo J, *et al. Int J Med Sci* 2013;10(4):427–33; 4. Chan S. *et al*. APASL, 2011; Poster PP05–101. 5. Chang TT, *et al*. *Hepatology* 2010;51:422–30; 6. Chang TT, *et al. Hepatology* 2010;52:886–93; 7. Yao G, *et al. Hepatol Int* 2011;17 (Suppl 1):51–58; 8. Seto WK, *et al. J Hepatol* 2011;54:S301; 9. Marcellin P, *et al*. *Lancet* 2013; 381(9865):468-75.

Real-world outcomes with long-term CHB management: Europe

Real-world outcomes with long-term CHB management: Europe

- What do the data from real-life clinical settings in Europe show?
  - The Italian ETV Cohort (5 years, Lampertico *et al.*)
  - The European TDF Cohort (3.5 years, Lampertico *et al.*)
  - The VIRGIL Study (20 months, Zoutendijk *et al.*)

European data: long-term ETV and TDF cohorts

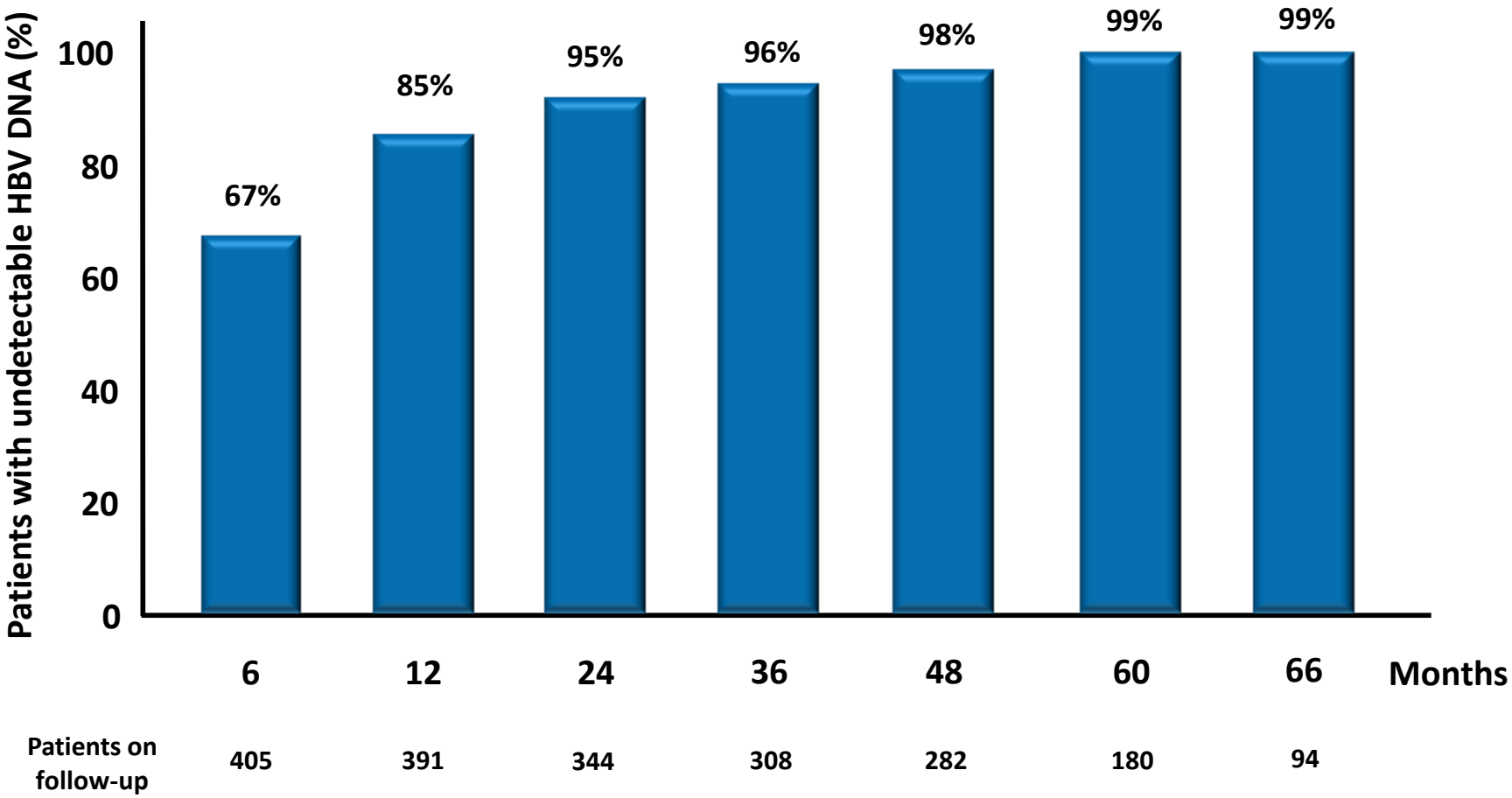
- Multi-centre retrospective/prospective cohorts of NUC-naive patients
- Aim: To assess the virological and clinical outcome of NUC therapy in two large cohorts of CHB patients

Baseline characteristics	Italian ETV cohort† (N = 418)	European TDF cohort‡ (N = 302)
Age (years)*	**58 (18–82)**	**55 (19–80)**
Male	316 (76%)	222 (74%)
HBeAg (–)	**346 (83%)**	**241 (80%)**
HBV DNA (log IU/mL)*	6.0 (1.5–9)	5.9 (1.4– > 9)
ALT (IU/L)*	92 (11–2241)	88 (11–3733)
Genotype D	**84/93 (90%)**	
Cirrhotics	**204 (49%)**	**105 (35%)**
HCC	41 (10%)	28 (10%)
BMI > 25 kg/m^2	168/365 (46%)	
Concomitant diseases	228 (56%)	129 (43%)
Reduced TDF dose		6 (2%)

* Median (range); † Retrospective/Prospective cohort of NUC-naive patients from 19 Italian centres; ‡ Retrospective/prospective cohort of NUC-naive patients from 19 European centres

† Lampertico P, *et al.* EASL 2013; Abstract 755;
‡ Lampertico P, *et al.* AASLD 2012; Poster 525.

The Italian ETV cohort: Virological response through 5 years



Lampertico P, *et al.* EASL 2013; Abstract 755.

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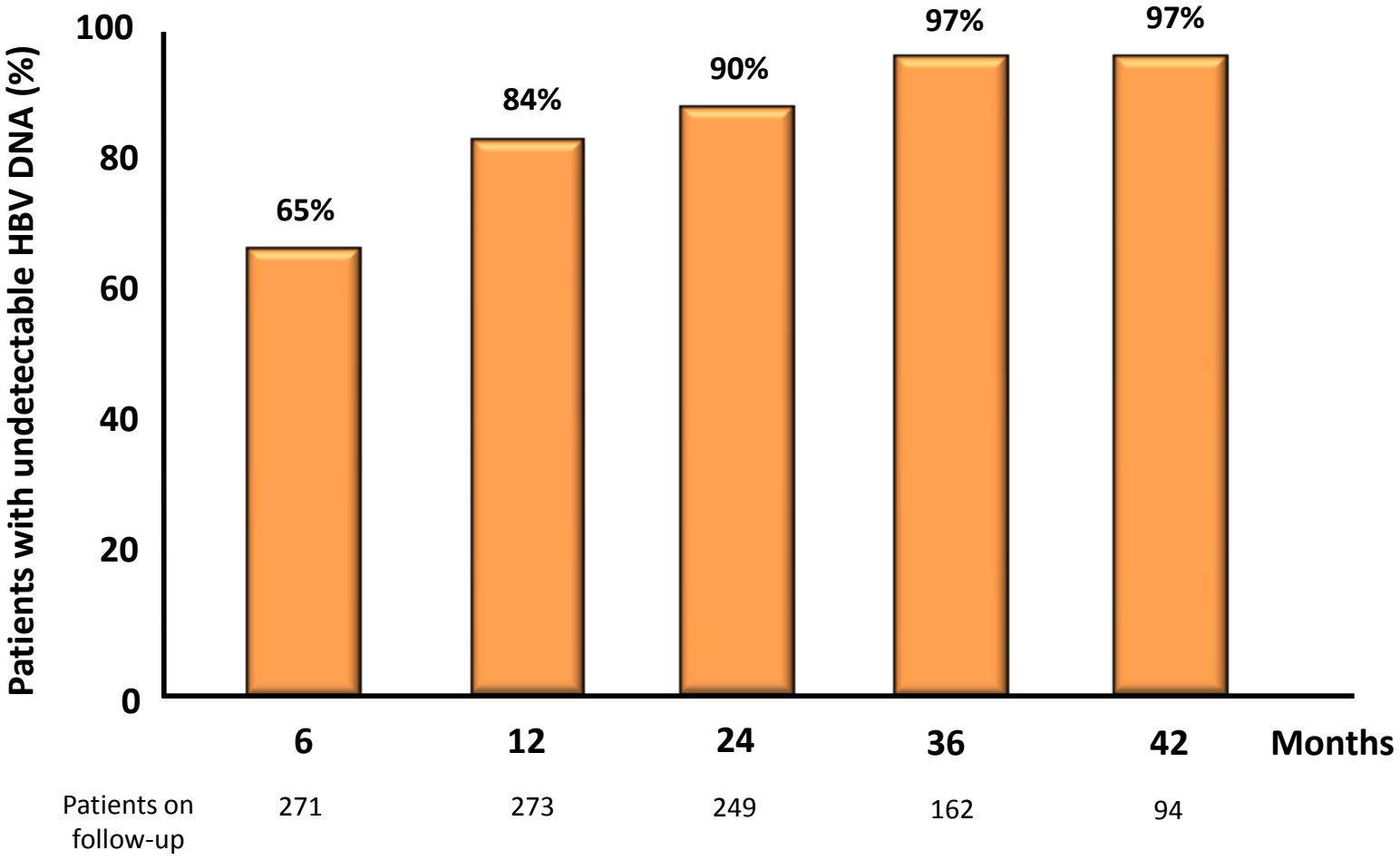
The European TDF cohort: Overall virological response



Lampertico P, *et al.* AASLD 2012; Poster 525.

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VIRGIL study: assessment of the effect of ETV on liver disease progression

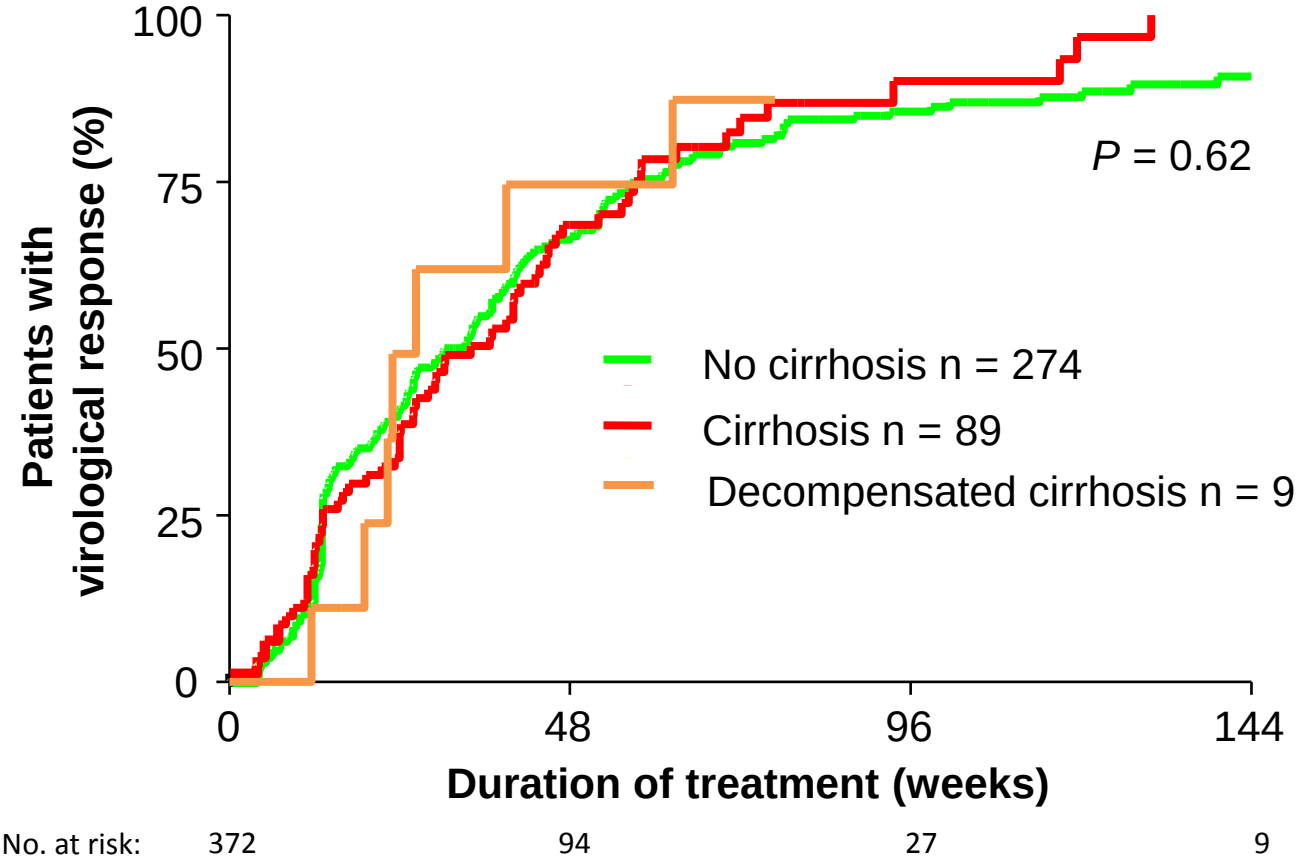
- Cohort study in 10 European expert centres
- Aim of this analysis: To investigate the effect of ETV on disease progression in 372 NUC-naive or NUC-experienced* CHB patients. Primary endpoint: Occurrence of clinical event (hepatic decompensation, HCC, death)

Baseline characteristics	No cirrhosis (n = 274)	Cirrhosis (n = 89)	Decompensated cirrhosis (n = 9)
Age, years	41	51	51
Male, n (%)	200 (73)	71 (80)	6 (67)
Caucasian, n (%)	137 (50)	41 (46)	3 (33)
HBeAg(+), n (%)	116 (42)	56 (63)	4 (44)
HBV DNA, $\log_{10}$ IU/mL	5.9	5.3	6.7
HBV genotype D, n (%)	104 (49)	29 (50)	2 (29)
Previous LVD, n (%)	56 (20)	29 (33)	4 (44)
Previous ADV, n (%)	36 (13)	28 (32)	2 (22)

* Patients treated with ETV for ≥ 3 months (during 2005–2010, median follow-up 20 months); ADV, adefovir; LVD, lamivudine.

Zoutendijk R, *et al. Gut* 2012; 62(5):760–65.

VIRGIL: virological response rate to ETV independent of severity of liver disease



- Cumulative probability of achieving a VR to ETV: 93% at Week 144

* VR, virological response; HBV DNA < 80 IU/mL

Zoutendijk R, *et al. Gut* 2012; 62(5):760–65.

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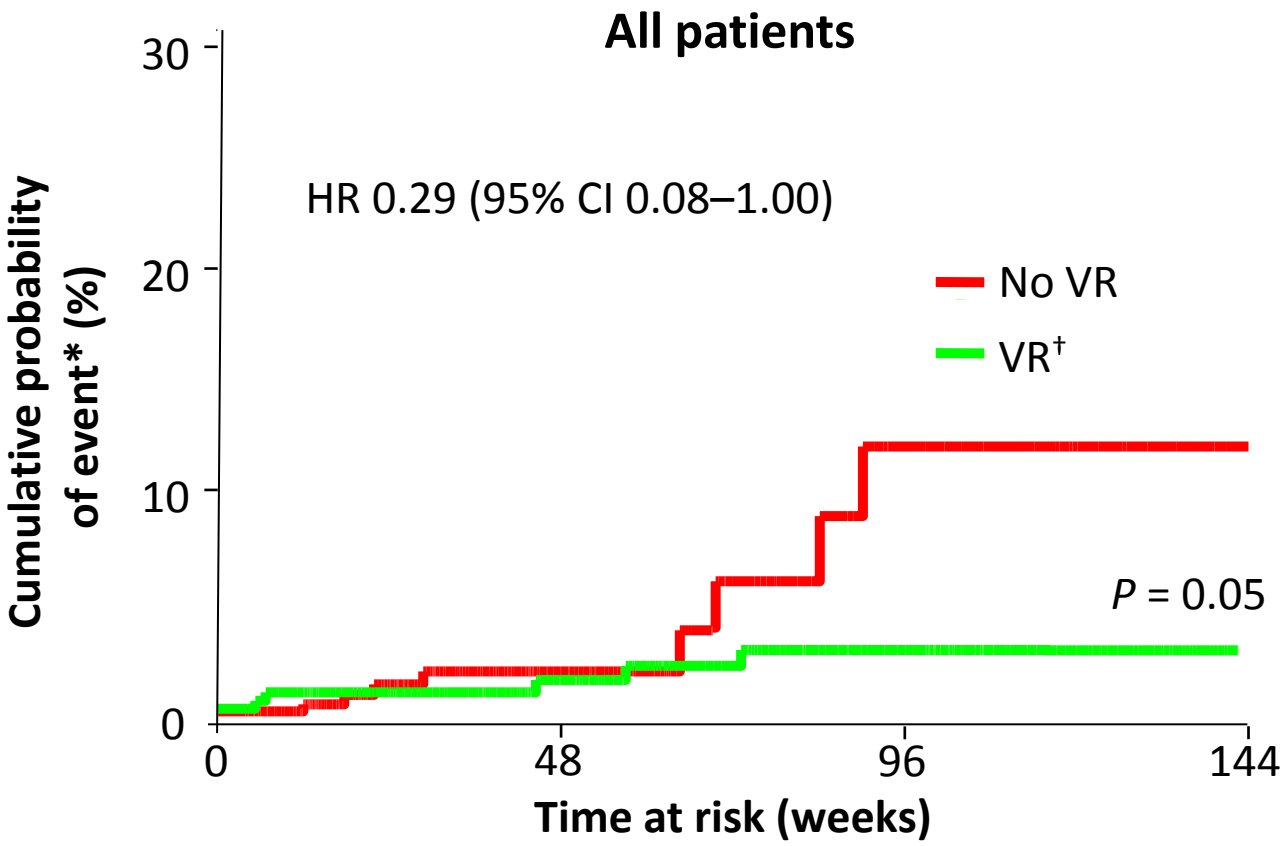
VIRGIL: virological response to ETV associated with lower risk of disease progression



- VR to ETV: > 70% lower risk of clinical event compared with no VR (all patients)
- HBV DNA < 2000 IU/mL: risk of clinical event not reduced (HR 0.20; *P* = 0.10)

* Hepatic decompensation, HCC, or death. † VR, virological response (HBV DNA < 80 IU/mL).

Zoutendijk R, *et al. Gut* 2012; 62(5):760–5.

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Real-world outcomes with long-term CHB management: Europe

- In a real-world setting in NUC-naive CHB patients in Italy, ETV monotherapy showed a favourable efficacy profile over 5 years of administration in clinical practice

The Italian cohort (5 years, Lampertico et al.)

- In a real-world setting in NUC-naive CHB patients in Europe, TDF monotherapy suppressed HBV in most NUC-naive patients in field practice

The European cohort (3.5 years, Lampertico et al.)

- In a real-world setting in ETV-treated European patients, virological response to ETV was associated with a reduced probability of disease progression

The VIRGIL study (20 months, Zoutendijk et al.)

Summary: ETV and TDF demonstrate long-term efficacy in real-world situations

- The efficacy and safety data for ETV and TDF in these real-world studies are consistent with results from global long-term clinical studies.[1–9]

- Long-term therapy with ETV and TDF results in high rates of virological response and low rates of resistance
  - Evidence from VIRGIL study that virological response to ETV reduces disease progression

- ETV and TDF are generally well-tolerated:
  - Individual long-term safety profiles vary and should be monitored

1. Hou JL, *et al.* APASL 2013. Abstract 456; 2. Seto WK, *et al.* EASL 2013. Poster 772; 3. Luo J, *et al. Int J Med Sci* 2013;10(4):427–33; 4. Chan S. *et al*. APASL, 2011. Poster PP05-101. 5. Chang TT, *et al*. *Hepatology* 2010;51:422–30; 6. Chang TT, *et al. Hepatology* 2010;52:886–93; 7. Yao G, *et al. Hepatol Int* 2011;17 (Suppl 1):51–58; 8. Seto WK, *et al. J Hepatol* 2011;54:S301; 9. Marcellin P, *et al*. *Lancet* 2013; 381(9865):468-75.