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- Panel discussion session
  - Please fill in question cards
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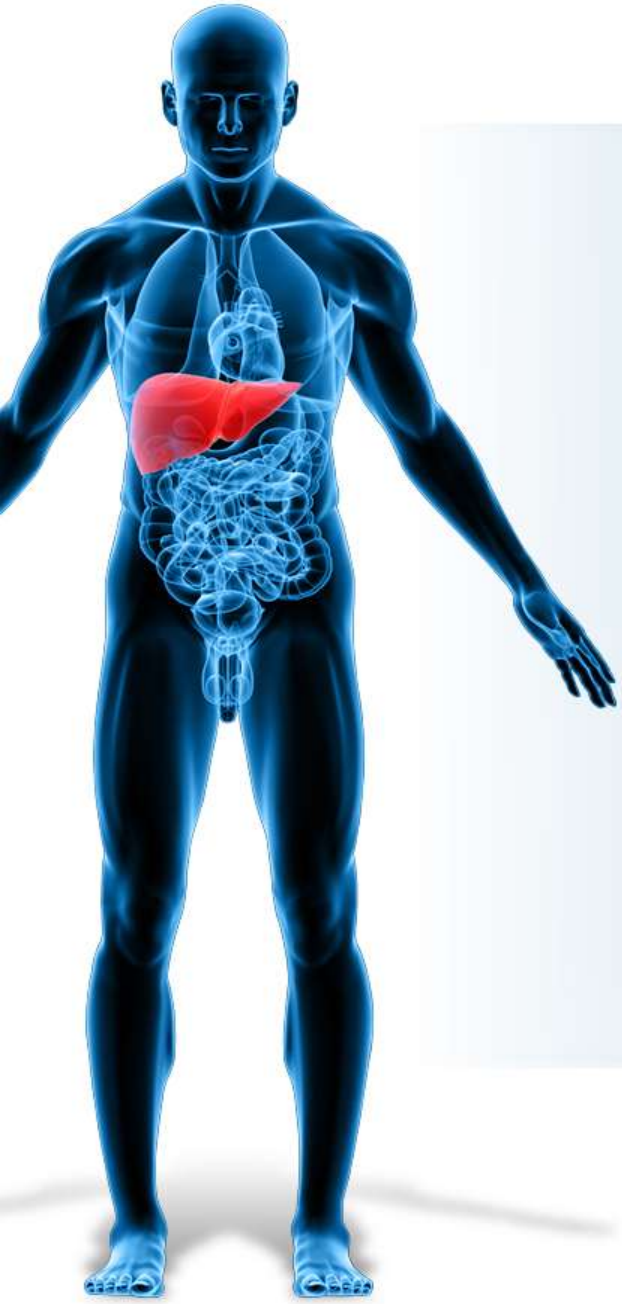
Symposium objectives

- Review the factors involved in reaching the ultimate goal of CHB therapy
- Highlight key considerations in the management of CHB: antiviral efficacy, safety and resistance
- Explore supporting real-world data from around the globe
- Discuss the role of antiviral therapy on HCC prevention in Asia

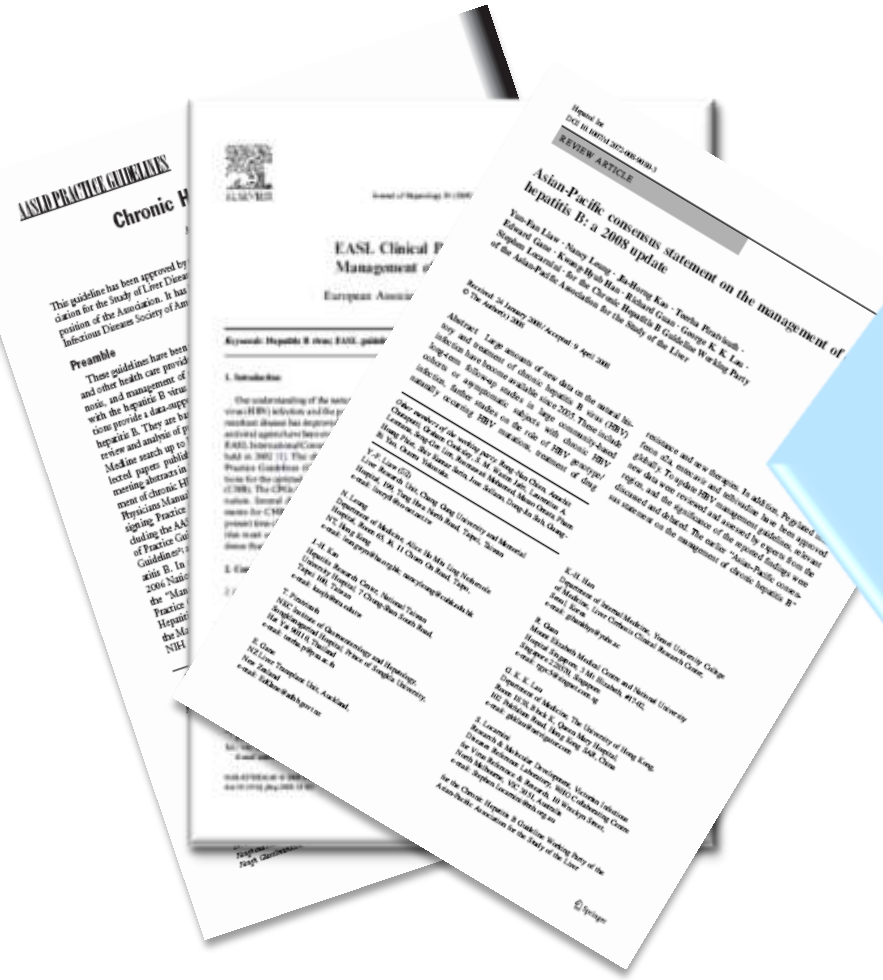


Playing the Long Game: Can We Reach the Ultimate Goal of CHB Therapy?

Jose D Sollano (Manila)

Bristol-Myers Squibb

International guidelines: long-term goal of HBV treatment



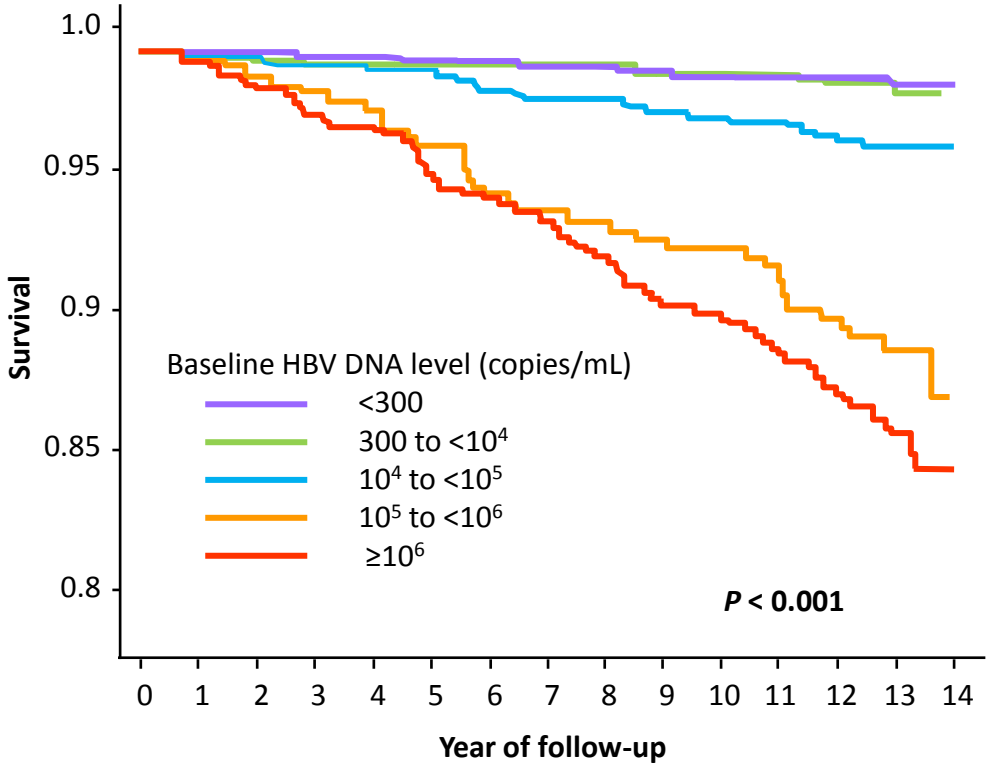
International guidelines agree: The goal of therapy for hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, end-stage liver disease, HCC and death

HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

1. EASL Clinical Practice Guidelines: *J Hepatol* 2009;50:227–42; 2. Lok ASF & McMahon BJ. AASLD practice guidelines. Chronic hepatitis B: Update 2009. At: http://www.aasld.org/practiceguidelines/Documents/Bookmarked Practice Guidelines/Chronic_Hep_B_Update_2009 8_24_2009.pdf (Feb 2012); 3. Liaw YF, *et al. Hepatol Int* 2008;2:263–83.

REVEAL: high HBV viral load associated with increased risk for HCC mortality

- REVEAL longitudinal cohort study: liver-related mortality among 3,653 HBsAg(+) patients by baseline HBV DNA level



Baseline HBV DNA (copies/mL)	Multivariate-adjusted HR death from HCC (95% CI)
< 300	Referent
300 to < 10^4	0.7 (0.3–1.9)
10^4 to < 10^5	2.1 (0.9–5.0)
10^5 to < 10^6	6.9 (3.1–15.4)*
≥ 10^6	5.7 (2.4–13.6)*

*P < 0.001

HR, hazard ratio. CI, confidence interval.

Iloeje UH, *et al. Clin Gastroenterol Hepatol* 2007;5:921-31.

HCC risk prediction – a future tool in managing CHB?

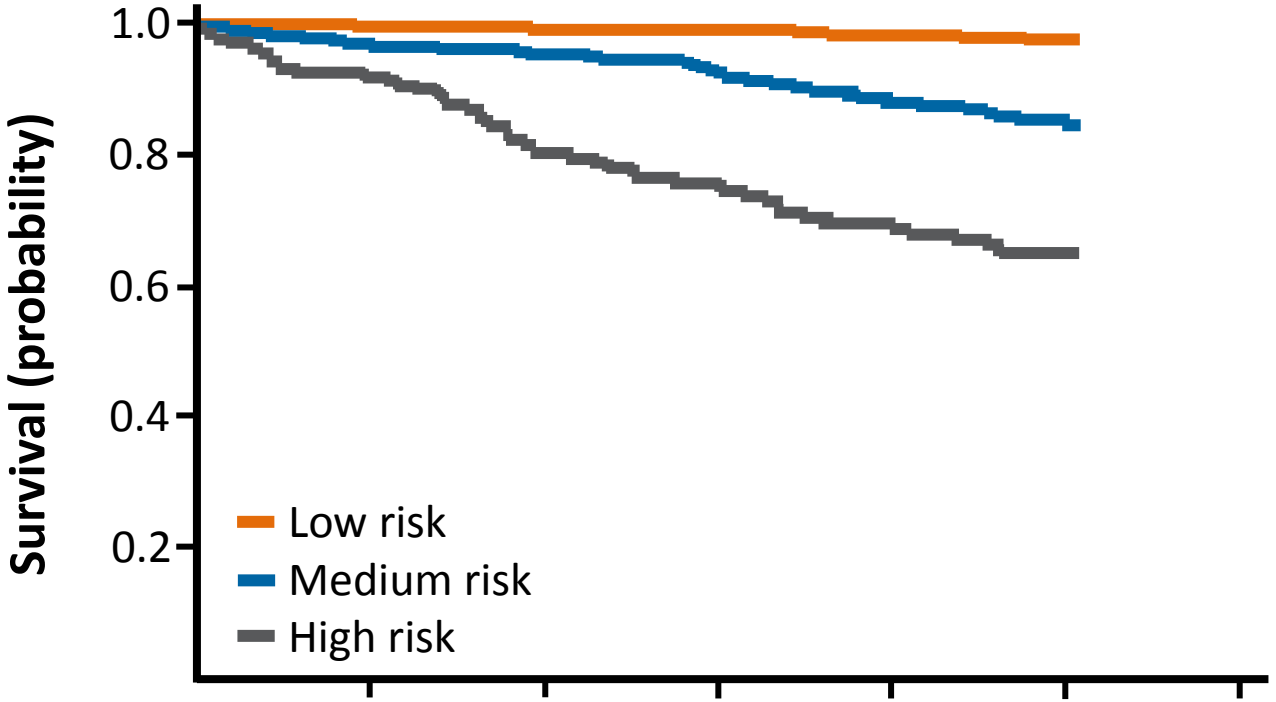
- Several important predictors of HCC risk in patients with CHB have been identified
  - REVEAL HCC score
  - REACH-B
  - CU-HCC score
  - GAG-HCC
- Well-designed clinical trials show that treatment can reduce these factors and decrease the risk of disease progression
- Data from long-term population-based studies now exist for developing these models

Risk scores for HBV-related HCC

Score	Patients	Components	Cut-off	Performance
CU-HCC[1]	Clinic patients: 1005 in training cohort, 424 in validation cohort	Age, albumin, bilirubin, HBV DNA, cirrhosis	5	97% NPV at 10 years
GAG-HCC[2]	820 clinic patients (leave-one-out cross-validation method)	Age, gender, HBV DNA, cirrhosis	101	99% NPV at 10 years
REACH-B[3]	Non-cirrhotic patients: 3584 in training cohort, 1505 in validation cohort	Age, gender, ALT, HBV DNA, HBeAg	8	98% NPV at 10 years

1. Wong VW, *et al. J Clin Oncol* 2010;28:1660–65; 2. Yuen MF, *et al. J Hepatol* 2009;50:80–88; 3. Yang HI, *et al. Lancet Oncol* 2011;12:568–74.

How do we identify which patients are at the highest risk of HCC / disease progression?



No. at risk	0	2	4	6	8	10	12
Low risk	297	285	279	278	265	217	
Median risk	63	56	55	55	47	32	
High risk	64	43	40	39	32	24	

Projected HCC risk is accurate and reproducible

Kaplan-Meier estimates of time to HCC in CHB patients with low, medium and high prediction scores in the validation cohort.

Wong VWS, *et al. J Clin Oncol* 2010; 28:1660–65.

Implications of risk prediction in clinical practice

- Risk prediction can help:
  - Assist in patient counseling
  - Risk stratification
  - Identify those most likely to benefit from treatment[1]
  - Assist with resource allocation in areas of high endemicity

1. Yuen MF, *et al*. *J Hepatol* 2009;50:80–88.

The best chance of achieving the ultimate goal: key considerations

Potency

"**Entecavir and tenofovir are the preferred nucs**."[1]

Resistance

"**Entecavir and tenofovir** are potent HBV inhibitors and they **have a high barrier to resistance**. Thus they can be confidently used as first-line monotherapies (A1)."[2]

Safety

"Therefore, age of patient, severity of liver disease, probability of sustained response, likelihood of drug resistance, **adverse events, and complications need to be carefully considered**."[1]

1. Liaw YF *et al*. APASL consensus statement on the management of chronic hepatitis B: a 2012 update. *Hepatol Int* 2012;6:531–61; 2. EASL Clinical Practice Guidelines: Management of chronic hepatitis B. *J Hepatol* 2009;50:227–42.

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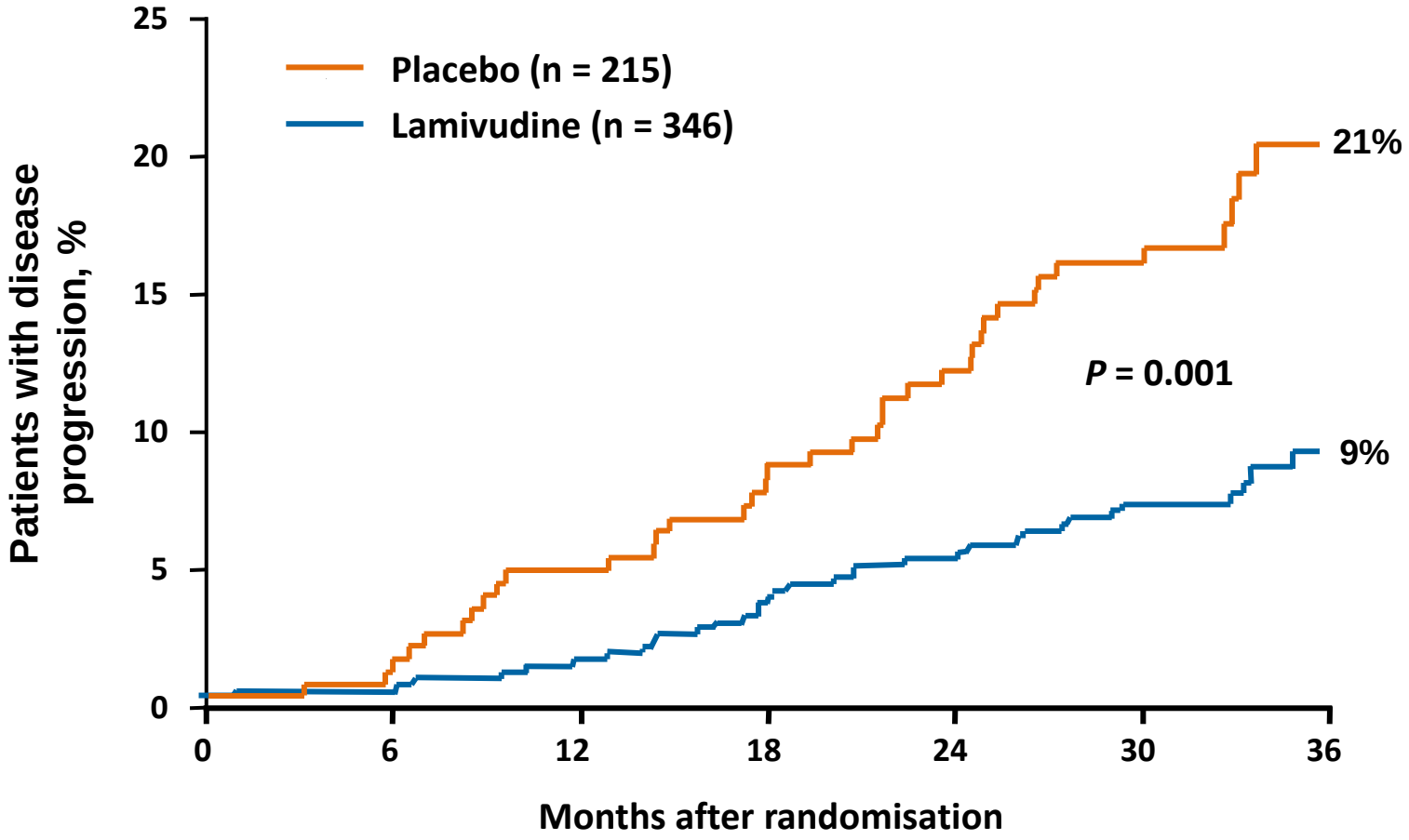
Potency / Efficacy

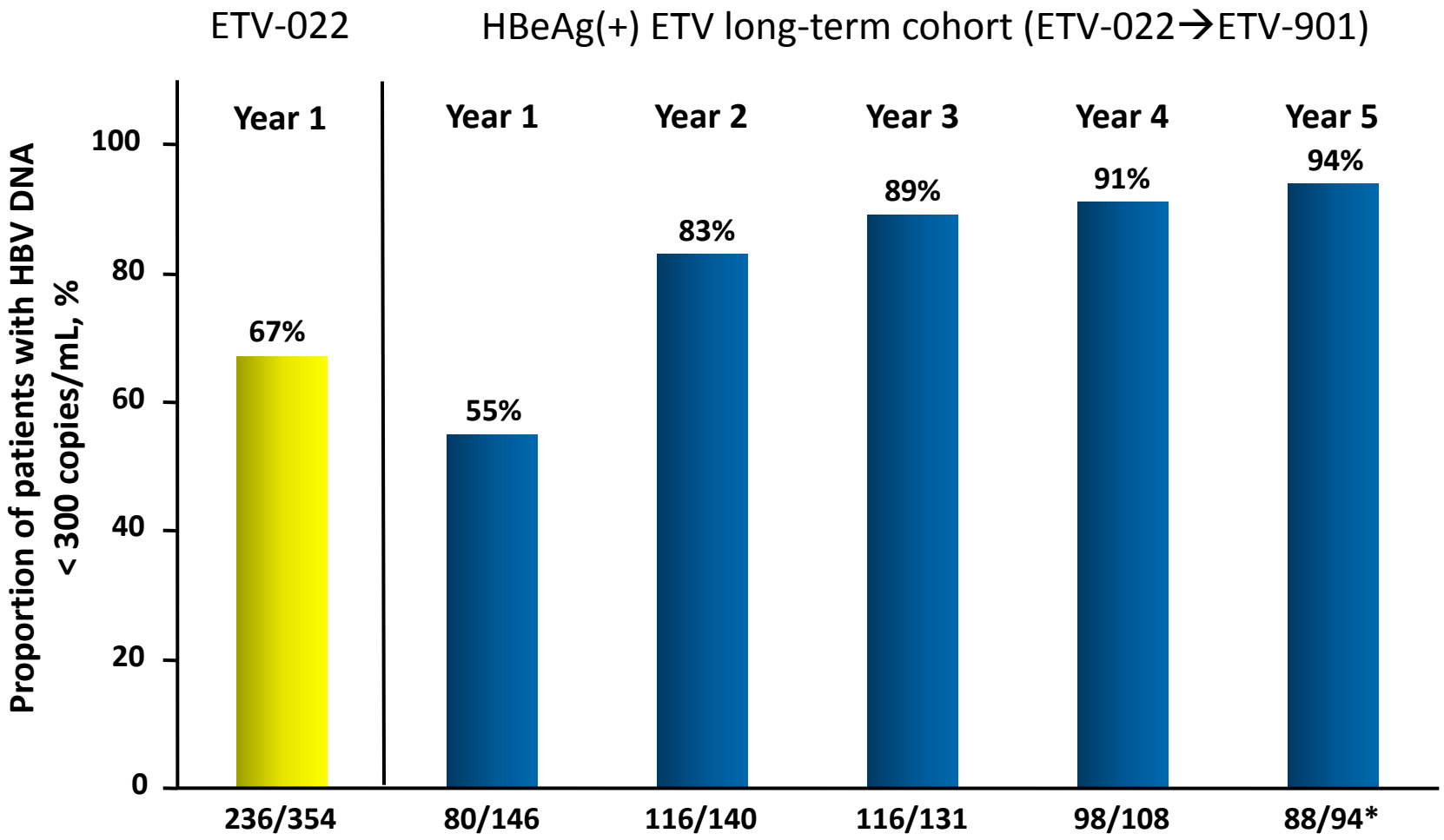
Antiviral agents delay disease progression



Intention to treat population.

Adapted from Liaw Y-F. *Semin Liver Dis* 2005;25:40–47; Liaw Y-F, *et al*. *N Engl J Med* 2004;351:521–31.

Long-term efficacy with entecavir: proportion of patients achieving HBV DNA < 300 copies/mL through 5 years



* Five patients who remained on treatment at the Year 5 visit had missing PCR values (non-completer = missing).

Adapted from Chang TT, *et al. Hepatology* 2010;51:422–30.

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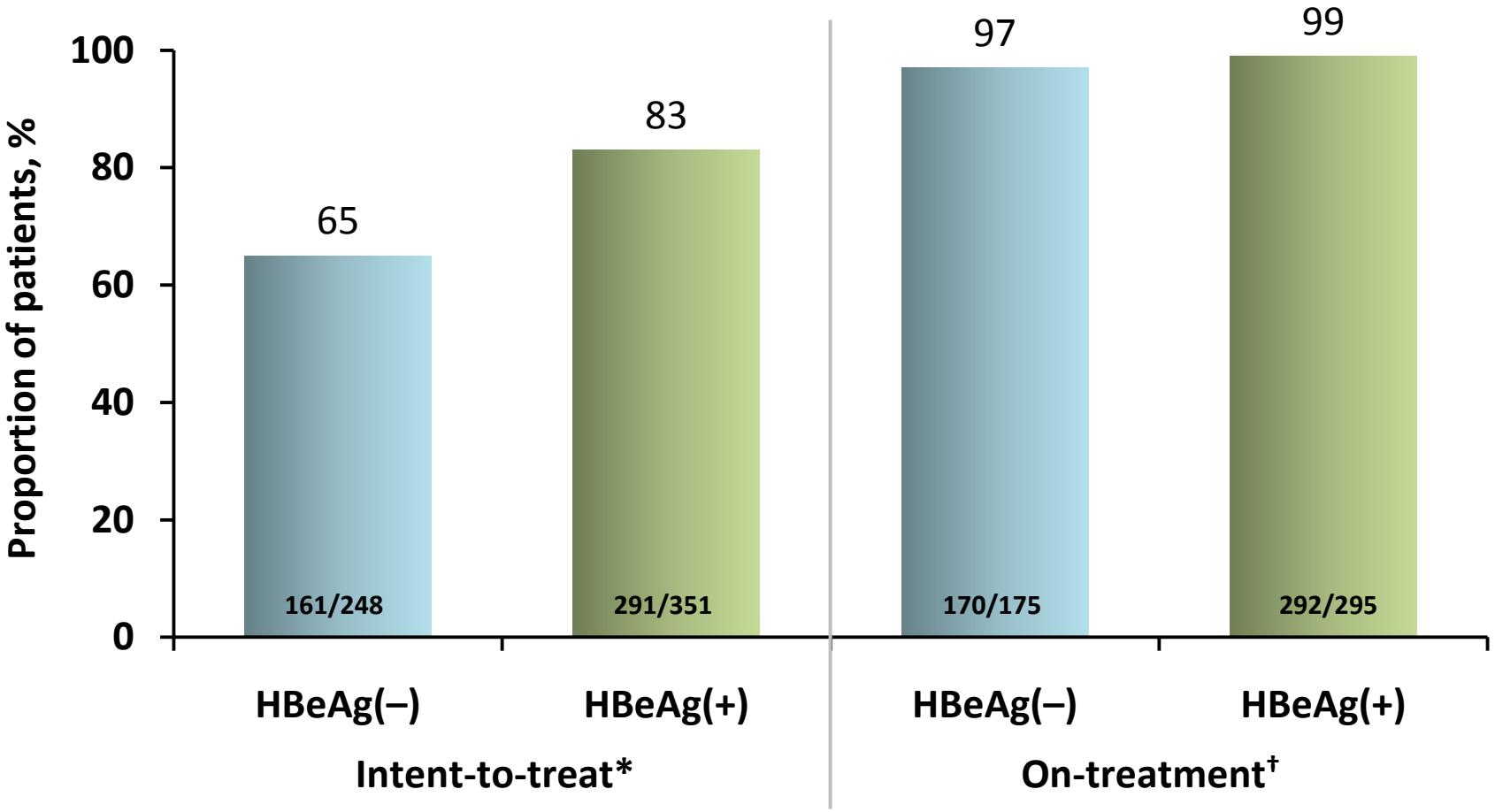
Long-term efficacy with tenofovir: proportion of patients achieving HBV DNA < 400 copies/mL at Year 5

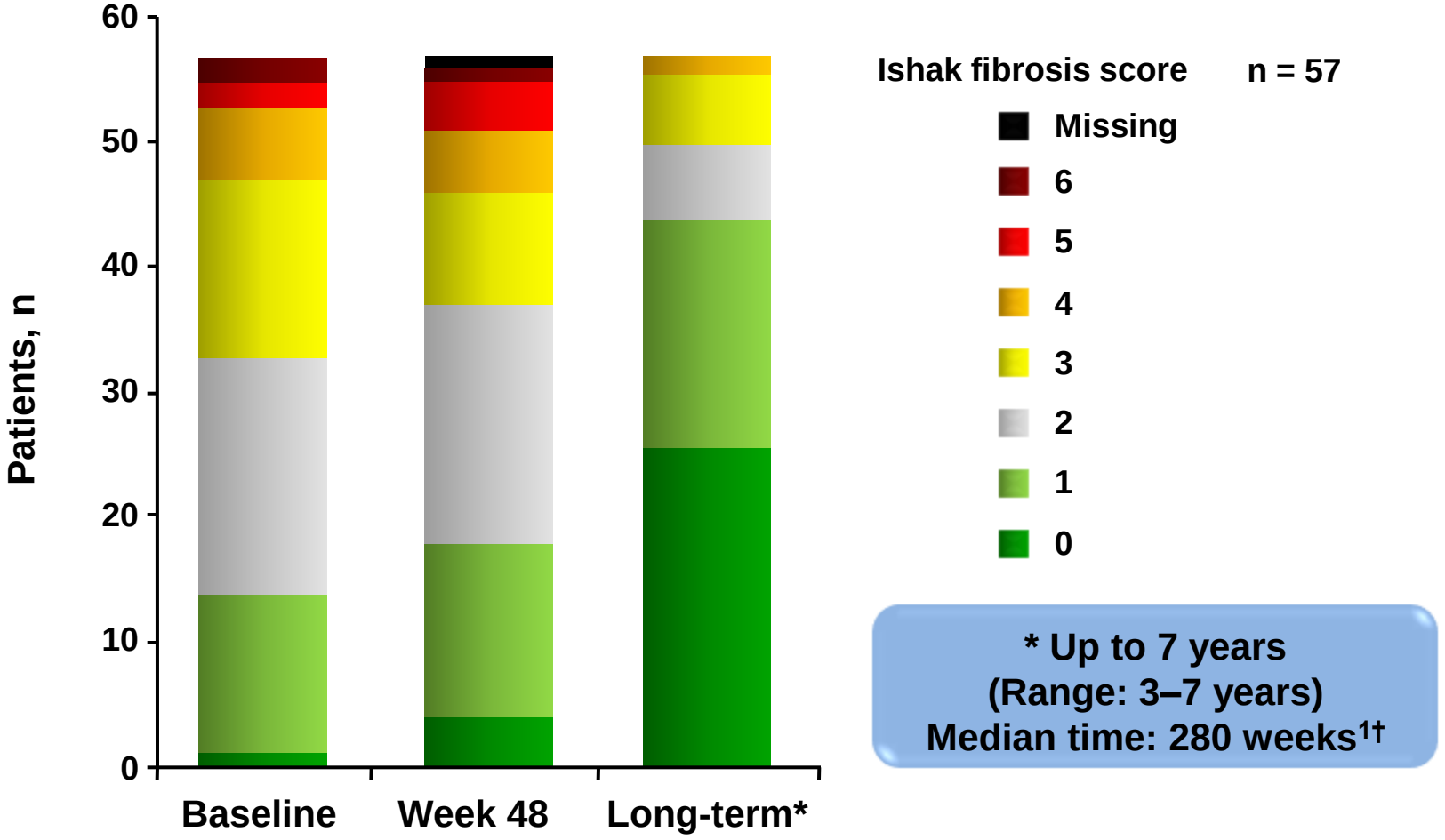


* Missing = failure; add emtricitabine (FTC) = failure.

† Includes patients who added FTC; missing = excluded.

Adapted from Marcellin P, *et al*. *AASLD* 2011; Poster 1375.

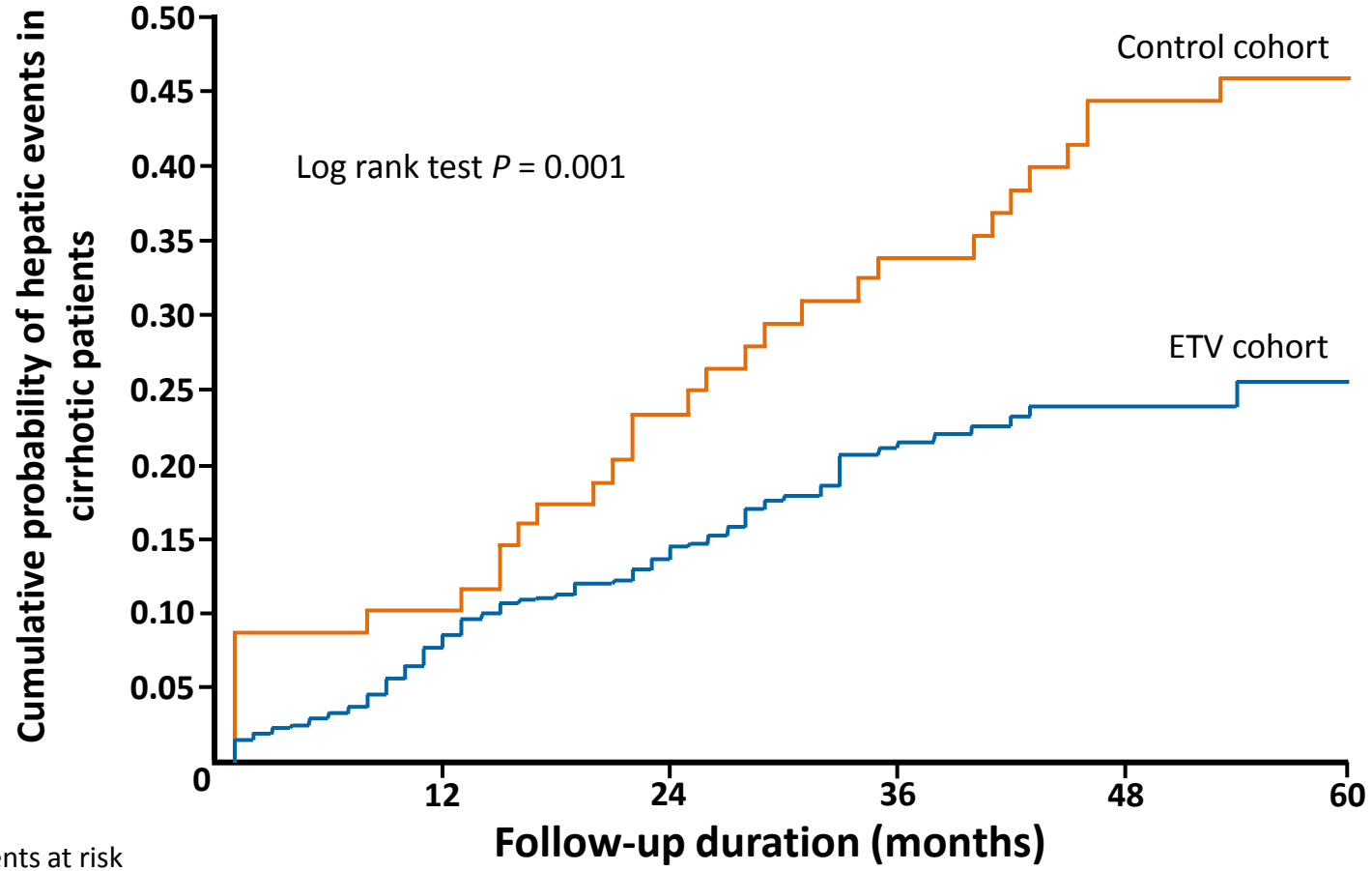
Long-term viral suppression leads to fibrosis reversal: Improvement in Ishak fibrosis score with ETV



† In the randomized controlled studies, patients received 0.5 mg ETV. In the 901 rollover study, patients received 1 mg ETV.

1. Adapted from Chang TT, *et al. Hepatology* 2010;52:886–93.
Bristol-Myers Squibb. Baraclude® (entecavir) Summary of Product Characteristics. May 2011.

Hong Kong ETV cohort: Kaplan-Meier analysis of cumulative probability of hepatic events



Patients at risk						
Entecavir cohort	482	442	342	179	74	20
Control cohort	69	62	51	44	37	36

Hepatic events defined as as any cirrhotic complications, HCC and/or liver-related mortality.

Wong GLH, *et al. Hepatology* 2013;*in press*.

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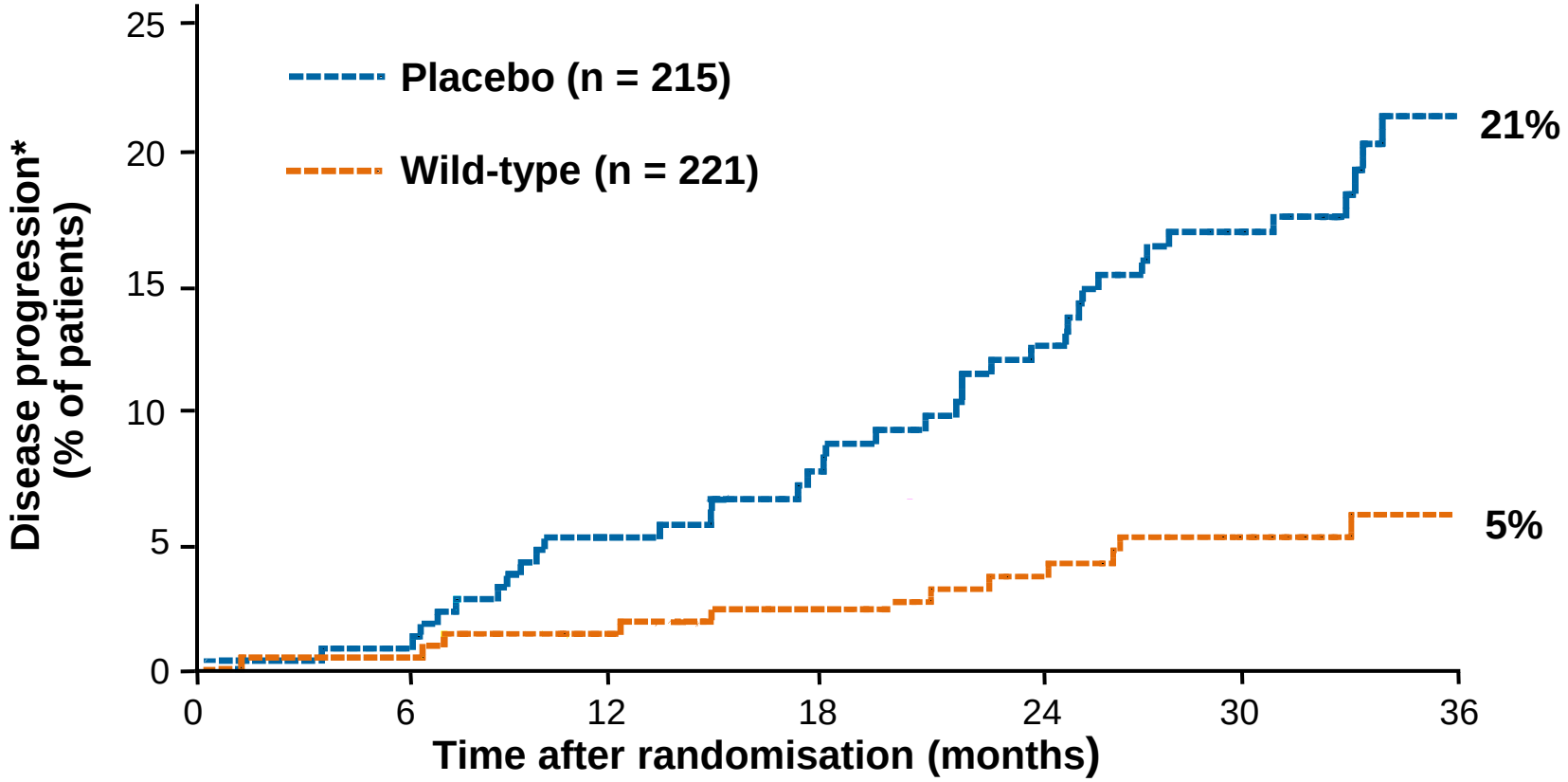
Avoiding drug resistance

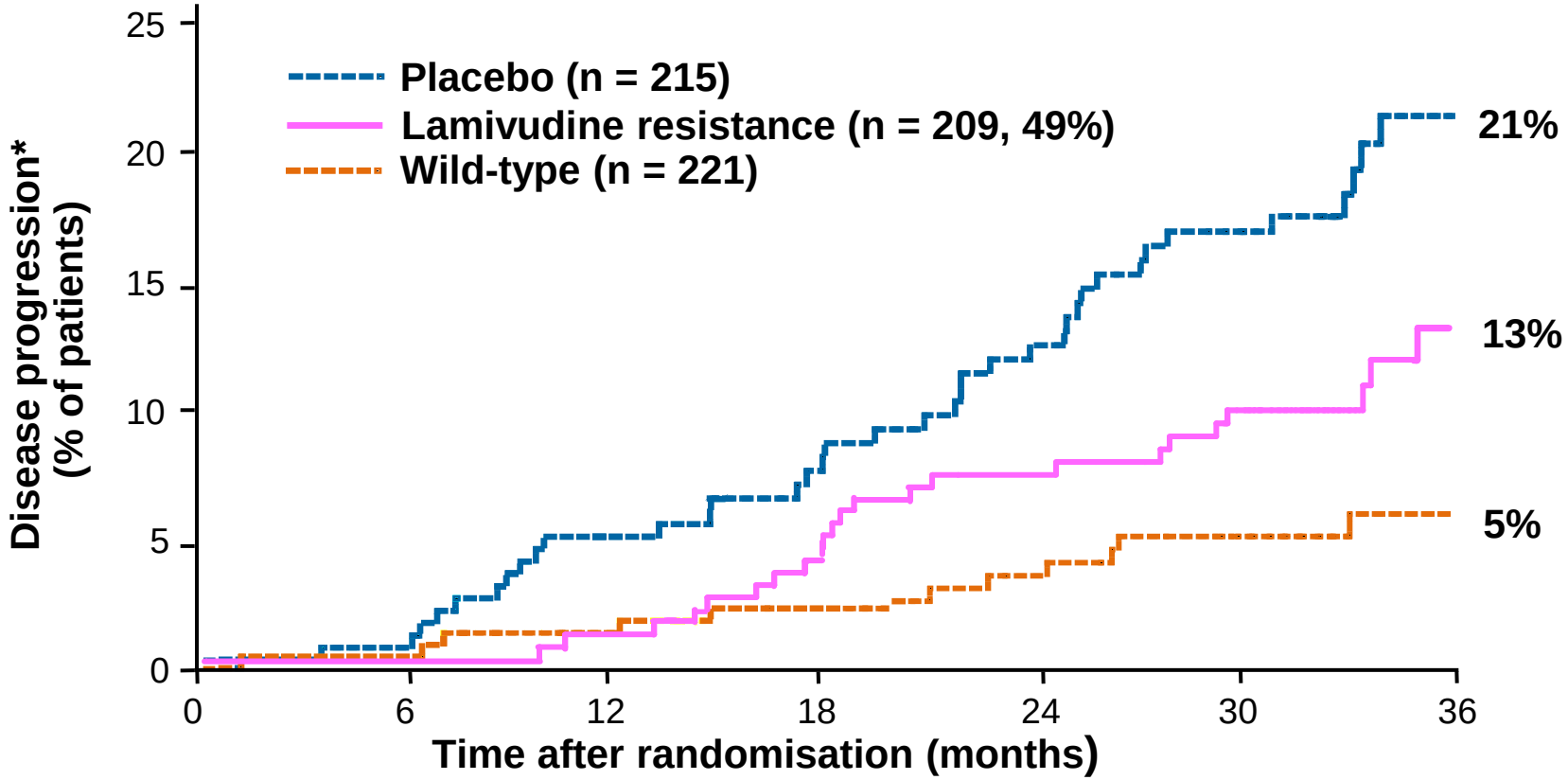
Development of resistance reduces antiviral effect on disease progression



* Time to disease progression defined as first occurrence of > 2 points increase in Child-Pugh score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding gastric or esopageal varices, the development of HCC, death related to liver disease.

1. Adapted from Liaw Y-F, *et al. Semin Liver Dis* 2005;25(Suppl.1):40–47;
2. Liaw Y-F, *et al. N Eng J Med* 2004;351:1521–31.

Development of resistance reduces antiviral effect on disease progression

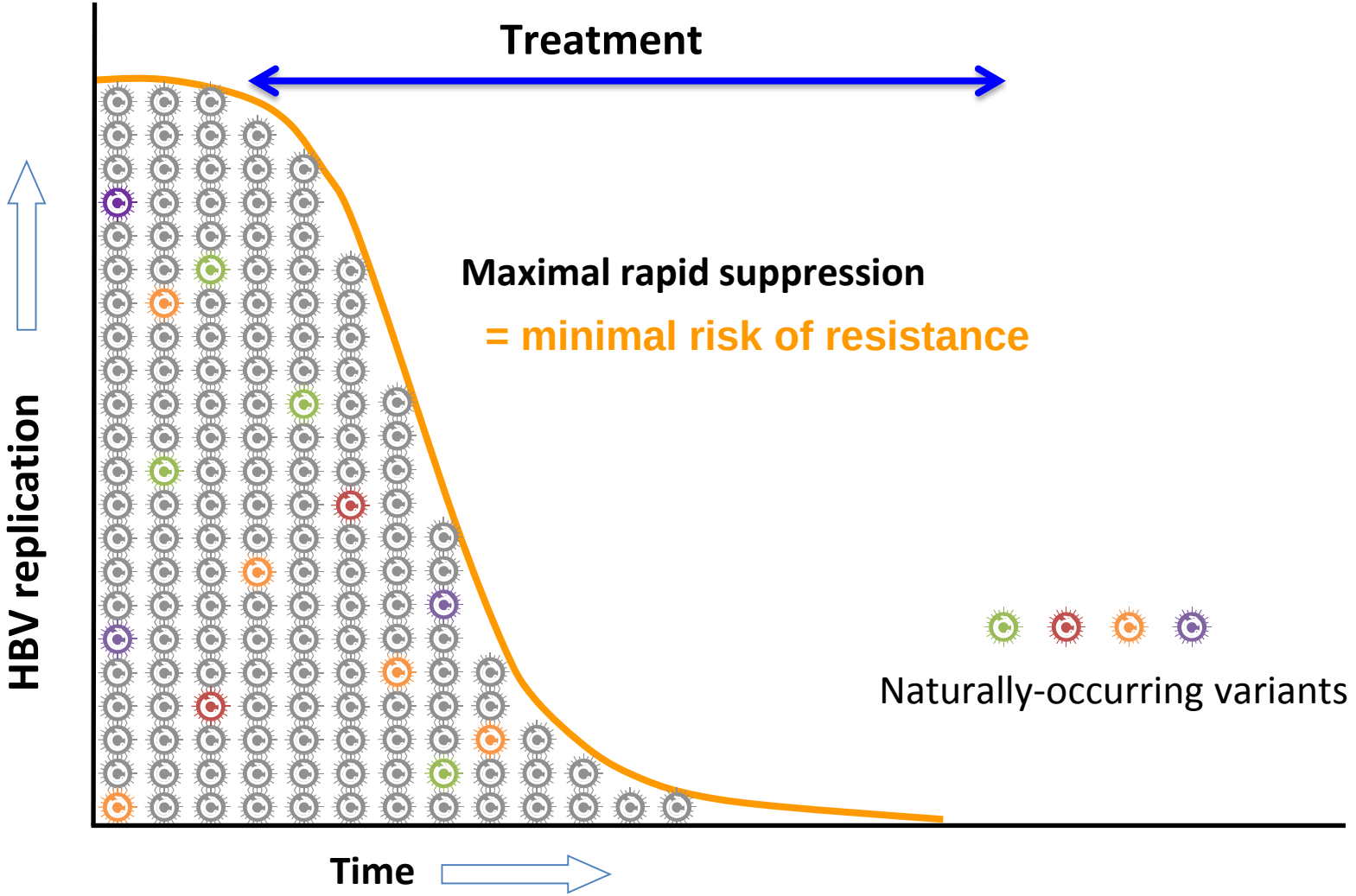


8/10 patients assigned to LVD who died after reaching a clinical endpoint showed evidence of YMDD mutations[2]

* Time to disease progression defined as first occurrence of > 2 points increase in Child-Pugh score, spontaneous bacterial peritonitis with proven sepsis, renal insufficiency, bleeding gastric or esopageal varices, the development of HCC, death related to liver disease.

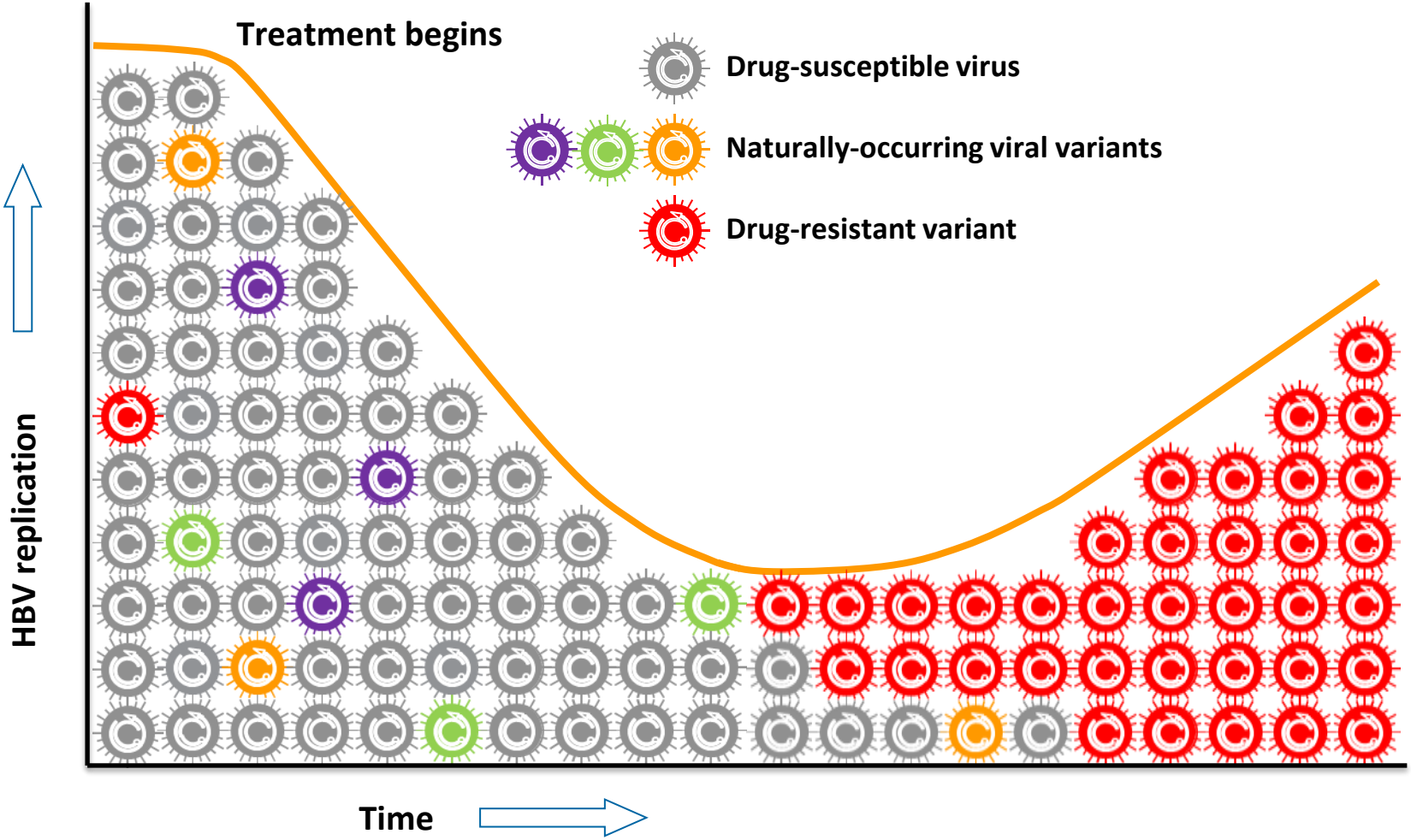
1. Adapted from Liaw Y-F, *et al. Semin Liver Dis* 2005;25(Suppl.1):40–47;
2. Liaw Y-F, *et al. N Eng J Med* 2004;351:1521–31.

Drug potency and maximal suppression of viral replication



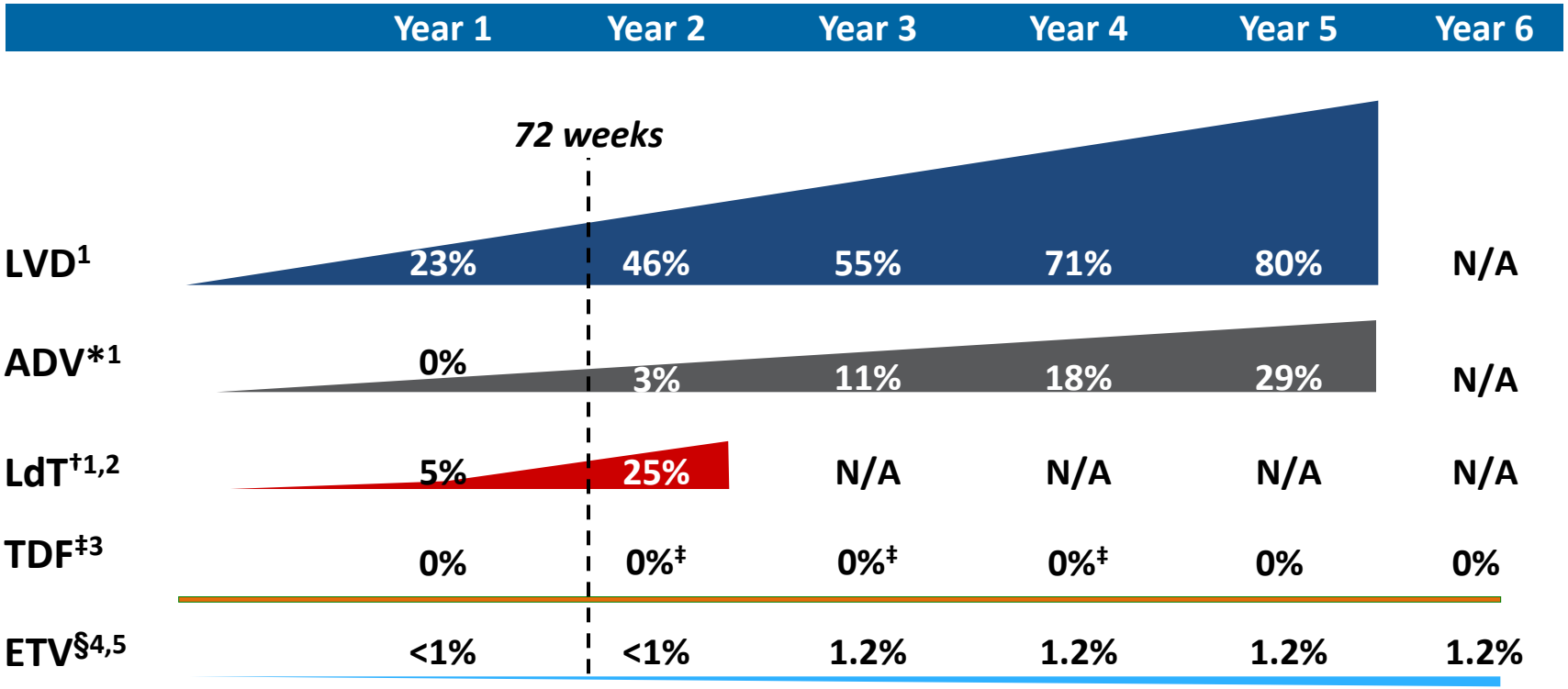
Locarnini S, *et al. Antivir Ther* 2004;9:679–93.

Incomplete suppression of viral replication allows the selection of resistant virus



Fung SK & Lok ASF. *Antivir Ther* 2004; 9:1013–26; Locarnini S, *et al. Antivir Ther* 2004; 9:679–93.

Resistance rates through 6 years among nucleos(t)ide-naive patients



* Naive HBeAg–; †Naive HBeAg+; ‡Patients with HBV DNA ≥ 400 copies/mL at week 72 could add emtricitabine to TDF; resistance to TDF monotherapy did not develop in 72 weeks of therapy[4]; §Cumulative probabilities of resistance
ADV, adefovir dipivoxil; FTC, emtricitabine; LdT, telbivudine; LVD, lamivudine; N/A, not available; TDF, tenofovir disoproxil fumarate; ETV, entecavir

1. Zoulim F, *et al.* Gastroenterol 2009;137:1593–1608; 2. Lai CL, *et al*. *N Engl J Med* 2007;357:2576–78; 3. Snow-Lampart A, *et al*. *Hepatology* 2011;53:763–73; 4. EU Summary of Product Characteristics for Baraclude (entecavir), October 2009; 5. Tenney D, *et al*. *J Hepatol* 2009;50(suppl 1):S10. Abstract 20.

Avoiding the development of resistance

- The risk of resistance can be minimised by choosing an antiviral that results in rapid, profound and durable viral suppression[1]

AND

- That has a high genetic barrier to resistance[1]

BUT... it won't work if patients don't take the pills![2]

1. Locarnini S, *et al. Antivir Ther* 2004;9:679–93. 2. Lok ASF & McMahon BJ. AASLD practice guidelines. Chronic hepatitis B: Update 2009. Available at http://www.aasld.org/practiceguidelines/Documents/Bookmarked Practice Guidelines/Chronic_Hep_B_Update_2009 8_24_2009.pdf (Feb 2012).

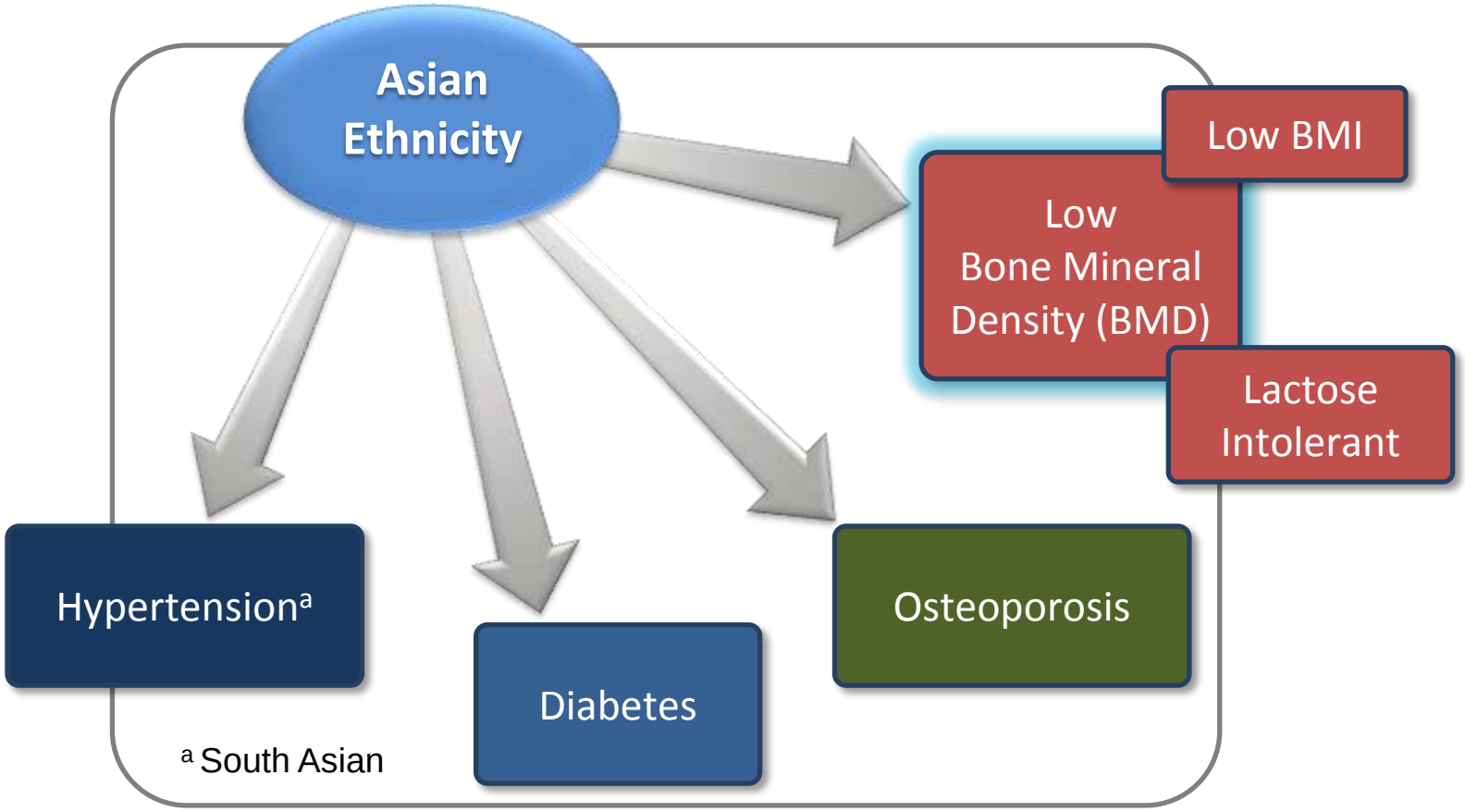
Long-term safety

Long-term safety

- The risks of AEs must be balanced against the benefits before initiating treatment[1]
- The long-term safety of nucleos(t)ide-analogues remains to be determined[1,2]
- All nucleos(t)ides are generally well tolerated
  - Individual safety profiles differ (e.g. renal impairment, myopathy, myalgia)[1]

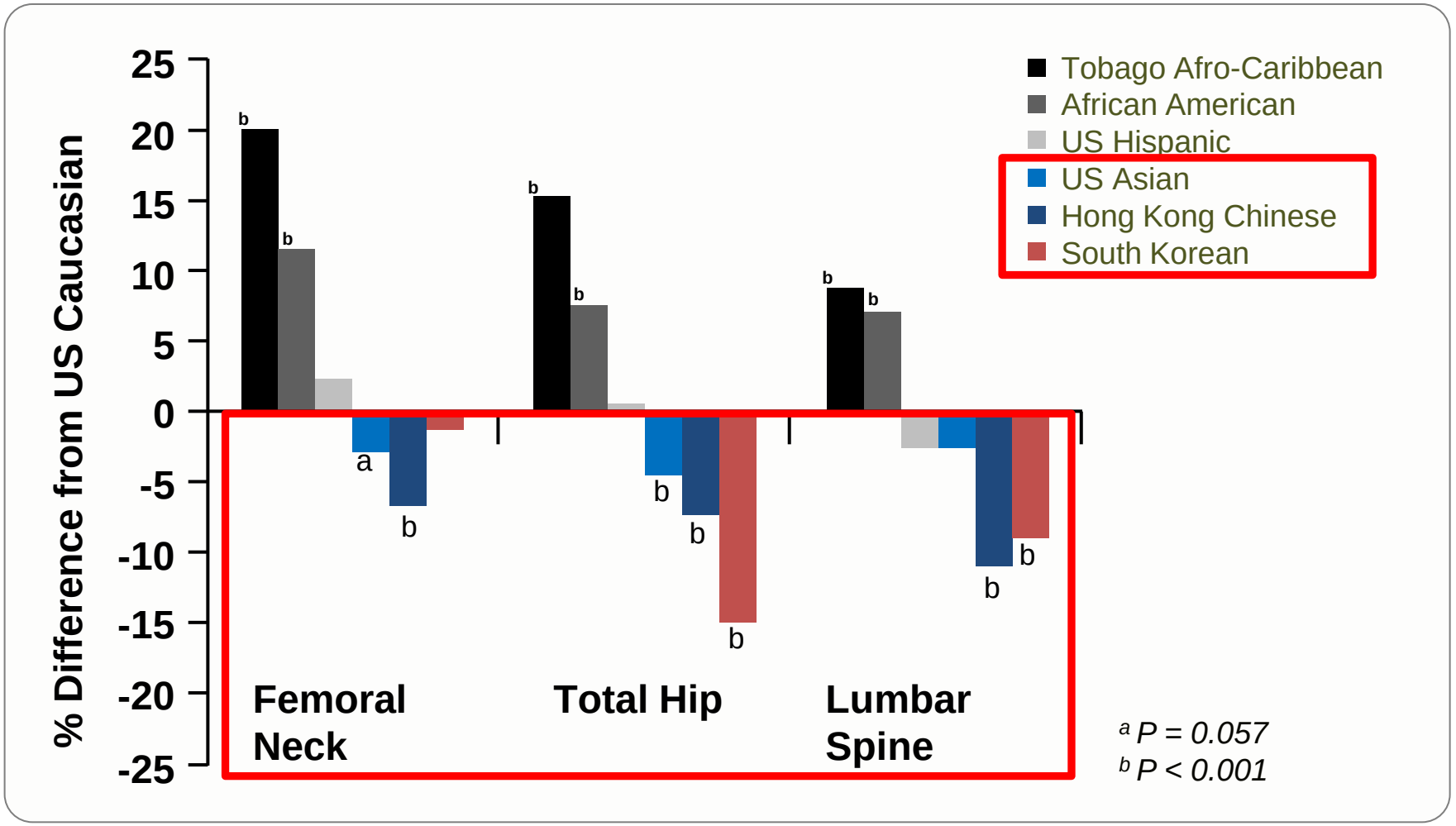
1. Fleischer RD & Lok ASF. *J Hepatol* 2009;51:787–91.
2. Keeffe EB, *et al*. *Clin Gastroenterol Hepatol* 2008;6:1215–1341.

Asian patients are predisposed to common comorbidities



American Heart Association. http://www.americanheart.org/. (Sep 2010). Dixon AN, *et al*. *Diabetes and Vascular Dis Res* 2006; 3:22–25. Li-Ng M, *et al*. *Digest Liver Dis* 2007;6:549–56. National Digestive Diseases Information Clearinghouse. http://digestive.niddk.nih.gov/ddiseases/pubs/lactoseintolerance/. (Sep 2010). National Osteoporosis Foundation. http://www.nof.org/osteoporosis/diseasefacts.htm. (Sep 2010).

Asian men have lower age-adjusted BMD than Caucasian men



BMD, bone mineral density

Nam HS, *et al. Osteoporos Int* 2010;21:2115–23.

Nucleotide therapy may increase the risk of reduced bone density in CHB patients

- Single-center, cross-sectional study of 319 CHB patients receiving nucleosides (LAM: n=20; ETV: n=60) or nucleotides (TDF/ADV + LAM: n=239)
- Dual X-ray absorptiometry (DEXA) of the lumbar spine and femoral neck LFTs, clinical examination, abdominal ultrasound
- Osteoporosis and osteopenia was found in 68% of patients (217/319)

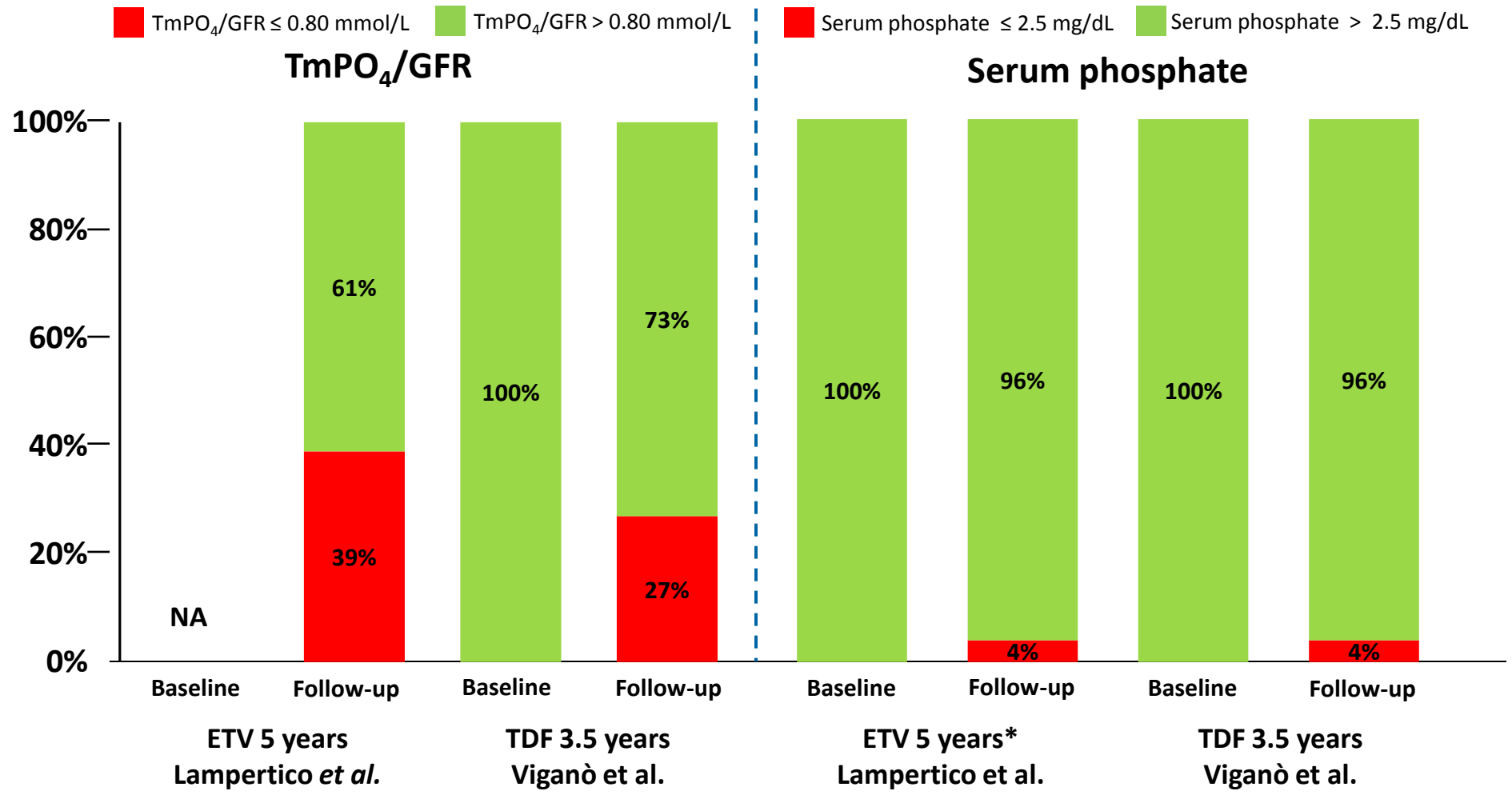
Predictors of osteoporosis and osteopenia by multivariate analysis*

Factors	OR	95% CI	*P*
Female	2.10	1.12–3.95	0.02
Age (per year)	1.03	1.0–1.05	0.011
Nucleotide treatment**	**1.87**	**1.08–3.23**	**0.025**

* Included were variables with *P* values < 0.1 at univariate analysis; ** ADV, TDF.

Vigano M. *et al*. 61st AASLD 2010; Poster 414.

Renal safety: monitoring is necessary



* Serum phosphate cut-off 2.0 mg/dL

Lampertico P, *et al.* EASL 2013. Abstract 755; Viganò M, *et al.* EASL 2013. Poster 777.

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How do we maximise the chances of achieving long-term goals?

- Use of potent/effective agents as first line therapy is crucial
- The development of resistance should be minimised
- Patients may be on therapy for long-term, therefore safety is an important consideration
- Adherence is essential
  - Make sure patients are taking medication as directed