Does Viral Cure Prevent HCC Development

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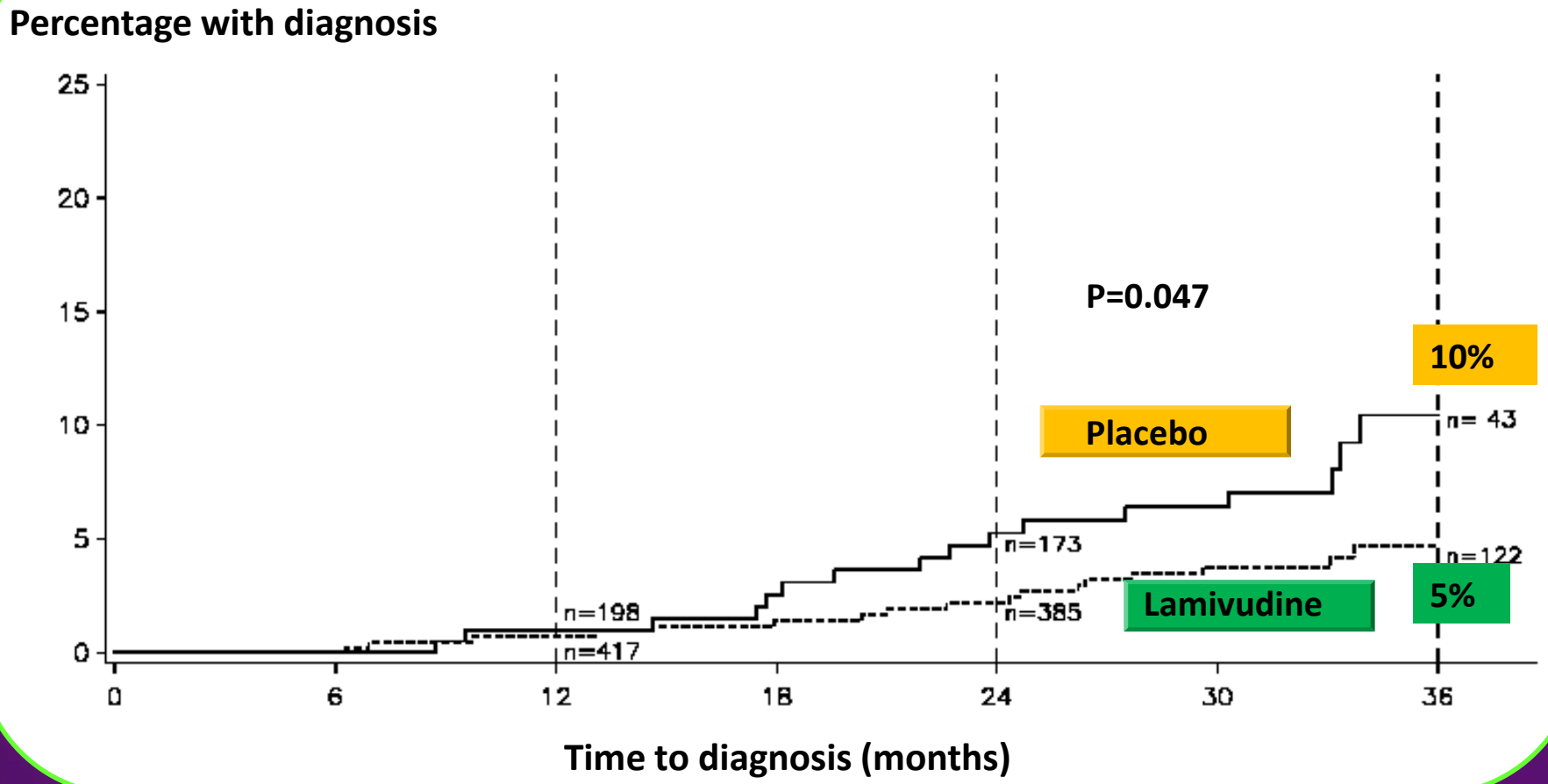
Lamivudine to reduce HCC in early HBV cirrhosis Controversial in Asian randomized controlled trial



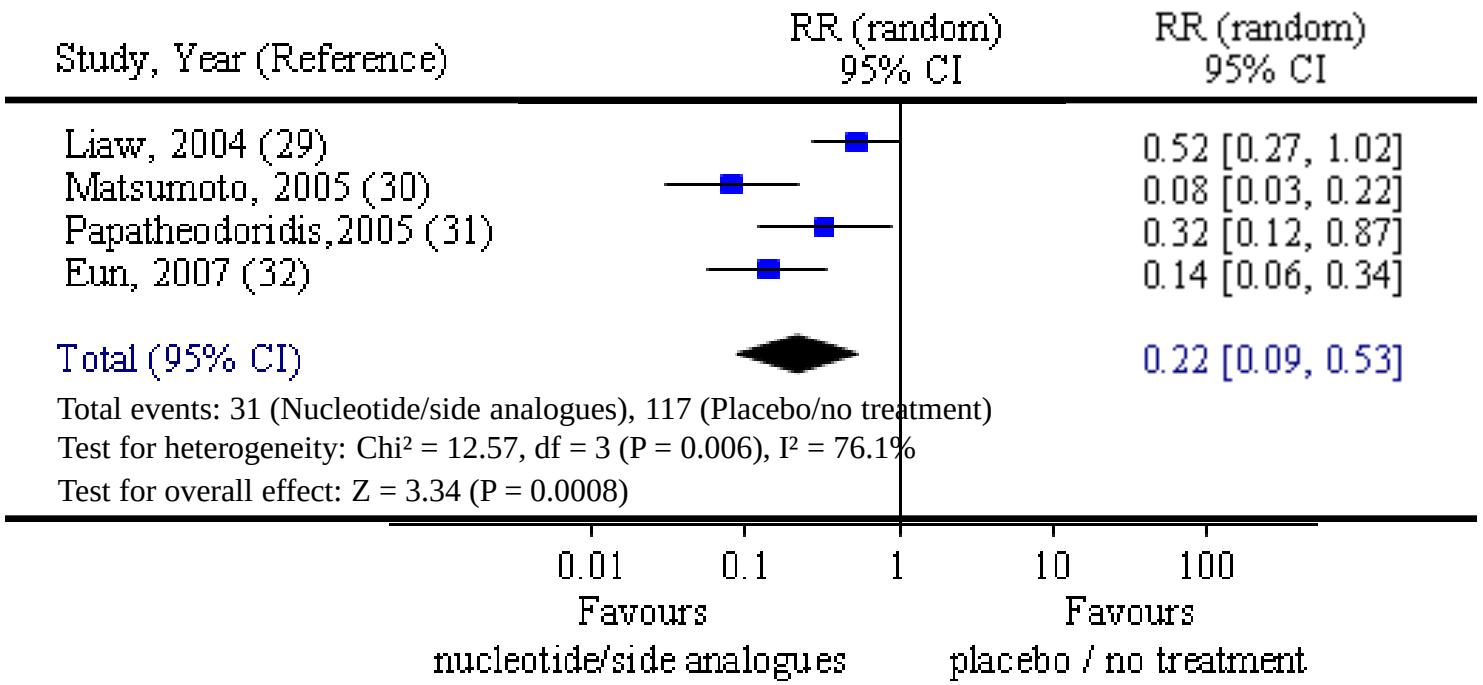
Placebo (n=215)

Lamivudine (n=436)

Excluding 5 cases in yr1: HR=0.47; P=0.052

Liaw YF et al. N Engl J Med 2004; 351: 1521-31

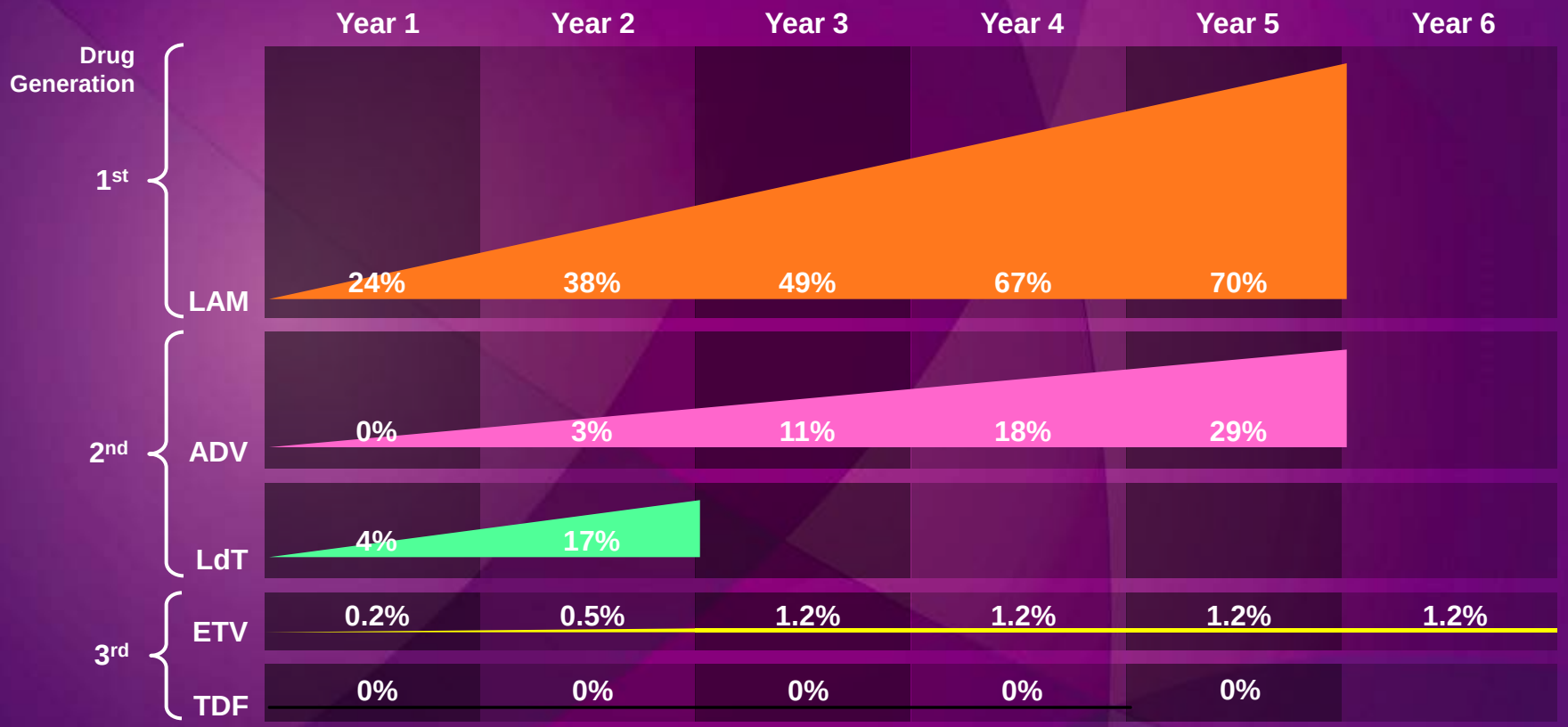
Meta-analysis
NA (lamivudine) can reduce risk of HCC



Sung JJ, et al. Aliment Pharmacol Ther 2008;28:1067-77

Entecavir and Tenofovir are the first line NA treatment for CHB

Not head-to-head trials; different patient populations and trial designs



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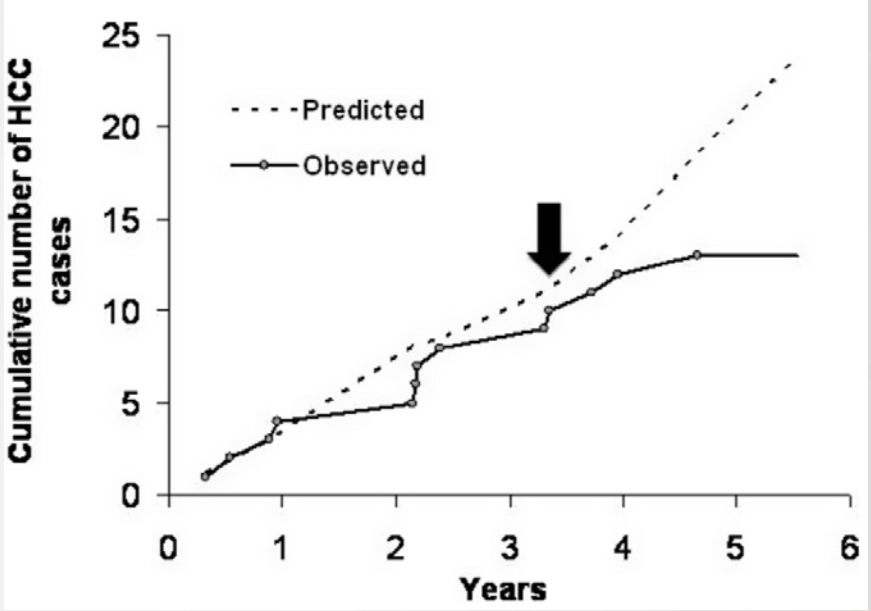
Adapted from 1. EASL. J *Hepatol*. 2009;**50**:227-42. 2. Tenney DJ, *et al*. *EASL* 2009. Oral presentation #20. 3. Marcellin P, *et al*. *Hepatology* 2009;**50(4, Suppl.)**:532A-3A. 4. Heathcote EJ, *et al*. *Hepatology* 2009;50(4, Suppl.):533A-4A 5. Marcellin P, *et al*. *Lancet* 2013;381:468-75.

HCC in TDF-treated patients - observed *vs.* predicted

6-year follow-up data of 641 patients, 13 cases of HCC

10th HCC case occurred at 3.3 years

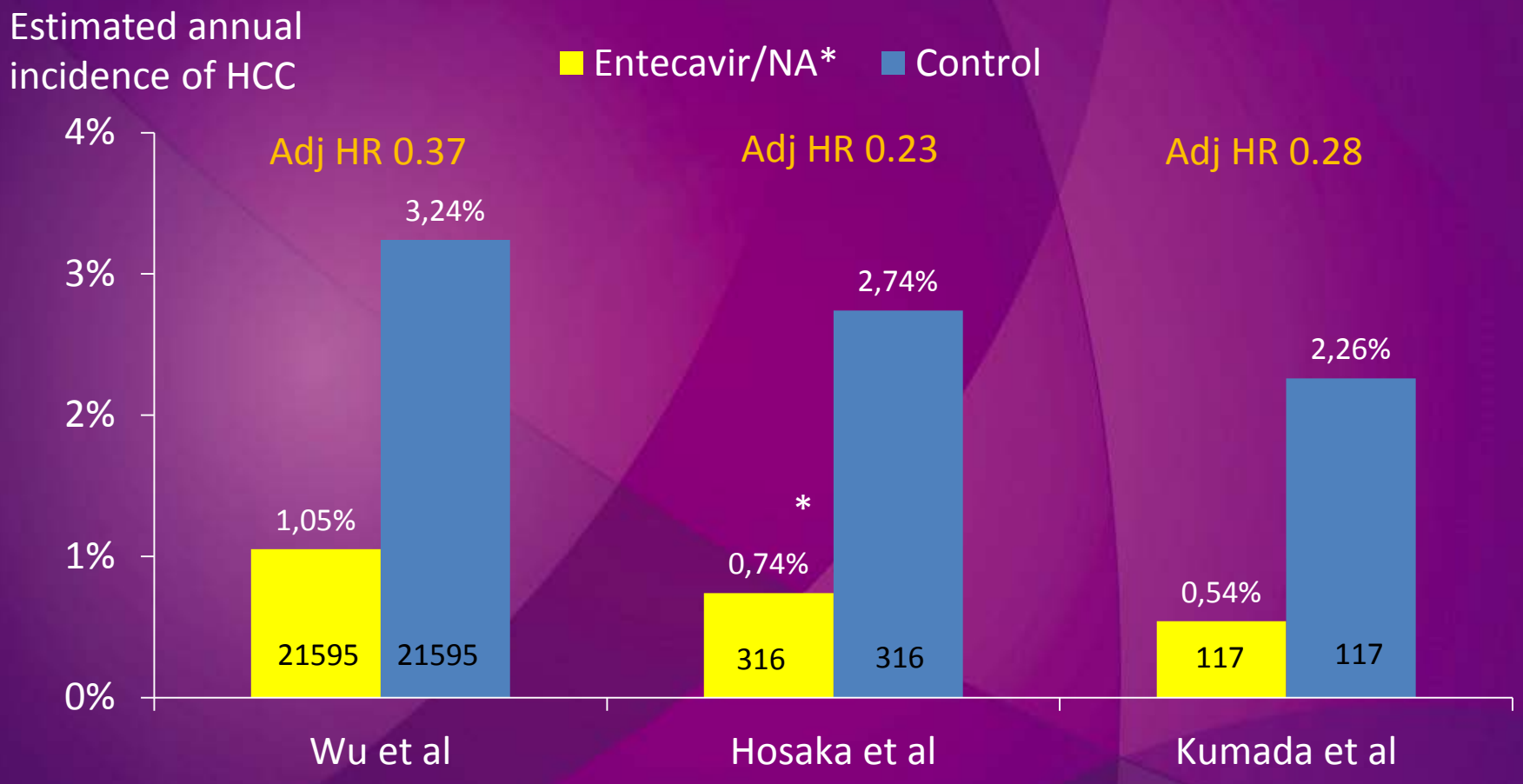
REACH-B model predicted 11.2 cases at this time point



- Progressive divergence between the predicted and observed no. of HCC beyond 3.3 years.
- Standardized incidence ratios
  - At 2.4 years = 0.94 (95% CI 0.47–1.88)
  - At 3.3 years = 0.89 (0.48–1.66)
  - At 5.5 years = 0.55 (0.32–0.94)

Kim R, et al. EASL 2013

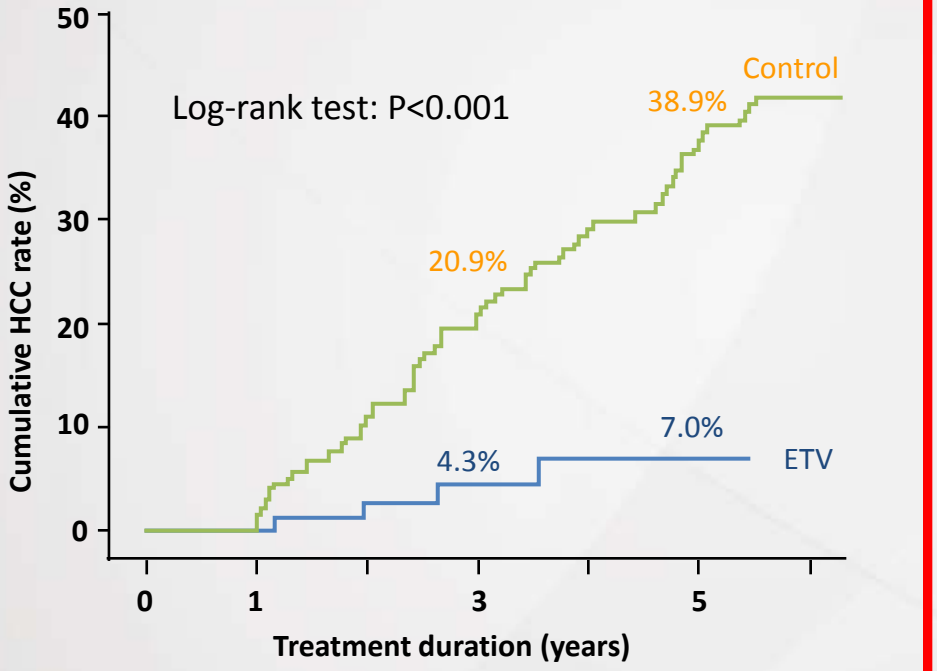
Estimated annual incidence of HCC in patients based on 5 year FU



Propensity score matched

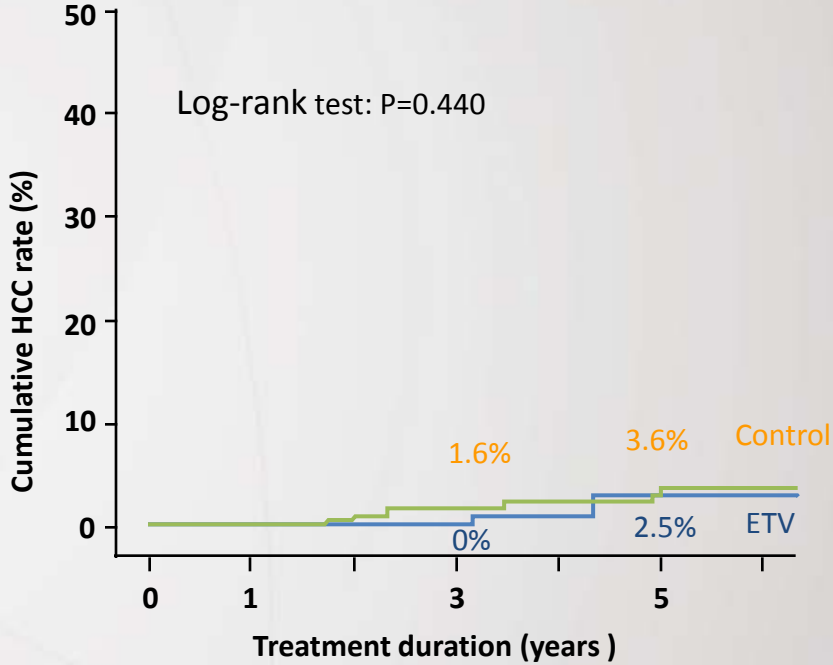
Wu CY, et al. Gastroenterology 2014;147:143-51;
Hosaka T, et al. Hepatology 2013;58:98-107;
Kumada T, et al. J Hepatol 2013;58:427-33.

Toranomon Hospital cohort: reduction in HCC incidence with ETV greater among cirrhotic patients



No at risk

ETV	79	79	72	53	35	17
Control	85	85	76	65	54	47



No at risk

ETV	237	237	192	132	66	27
Control	231	231	201	181	169	143

Hosaka T, et al. HEPATOLOGY 2013;58:98-107

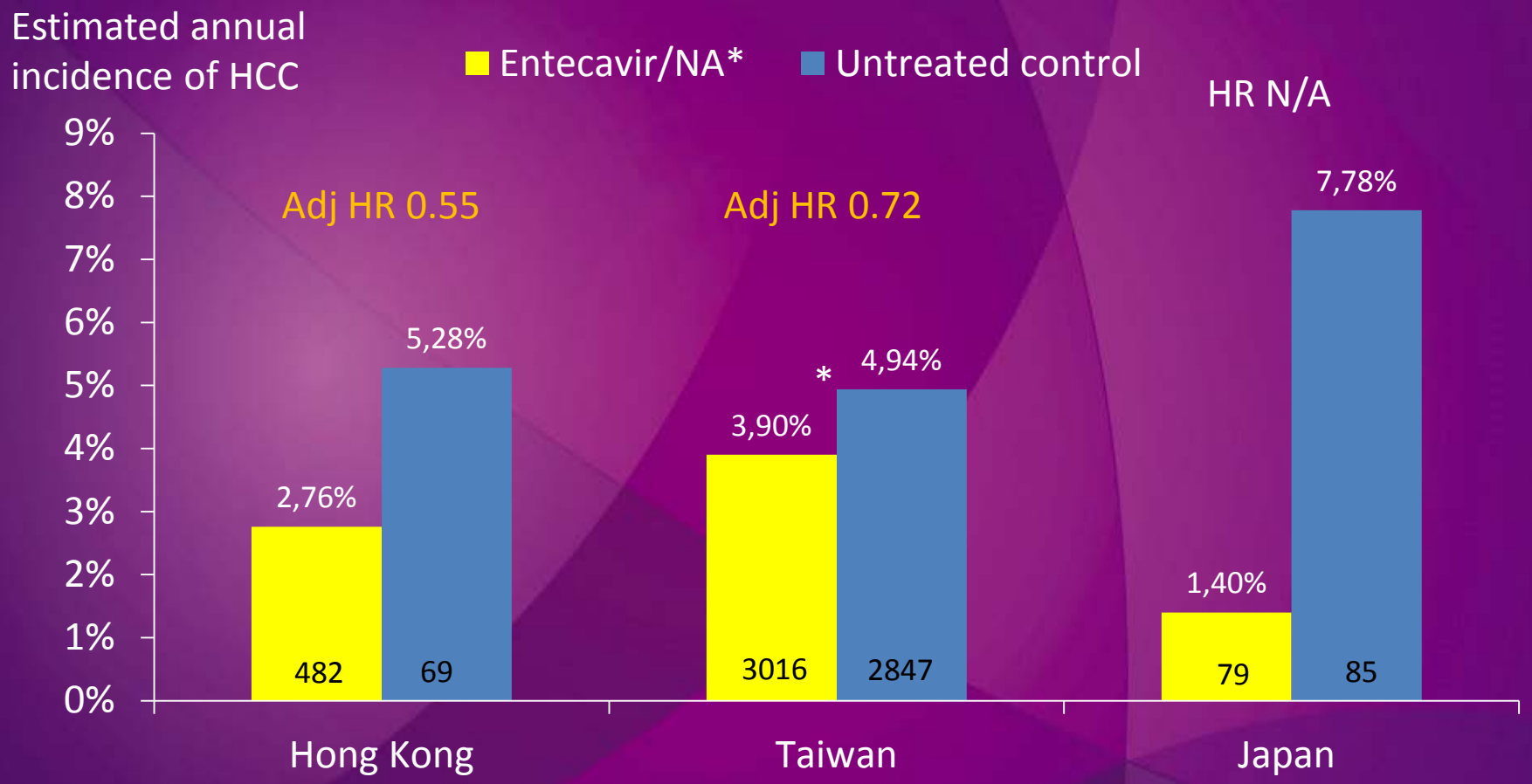
Efficacy of entecavir therapy adjusted for MELD score and maintained viral suppression in cirrhotic patients

482 ETV treated (mean 36 months) vs 69 untreated historic control patients (mean FU 114 months) with radiological liver cirrhosis in Hong Kong

Clinical outcomes	Hazard ratio	95% CI	P values
Hepatic events	0.51	0.34 – 0.78	0.002
HCC	0.55	0.31 – 0.99	0.049
Liver-related mortality	0.26	0.13 – 0.55	<0.001
All-cause mortality	0.34	0.18 – 0.62	<0.001

Wong GLH, Chan HLY, et al. Hepatology 2013;58:1537-47

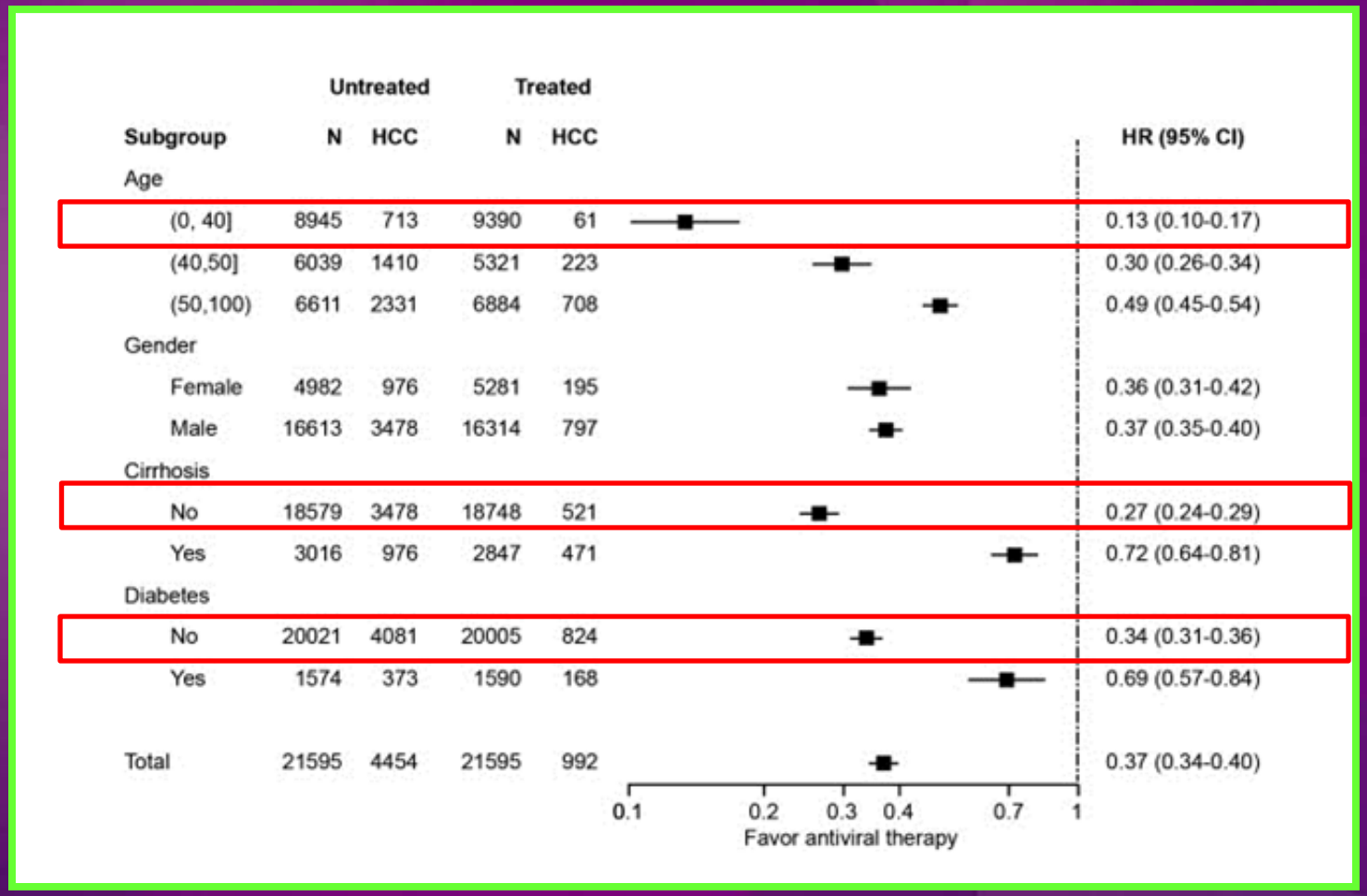
Estimated annual incidence of HCC in cirrhotic patients based on 5 year FU



Wong GL, et al. Hepatology 2013;58:1537-47;
Wu CY, et al. Gastroenterology 2014;147:143-51;
Hosaka T, et al. Hepatology 2013;58:98-107

Benefit of NA especially significant among younger, non-cirrhotic and non-diabetic patients

Propensity score matched study from Taiwan national database

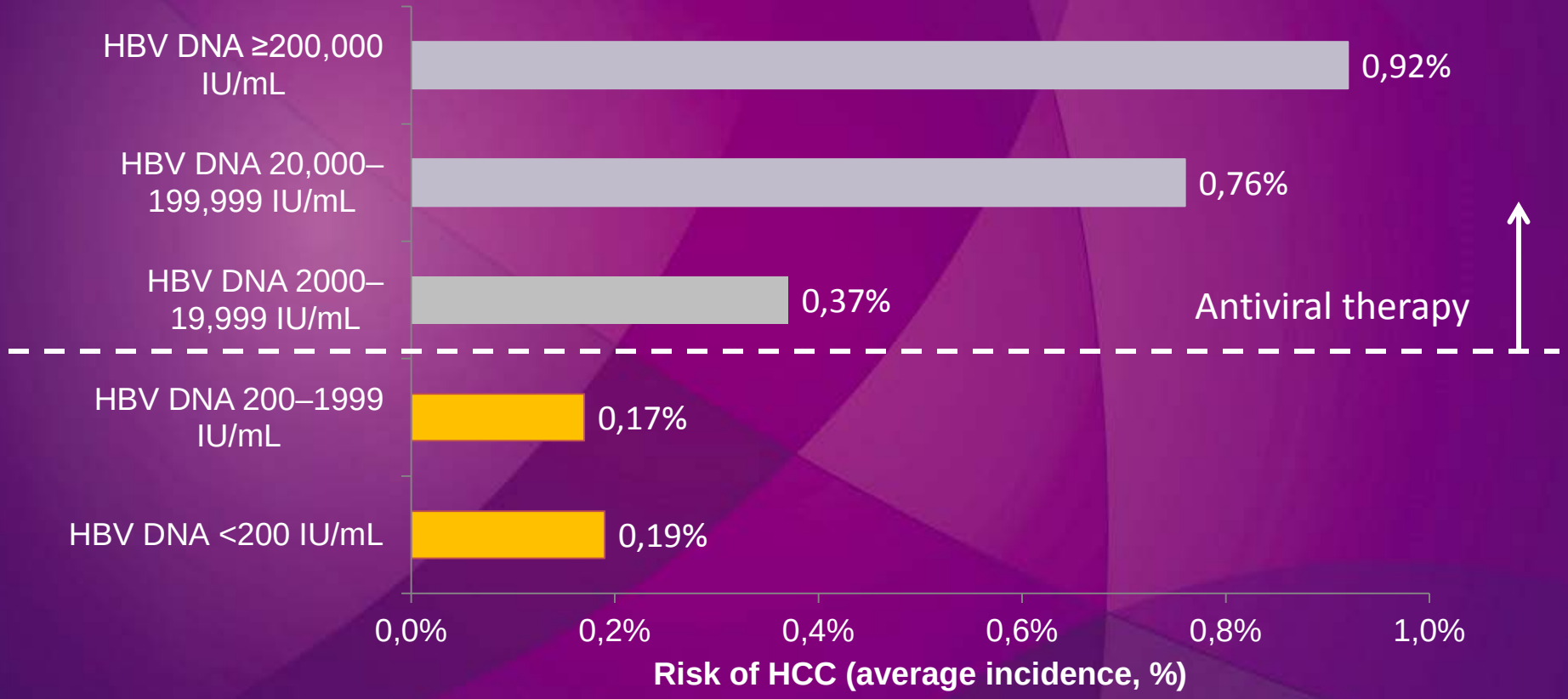


Wu CY, et al. Gastroenterology 2014;147:143-51

Non-cirrhotic patients
Annual incidence of HCC <1%

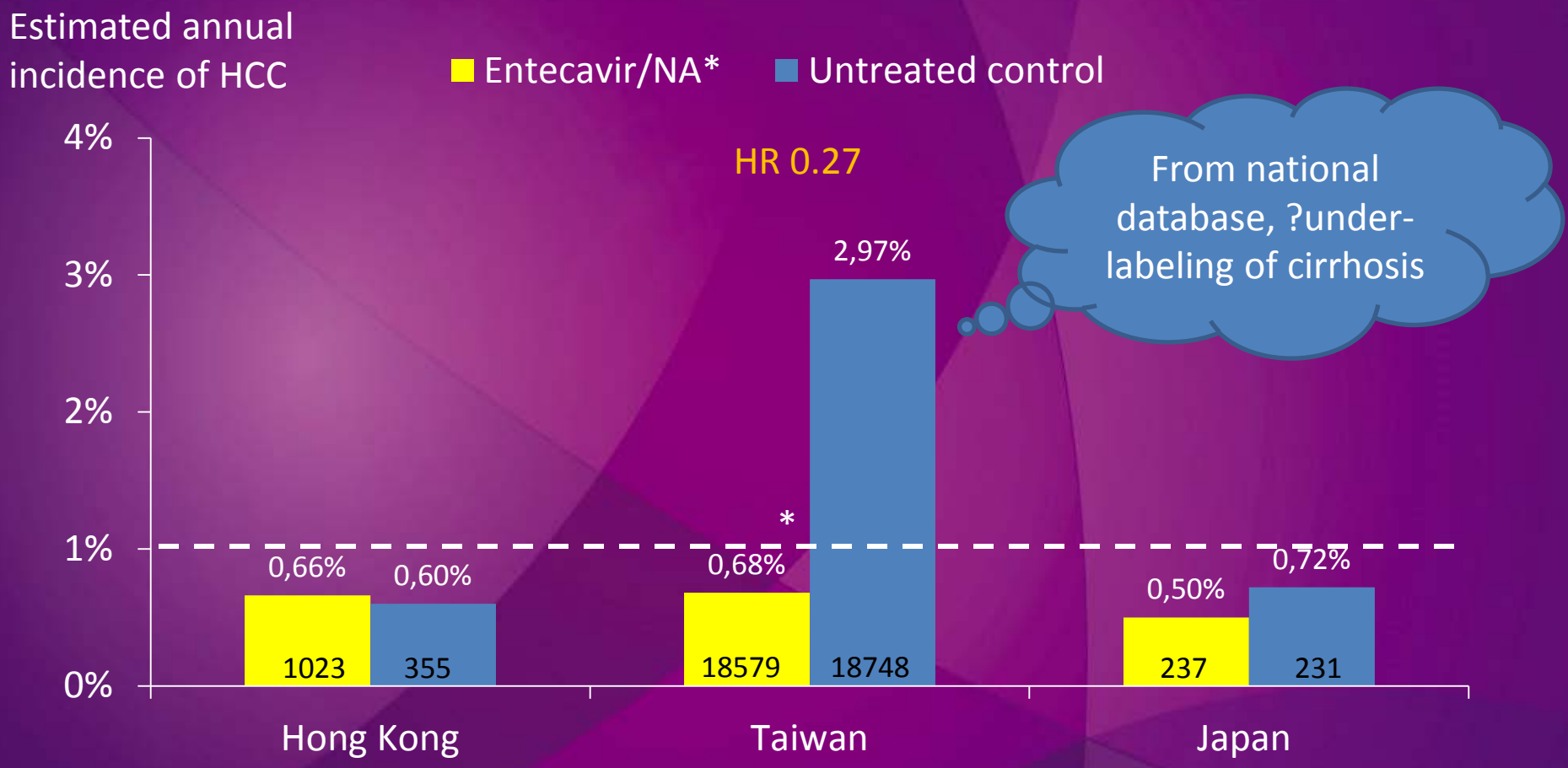
ERADICATE-B Study

2,688 non-cirrhoic Taiwanese CHB patients followed for a mean of 14.7 years



Modified from Tseng et al. Gastroenterology 2012 and Chan HL. Gastroenterology 2012

Estimated annual incidence of HCC in non-cirrhotic patients based on 5 year FU

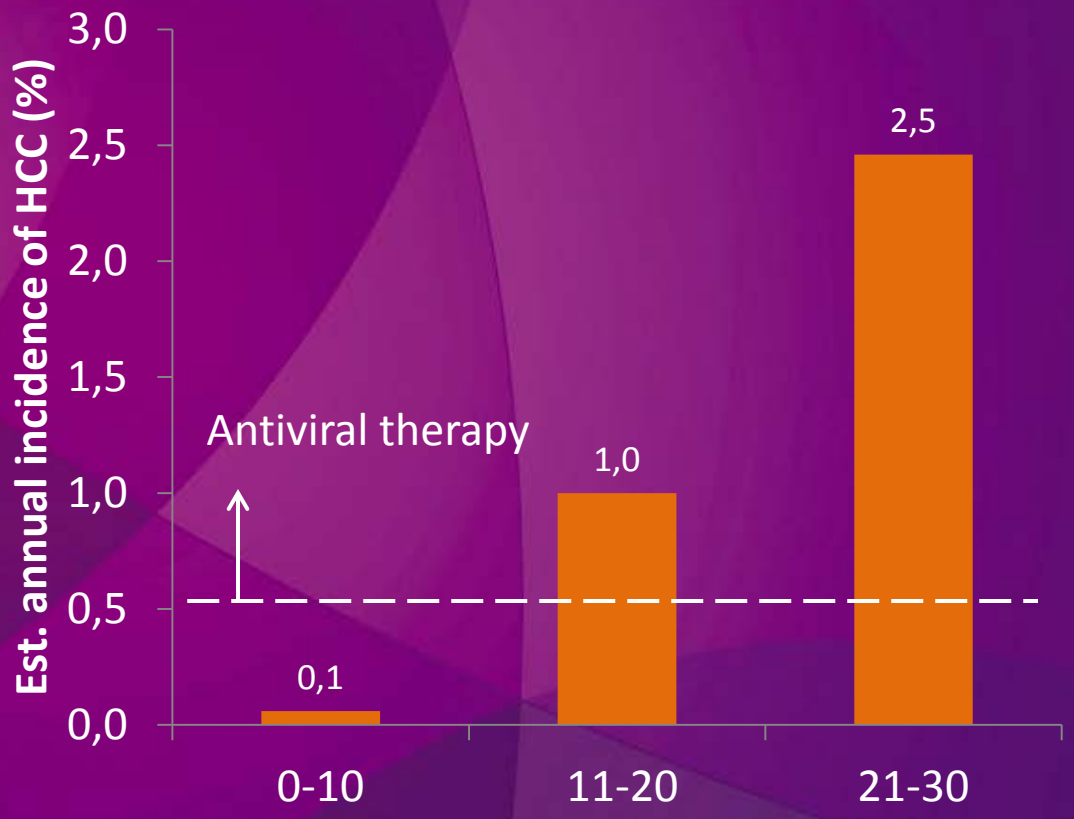


Wong GL, et al. Hepatology 2013;58:1537-47;
Wu CY, et al. Gastroenterology 2014;147:143-51;
Hosaka T, et al. Hepatology 2013;58:98-107

LSM-HCC Score – combining HBV DNA and cirrhosis for treatment indication

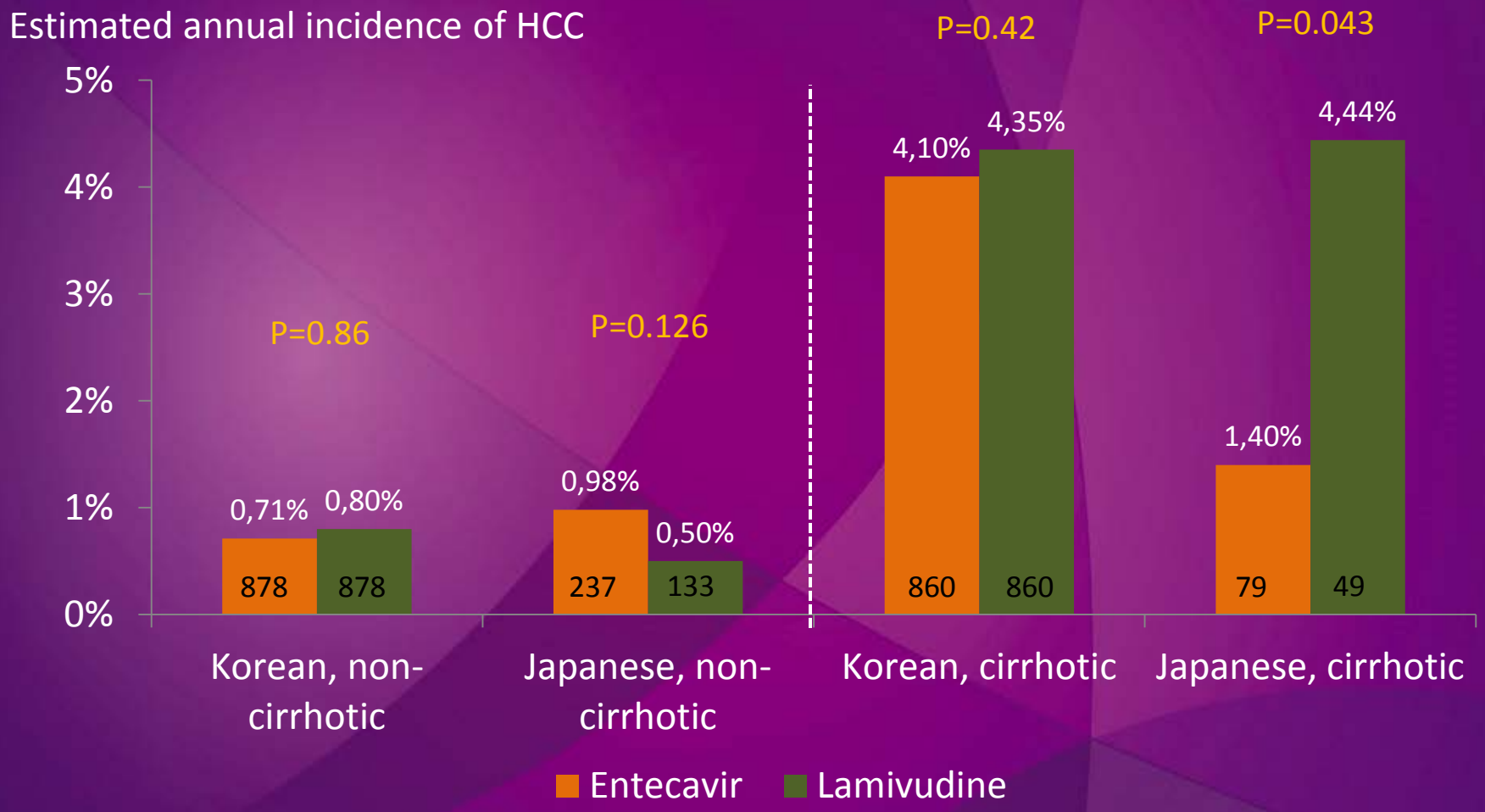
Factors	Score
Age	
> 50 years	+10
≤ 50 years	0
Albumin	
≤ 35g/l	+1
> 35g/l	0
HBV DNA	
> 200,000 IU/ml	+5
≤ 200,000 IU/ml	0
Liver stiffness	
≤ 8.0 kPa	0
8.1-12.0 kPa	+8
> 12.0 kPa	+14

1555 CHB patients (38% received antiviral therapy)
FU 69±9 months
38 patients developed HCC



Modified from Wong GL, et al. J Hepatol 2014;60:339-45

Choice of NA makes a difference? Controversial among cirrhotic patients

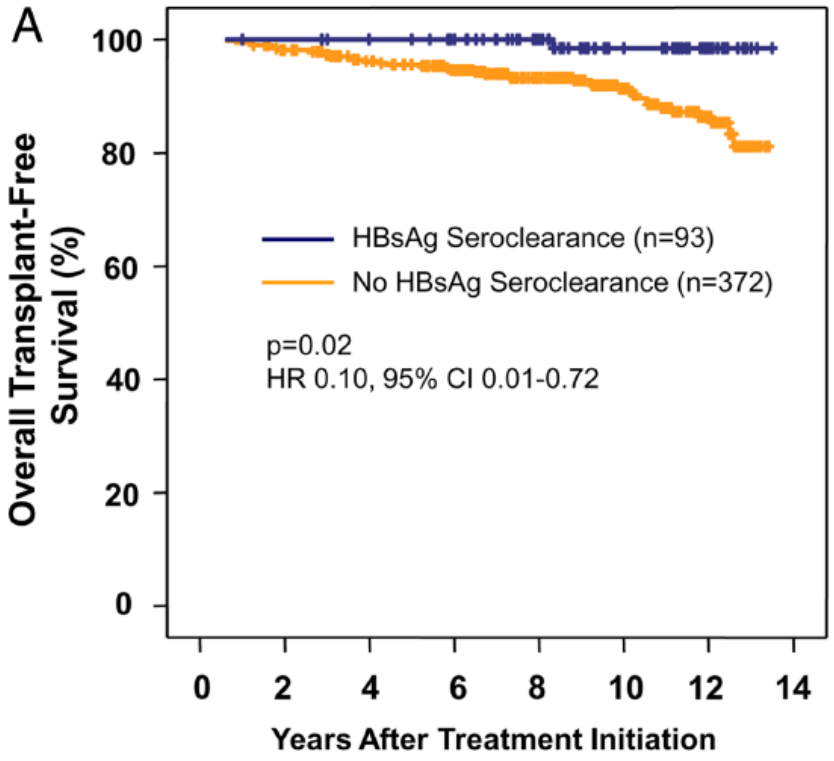


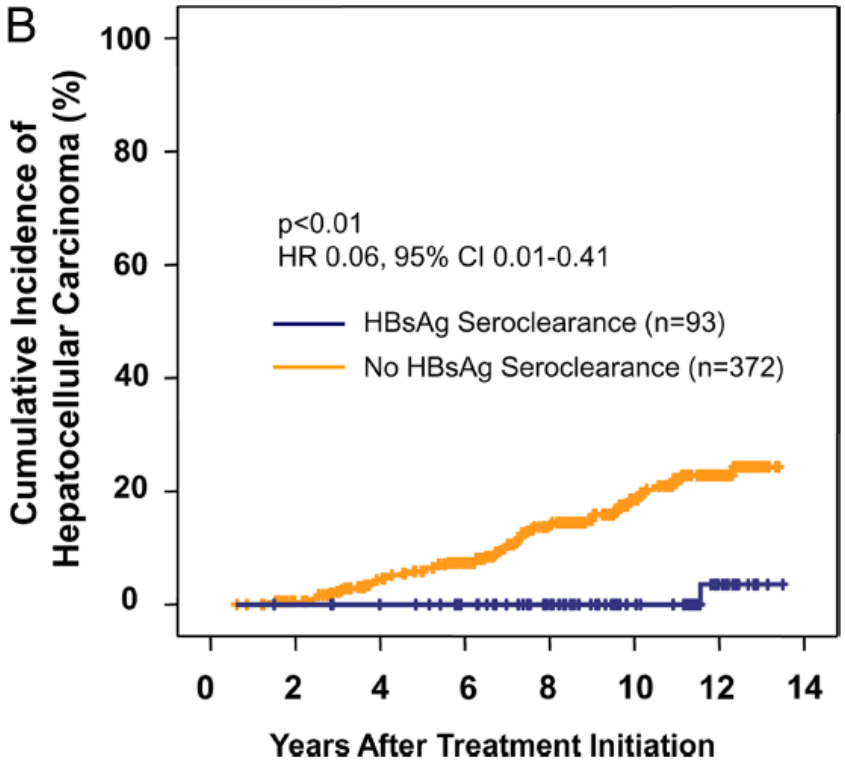
Lim YS, et al. Gastroenterology 2014;147:152-61
Hosaka T, et al. Hepatology 2013;58:98-107

Lamivudine resistance: unrescued in Japanese study

HBsAg seroclearance is associated with excellent clinical outcome

Treatment naïve patients on lamivudine (adefovir rescue for resistance) or entecavir
Propensity score matched (1:4)





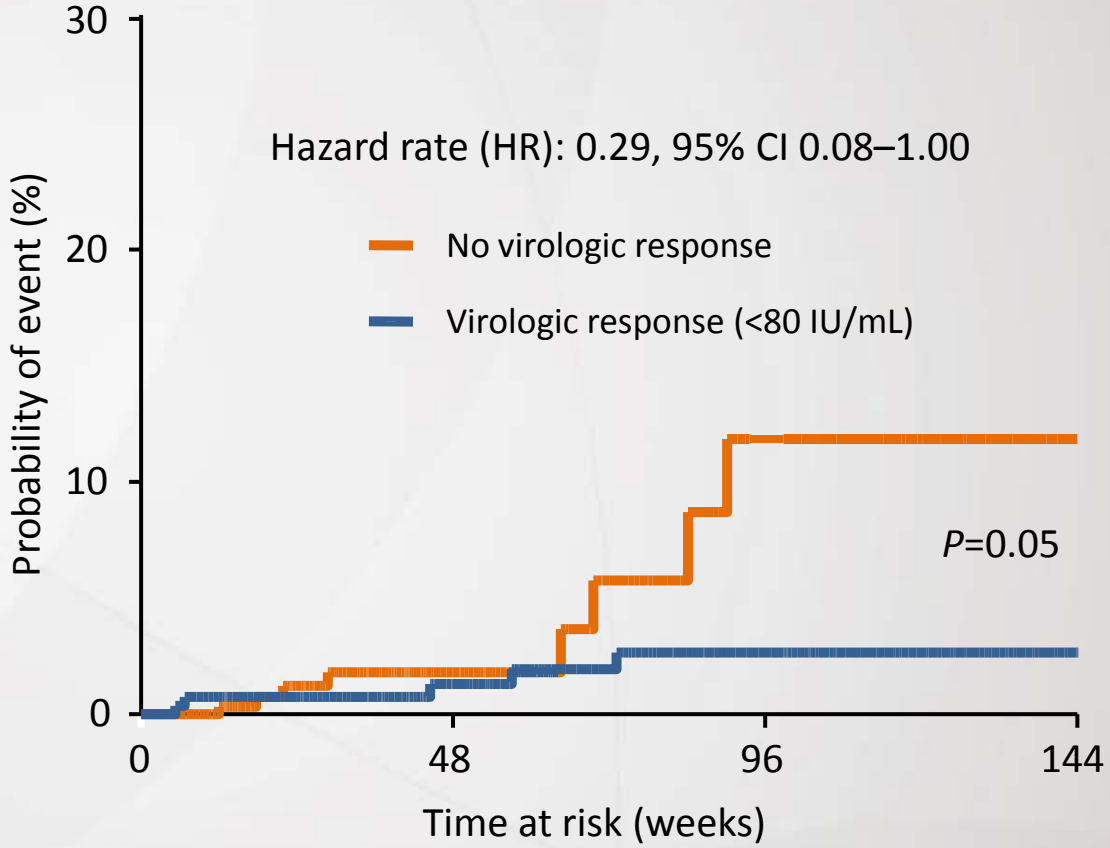
Kim GA, et al. Gut 2014;63:1325-32

VIRGIL ETV study
Virologic response is associated with a lower probability of disease progression

Retrospective cohort study in 10 large European centers
Study population (N=372)

Median follow-up 20 (3–51) months

98 patients have liver cirrhosis



*** Composite endpoint: Hepatic decompensation, jaundice, variceal bleeding, ascites or encephalopathy, HCC, death.**

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Zoutendijk R, et al. Gut 2013 May;62(5):760-5

Virologic remission is an independent factors preventing HCC development in cirrhotic patients under ETV treatment

1531 CHB patients (69% treatment naïve) on ETV for 42±13 months
332 (22%) had liver cirrhosis

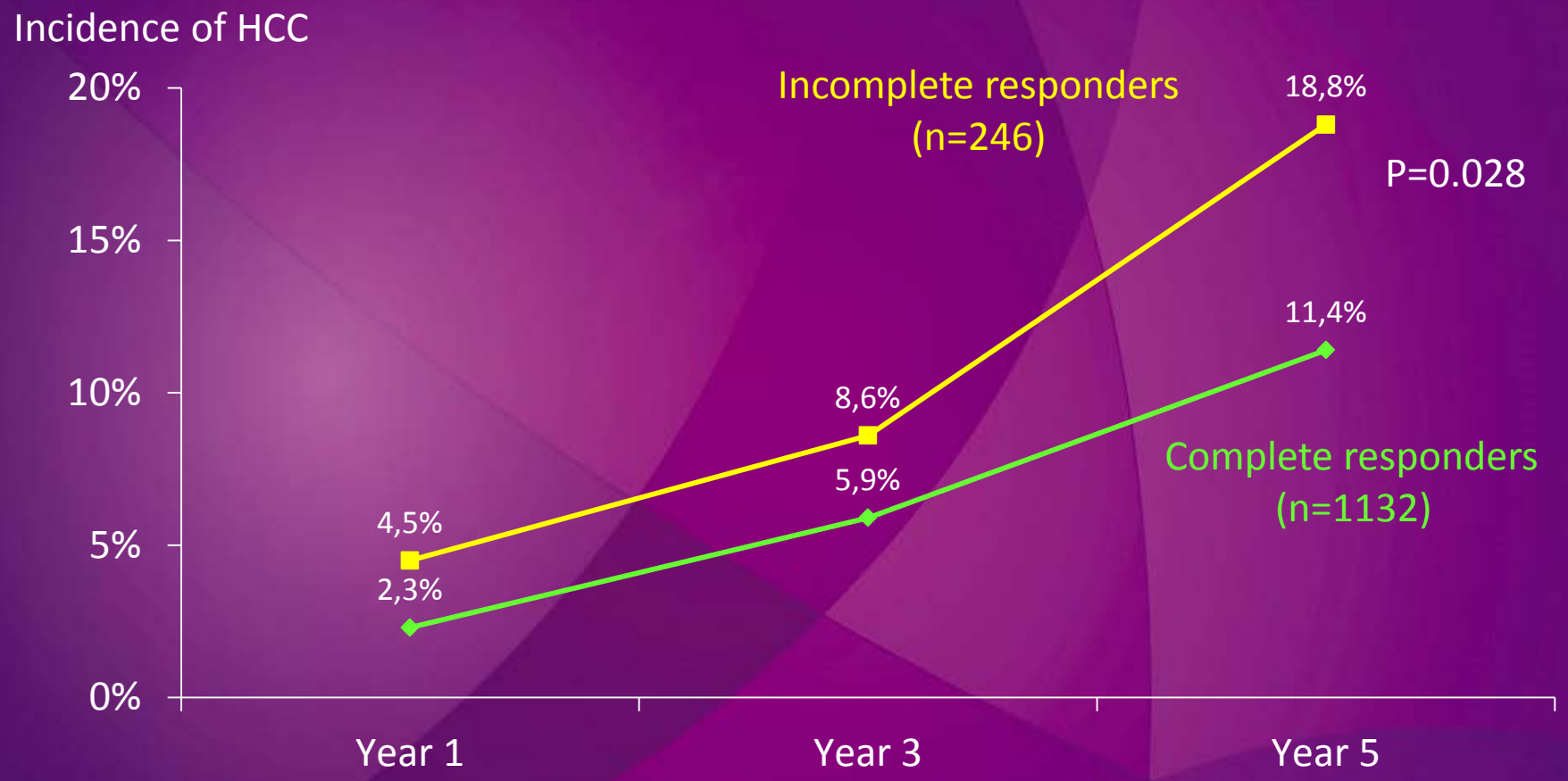
Non-cirrhotic patients	Adjusted HR	95% CI	P value
Albumin <35 g/L	17.5	2.0-63.4	0.04
Duration of virologic remission ≥24 months	0.6	0.4-1.1	0.08

Cirrhotic patients	Adjusted HR	95% CI	P value
Albumin <35 g/L	7.1	1.8-28.7	0.02
Total bilirubin ≥18 umol/l	5.9	0.5-59.5	0.48
Duration of virologic remission ≥24 months	0.3	0.2-0.7	0.003

Adjusted for age, gender, albumin, bilirubin, ALT, HBeAg, baseline HBV DNA and HBsAg

Wong GL, et al. Gastroenterology 2013;144:933-44

Cumulative incidence of HCC among incomplete NA responders is higher than complete responders



1378 treatment naïve patients on NA for mean of 42.4 months
Liver cirrhosis 32.3%
Complete response = HBV DNA <2000 IU/ml

Cho JY, et al. Gut 2014 (Epub ahead of print)

5 year cumulative HCC in HBeAg-negative pts Complete NA responders > inactive carriers

		N	5-year cumulative incidence	P
No cirrhosis	Complete responder	316	6.9%	<0.001
	Inactive carrier	884	0.8%	
Cirrhosis	Complete responder	223	15.3%	<0.001
	Inactive carrier	130	6.0%	

HBeAg-negative complete responders have higher baseline HBV DNA (5.52 vs 1.82 log IU/ml) , ALT and baseline cirrhosis (41% vs 13%) than inactive carriers

Cho JY, et al. Gut 2014 (Epub ahead of print)

Primary non-response from treatment naïve CHB to entecavir 0.5mg daily NOT predictive of maintained response

	Yang et al Korea	Bang et al Korea
N	1254	355
HBeAg positive	55%	58%
Primary non-response	1.2-1.3%	1.7%

Primary non-response
<2 log reduction at month 6 (AASLD); <1 log reduction at month 12 (EASL)

FU (months)	54	8-36
Undetectable HBV DNA	**100%**	**100%**

Yang YJ, et al. Hepatology 2014;59:1303-10; Bang SJ, et al. Dig Dis Sci 2013;45:600-5.

Partial response from treatment naïve CHB to entecavir 0.5mg daily

Predictive of maintained response at 3 years

	Wong et al Hong Kong	Bang et al Korea	Kwon et al Korea	Ko et al Korea
N	440	355	227	128
HBeAg positive	36%	58%	65%	66%
Partial response	23.5%	17.7%	28.2%	14.1%

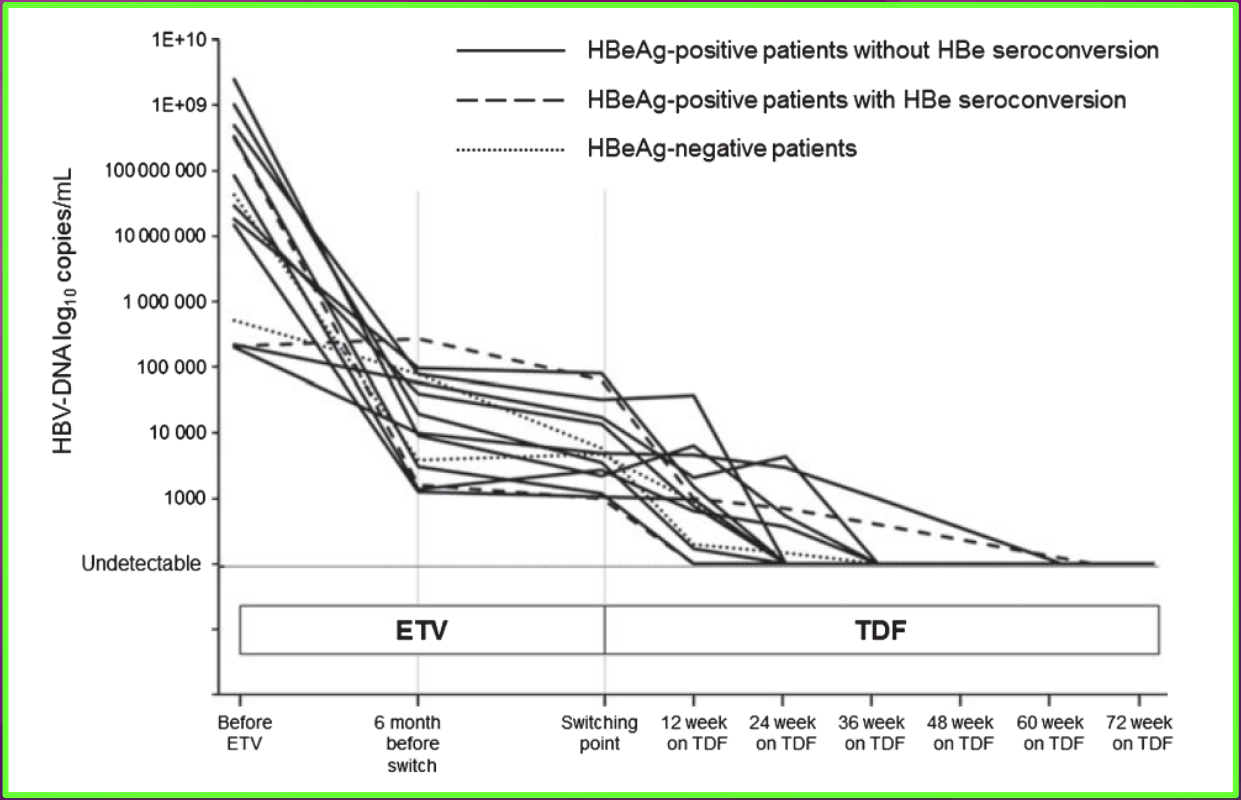
Partial response = > 1 log reduction but detectable HBV DNA at month 12

UD HBV DNA				
Month 24	NA	31%	45%	NA
Month 36	**58%**	**45%**	**74%**	**NA**

Wong GL, et al. Aliment Pharmacol Ther 2012;35:1326-35; Bang SJ, et al. Dig Dis Sci 2013;45:600-5; Kwon DH, et al. Gut Liver 2013;7:712-8; Ko SY, et al. Scand J Gastroenterol 2012;47:1362-7.

Tenofovir is effective to suppress HBV DNA in ETV suboptimal responder

14 patients (12 HBeAg-positive) on ETV for 65.4 (26-126 weeks)
12 patients treatment naïve, 1 LMV exposed, 1 pegIFN exposed
HBV DNA 7.55 (5.30-9.40) log copies/ml



Pan CQ, et al. J Viral Hepat 2012

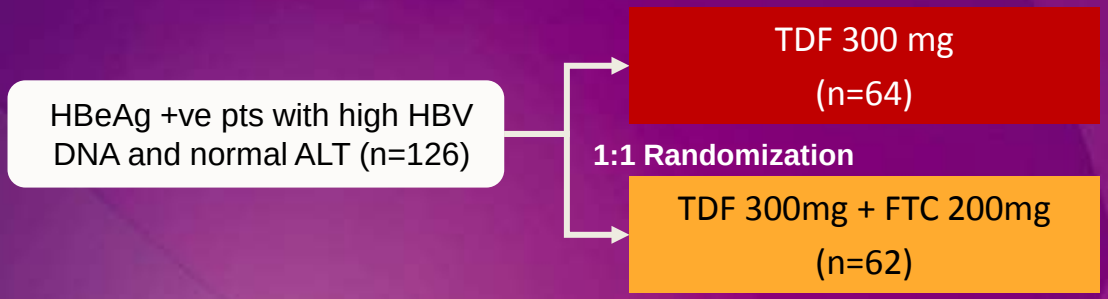
TDF is equally effective as TDF+ETV for ETV partial responders

42 patients on entecavir with incomplete viral suppression with no drug resistance
All Asian, 95% HBeAg positive
HBV DNA at time of switch = 3.32±0.74 log IU/ml
Rescue treatment 14 (3-30) months; one patient has complete viral suppression by ETV+TDF at month 3 and other have treatment >6 months

Complete viral suppression	ETV+ADV (n=5)	TDF (n=6)	ETV+TDF (n=31)
6 months	20%	83%	83%
12 months	20%	100%	97%

Yip B, et al. Dig Dis Sci 2012;57:3011-6.

Combination of tenofovir and emtricitabine improves viral suppression in HBeAg-positive patients with high viral load

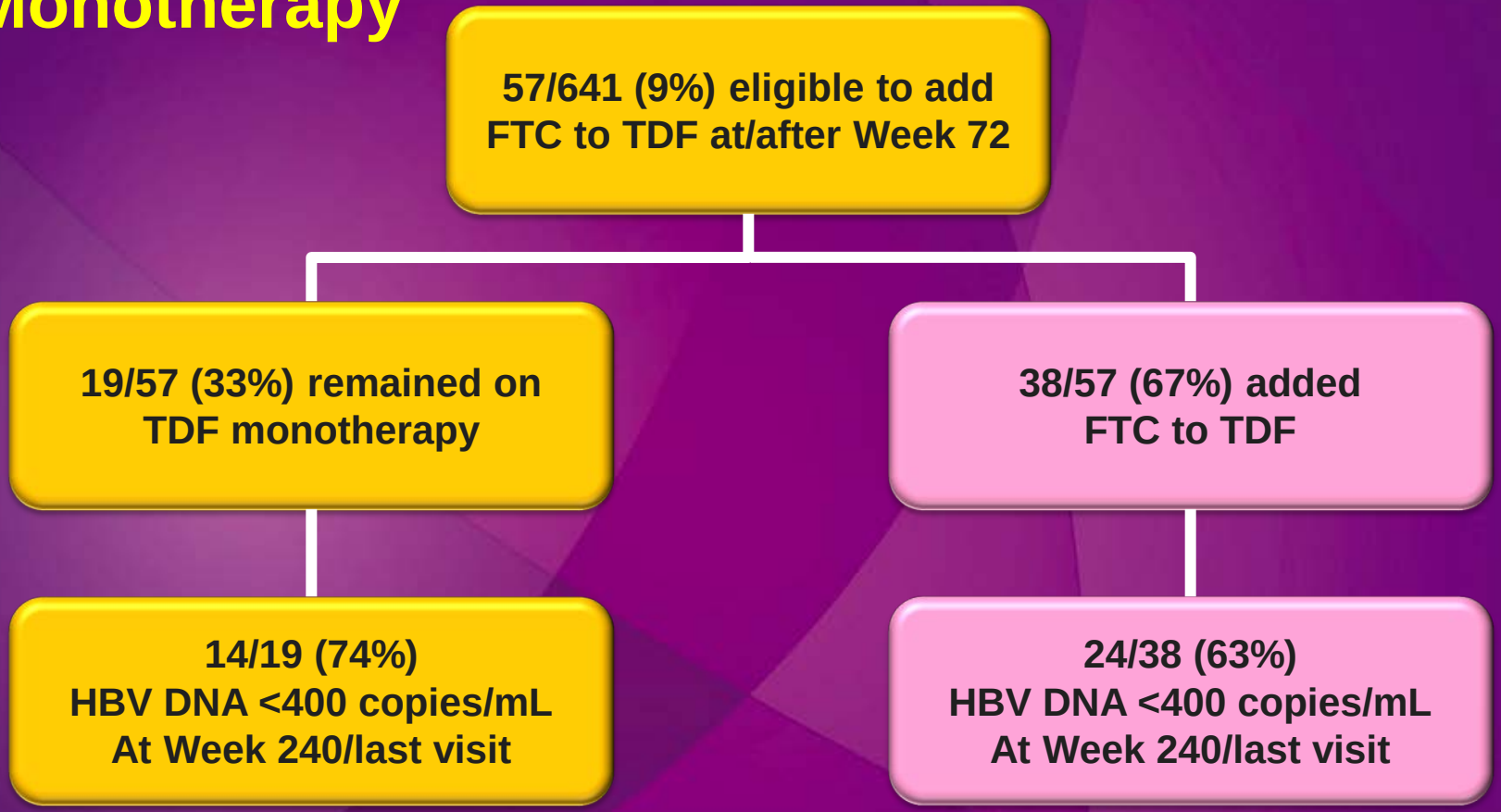


Response = HBV DNA < 69 IU/ml at week 192

	Univariate analysis			Multivariate analysis	
	Non-responders N=25	Responders N=82	p-value	Odds ratio	95% CI
Female, n (%)	5 (20)	46 (56)	0.002	6.0	1.9-18.2
Baseline HBsAg, mean $\log_{10}$	4.88	4.69	0.010		
TDF/FTC treatment, n (%)	7 (28)	47 (57)	0.012	3.9	1.4-11.1
Baseline HBV DNA, mean $\log_{10}$	9.26	9.13	0.036		

Chan HL, et al. Gastroenterology 2014; 146:1240-8.

Studies 102/103: Adding FTC does not improve viral suppression vs Maintaining TDF Monotherapy



All subjects analyzed with >400 copies/mL had no TDF resistance detected.

Marcellin P, et al. AASLD 2011. Oral 238.

Summary

- There is sufficient data to suggest antiviral therapy can reduce the risk of HCC in Asian cirrhotic patients
  - Annual incidence of HCC – 1.4% - 3.9%
- Conflicting data on benefit of antiviral therapy among non-cirrhotic patients
  - Annual incidence of HCC – 0.5% - 0.7%
- Complete viral suppression can improve HCC prevention
- Only 58%-74% partial responders at 1 year have complete HBV DNA suppression at 3 years
- Tenofovir switch is effective for entecavir partial responders