Don’t interfere
My first choice is always nucs !

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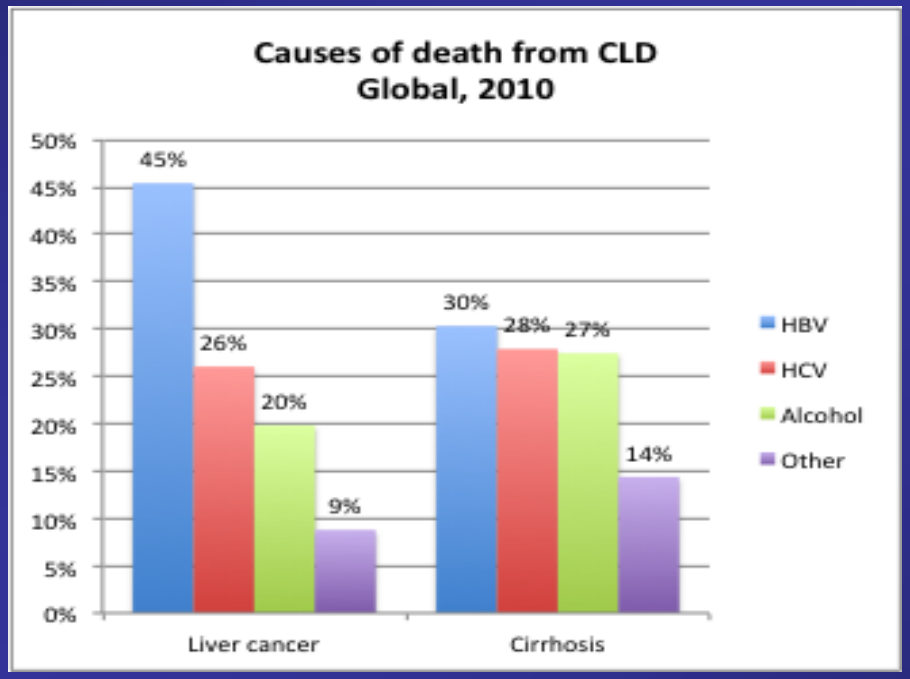
Disclosures

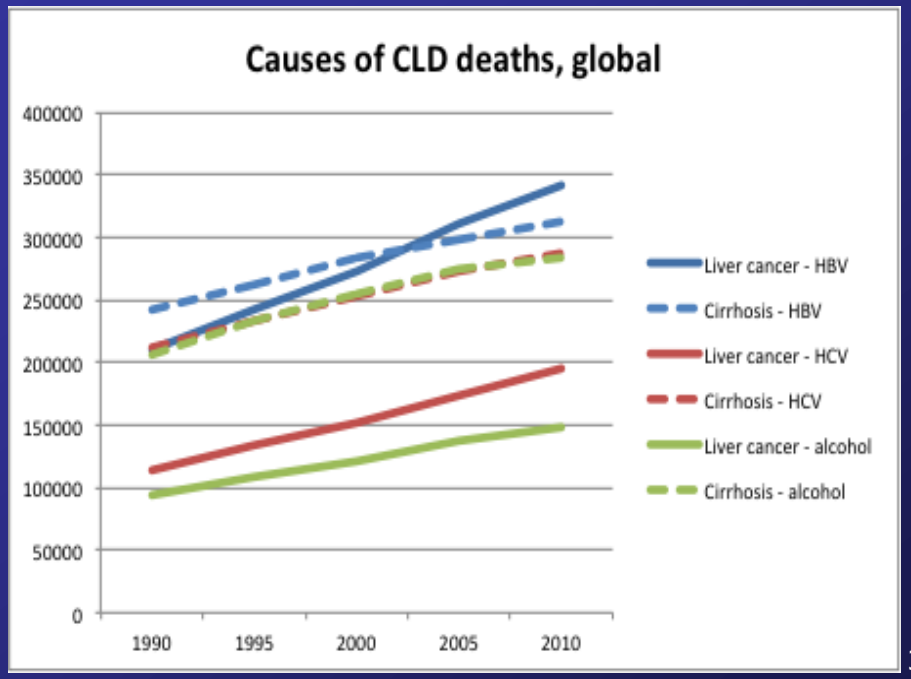
- Dr Gish has consulting relationships, advisory boards and speakers bureaus with

- BMS
- Gilead
- Roche
- Genentech

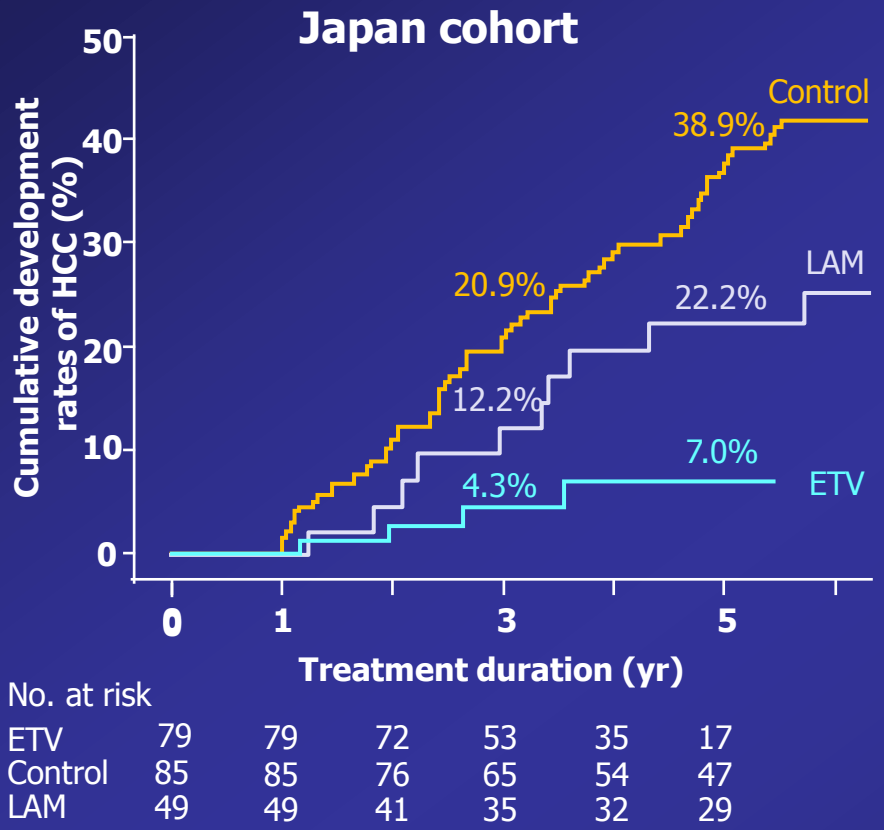
Global Deaths – Cirrhosis and Liver Cancer, 2010

- 750,000 liver cancer deaths and 1.03 million cirrhosis deaths
- Total deaths increased from 1.25 to 1.75 million per year
- An increasing proportion due to liver cancer
- HBV associated with 45% of liver cancer & 30% of cirrhosis
- HCV and alcohol each cause approximately 25% of deaths



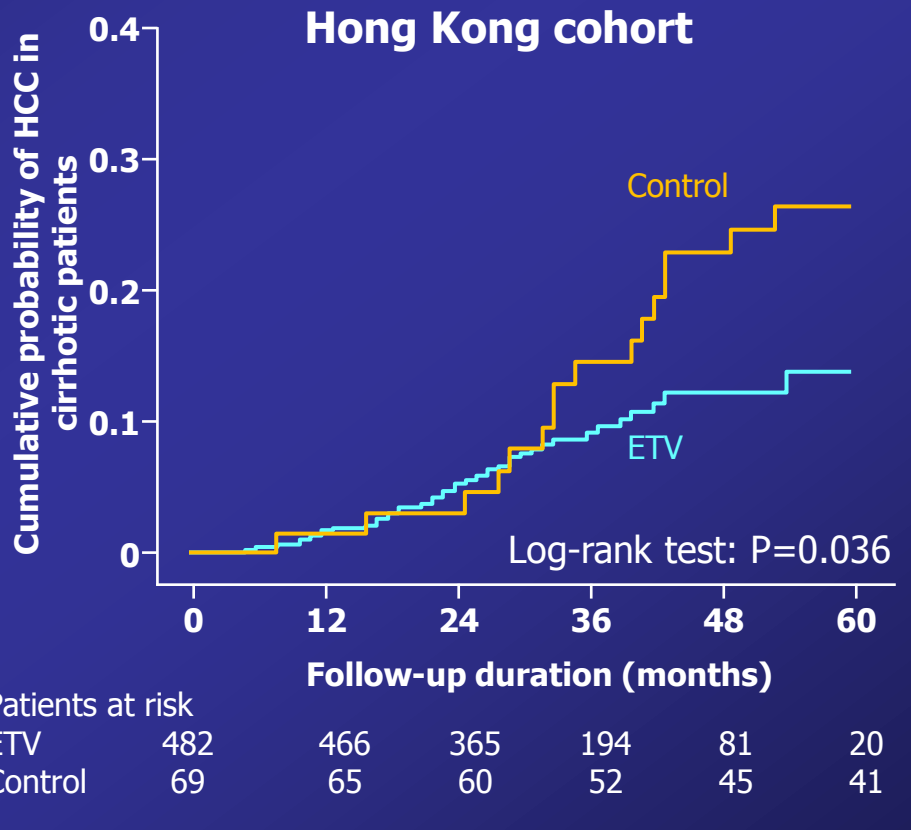


Discussion:
Benefit of Long-term Entecavir Treatment



No. at risk

ETV	79	79	72	53	35	17
Control	85	85	76	65	54	47
LAM	49	49	41	35	32	29



Patients at risk

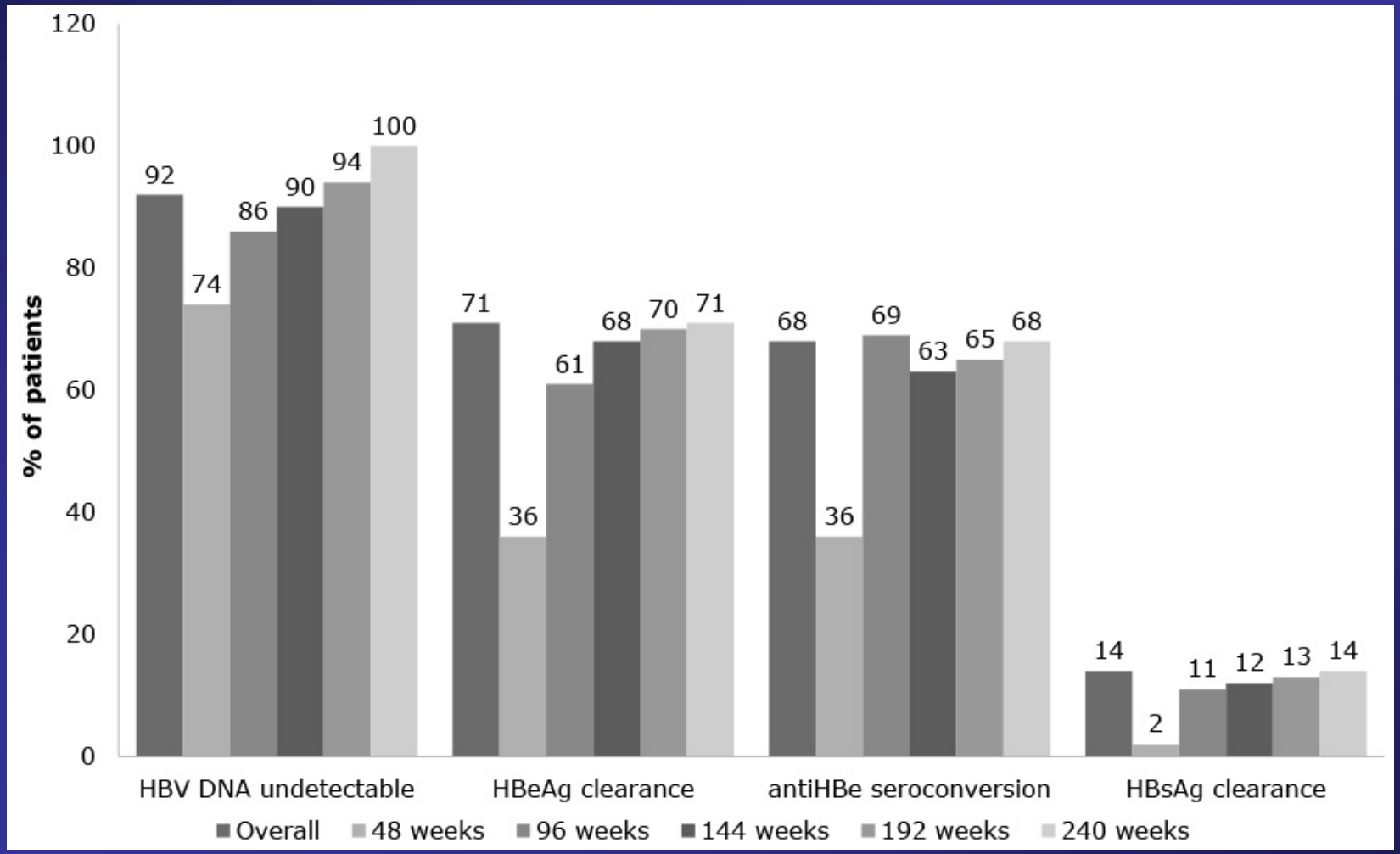
ETV	482	466	365	194	81	20
Control	69	65	60	52	45	41

- Cirrhotic patients benefit more to prevent HCC development

Hosaka, et al. Hepatology 2013.
Wong, et al. Hepatology 2013.

Su T-H, et al. AASLD 2013, Washington, DC. Oral 189.

Figure 1: Serologic and Virological Response According to ETV Week of Treatment



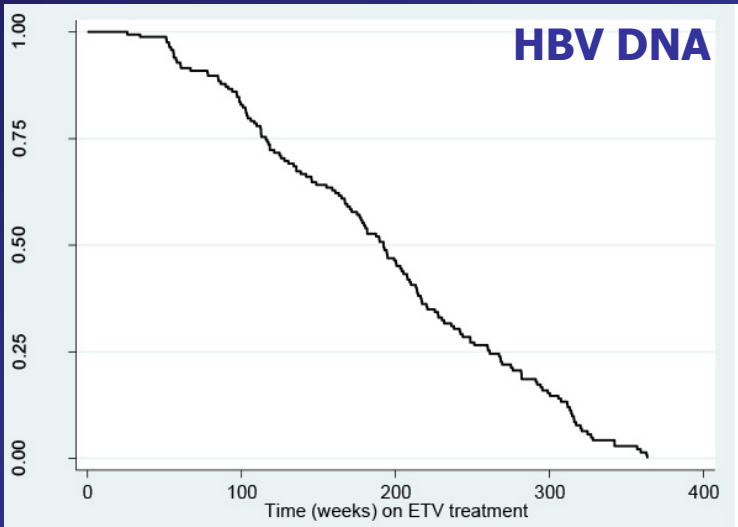
Ridruejo E, et al. AASLD 2013, Washington, DC. Poster 901.

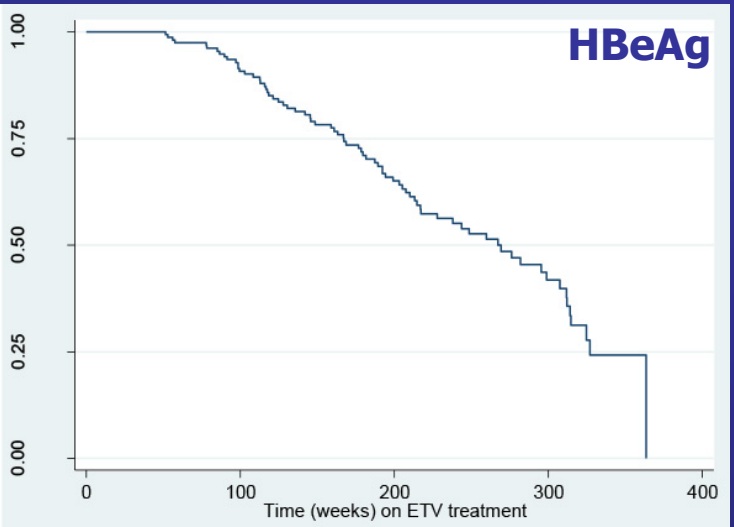
Table 3: Predictors of Serologic Response, Multivariate Analysis by Cox Proportional Hazard Model

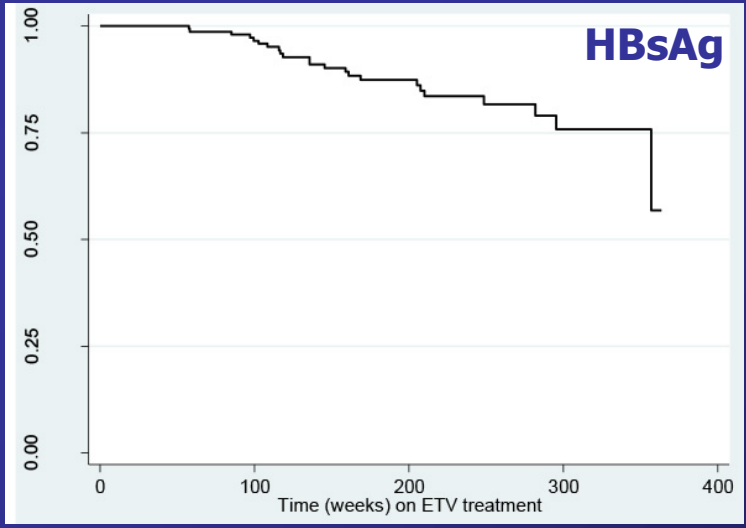
	Variable	Hazard Ratio	95CI%	P value
HBeAg Clearance	Gender	1.03	0.41-2.58	0.949
	ALT > 5 times ULN	1.85	0.74-4.59	0.182
	HBV DNA ≥7 $\log_{10}$ IU/ml	9.40	3.46-25.54	<0.001
	Metavir A score ≥2	2.48	1.39-4.40	0.002
	HBV negativization after week 192	1.01	0.46-2.19	0.969
HBsAg Clearance	HBeAg positive at baseline	11.1	0.96-128	0.053
	HBV negativization before week 48	7.76	0.96-62.4	0.054
	Metavir A score ≥2	2.34	0.81-6.79	0.116
	HBV DNA ≥7 $\log_{10}$ IU/ml	0.93	1.01-15.48	0.937

Ridruejo E, et al. AASLD 2013, Washington, DC. Poster 901.

Figure 2: Cumulative HBV DNA, HBeAg and HBsAg Response in the Overall Population (Kaplan Meier Survival Estimates)







Ridruejo E, et al. AASLD 2013, Washington, DC. Poster 901.

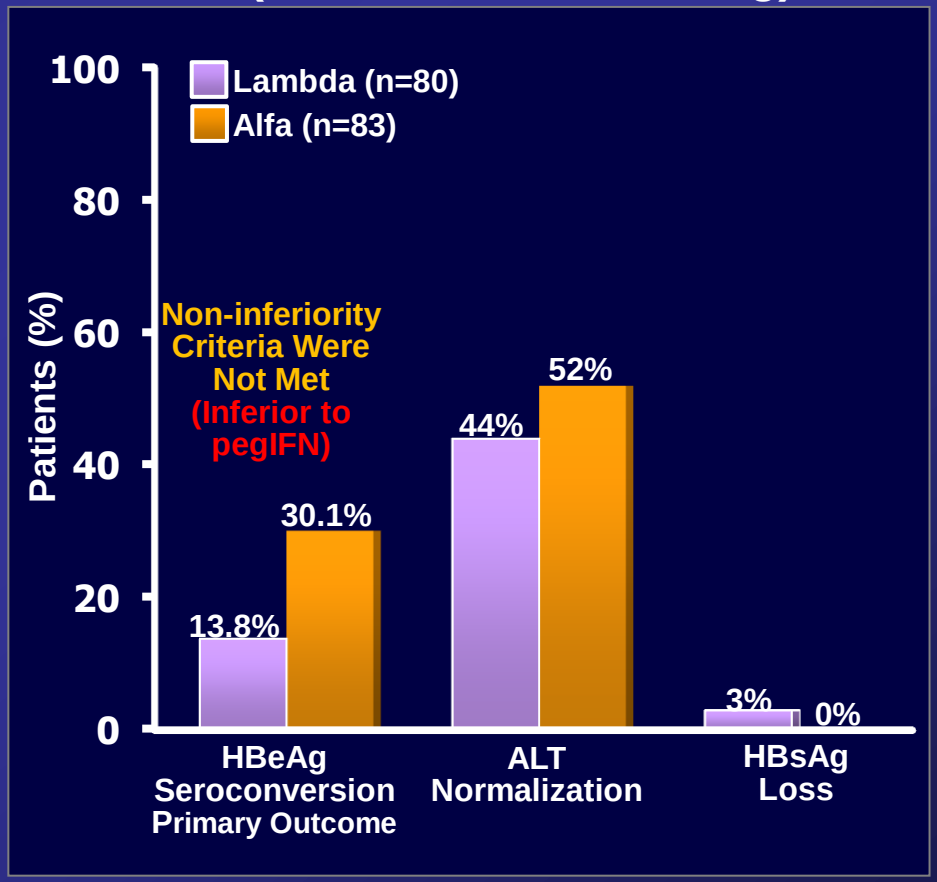
Figure 1. Ratio of Undetectable HBVDNA in Patient Groups

Idilman R, et al. AASLD 2013, Washington, DC. Poster 1030.

LIRA-B Study: PegIFN Lambda Versus PegIFN Alfa in HBsAg-Positive Patients

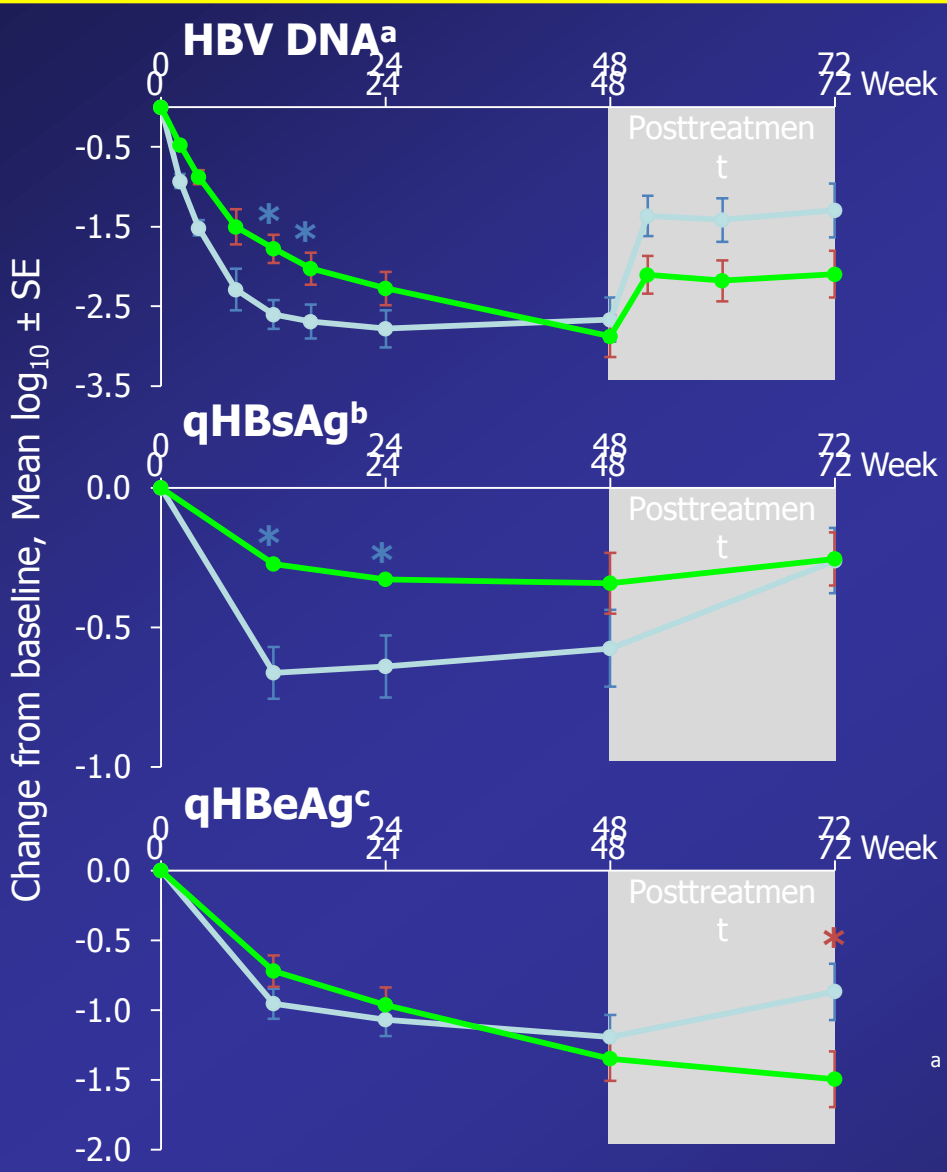
- Lambda was not non-inferior to alfa pegIFN for HBeAg seroconversion
  - End-of-treatment responses between the 2 arms were similar
- Safety was similar between lambda and alfa arms
  - Discontinuations due to adverse events (9.6% versus 7.5%)
  - Serious adverse events (8.8% versus 6.0%)
  - Traditional INF-associated adverse events
- Grade 3/4 elevations in liver measures were more common in lambda (ALT flares), whereas cytopenias were more common with alfa (more dose reductions)

Week 72 Outcomes (24 Weeks Post-Dosing)



Chan HL, et al. *J Hepatol.* 2014;60(suppl 1):S48. Abstract O115.

Quantitative Virologic and Serologic Responses



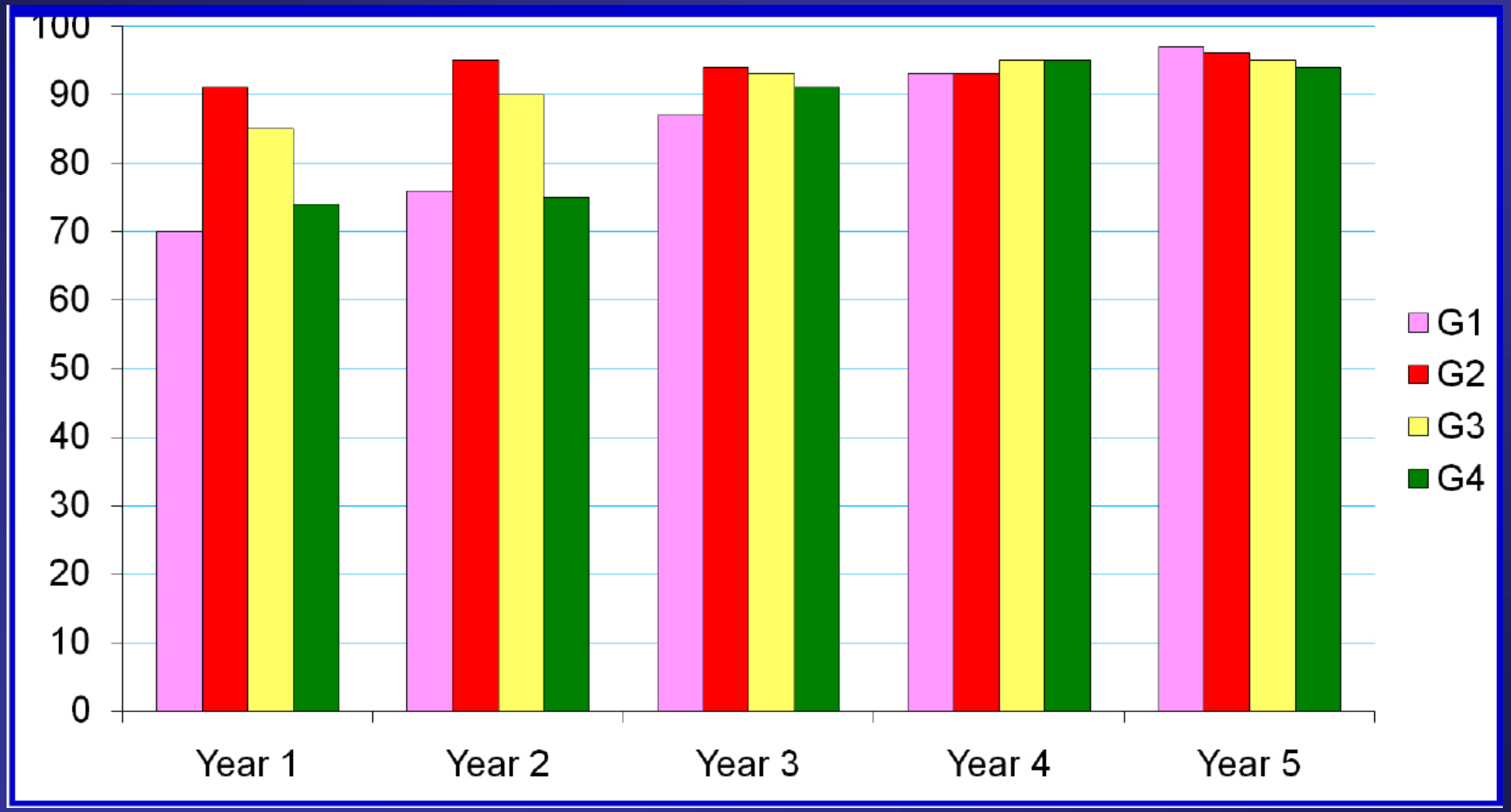
- **First 24 weeks:** greater early declines in HBV DNA and qHBsAg with Lambda
- **End of treatment:** responses comparable for Lambda vs alfa
- **Posttreatment:** HBV DNA and qHBeAg responses favor alfa

* Significant difference ($P < 0.05$)

[a] Roche COBAS® TaqMan HPS assay LLOQ 29 IU/mL, LLOD 10 IU/mL
[b] Abbott Architect assay, linear range, 0.05–250 IU/mL
[c] Abbott Architect assay, linear range 0.22–56.70 PEIU/mL

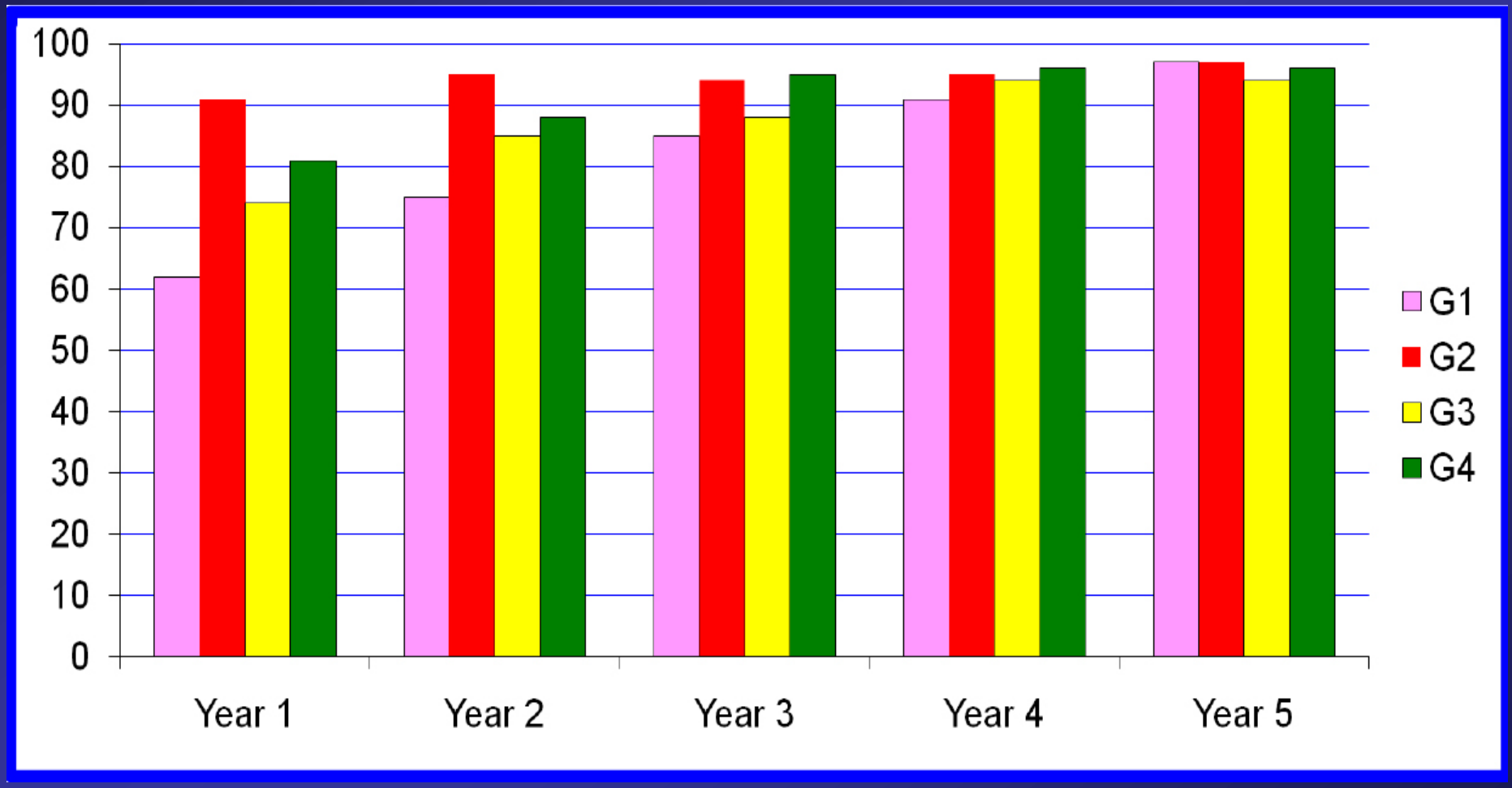
Chan HL, *et al.* EASL 2014

Nuc real life: Percent of ALT Normalization



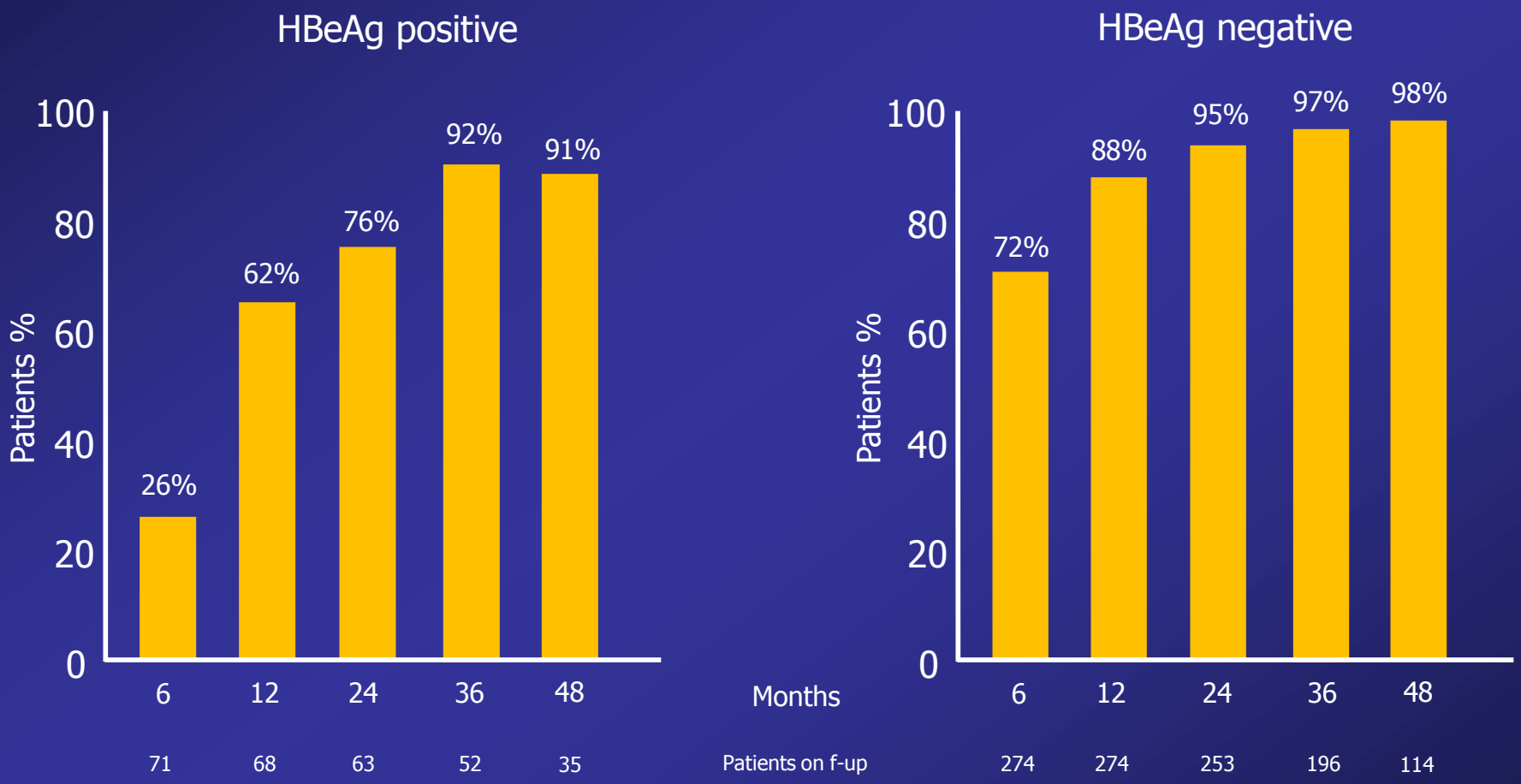
Tanwandee T, et al. AASLD 2013, Washington DC, Poster 968.

Nuc: real life: Percent of Undetectable HBV DNA



Tanwandee T, et al. AASLD 2013, Washington DC, Poster 968.

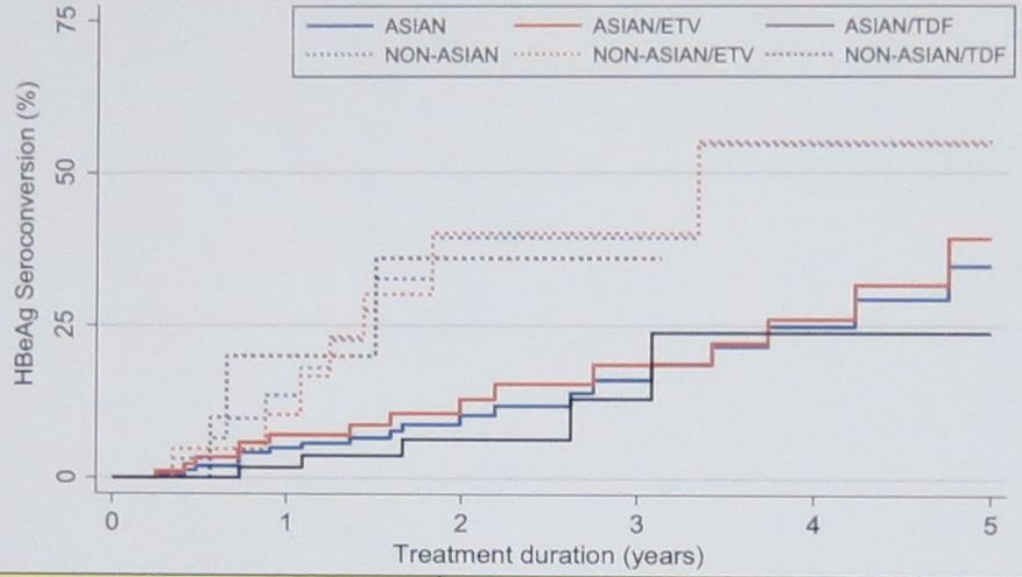
Real Life Nucs: Italy: Virological Response* by HBeAg Status



*Undetectable HBV DNA.

Lampertico P, et al. AASLD 2013, Washington, DC. Poster 933.

Figure 2: Cumulative Incidence of HBeAg Seroconversion Among Asians Versus Non-Asians Treated with ETV or TDF Monotherapy



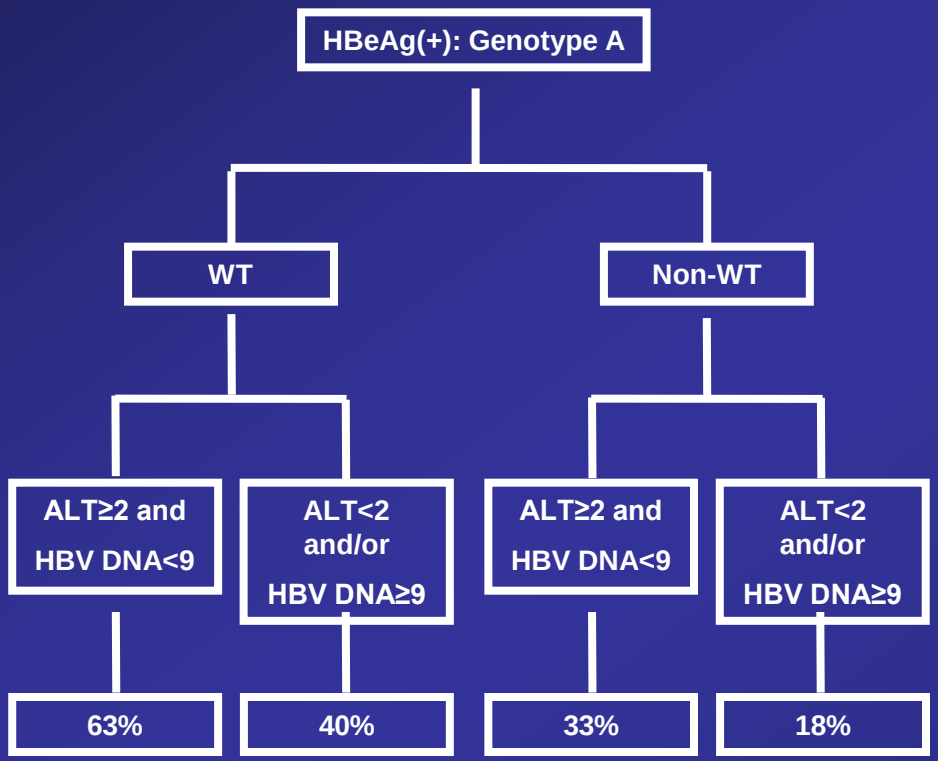
Cumulative incidence of seroconversion on ETV or TDF monotherapy	Year 1	Year 2	Year 3	Year 4	Year 5
Asian (n=155)	5%	10%	16%	25%	35%
non-Asian (n=32)	14%	39%	39%	55%	55%
p-value	0.07	<0.001	0.001	0.001	0.002

Cumulative incidence of seroconversion by drug type		Year 1	Year 2	Year 3	Year 4	Year 5
ETV	**Asian** (n=93)	7%	13%	19%	26%	39%
	non-Asian (n=21)	10%	40%	40%	55%	55%
	p-value	0.63	0.02	0.04	0.02	0.04
TDF	**Asian** (n=62)	2%	6%	13%	24%	
	non-Asian (n=11)	20%	36%	36%		
	p-value	0.005	0.002	0.005		

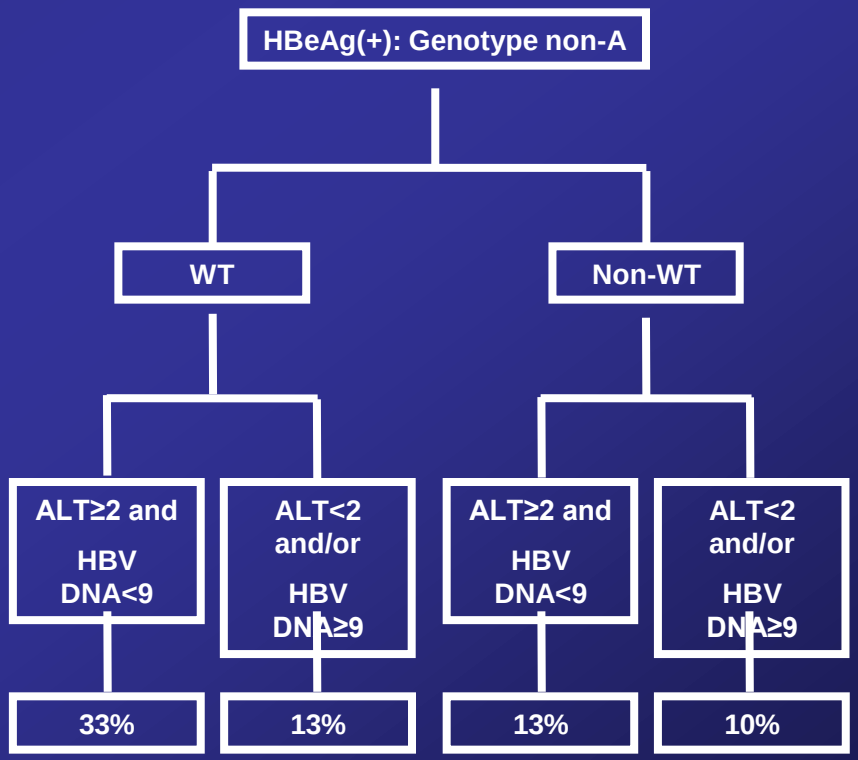
Jo KJ, et al. AASLD 2013, Washington, DC. Poster 961.

Probability of response (DNA <2,000 and eAg clearance) to Interferon by HBV genotype, presence of mutants and baseline ALT and HBV DNA

Genotype A



Genotype non-A



Observations in non-A genotypes need to be confirmed in studies enrolling more Asian patients

Extention of the previously published PEG-IFN treatment index (Buster et al. *Gastroenterology* 2009)

Summary

- Nucs are superior to interferon
  - Side effects <1% per year
  - DNA negativity over 70% ITT, over 95% PP
  - sAg loss is over 10% at 5 years

- Interferon
  - Complex treatment
  - Many side effects
  - Poor stopping rules
  - <20% of patients have DNA < LOQ long-term
  - HBsAg < 10% at 5 years of follow up