NUCs for Chronic Hepatitis B

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Disclosures

- Advisory board of, and/or, received speaker fee from BMS, Gilead, GSK, MSD, and Novartis

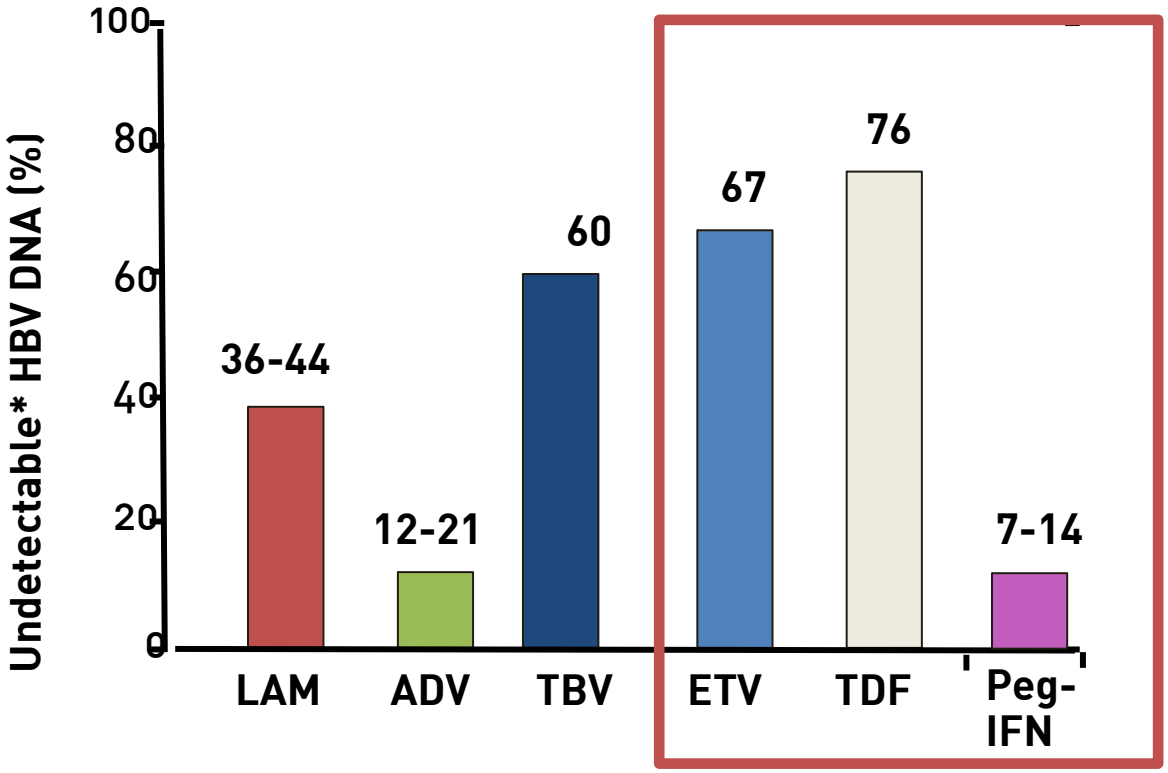
First Argument

- Nucleos(t)ide Analogues are currently the most potent drugs for suppressing hepatitis B virus replication

- HBV DNA suppression is associated with an improvement in disease outcomes

Undetectable* HBV DNA in HBeAg-positive patients After 1 Year of Treatment

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

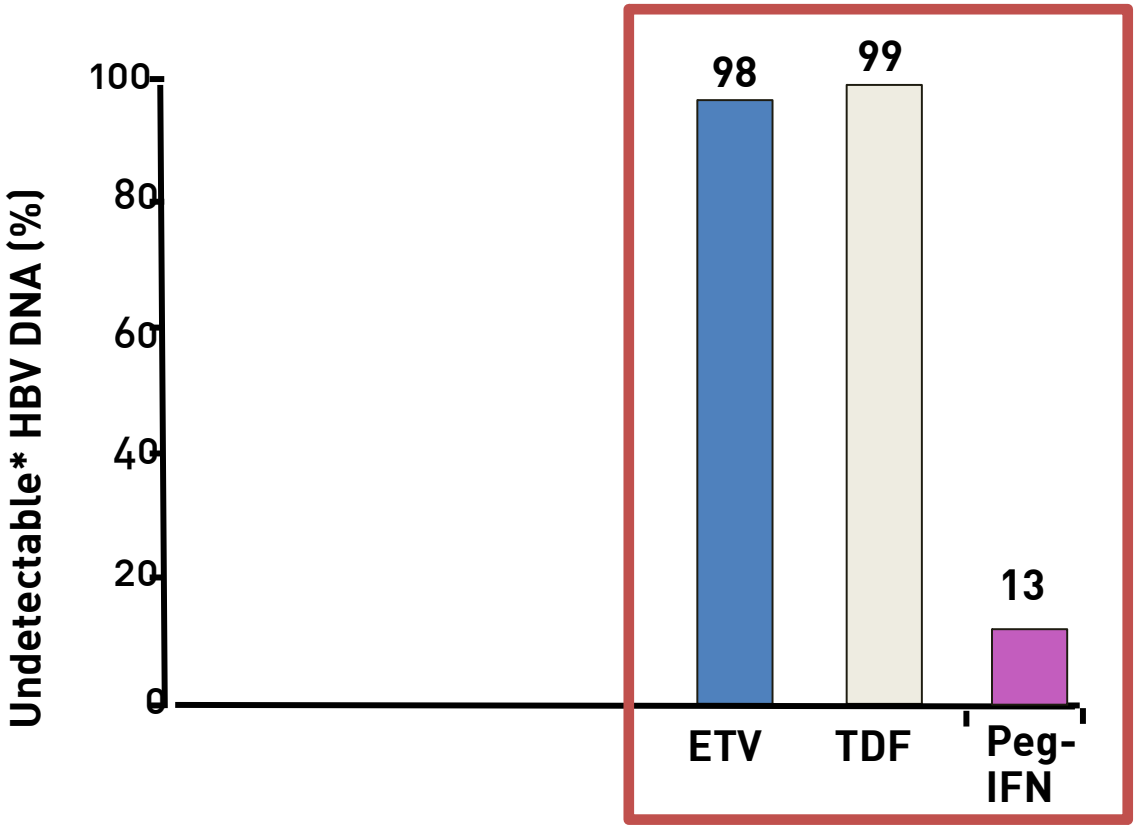


*Undetectable means HBV DNA ↓60-80 IU/ml (%)

EASL Guidelines 2012. J of Hepatol 2013

Maintained Undetectable* HBV DNA in HBeAg-Positive Patients after 5 Years of Treatment

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



*Undetectable means HBV DNA ↓60-80 IU/ml (%)

Chang TT et al.Hepatology 2010. Marcellin P et al Lancet 2012. Wong VW et al, Hepatology. 2010

Studies 102/103

Efficacy Results at Year 8

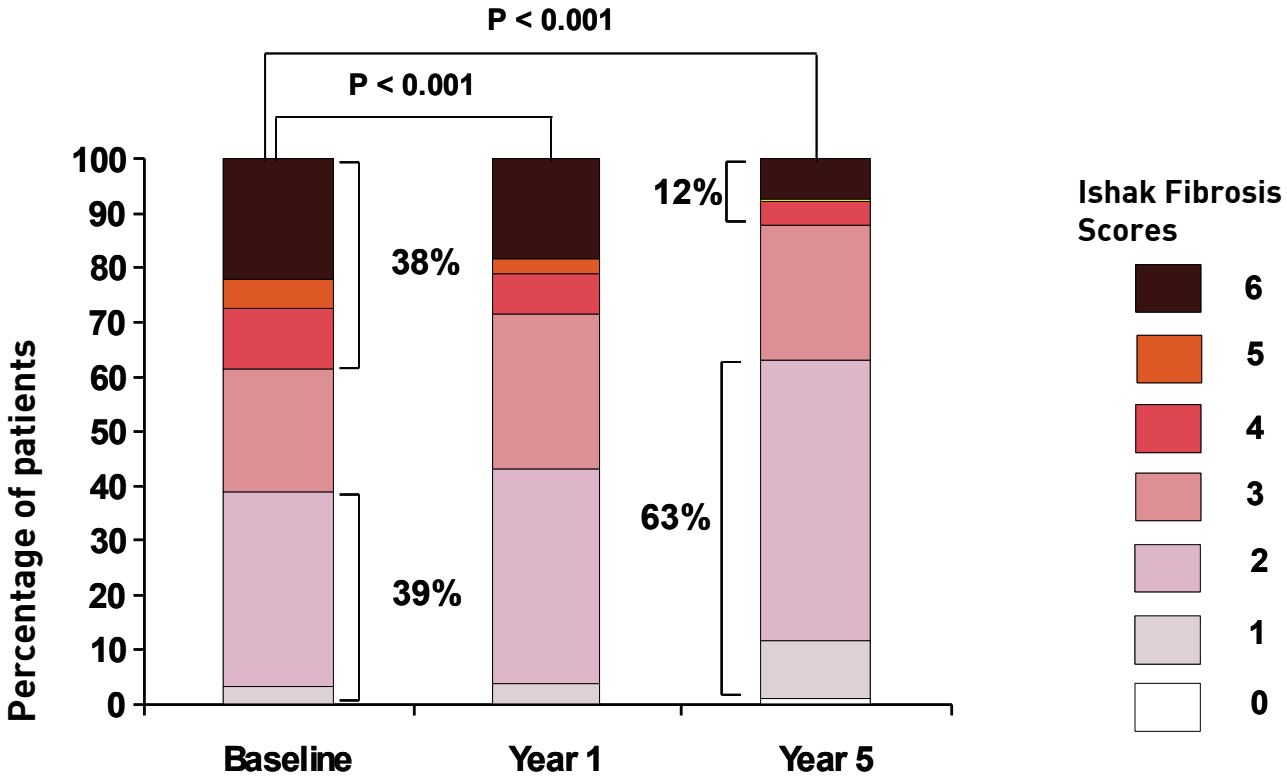
% (n/N)	HBeAg-	HBeAg+
HBV DNA ↓29 IU/mL (ITT)*	75 (260/349)	58 (139/241)
HBV DNA <29 IU/mL (Observed)	99 (261/264)	97 (142/146)
HBeAg loss / seroconversion (Observed)†	NA	47 (55/118) / 31 (36/115)
HBsAg loss/seroconversion (KM%) ‡	1.1 (n=3) / 0.7 (n=2)	13 (n=28) / 10 (n=22)

* Missing = failure; add FTC = failure[LTE-TDF])
† Missing = excluded; add FTC = included)
‡ KM% = Kaplan-Meier % (KM-ITT)
NA, not applicable

Marcellin, AASLD, 2014, Oral #229

Tenofovir Treatment reduces Fibrosis in the majority of patients after 5 years

- Patients with Ishak score ↘4: 38% at Baseline, 12% at Year 5
- Patients with cirrhosis (score ↘5): 28% at Baseline, 8% at Year 5



96% (335/348) of patients improved fibrosis score or did not change at Year 5
71/96 (74%) cirrhotic patients had regression of fibrosis (Ishak score ↖4)

Marcellin, P, et al. Lancet 2012

Nucleos(t)ide Analogues

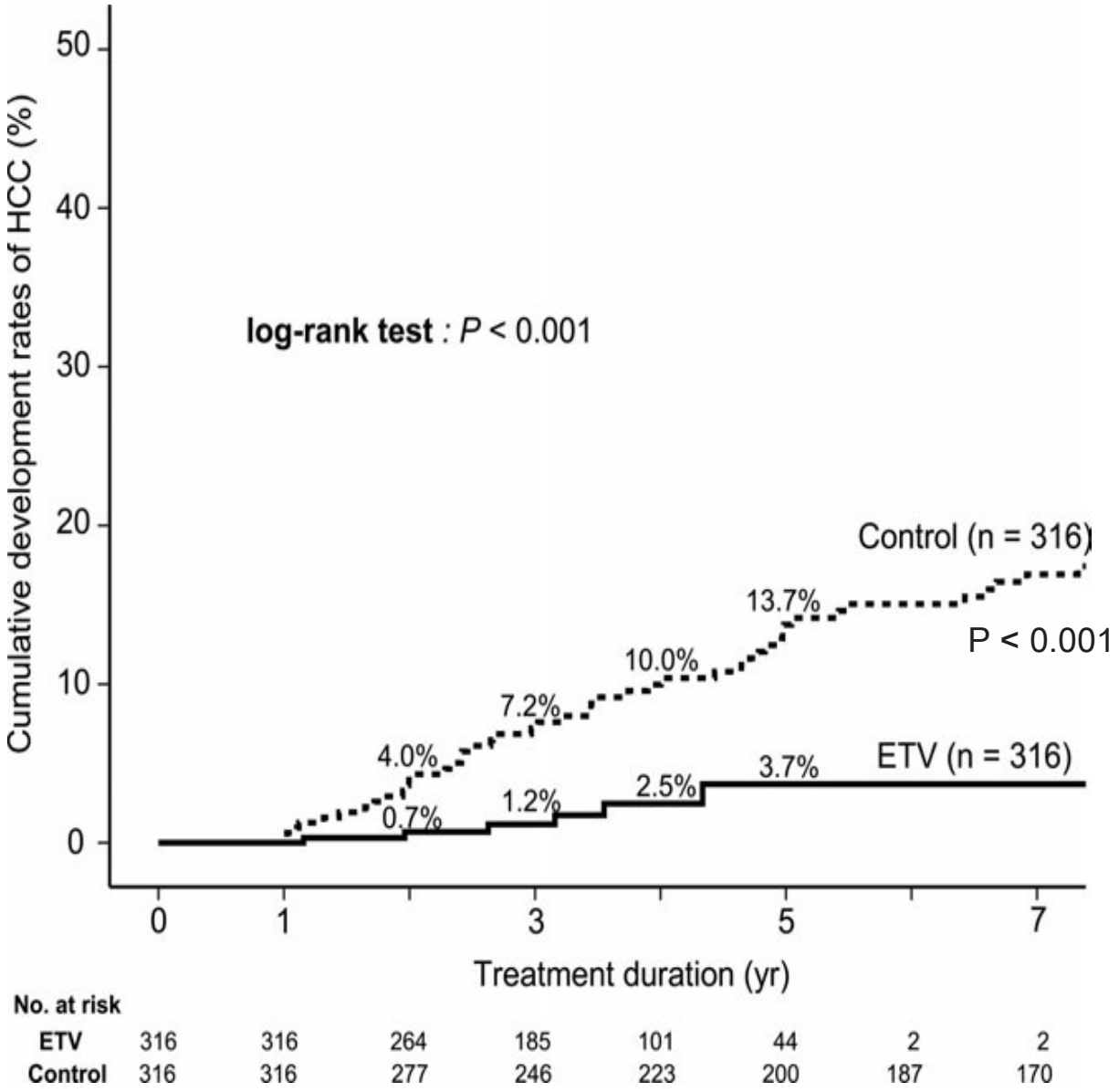
- Prevention of HBV-related HCC

  Lamivudine/ adefovir vs no treatment:

  - 5 studies; **ALL** showed beneficial effects
  - Consistent reduction of HCC in patients with and without cirrhosis (effect blunted but still present with resistance development)

Lai CL. Yuen MF. Hepatology 2013; 57: 399

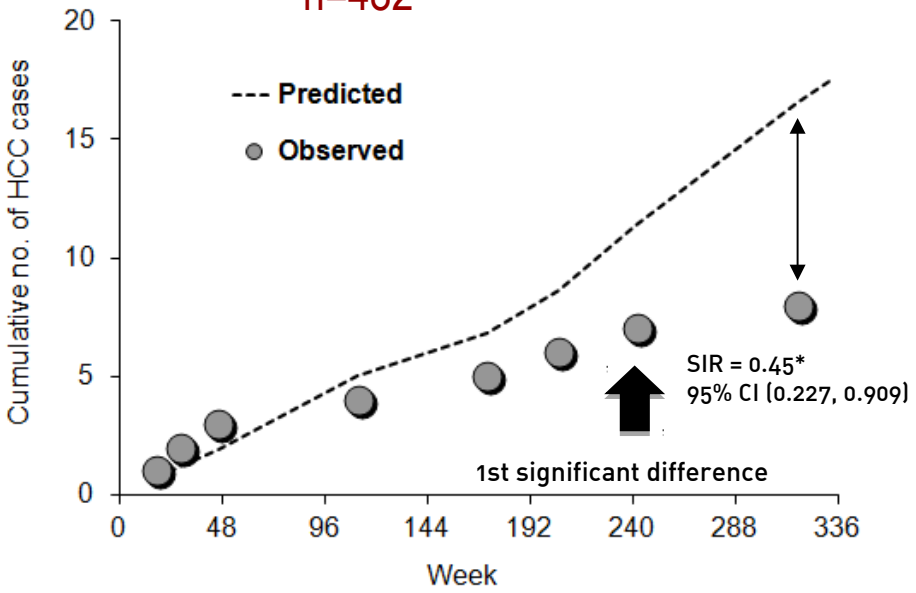
HCC cumulative incidence rates between entecavir-treated group and the non treated control group



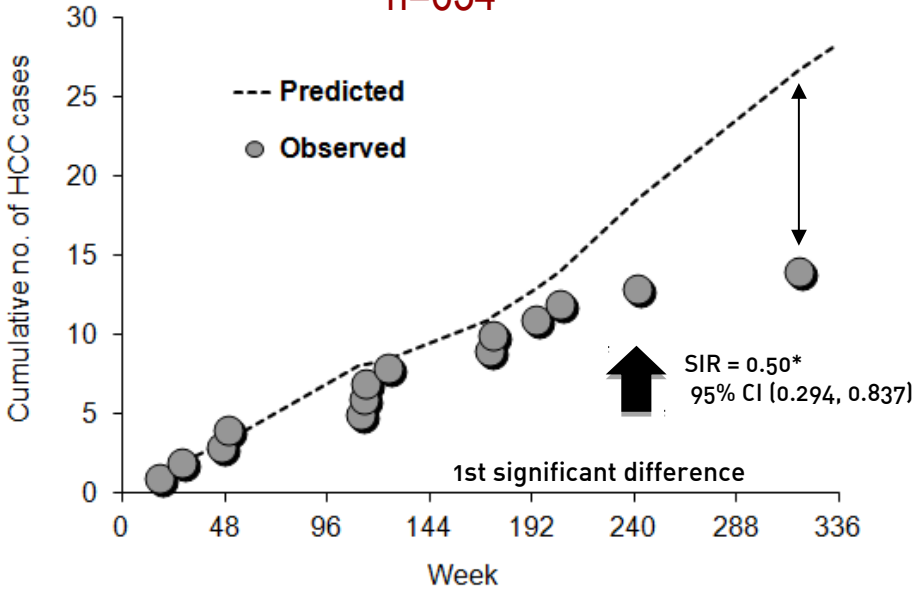
Hosaka et al Hepatology 2013

Observed vs. Predicted HCC Cases in TDF Studies 102/103

Non-cirrhotics
n=482



All Patients
n=634



- Incidence of HCC in patients on TDF in Studies 102/103 was lower than predicted by the REACH-B model
- In non-cirrhotic patients, the effect of TDF becomes noticeable between 2–3 years of therapy and became statistically significant (55% reduction) at 6 years of therapy

*Statistically significant at nominal α-level of 0.05.
Kim WR, et al. J Hepatol 2013 Supp 1;58(43):S19 - Oral#43

REACH-B is a risk calculator developed in non-cirrhotic pts so It may underestimate the risk

Prevention of HBV-related HCC
Interferon vs no treatment

Authors	Number of Studies	Number of Patients Treated Versus Controls	RR/Risk Difference* (95% CI)	*P* Value
Cammà et al.[17]	7	853 versus 652 (all cirrhotic patients)	4.8%* (0.11-0.015)	NS
Miyake et al.[18]	8	553 versus 750	5.0%* (9.4-0.5)	0.028
Sung et al.[19]	12	1,292 versus 1,458	0.66 (0.48-0.89)	0.006
Yang et al.[20]	11	1,006 versus 1,076	0.59 (0.43-0.81)	0.001
Zhang et al.[21]	2	176 versus 171	0.23 (0.05-1.04)	NS (0.056)
Jin et al.[22]	9	1,291 versus 1,048	0.274 (0.059-1.031)	NS

Only 3 showed some improvement; 7 showed **NO** difference
Conclusion: inconsistent results; beneficial effect of interferon possibly in responders (ie, ~30%) with pre-existing cirrhosis

Lai CL. Hepatology 2013; 57: 399

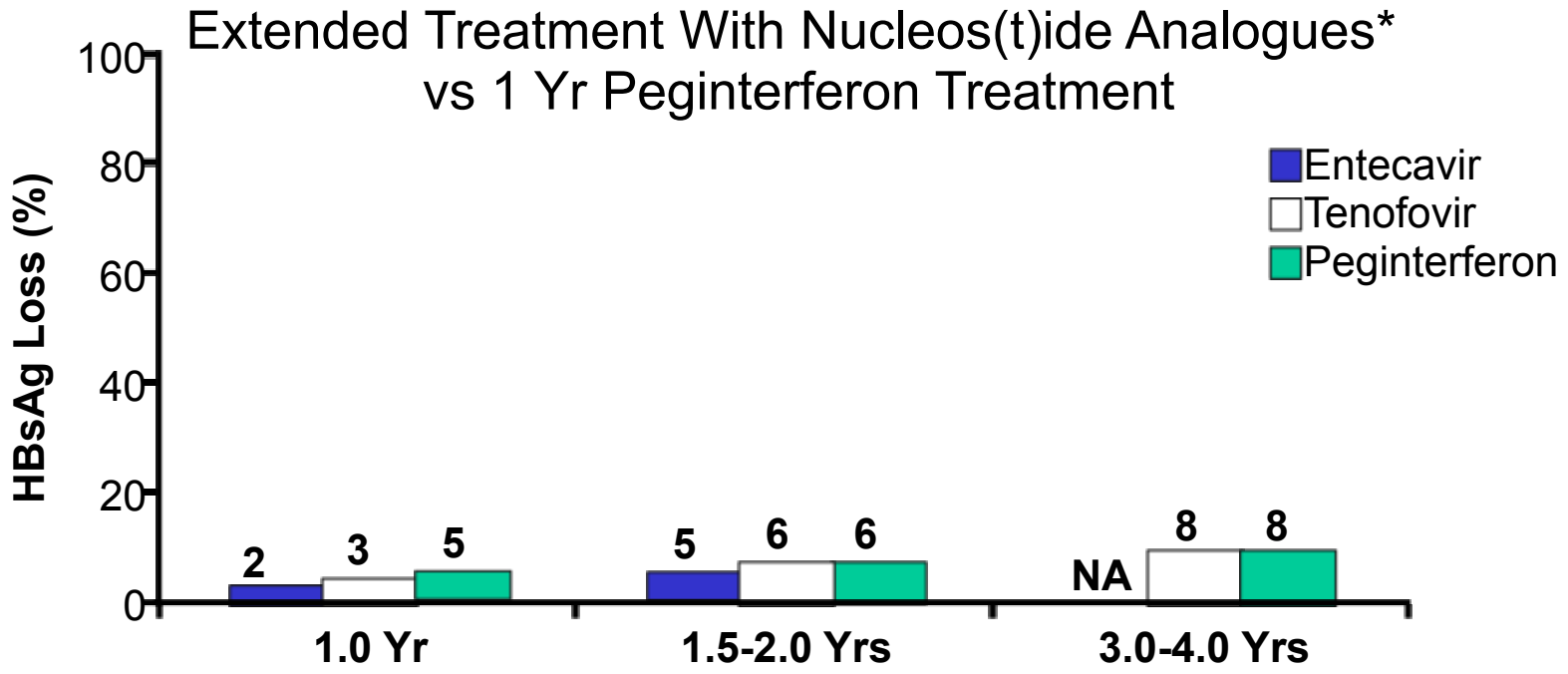
Second Argument

- In HBeAg-positive patients, the ideal end point is sustained off-therapy HBsAg loss, with or without seroconversion to anti-HBs

- This is associated with a complete and definitive remission of the activity of CHB and an improved long-term outcome

HBsAg Loss Over Time in HBeAg-Positive Patients

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



*With sustained undetectable HBV DNA.

Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129. CCO Hepatitis

Predictors of HBsAg Loss in HBeAg-Positive Patients

- Race: whites > nonwhites[1]
- Genotype[1-3]
  - Nucleos(t)ide analogues: A and D
  - Peginterferon: A
- HBeAg loss during the first 24 wks of Nucs[1]
- Serum HBsAg decline during first 24 wks with Nucs[1]

1. Heathcote EJ, et al. EASL 2009. Abstract 909. 2. Gish RG, et al. J Viral Hepat. 2010;17:16-22.
3. Buster EH, et al. Gastroenterology. 2008;135;459-467. CCO Hepatitis

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Marcellin, AASLD, 2014, Oral #229

THird Argument

- NAs have an excellent safety profile

- No Resistance

Most Common Adverse Events (Occurring in ↑10% of Patients) in Nucs-Naive HBeAg-Positive Entecavir Long-Term Cohort

	Number of Patients (%) n=146
Any adverse event	132 (90)
Upper respiratory tract infection	45 (31)
Headache	31 (21)
Cough	25 (17)
Influenza	25 (17)
Diarrhea	23(16)
Nasopharyngitis	23 (16)
Pyrexia	18 (12)
Upper abdominal pain	14 (10)

Chang TT et al.Hepatology 2010

Tenofovir Adverse Events in Studies 102/103

Safety Summary During the Open-Label Period

	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 Argument

- All patients can be treated with NAs
  - NAs therapy is widely applicable with excellent and similar results
    - All stages of disease
    - Decompensated Patients
    - After Liver transplantation
    - Immunesuppressed Patients
    - Even in case of pregnancy (TDF, Telbivudine, LAM)

It is just an easier treatment regimen

- A pill per day

- No injections

- It is the prefer option for physicians and patients

IVer

Drawbacks of a NA

- Long therapy probably indefinite
- Potential side effects during long-term therapy
- Educate patients regarding adherence

In summary, I treat my HBeAg positive patient with a NA because

- NAs prevent the negative disease outcomes, and there is increasing evidence indicating a reduction on the risk of HCC
- NAs can be used in all patients, even those with contraindications to PEG-IFN
- NAs is preferred treatment by patients and physicians because their easier management and excellent tolerance and safety