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Long-term Efficacy and Safety of Nucleos/tide Analogues

- Long-term follow up data of entecavir and tenofovir

- Safety of nucleos/tide analogues


Entecavir Long-Term Data

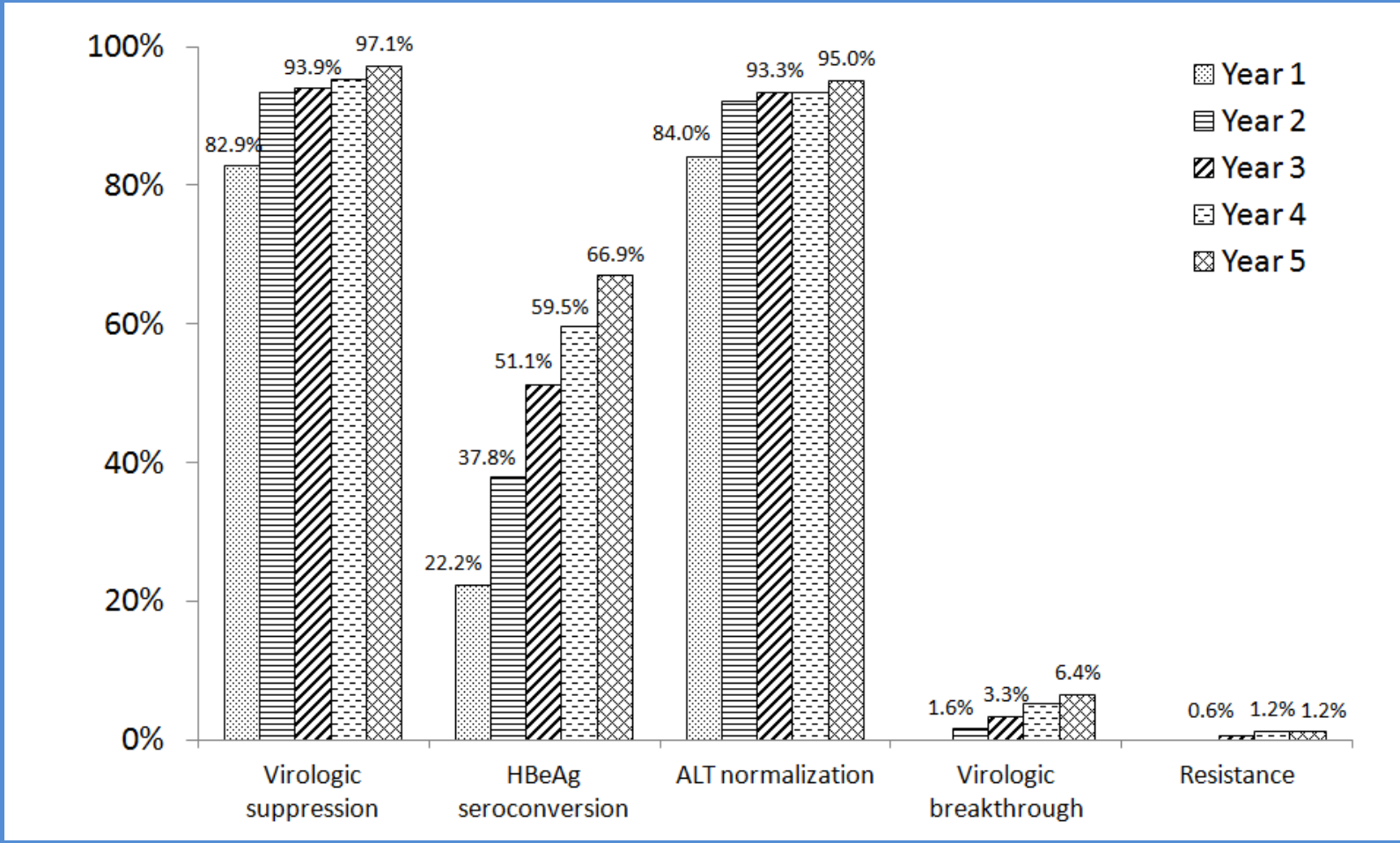
5 Year Continuous Entecavir

Hong Kong real-life cohort

- 222 patients
- 157 males (70.7%)
- HBeAg positive 90 (40.5%)
- HBV DNA 6.40 log IU/mL (range 3.3- > 8.1)

Seto WK et al. J Gastroenterol Hepatol (in press)

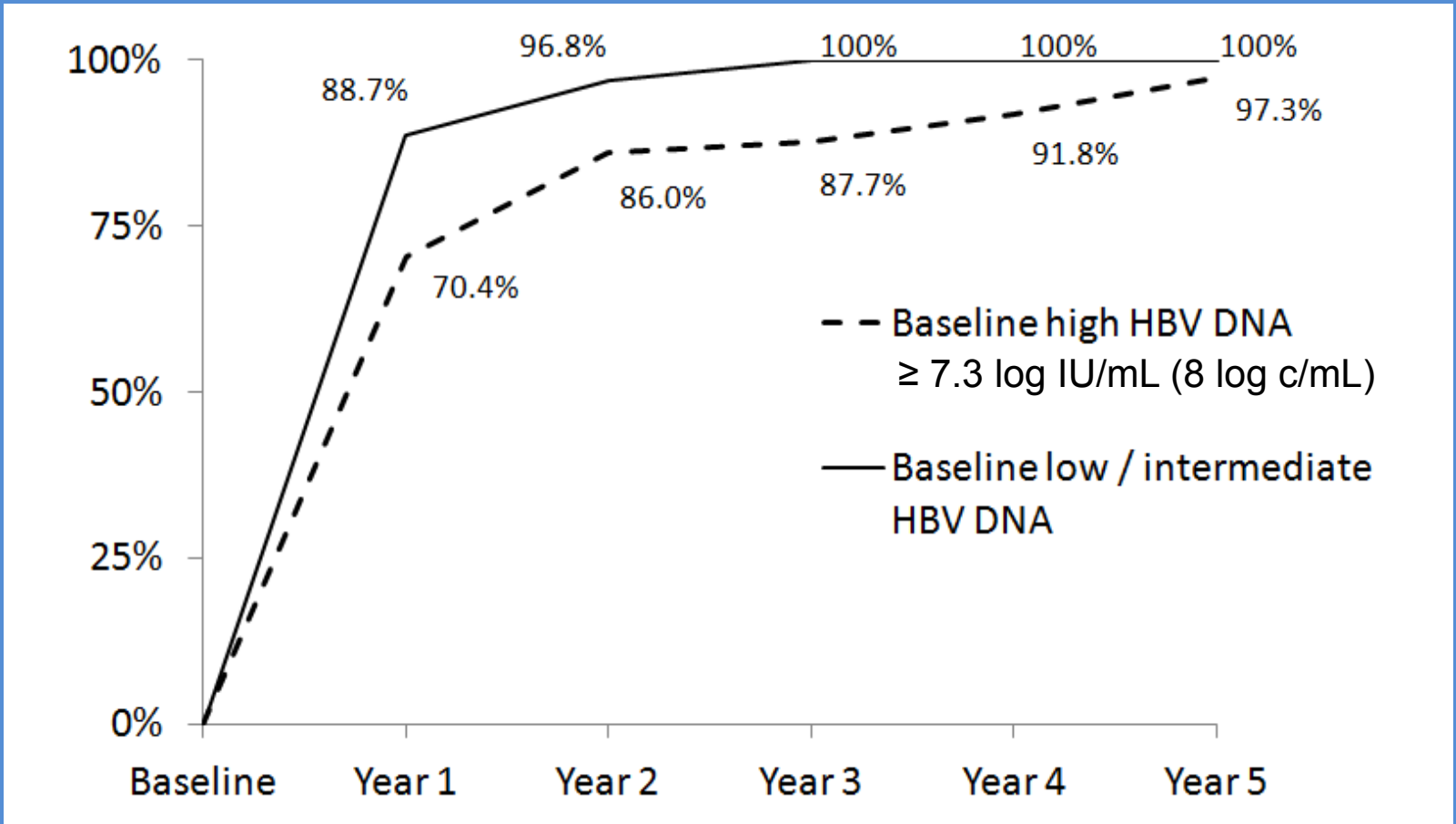
ETV 5-year Cumulative Outcomes



1 patient lost HBsAg at year 3.

Seto WK et al. J Gastroenterol Hepatol (in press)

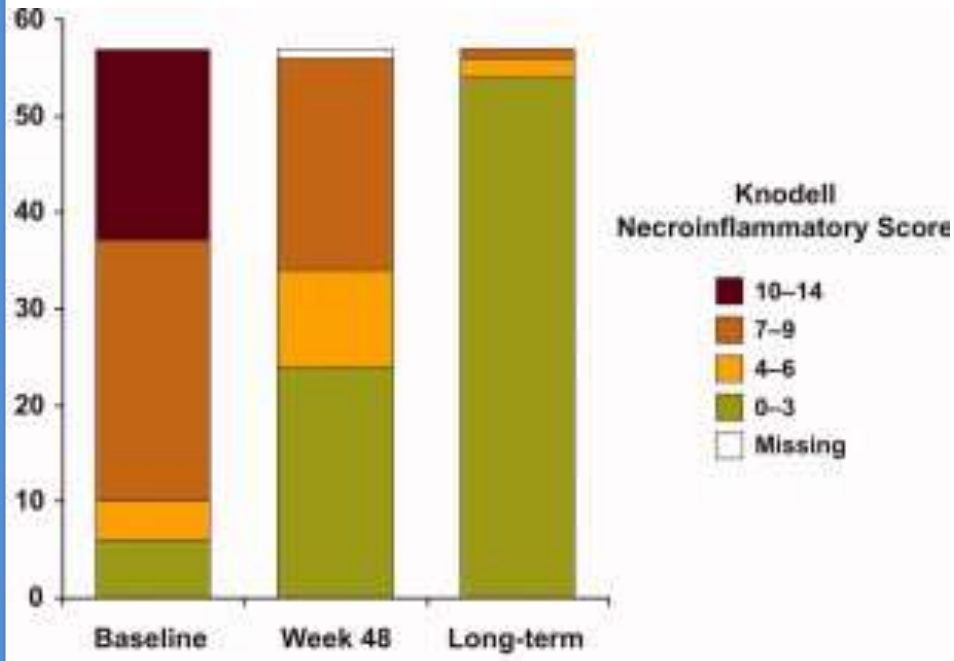
Virologic Suppression Stratified According to Baseline HBV DNA



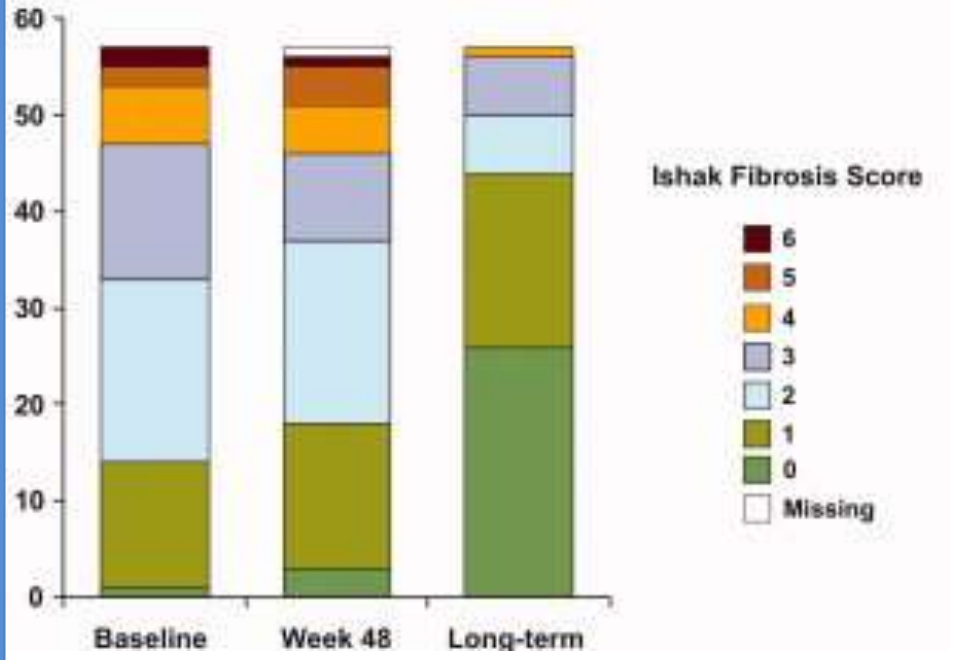
Lower limit of HBV DNA detection 20 IU/mL (COBAS assay)

Seto WK et al. J Gastroenterol Hepatol (in press)

Number of Patients



Number of Patients

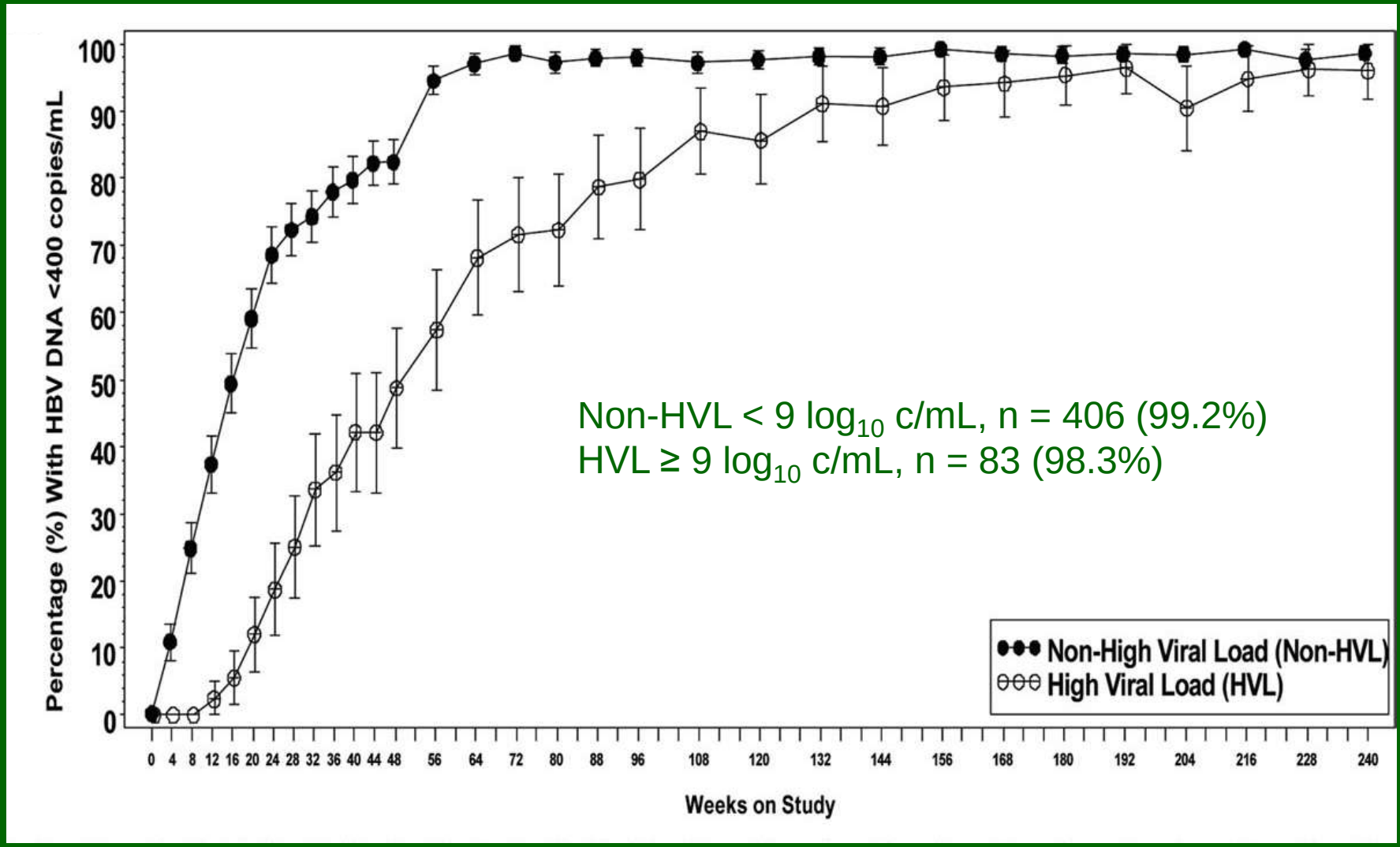


Histology Data from 57 patients with 3 Biopsies (Median time for third Bx 6 years)

ChangTT et al. Hepatology 2010; 52:886

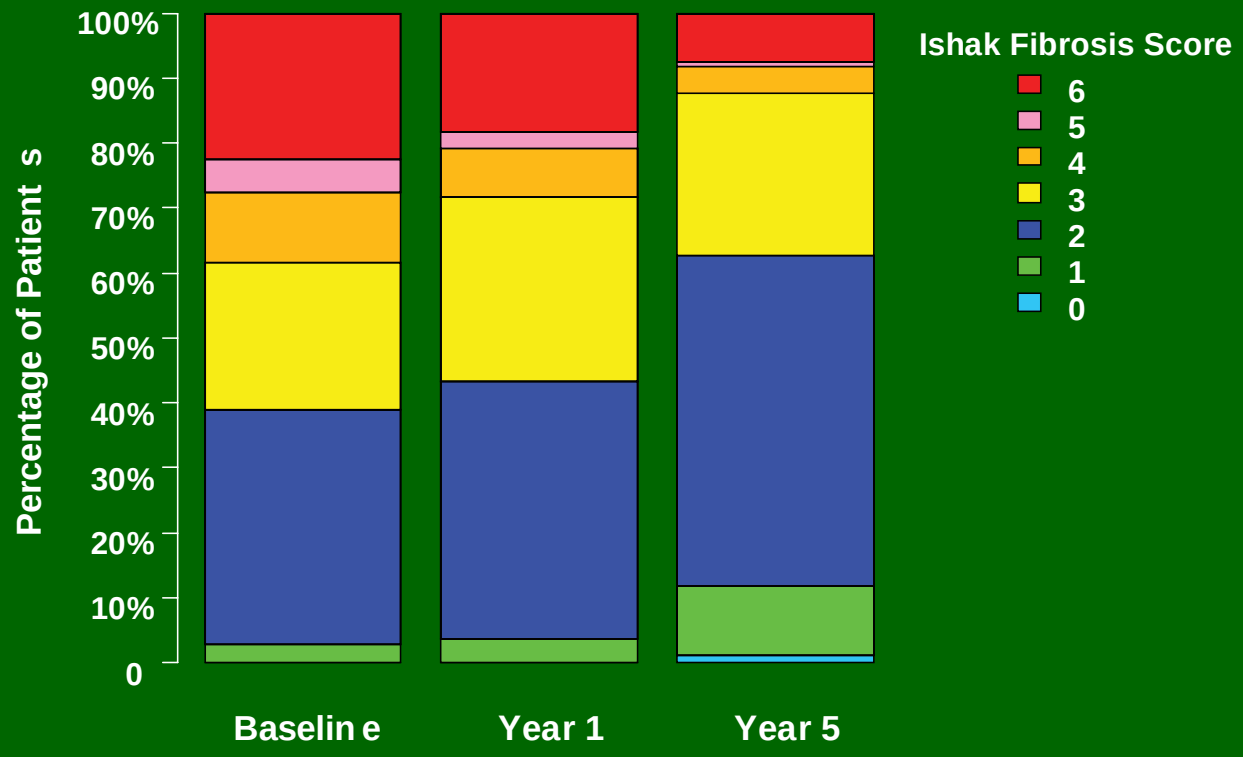
Tenofovir Long-Term Data

Continuous Tenofovir (± Emtricitabine)



Gordon SC et al. Hepatology 2013 ; 58: 505.

Fibrosis Scores at Baseline, Year 1, and 5



- 96% (335/348) either improved or did not change
- Percentage with cirrhosis (Ishak Score ≥5) decreased from 28% at baseline to 8% at Year 5

Marcellin et al. 2013; 381: 468.

Long-Term Tenofovir in Multi-Resistant CHB

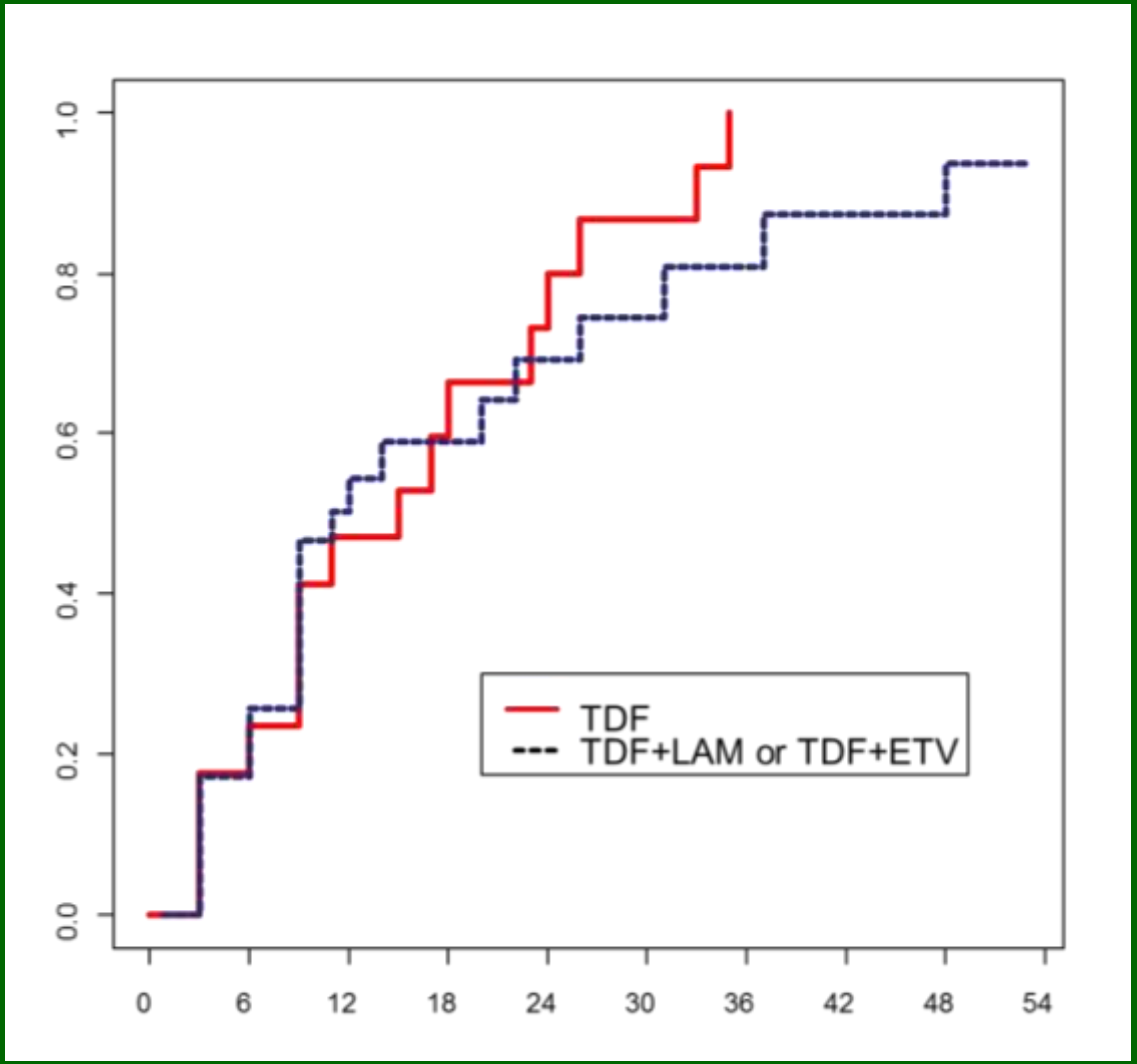
- 52 patients (75% males)
- Prior exposure:

LAM + ADV	12 (23.1%)
LAM + ADV + ETV	39 (75%)
ETV + ADV	1 (1.9%)

- Treatment regime: TDF 32.7% / TDF + LAM 28.9% / TDF + ETV 1.9%

Kim HJ et al. AASLD 2013

Cumulative Probability of HBV DNA PCR-ve



Probability of becoming PCR –ve:
25.0% at 3 mos; 74.2% at 24 mos; 96,7% at 48 mos

Kim HJ et al. AASLD 2013

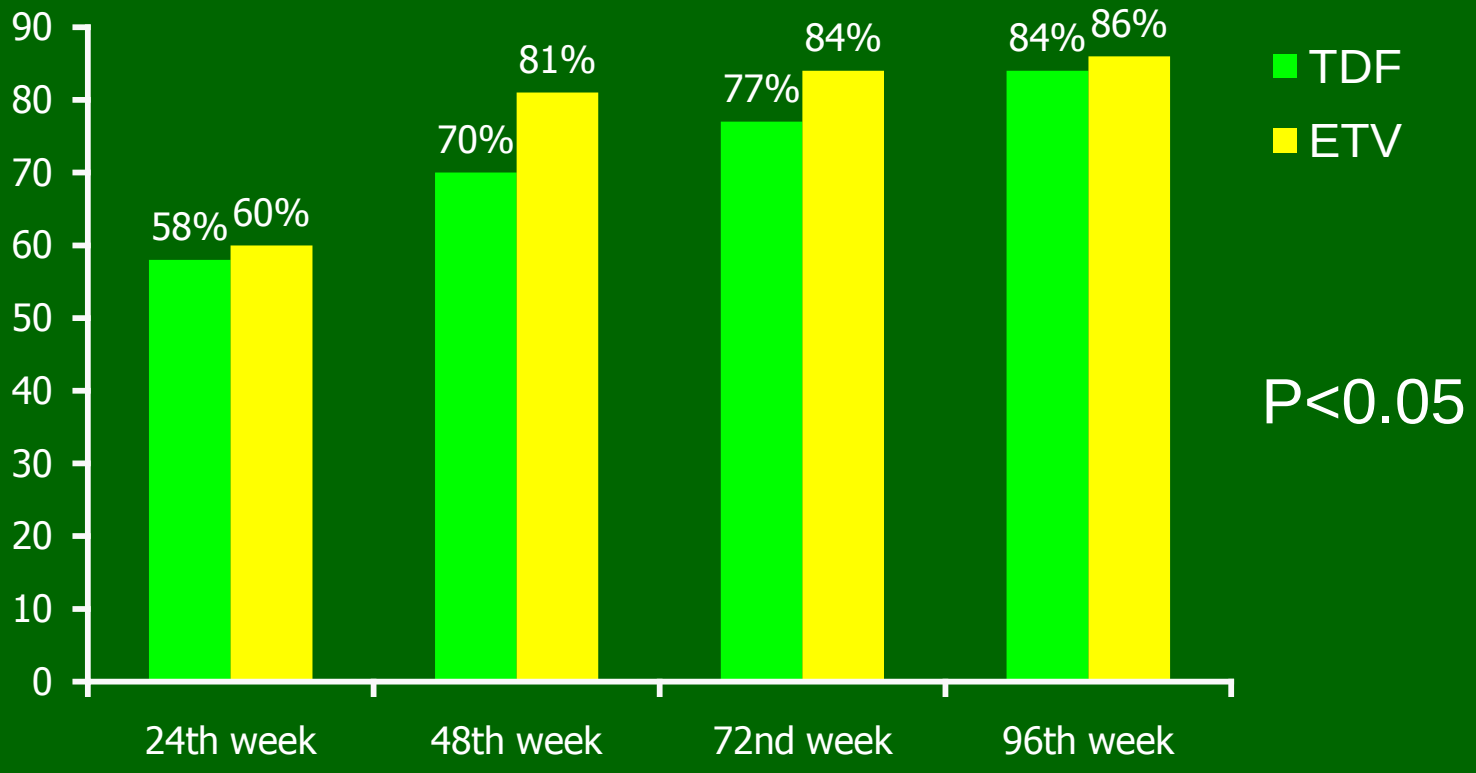
Entecavir vs Tenofovir: Real World Practice from Turkey

- 511 patients, 76% nucs naïve
- 32% HBeAg +, 38% cirrhosis

	entecavir	tenofovir	p
n	201	310	
HBV DNA (copies/mL)	6.88± 1.69	6.30 ± 1.82	<0.01
Rx naïve (%)	95	63	0.01

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

Undetectable HBV DNA on Treatment



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

Summary

- 5-7 years of entecavir and tenofovir induce viral suppression to below PCR detectability in 97-100% of patients
- Both agents cause improvement in necro-inflammation and fibrosis
- Tenofovir monotherapy is efficacious for patients with lam/adv/ent resistance

Safety/ Extrahepatic Effects of Nucs

Muscular Function

- Both clevudine and fialuridine cause severe myopathy (clinical trials terminated)
- Both preferentially phosphorylated by mitochondrial (rather than cytoplasmic) thymidine kinase
- Accumulated in mitochondria with ↑oxidative stress and toxicity

Tehrani OS et al. Eur J Nucl Med Mol Imaging 2008; 35: 1480.
Yoo BC et al. Hepatology 2007; 45: 1172.

Muscular Function

- In the licensed nucs
  - telbivudine associated with gr 1-2 CK elevation in 71% and grade 3-4 in 16% of 655 patients with 4 year FU
  - mostly no symptoms
  - muscle event in 40 patients (6.1%), myopathy in 4 patients
  - no correlation with CK elevation

Jung M et al. Hepatol Int 2011; 5: 117.

Muscular Function

- The incidence of CK elevation with adefovir, entecavir, tenofovir similar to comparative arms
- Overt myopathy rarely observed

Renal Function

- Adefovir
  - nephrotoxicity at week 48 with 30, 60, 120 mg were 13%, 27%, 50%
  - at 10 mg dose, up to year 5, 3% had rise in creatinine
  - site of injury proximal tubules where adefovir is taken up by the human organic anion transporter-1 (HOAT-1)

Hazdziyannis SJ et al. Gastroenterology 2006; 131: 1743.
Law ST et al. Clin Pharma Ther 2012; 37: 128.

Renal Function

- Tenofovir:
  - renal toxicity much lower
  - pooled data of 426 patients over 144 weeks, 2% rise in creatinine and none with eGFR <50 mL/min
  - hyperphosphaturia may occur

Marcellin P et al. J Hepatol 2011; 54: S296.
Vigano et al. J Hepatol 2013; 58: S316.

- Lamivudine and entecavir: no renal toxicity

Renal Function

- Telbivudine:
  - 2 year treatment in the GLOBE study showed increase in eGFR of 8.5%, and maintained for 4-6 years of FU
  - renal function also improved in patients with baseline eGFR of 60-89 mL/min/1.73 m^2, >50 years old, cirrhosis and liver decompensation

Gane E et al. Gastroenterology 2013; Epub.

Bone Mineral Density

- Mainly with adefovir and tenofovir
  - hypophosphatemia leading to osteomalacia
  - reported mainly in HIV patients
  - in CHB patients, may actually be related to vitamin D deficiency rather than nucleoside treatment
  - in a cohort of 217 patients (142 on TDF, 75 on ETV), baseline vit D was low, with no change after 12 months of treatment

Nguyen HL et al. Hepatology 2011; 54: 610A

Neuropathy

- Increased risk of peripheral neuropathy (PN) in a study of 159 HBeAg-positive patients on telbivudine, peg IFN or tel + peg IFN, 9 (5.66%) develpoed PN, with 8 in the combo arm
- ? related to mitochondrial DNA reduction and carnitine reduction

Marcellin p et al. J Hepatol 20152: S6-7
Famularo G et al. AIDS 1997; 11: 185.

Pregnancy

- No significant effect
- Studies with LAM, TEL and TDF, no increase in abortion or birth abnormalities
- In fact LAM and TEL have been used in the third trimester to reduce maternal HBV DNA with resultant decrease in transmission to infants

Han GR et al. J Hepatolol 2011; 55: 1215.
Siberry GK et al. AIDS 2012; 26: 1151.

Lactic Acidosis

- Black box warning for all nucs
- LAM & TDF reported only in HIV patients with other antiretroviral agents
- A single report of 5 /16 patients with severe liver decompensation and high MELD score on entecavir developed lactic acidosis; no other report

Lang CM et al. Hepatology 2009; 50: 2001.


Conclusions

Conclusions

- The two first line nucleos/tide analogues, entecavir and tenofovir, suppresses HBV DNA to below PCR detectability in 97-99% of patients by year 5 of treatment
- Both agents decrease necroinflammation and fibrosis (with tenofovir shown to reverse cirrhosis)

Conclusions

- Licensed nucleos/tides are essentially safe
- Telbivudine may cause myopathy in a small percent of patients
- Tenofovir may cause hypophosphatemia and mild elevation of creatinine in a small proportion of patients


FORWARD

Thank You!!