2018 11th Paris Hepatology Conference

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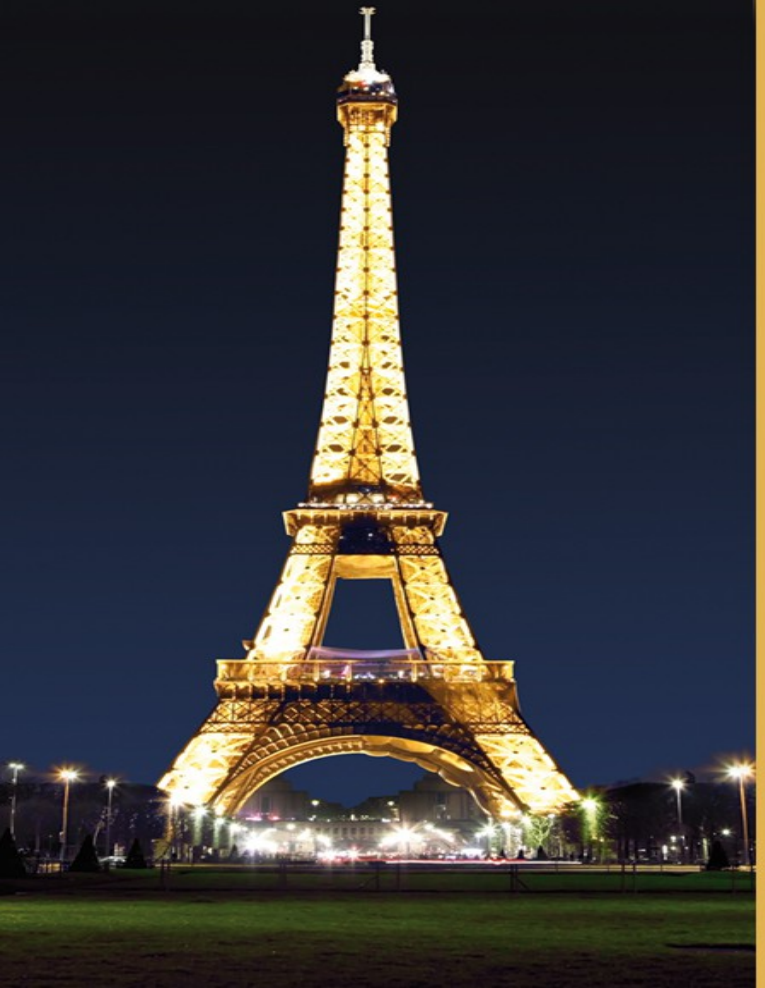

Long term safety and efficacy of NUCs

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Disclosures

- Received honoraria for speaking at educational events or consulting from:
  AbbVie, Arrowhead Pharmaceuticals,
  Bristol-Myers Squibb, Gilead Sciences, Janssen,
  Merck Sharp & Dohme

EASL JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

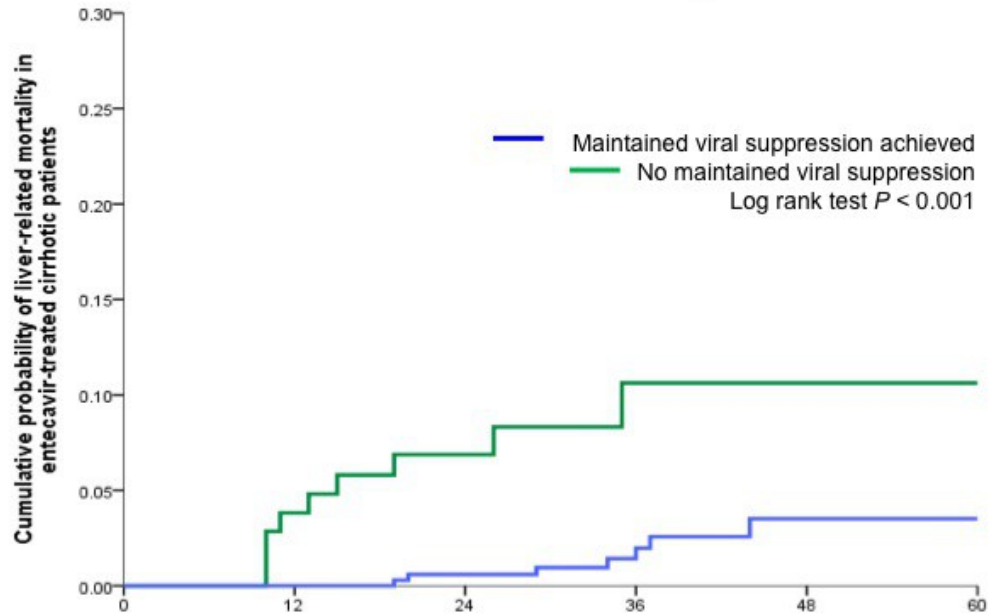
European Association for the Study of the Liver*

Goals of therapy

The main goal of therapy for patients with chronic HBV infection is to improve survival and quality of life by preventing disease progression, and consequently HCC development. Additional goals of antiviral therapy are to prevent mother to child transmission, hepatitis B reactivation and the prevention and treatment of HBV-associated extrahepatic manifestations.

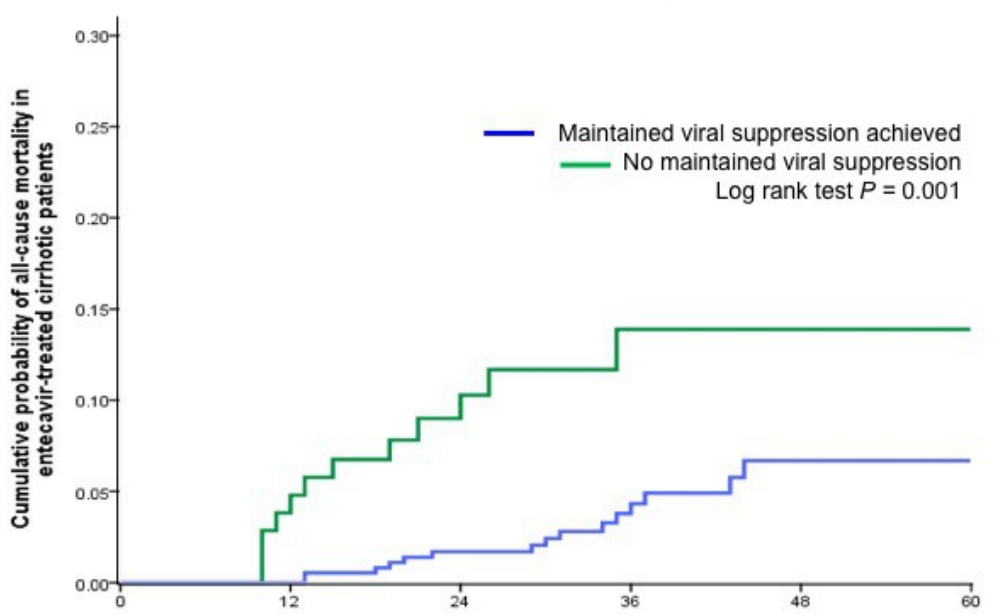
Maintained virologic response is associated with a lower probability of mortality in cirrhotic patients

Liver Related Mortality



Patients at risk						
Maintained viral suppression	377	374	312	178	80	21
No maintained viral suppression	105	99	71	36	13	2

All Cause Mortality



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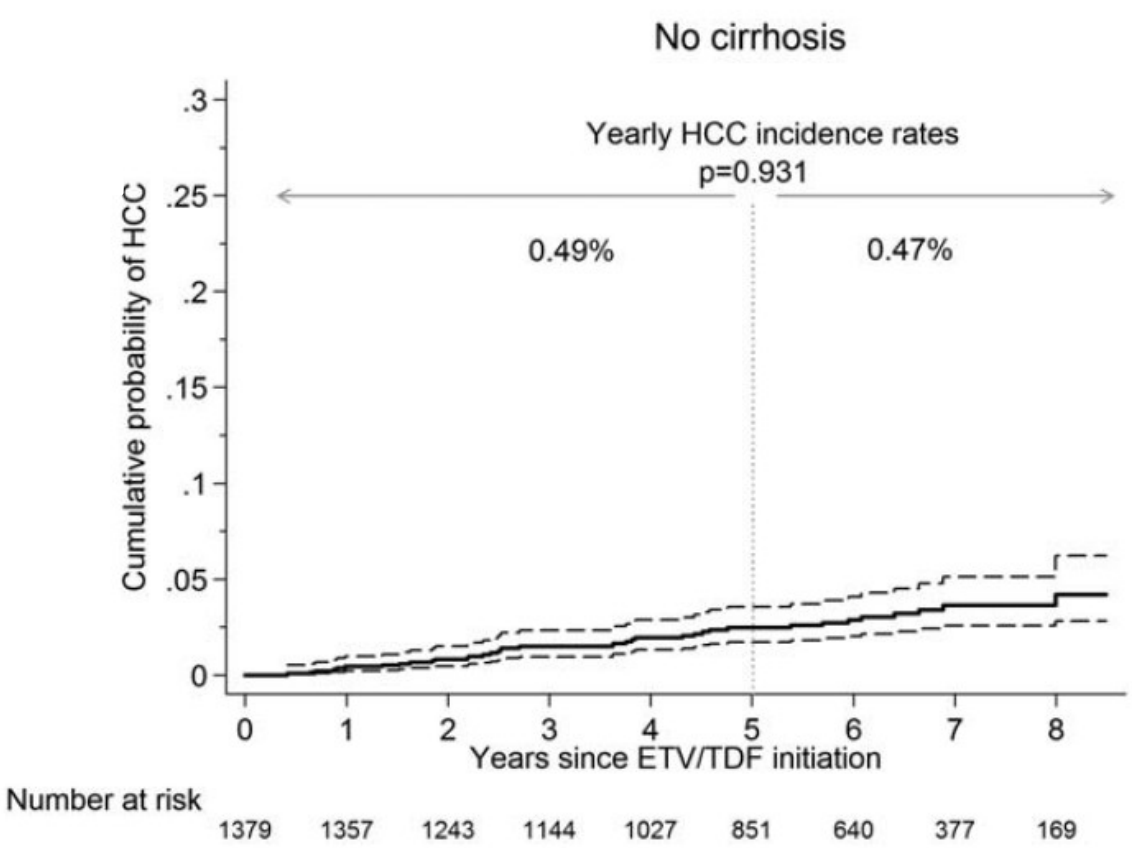
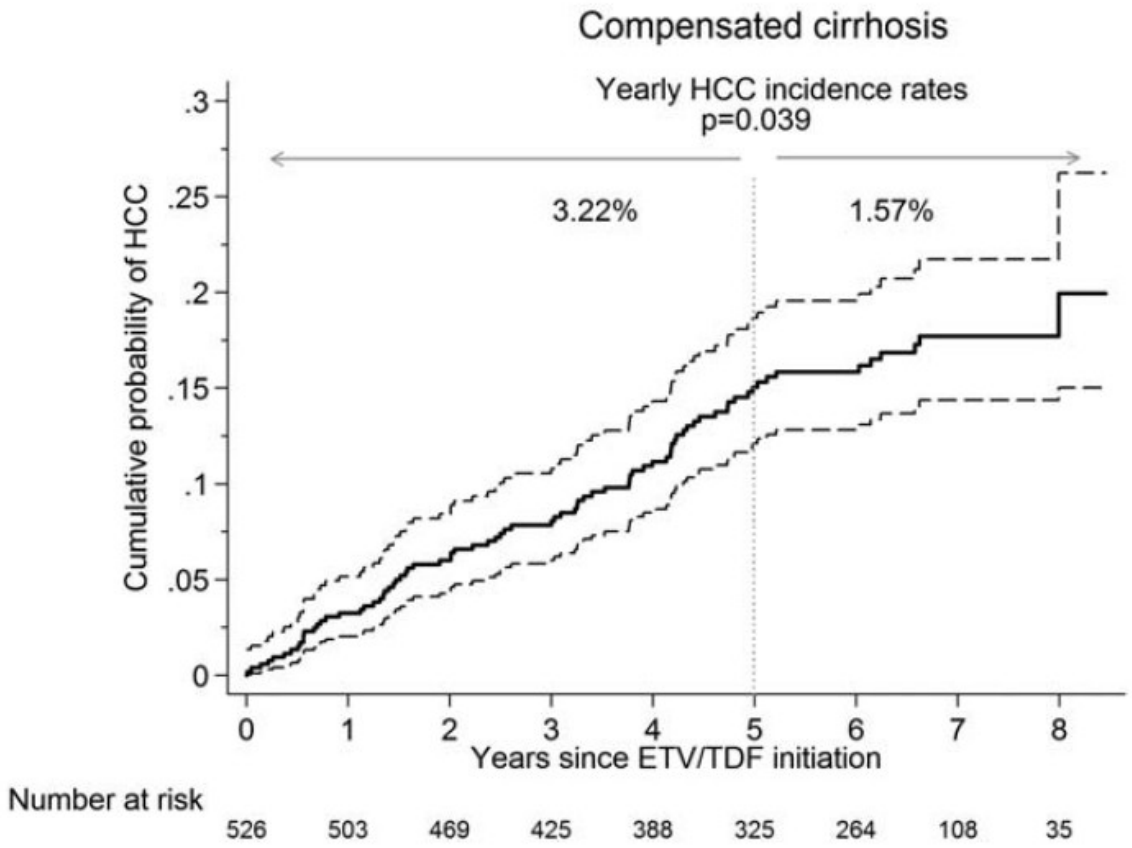
No maintained viral suppression	105	99	71	36	13	2

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

Risk of Hepatocellular Carcinoma Decreases After the First 5 Yrs of ETV or TDF in Caucasians With Chronic Hepatitis B

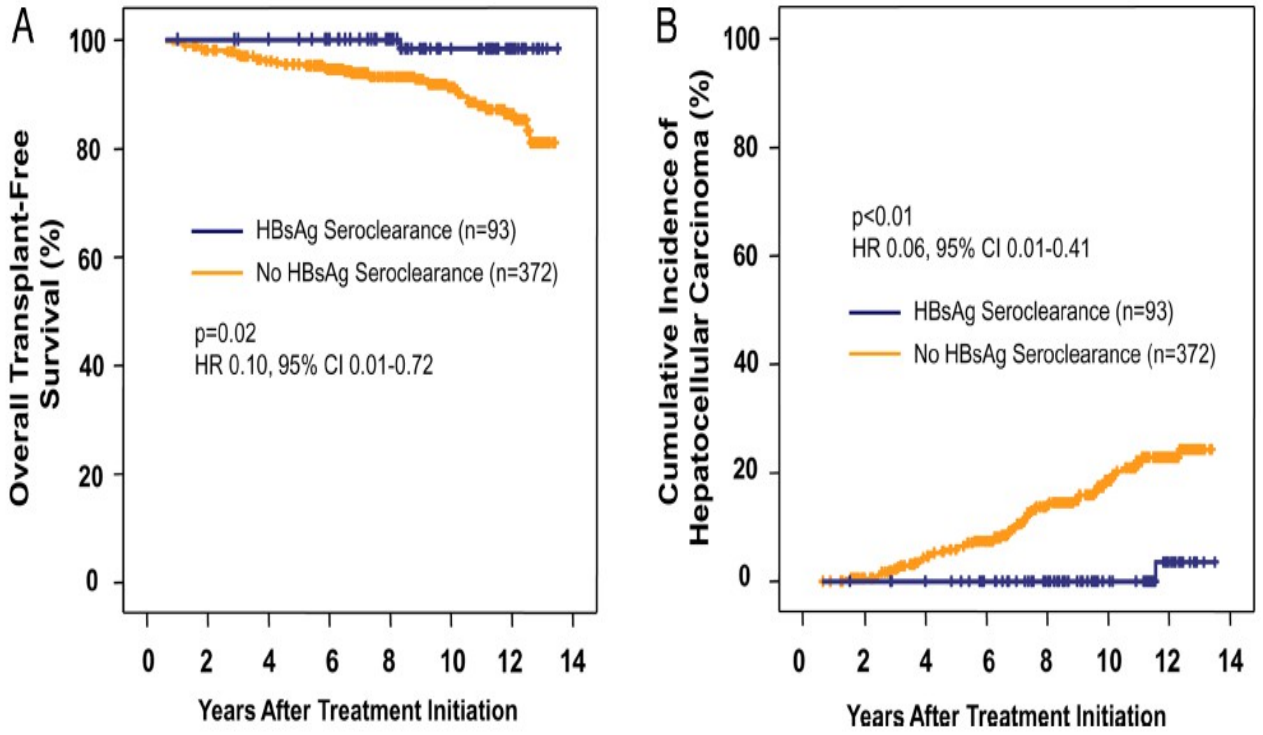




Papatheodoridis G V et al. Hepatology 2017;66:1444-1453

Clinical Outcomes After NUCs Therapy in Relation to HBsAg Loss

6-year follow-up of 5409 CHB patients who were treated with lamivudine or entecavir
110 achieved HBsAg loss (0.33% annual)

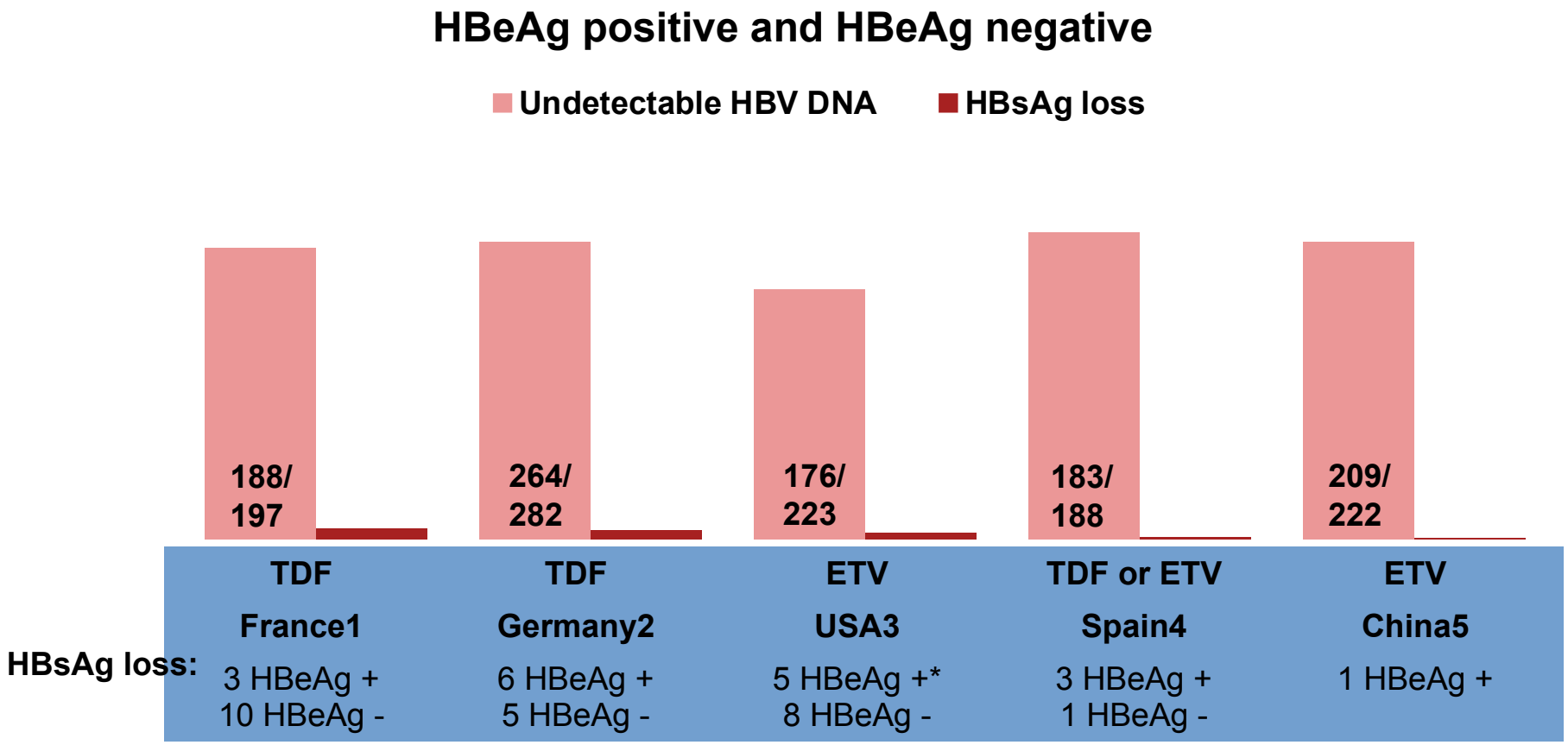


HBsAg loss after NAs was associated with favourable clinical outcomes

Kim GA et al- Gut 2014;63:1325-–32

ETV or TDF in Real-world Setting

HBV DNA suppression and HBsAg loss at Year 3 of Therapy



*Data at year 5 of therapy; σ estimated data
TDF: tenofovir disoproxil fumarate; ETV: entecavir

1. Marcellin P, et al. Dig Dis Sci 2016;61(10):3072-83; 2. Petersen J, et al. Dig Dis Sci 2016;61(10):3061-71; 3. Ahn J, et al. Aliment Pharmacol Ther 2016;43(1):134-44; 4.Riveiro-Barciela M, et al. Dig Dis Sci 2017;62(3):784-793; 5. Seto KW, et al. J Gastroenterol Hepatol 2014;29(5):1028-34

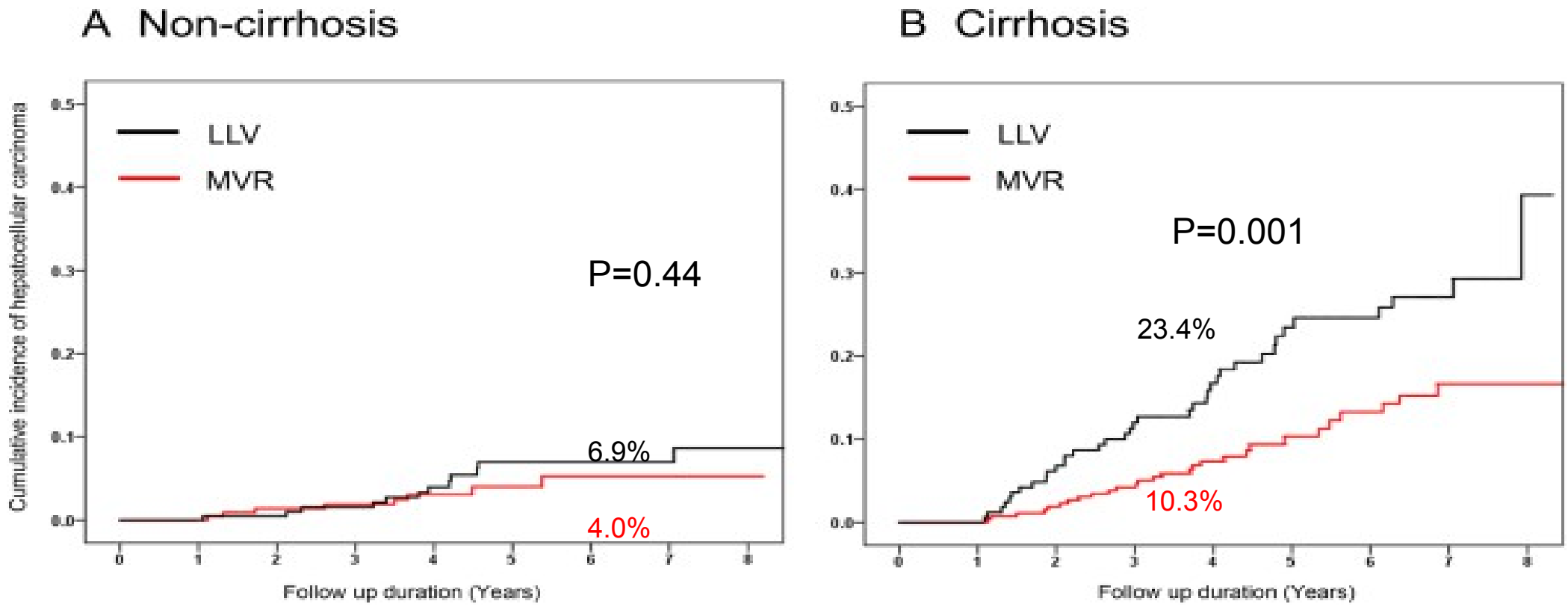
Persistent low-level viremia on ETV and TDF

AASLD Recommendations	EASL Recommendations
• Persistent HBV DNA < 2. 000 UI/mL but detectable • On ETV and TDF to continue monotherapy • Must ensure drug adherence	• Still matter of debate • No relevant in patients without cirrhosis • Patients with decompensated cirrhosis have a higher risk of HCC • Combining NUCs can be considered

Terrault N, et al. Hepatology 2016;63:261-83

Low level viremia is associated with increased HCC risk in cirrhotic patients

337 patients on ETV with low level viraemia (HBV DNA <2000 IU/ml) vs 498 patients with maintained virological response (HBV DNA <12 IU/ml)

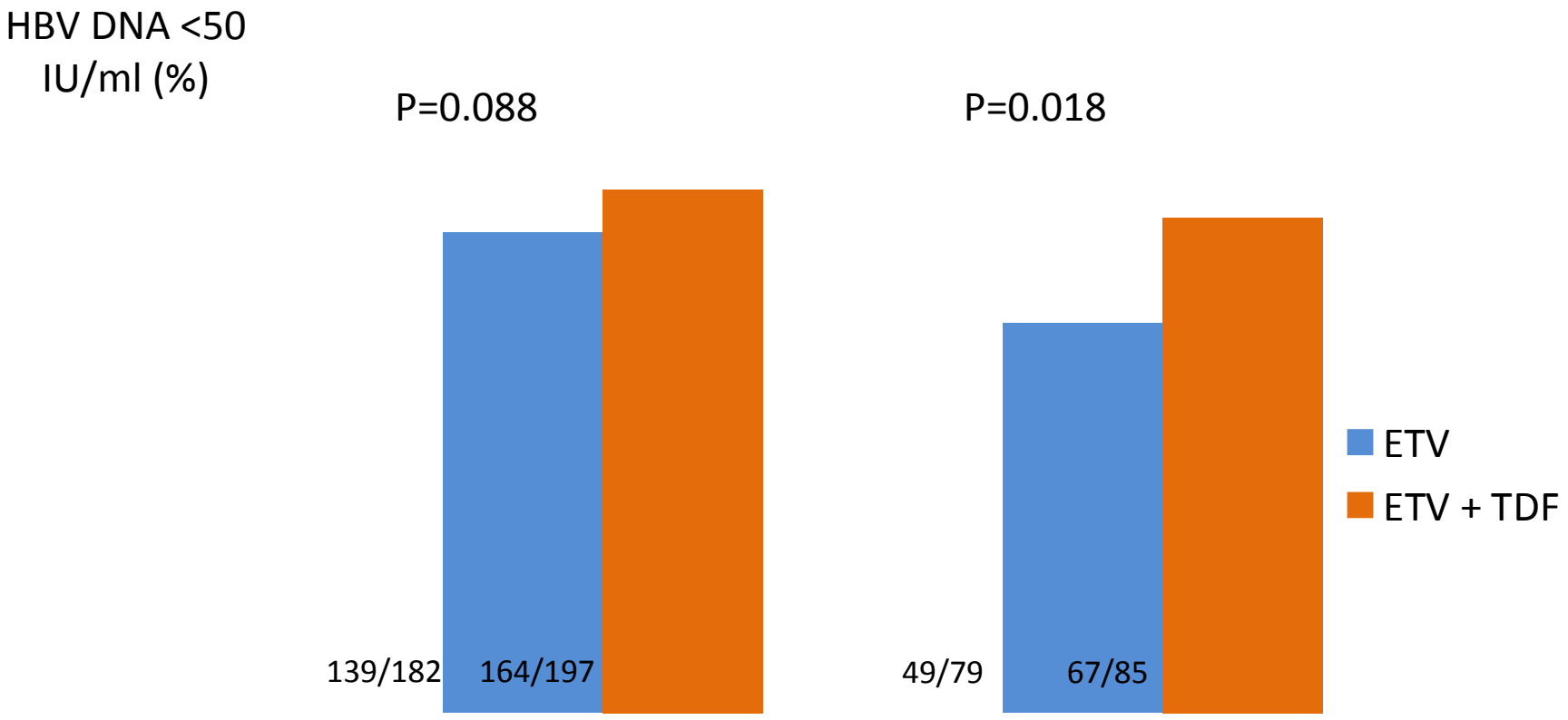


Adjusted HR = 1.65, 95% CI 0.65-4.71

Adjusted HR = 2.2, 95% CI 1.34-3.60

Kim JH, et al. Hepatology 2017;66:335-343

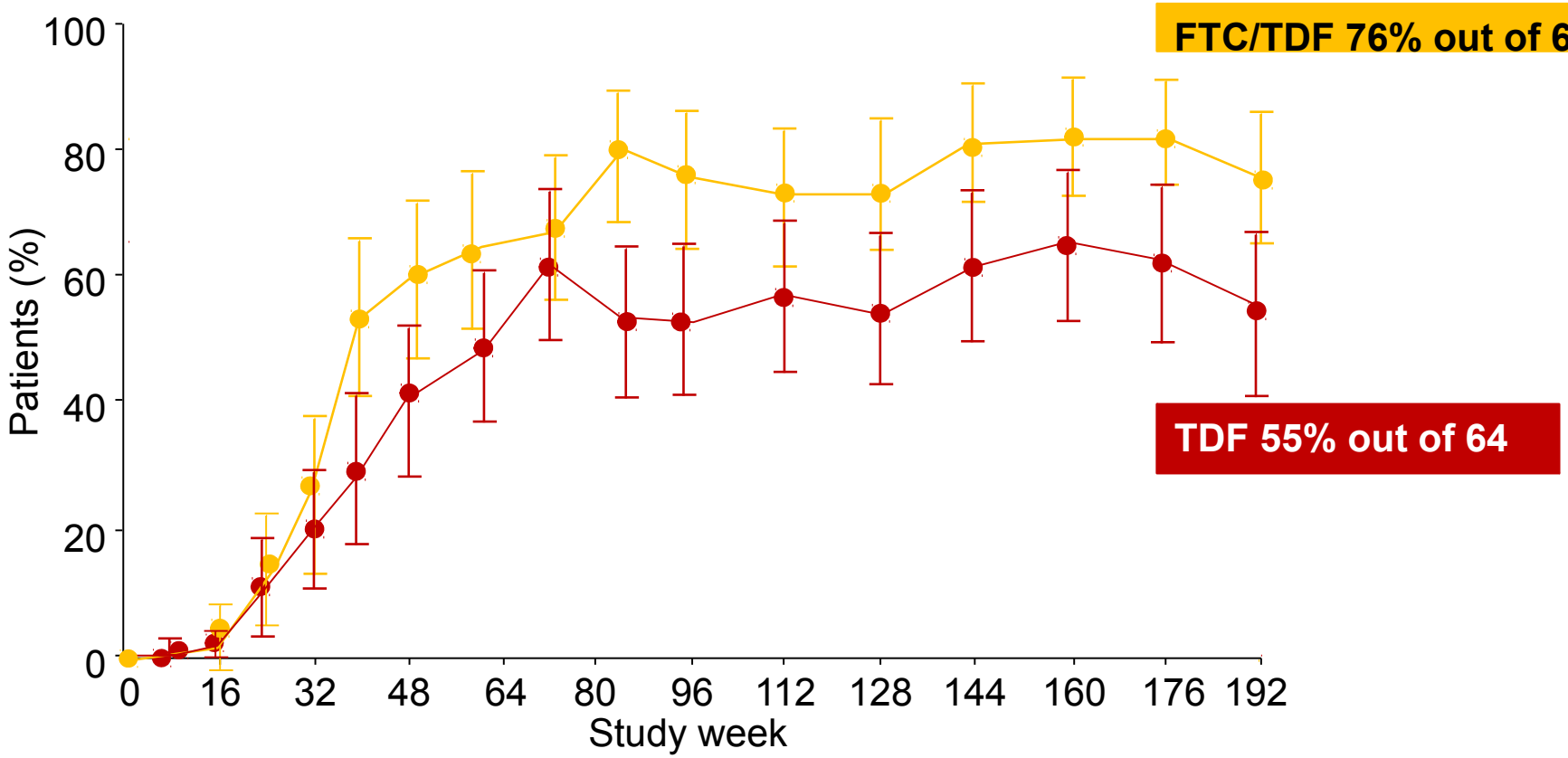
Combination of ETV and TDF has higher HBV DNA suppression in HBeAg positive patients with high viral load (BELOW study)



Randomized, open-label, multi-center trial
Treatment naïve HBeAg positive (n=264) and HBeAg negative (n=115) CHB patients
ETV vs ETV + TDF for 96 weeks

Lok AS, et al. Gastroenterology 2012;143:619-28

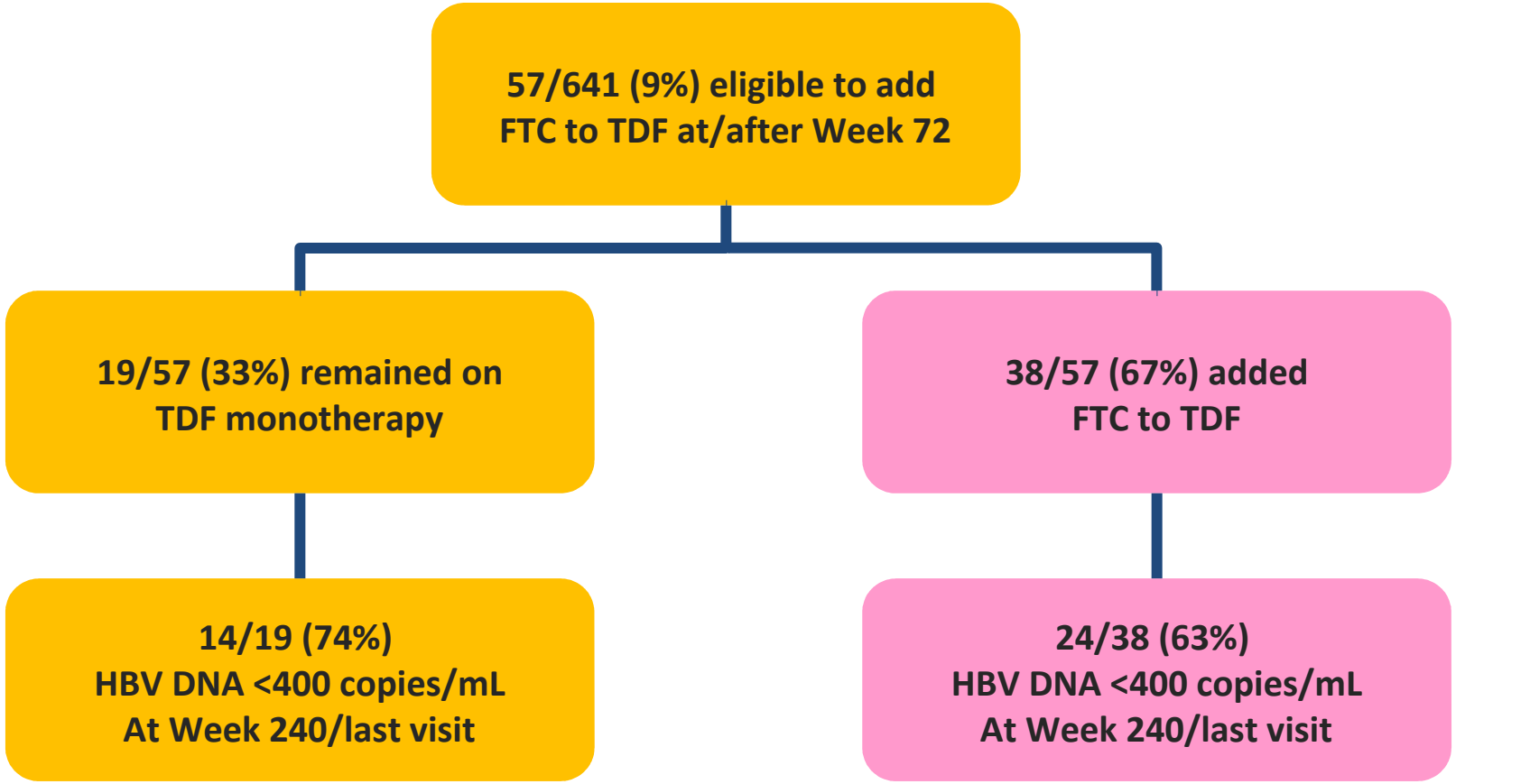
Combination of tenofovir and emtricitabine improves viral suppression in HBeAg-positive patients with high viral load and normal ALT levels



- 6% TDF patients and 2% TDF/FTC achieved HBeAg loss
- 5% TDF patients and 0% TDF/FTC achieved HBeAg seroconversion
- There were no cases of HBsAg loss/seroconversion
- No patients developed HCC or clinical events

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

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

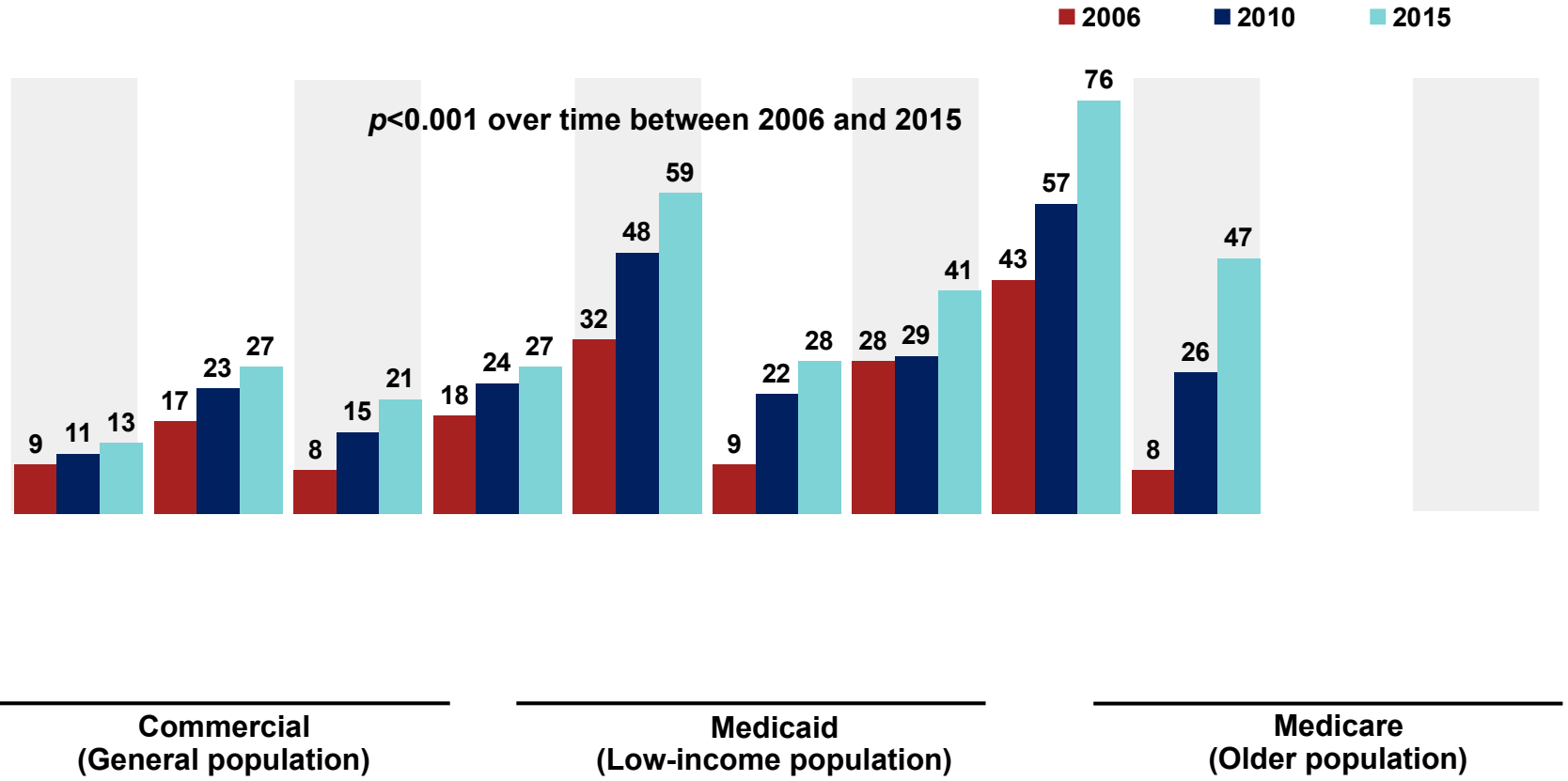


All subjects analyzed with >400 copies/mL had no TDF resistance detected.

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

The Proportion of CHB Patients with Metabolic Comorbidities

Retrospective, observational study to determine prevalence of comorbidities in 44,026 CHB patients from Commercial, Medicare, and Medicaid databases from 2006–2015



The proportion of CHB patients with metabolic comorbidities significantly increased between 2006 and 2015

Nguyen, EASL 2017, PS-107

Long-Term Safety of Nucleos(t)ides Analogues in Real-world

Study	Follow-up (years)	No	NAs	AEs Discontinuation	Lactic Acidosis	Renal-related Events	
						TDF	ETV
USA1	5	658	ETV	8 (1.2%)	2 (0.3%)	—	2 (0.3%)
China2	5	222	ETV	0 (0%)*	0 (0%)	—	N/A
Spain3	4	611	TDF/ETV	0 (0%)	0 (0%)	7 (1.7%)	4 (2.1%)
USA4	N/A	160	TDF/ETV	0 (0%)	0 (0%)	3 (3.8%)	11 (13.8%)
Spain5	3	158	TDF/ETV	0 (0%)	0 (0%)	2 (2%)	2 (3%)
France6	3	440	TDF	23 (5%)	0 (0%)	7 (1.6%)	—
Germany7	3	400	TDF	11 (2.8%)	0 (0%)	5 (1.3%)	—

*2 patients discontinued therapy for ETV resistance and 1 for pregnancy

1Ahn J, *et al.* Aliment Pharmacol Ther 2016;43(1):134-44; 2Seto KW, *et al.* J Gastroenterol Hepatol 2014;29(5):1028-34; 3Riveiro-Barciela M, *et al.* Dig Dis Sci 2017;62(3):784-793; 4Gish RG, *et al.* Clin Gastroenterol Hepatol 2012;10(8):941-6; 5Rodríguez-Nóvoa S, *et al.* J Clin Gastroenterol 2016;50(9):779-89; 6Marcellin P, *et al.* Dig Dis Sci 2016;61(10):3072-83; 7Petersen J, *et al.* Dig Dis Sci 2016;61(10):3061-71

Review of Long-term safety of NUCs in HBV-Monoinfected patients

- TDF registration study (8 years) showed minimal event (2%) in subjects with normal eGFR
- Real Life studies with TDF showed controversial results
- Different parameters and definitions to measure renal alterations
- 8 cases of TDF-induced Fanconi syndrome have been published
- Optimal management of the few cases of renal alterations remains to be defined
  - -Dose adjustment of ETV
  - - TAF

Lampertico P et al . Aliment Pharmacol Ther. 2016 Jul;44(1):16-34.

ETV discontinuation or dose adjustment in the Enumerate Study

Cohort of 658 patients
(Naïve; median FU 4 yrs)

→ **108 discontinued ETV (16.4%)**

Reasons for ETV discontinuation (N= 108)	
Self discontinuation or loss FU	54 (50%)
Reached therapeutic endpoint	25 (23%)
Suboptimal clinical response	11 (10%)
Adverse events • Lactic acidosis • GI or dermatologic	8 (7%) 2 6
Pregnancy related	6 (6%)
Suspected ETV resistance	4 (4%)

27 ETV was substituted

- 24 TDF
- **3 TDF + 3TC**

- **Two patients required dose reduction due to deterioration of renal function**
- **No patients required haemodialysis or ETV discontinuation due to renal insufficiency**

Ahn J, *et al.* Aliment Pharmacol Ther 2016;43(1):134-44

ETV Regimen adjustment in The Enumerate study

Cohort of 658 patients with a median follow up of 4 years

53 (8%) increase ETV from 0.5 to 1 mg

- **40 Incomplete suppression**
- **2 Viral Breakthrough**
- **11 Unspecified reasons**

27 (4.1%) treatment adjustment

25 TDF was added

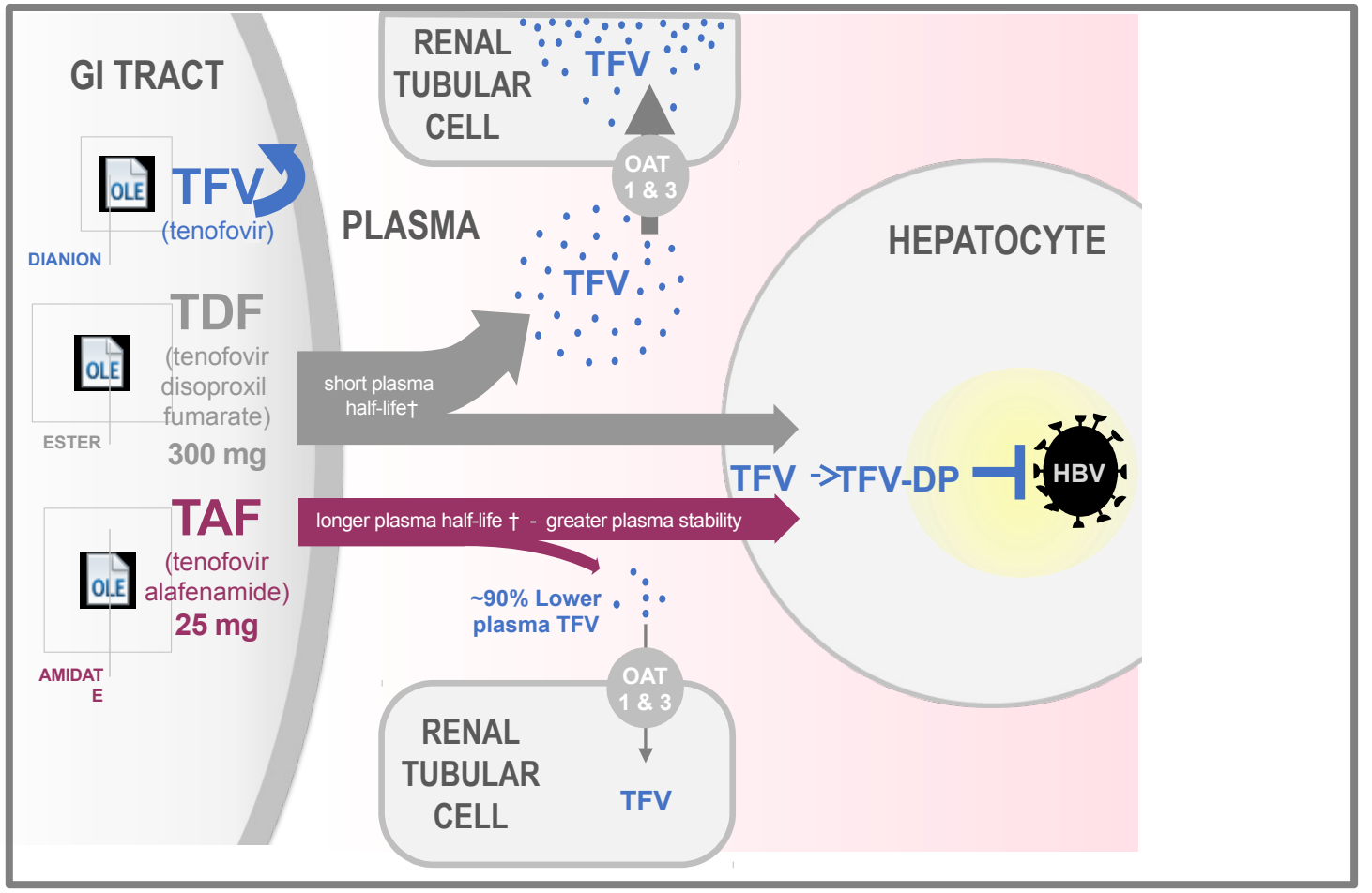
- **2 suspected resistance**
- **22 incomplete suppression**
- **1 unknown reasons**

2 ADV was added

- **1 suspected resistance**
- **1 incomplete suppression**

Ahn J, *et al.* Aliment Pharmacol Ther 2016;43(1):134-44

Tenofovir Alafenamide (TAF): Prodrug of Tenofovir Mechanism of the action



† T1/2 based on *in vitro* plasma data - TDF = 0.4 minutes, TAF = 30-90 minutes.

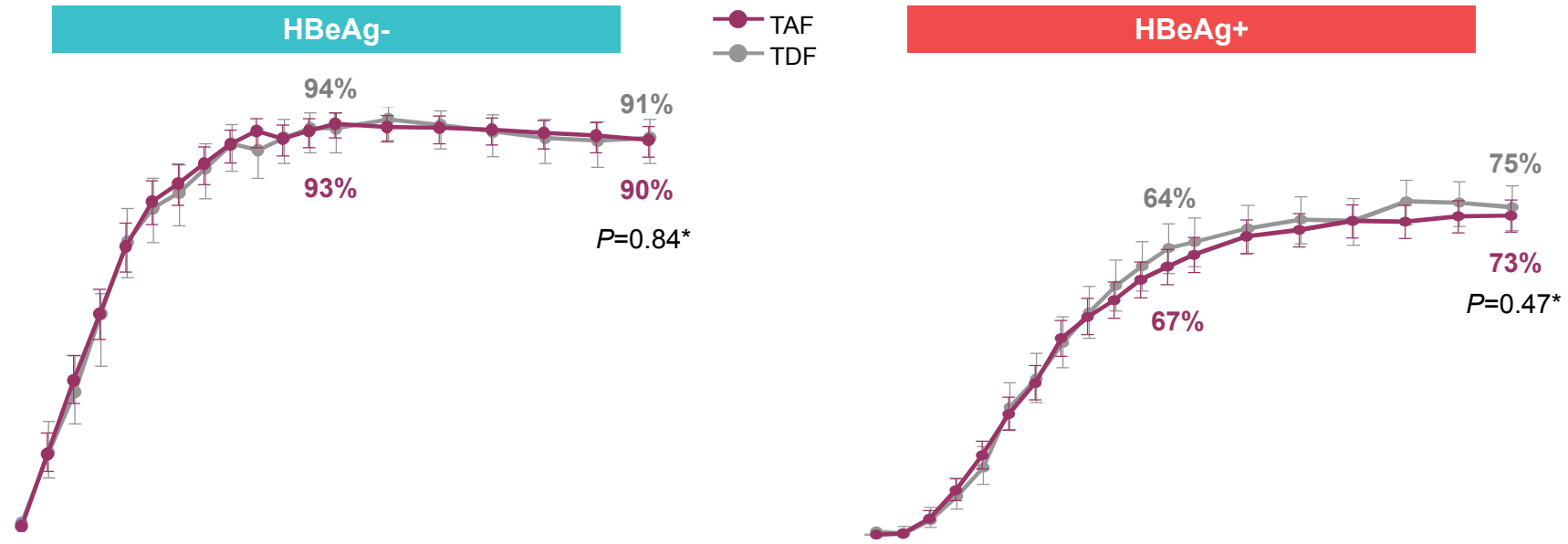
Lee W et. *Antimicr Agents Chemo* 2005;49(5):1898-1906. Birkus G et al. *Antimicr Agents Chemo* 2007;51(2):543-550. Babusis D, et al. *Mol Pharm* 2013;10(2):459-66; Ruane P, et al. *J Acquir Immune Defic Syndr* 2013; 63:449-5. Sax P, et al. *JAIDS* 2014. 2014 Sep 1;67(1):52-8. Sax P, et al. *Lancet* 2015. Jun 27;385(9987):2606-15. Agarwal K et al. *J Hepatology* 2015; 62: 533-540; Buti M et al. Lancet G&H 2016; doi: 10.1016/S2468-1253(16)30107-8; Chan HLY et al. Lancet G&H 2016; doi: /10.1016/S2468-1253(16)30024-3

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Antiviral Efficacy of TAF and TDF at Week 96

Rates of Viral Suppression (ITT; M=F)

HBV DNA <29 IU/mL



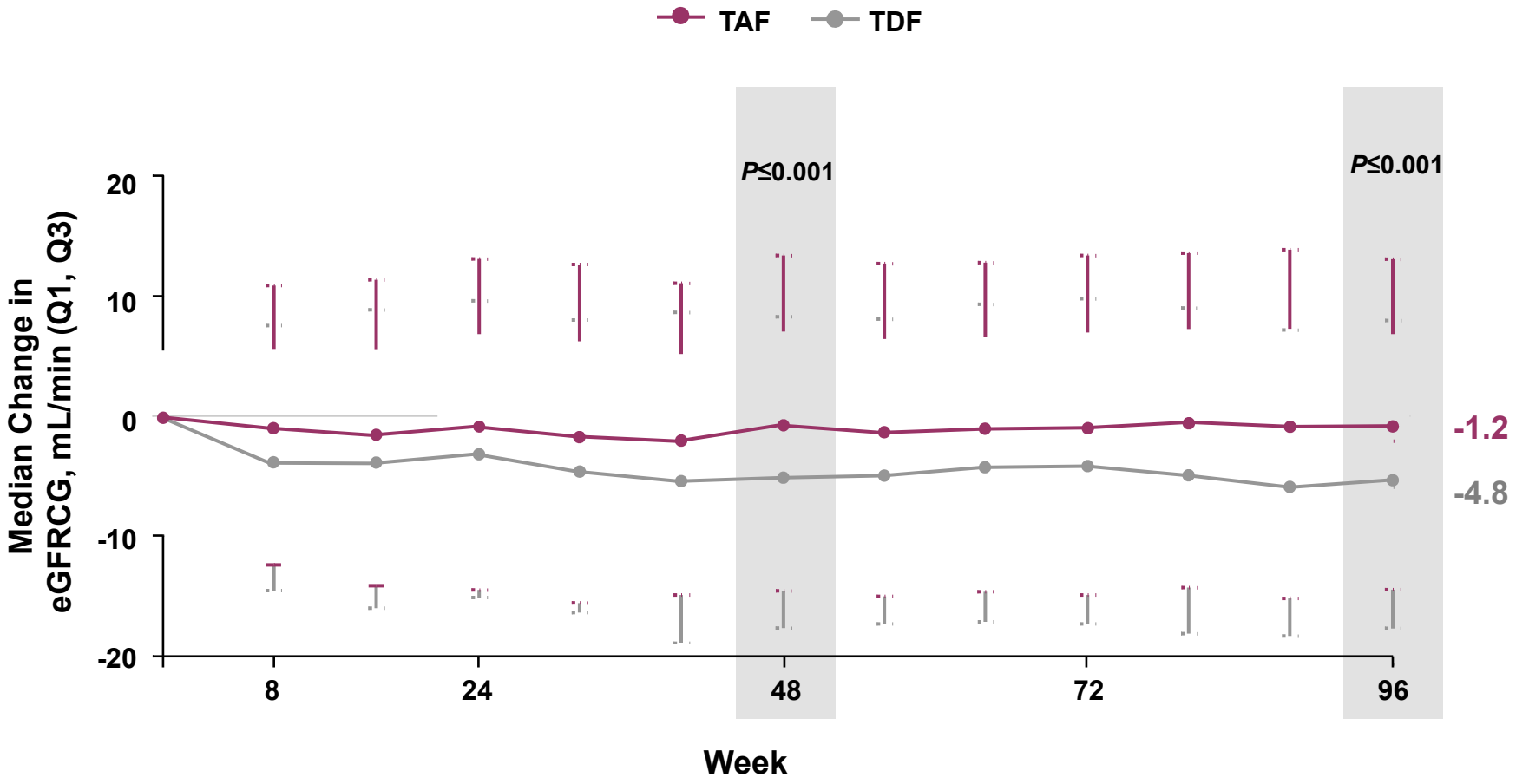
- **No resistance was detected through 96 weeks**
- **HBsAg loss < 1%**

*Adjusted for baseline HBV DNA level and oral antiviral treatment status strata
M=F: Missing =Failure

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206; Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95. Agarwal, EASL 2017, FRI-153; Brunetto, EASL 2017, PS-042; Gilead,

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Renal Safety Through Week 96

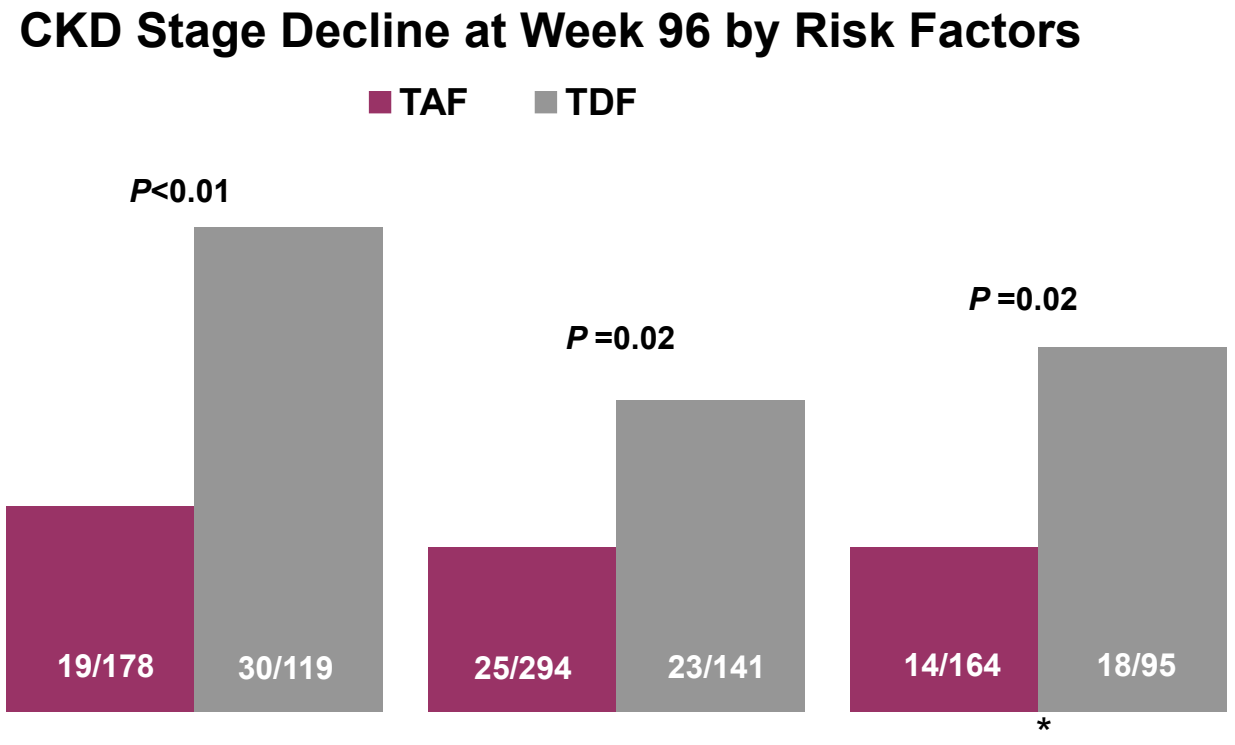


TAF treatment had significantly less impact on eGFR than TDF at all time points

Chuang, EASL 2017, SAT-171

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Renal Laboratory Parameters in CHB Patients Treated with TAF or TDF

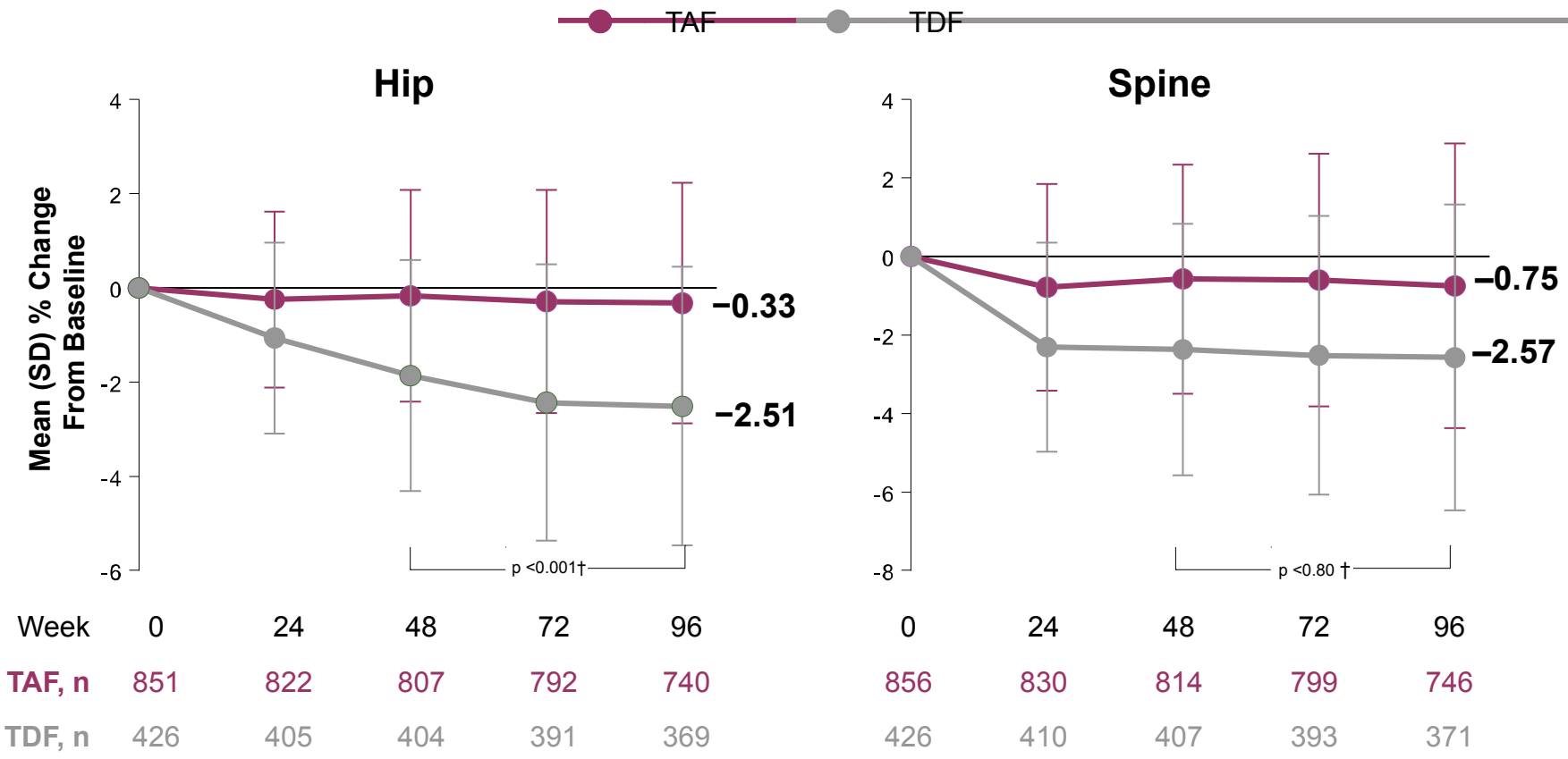


CHB patients with known risk factors for CKD showed smaller declines in their CKD stage with TAF vs TDF

*As determined by medical history or concomitant medication; p-values from rank analysis of covariance adjusting for baseline clinical status for treatment comparison
CVD, cardiovascular disease; DM, diabetes mellitus, HTN, Hypertension; HL, hyperlipidemia
Chuang, EASL 2017, SAT-171

Study 108 and 110: Phase 3 CHB Studies: TAF vs TDF

Mean Change in BMD Through Week 96

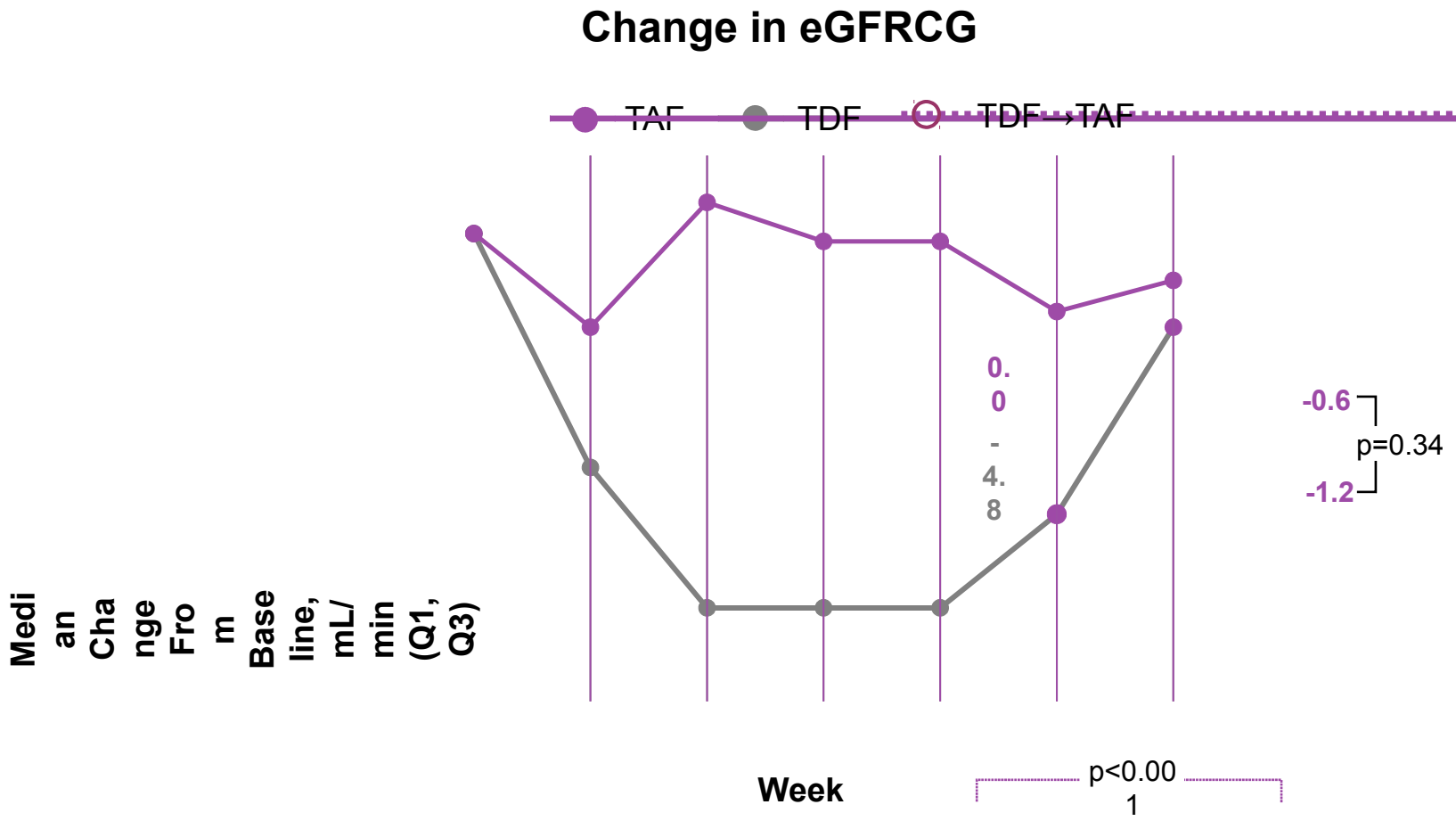


TAF treatment resulted in smaller declines* in hip and spine BMD compared with TDF

*All p-values from Week 24-96 are < 0.001; p-values from analysis of variance model including treatment as a fixed effect; † p-values from mixed model repeated measures
Fung, EASL 2017, SAT-162

Study 108 and 110: Phase 3 CHB Studies: TDF to TAF Switch Population (144 Week Analysis)

Renal Laboratory Parameters in CHB Patients Treated with TAF or TDF



eGFRCG increased significantly at Week 144 in patients who switched from TDF to TAF at Week 96

eGFRCG, estimated glomerular filtration rate as measured by the Cockcroft-Gault equation

Pan, AASLD 2017, Poster 904

Summary

- Long-term Nucs can prevent development of liver cirrhosis and related complication, and reduce risk of HCC especially in cirrhotic patients

- Complete Viral suppression maximize the benefits of NUCs in patients with cirrhosis

- Safety in long term therapy should be considered. Tenofovir alafenamide and entecavir are recommended over TDF for patients with risk of renal and bone diseases