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DE MÉDECINE

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Clinical Case

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Links of interest and Disclaimer

Adviser, speaker, investigator for:

Abbvie, BMS, Gilead, Janssen, MSD

Patient case

Age / Gender	59-years / male
HBV diagnosed	2012
Route of transmission	Injectable drugs
ALT	83 IU/mL
HBeAg	Negative
HBV DNA	5.4 log IU/mL
Fibrosis	Severe fibrosis (Fibroscan = 11.2 kPa)
GFR (mL/min)	80
US	Normal
Antiviral treatment	TDF 245 mg/d since 2012

Patient case

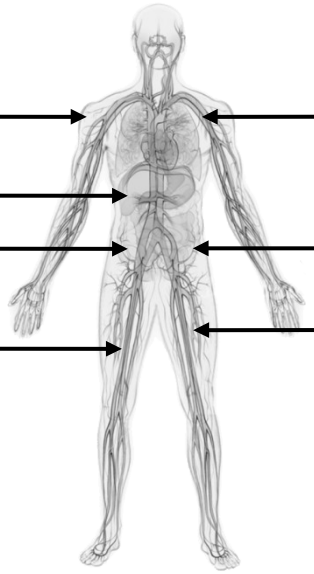
TDF started in 2012

	2012 (W24)	2013 (Year 1)	2014 (Year 2)	2015 (Year 3)
ALT (IU/L)	30	21	26	25
HBV DNA (IU/mL)	98	<20	<20	<20
GFR (mL/min)	79	77	73	68
Platelets	192	204	177	236
LS (kPa)	-	-	-	7.1
US	Normal	Normal	Normal	Normal

Do you think that this patient is at risk for comorbidities?

HBV-infected patients have a significantly higher risk of co-morbidities than non-HBV patients

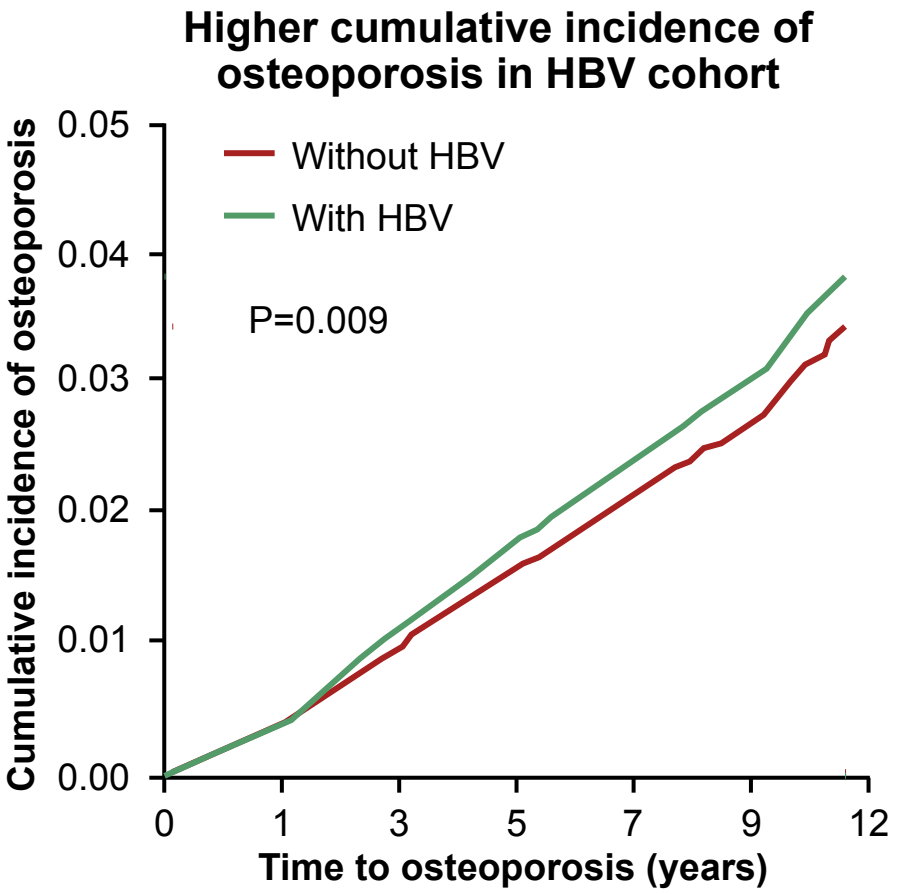
HBV in Europe: ~60,000 deaths/year1
US survey (NHANES III) indicated that adults >50 years have a 1.5 to two-fold higher prevalence compared with younger individuals2
Increased risk of co-morbidities, such as diabetes, hypertension, osteoporosis and renal disease compared with the non-HBV population3–5

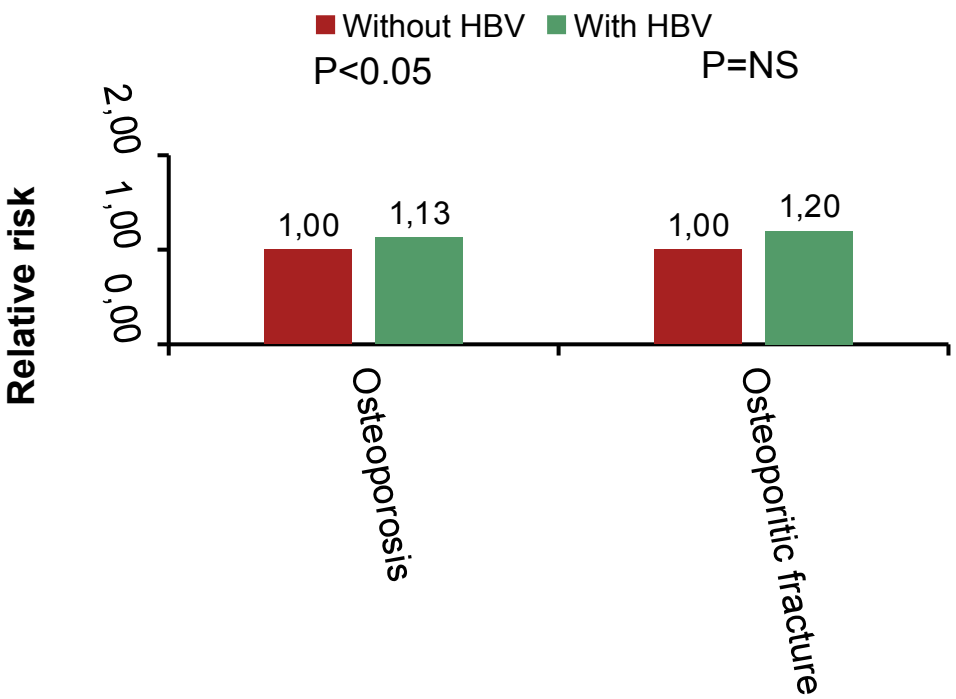


*Prevalence of co-morbidities in HBV patients compared with non-HBV patients, respectively.
aHR: adjusted hazard ratio comparing HBV patients to non-HBV patients;
ESRD: end-stage renal disease

1. WHO. Hepatitis B in the European region. Available at: http://www.euro.who.int/__data/assets/pdf_file/0009/283356/fact-sheet-en-hep-b.pdf (accessed November 2017).
2. Carrion AF, Martin P. Am J Gastroenterol 2012;107:691–7; 3. Chen Y-C, et al. Kidney Int 2015;87:1030–8;
4. Chen CH, et al. Medicine 2015:94:e2276

Association between HBV and osteoporosis

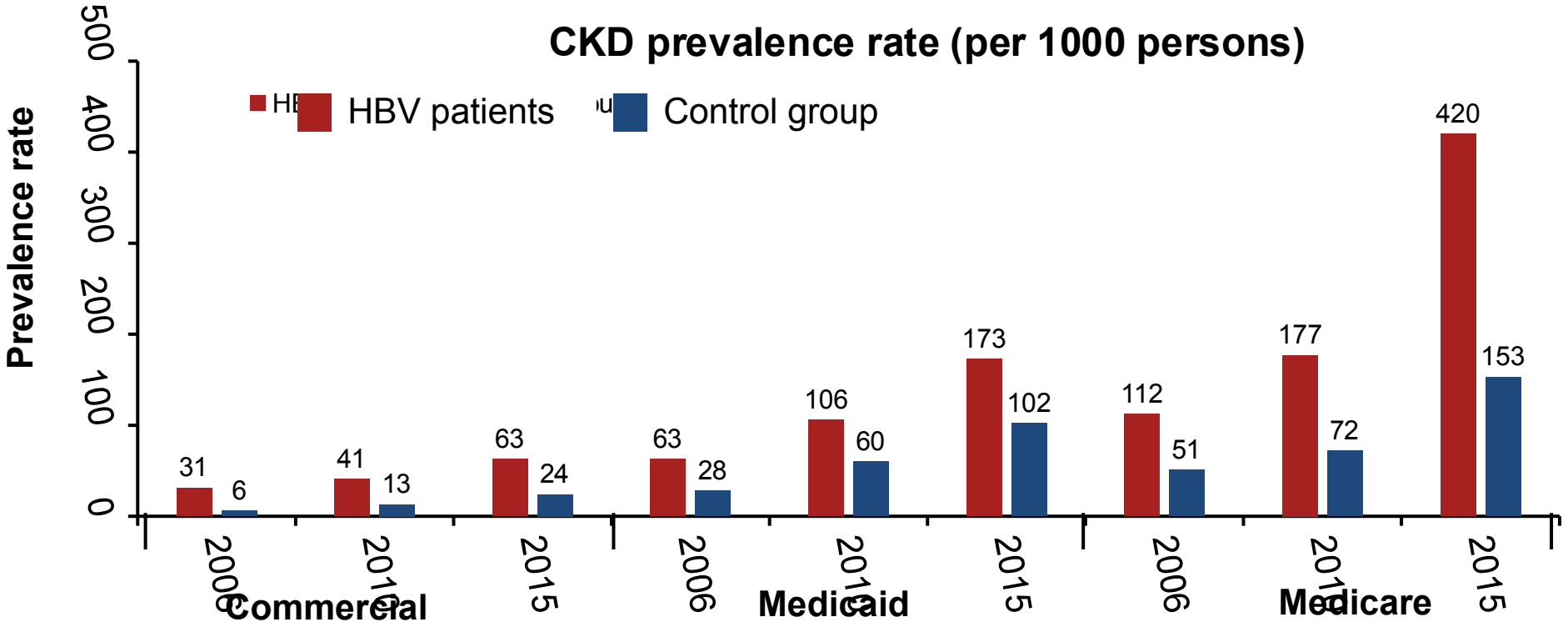




Chen CH, et al. Medicine 2015:94:e2276

NS: non-significant

Substantial increases in the number of CHB patients with CKD in the past decade in the USA



Nguyen M, et al. ILC 2017; Abstract #SAT-132

P<0.001 in all HBV patients and control group comparisons.
CKD: chronic kidney disease

Patient case

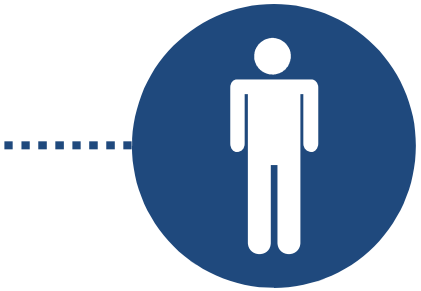
TDF started in 2012

	2016 (Year 4)	2017 (Year 5)
ALT (IU/L)	19	27
HBV DNA (IU/mL)	<20	<20
GFR (mL/min)	58	48
Phosphorus	-	Low
LS (kPa)	-	5.4
US	Normal	Normal
αFP		6.2

How do you manage the patient in terms of renal function, etc…?

Patient case

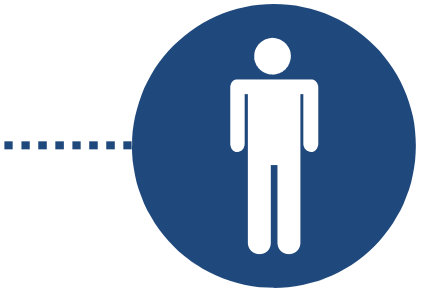
- Renal tubulopathy
- Osteoporosis



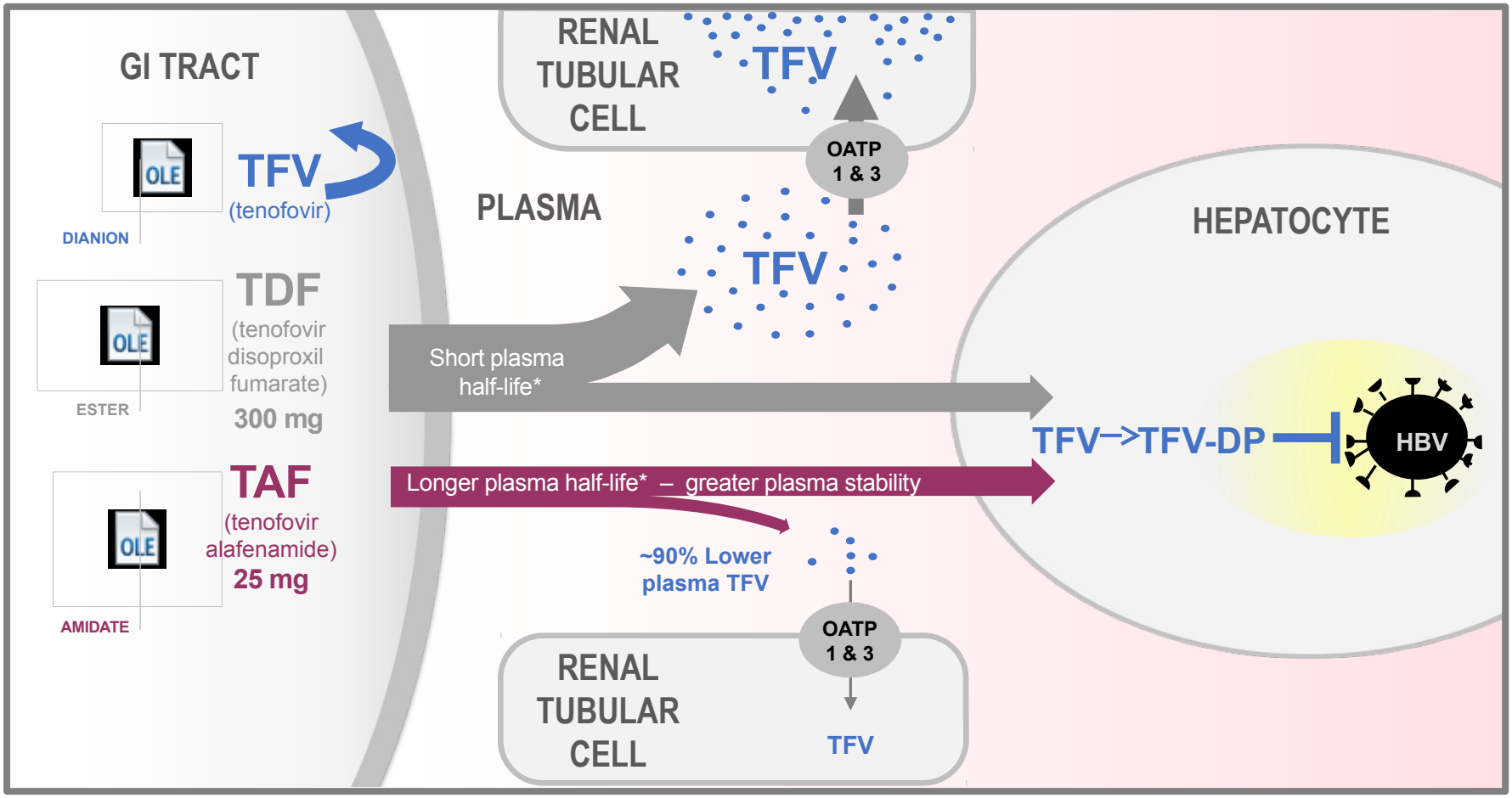
How do you manage the patient in terms of antiviral treatment?

Patient case

- Renal tubulopathy
- Osteoporosis
- Switch for TAF in April 2017



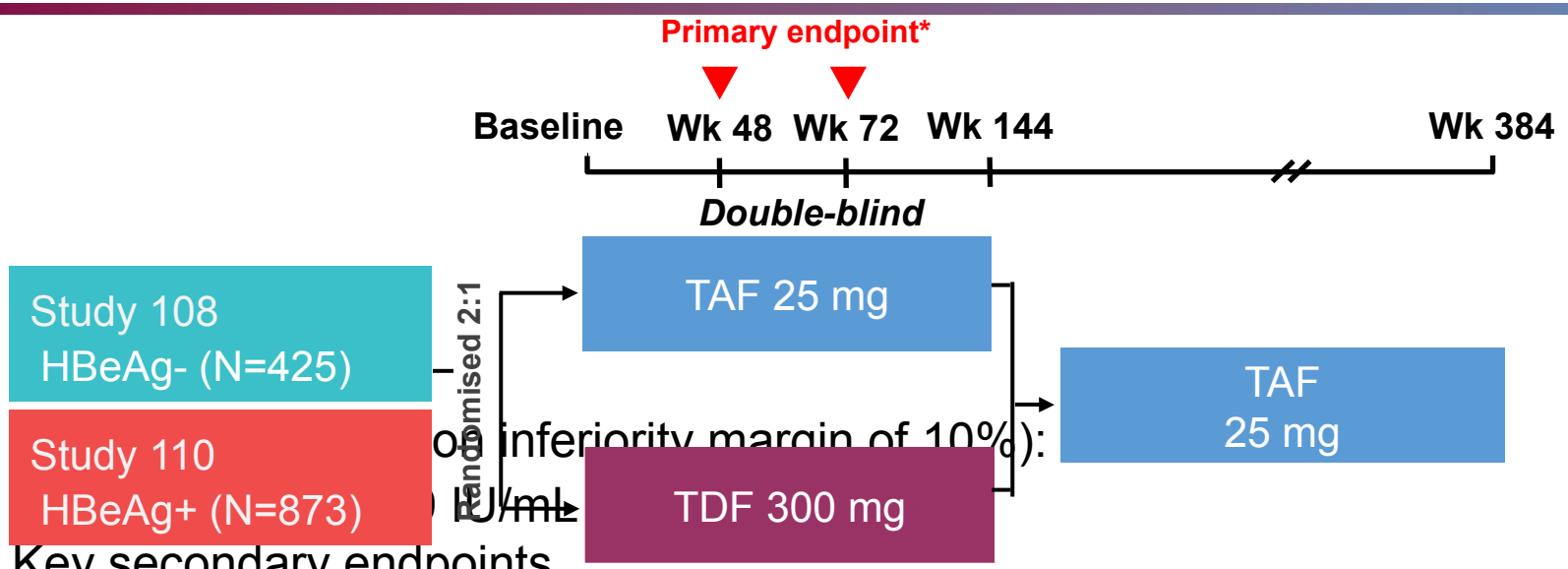
TDF and TAF: mechanism of action overview



Ray AS, et al. Antivir Res 2016;125:63–70

*T1/2 based on non-clinical data; TDF: 0.4 minutes, TAF: 30–90 minutes.
GI: gastrointestinal; OATP, organic anion-transporting polypeptide; TFV-DP, tenofovir diphosphate

TAF HBV Phase 3 programme (Study 108 and Study 110)



- o inferiority margin of 10%):
-) IU/mL

Key secondary endpoints

- ALT normalisation at Week 48
- Renal parameters and bone mineral density at Week 48

95% retention rate through Week 48

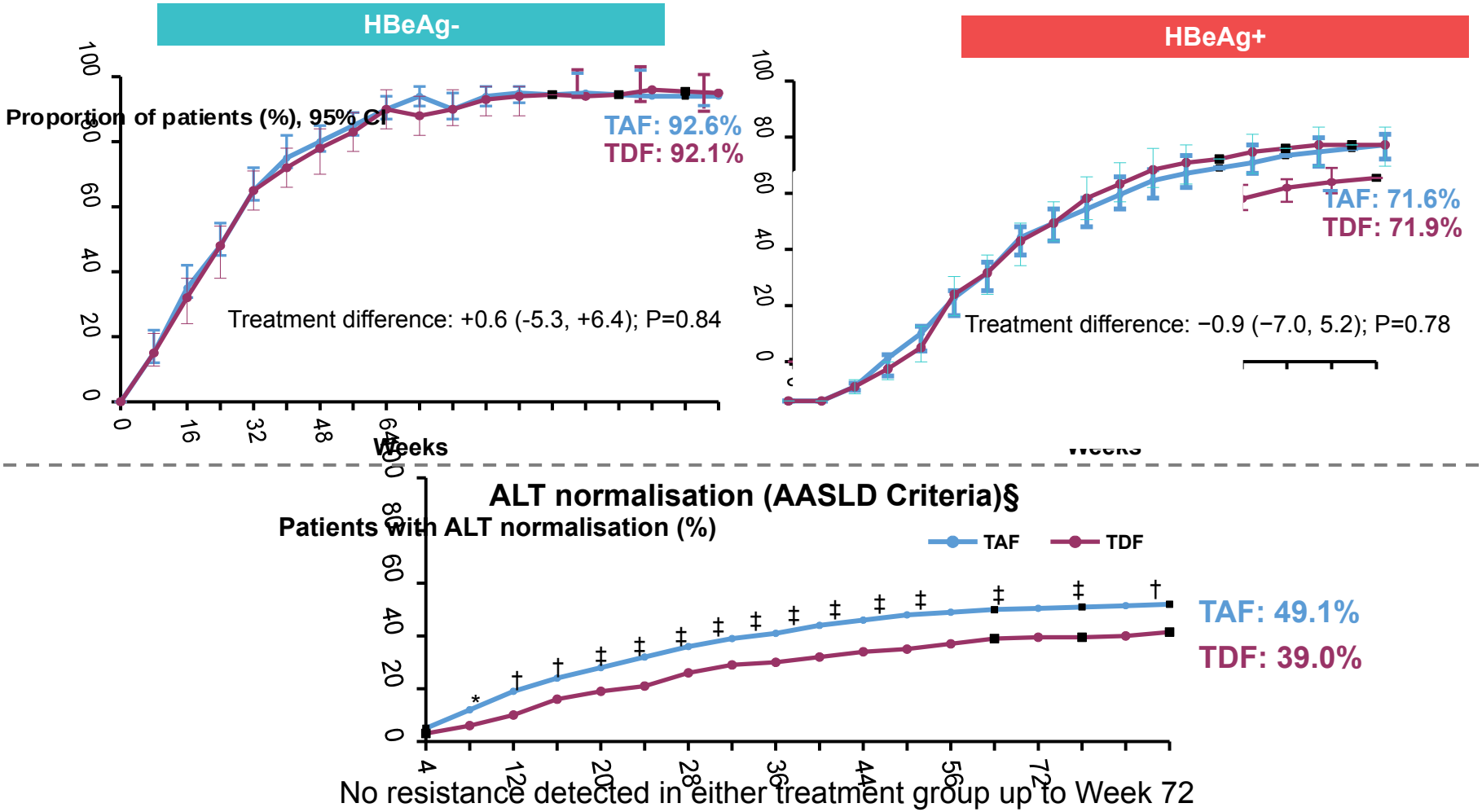
Inclusion criteria: HBV DNA ≥20,000 IU/mL; ALT >60 U/L (males), >38 U/L (females),

eGFRCG >50 mL/min

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206;
Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95;
https://www.clinicaltrials.gov/ct2/show/NCT01940471?term=TAF&rank=34 (Accessed September 2017)

*Amendment to extend double-blind to Week 144 and open-label phase to ≥Week 384 (Year 8) has recently been enacted.
The label is based on data at Week 48 and Week 72;
The licensed dose of TDF in Europe in CHB patients is 245 mg.
eGFRCG: estimated glomerular filtration rate Cockcroft–Gault

Study 108 and 110 (TAF vs. TDF): summary of efficacy up to Week 72



No resistance detected in either treatment group up to Week 72

Seto WK, et al. AASLD 2016; Oral #67;
Fung S, et al. AASLD 2016; Poster #185;
Gilead Sciences Europe Ltd. VEMLIDY▼ (tenofovir alafenamide) SmPC, January 2017

*P<0.05; †P<0.005; ‡P≤0.001; §<19 and <30 U/L for females and males, respectively.
AASLD: American Association for the Study of Liver Diseases;
Choice: Science, Interest

TAF and TDF are well tolerated in patients with CHB (Study 108 and Study 110)

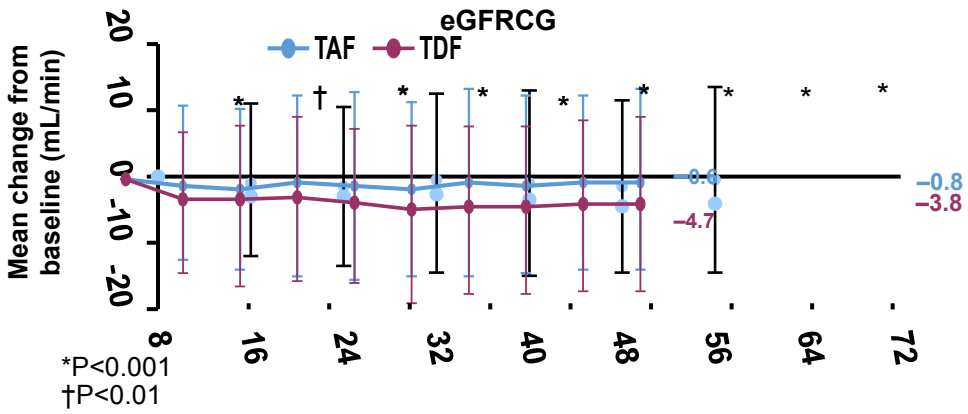
	Patients, n (%)	TAF n=866	TDF n=432
AEs	AEs	608 (70)	291 (67)
	Grade 3–4 AEs	39 (5)	17 (4)
	Serious AEs	36 (4)	21 (5)
	Discontinuations due to AEs	9 (1)	5 (1)
	Deaths	1*	1†
	HCC	1 (<1)	5 (1)
Laboratory abnormalities, ≥1%	Grade 3–4	269 (31)	126 (29)
	ALT >5 x ULN	70 (8)	40 (9)
	AST >5 x ULN	28 (3)	23 (5)
	Amylase >2 x ULN	23 (3)	10 (2)
	GGT	3 (<1)	6 (1)
	Glycosuria	41 (5)	5 (1)

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206;
Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95;
Buti M, et al. ILC 2016; Oral #GS-06;
Chan HLY, et al. ILC 2016; Oral #GS-12

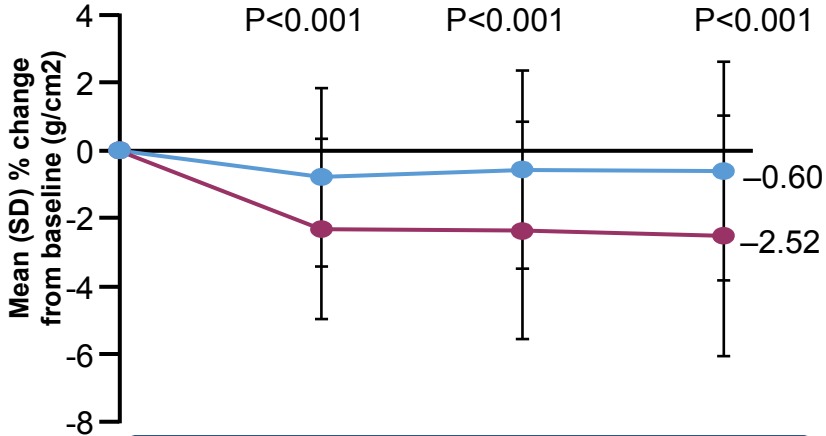
*54-year-old Asian woman died due to H1N1 influenza at Week 14 (non-treatment-emergent);
†51-year old Asian man with cirrhosis died due to HCC at Week 56 (non-treatment-emergent).
AST: aspartate aminotransferase;
GGT: gamma-glutamyl transferase; ULN: upper limit of normal

Study 108 and 110 (TAF vs. TDF): summary of bone and renal safety up to Week 72

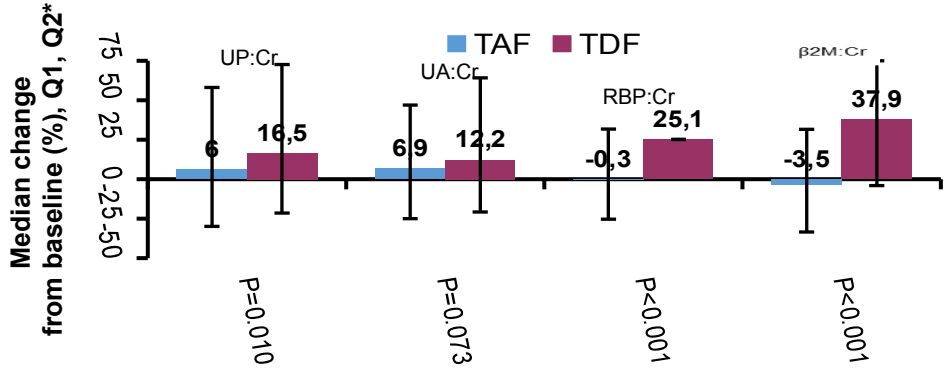
eGFRCG



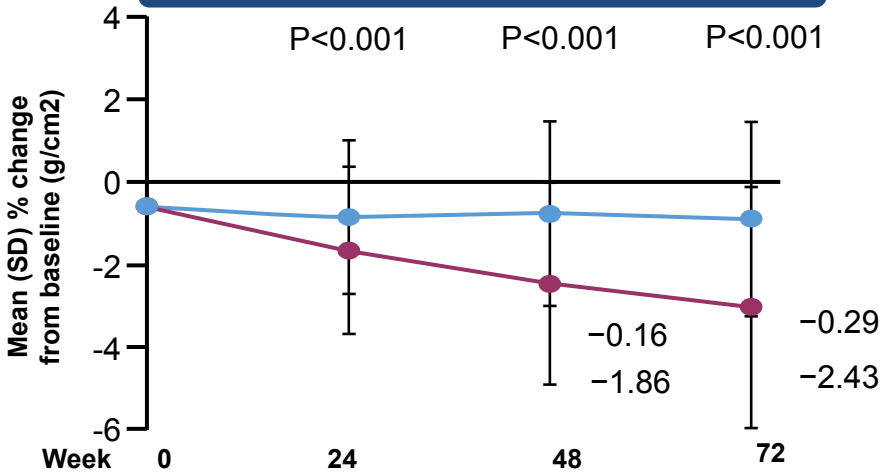
Spine BMD



Urine protein to creatinine ratio at Week 48 , median (%)



Hip BMD



Agarwal K, et al. AASLD 2016, Poster #1844;
Lim Y, et al. AASLD 2016; Poster #1901;
Seto W, et al. AASLD 2016; Oral #67;
Gilead Sciences, Data on File

BMD: bone mineral density; UA:Cr: urine albumin:creatinine ratio; UP:Cr: urine protein:creatinine ratio; RBP:Cr: retinol-binding protein:creatinine ratio; β2M:Cr: β2 microglobulin:creatinine ratio

Study 108 and 110 (TAF vs. TDF): authors' conclusions

Treatment with TAF through 72 weeks demonstrated:

- Comparable viral suppression (HBV DNA <29 IU/mL) to TDF
- Improved rates of ALT normalisation
- No resistance development in either treatment group at Week 48
- Rates of HBeAg loss and seroconversion similar to TDF in Study 110

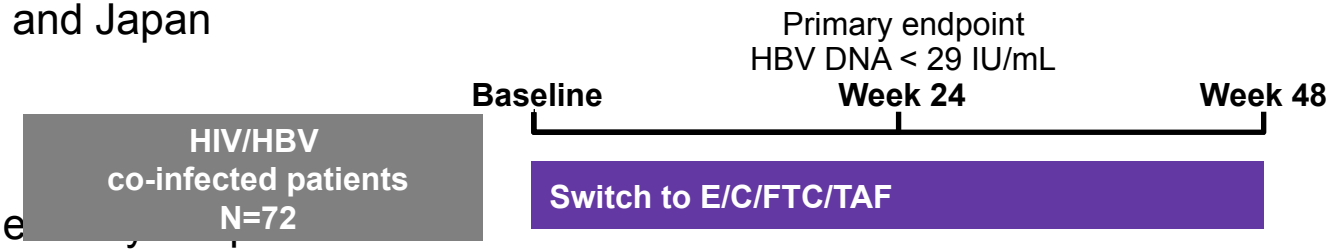
TAF was well tolerated in HBeAg-negative and -positive patients

- Treatment-emergent AEs similar to TDF
- Significantly less declines in hip and spine BMD compared to TDF
- Significantly smaller decreases in eGFRCG compared to TDF, with improved markers of renal tubular function

Buti M, et al. Lancet Gastroenterol Hepatol 2016;3:196–206; Chan HLY, et al. Lancet Gastroenterol Hepatol 2016;3:185–95;
Buti M, et al. ILC 2016; Oral #GS-06; Chan HLY, et al. ILC 2016; Oral #GS-12; Agarwal K, et al. AASLD 2016, Poster #1844;
Lim Y, et al. AASLD 2016; Poster #1901; Seto W, et al. AASLD 2016; Oral #67

Switching from TDF to TAF in HIV/HBV co-infected patients: study design

Evaluation of the efficacy and safety of switching to single tablet E/C/FTC/TAF in HIV/HBV co-infected patients in a Phase 3b, open-label, multicentre study in North America and Japan



Primary e

- Proportion with HIV RNA <50 copies/mL and HBV DNA <29 IU/mL at Week 24 and Week 48

Secondary endpoints:

- Safety and tolerability, ALT normalisation, HBsAg to HBsAb and HBeAg to HBeAb seroconversion, changes in liver fibrosis stage at Week 24 and Week 48

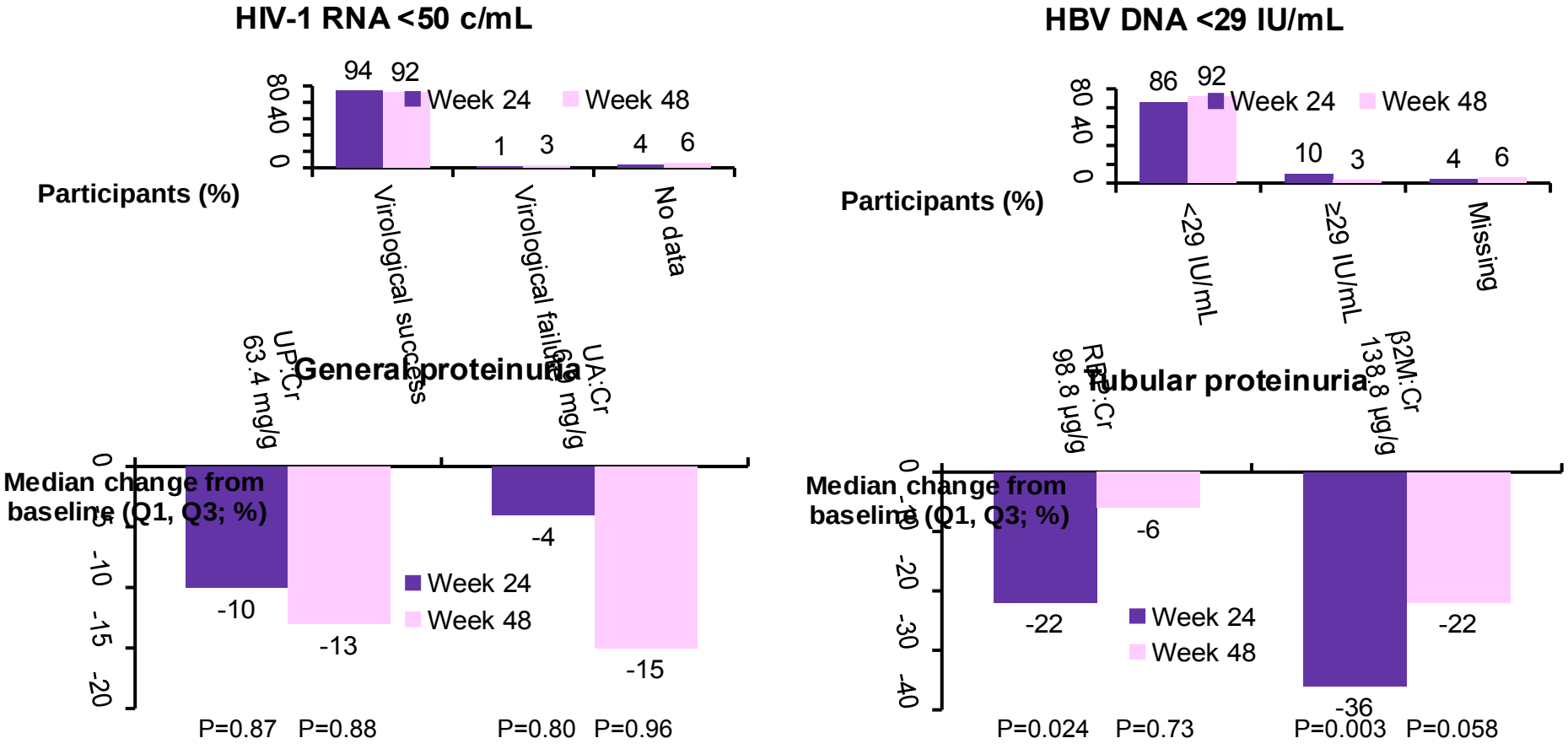
Inclusion criteria:

- HIV-1 RNA <50 copies/mL for ≥6 months, HBsAg+ >6 months, HBV DNA <9 log10 IU/mL, eGFR >50 mL/min (by CG) no current or prior regimen containing 3 active anti-HBV agents, no cirrhosis or HCC

Gallant J, et al. J Acquir Immune Defic Syndr 2016;73:294–8

Use of E/C/FTC/TAF in HIV/HBV is not included in the SmPC posology table.
C: cobicistat; E: elvitegravir

Efficacy and renal safety profile of E/C/FTC/TAF in HIV/HBV co-infected patients (Study 1249)



Switching to E/C/FTC/TAF resulted in high rates of HIV and HBV suppression with favourable effects on liver safety endpoints

Gallant J, et al. J Acquir Immune Defic Syndr 2016;73:294–8

Use of E/C/FTC/TAF in HIV/HBV is not included in the SmPC posology table

What do the EASL guidelines recommend?

EASL Clinical Practice Guidelines 2017: NA treatment recommendations

The long-term administration of a potent NA with a high barrier to resistance is the treatment of choice regardless of the severity of liver disease (I-1)

The preferred regimens are ETV, TDF and TAF as monotherapies (I-1)

LAM, ADV and TBV are not recommended in the treatment of CHB (I-1)

EASL. J Hepatol 2017;67:370–98

LAM: lamivudine; TBV: telbivudine

EASL Clinical Practice Guidelines: indications for selecting ETV or TAF over TDF*

1. Age >60 years
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
3. Renal alteration†
eGFR <60 min/mL/1.73 m2
Albuminuria >30 mg or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dL)
Haemodialysis

*TAF should be preferred to ETV in patients with previous exposure to NAs;
†ETV dose needs to be adjusted if estimated glomerular filtration rate (eGFR) <50 mL/min; no dose adjustment of TAF is required in adults or adolescents (aged at least 12 years and of at least 35 kg body weight) with estimated creatinine clearance (CrCl) ≥15 mL/min or in patients with CrCl <15 mL/min who are receiving haemodialysis

EASL. J Hepatol 2017;67:370–98

Patient case

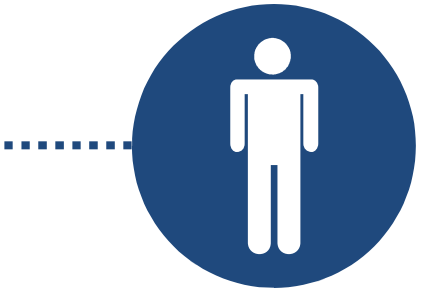
Switch TAF in April 2017

	2016 (Year 4)	April 2017 (Year 5)	Oct 2017 (W24)
ALT (IU/L)	19	27	24
HBV DNA (IU/mL)	<20	<20	<20
GFR (mL/min)	58	48	51
Phosphorus	-	Low	Treatment
LS (kPa)	-	5.4	
US	Normal	Normal	Normal
αFP		6.2	58.4

How do you manage the elevation of αFP?

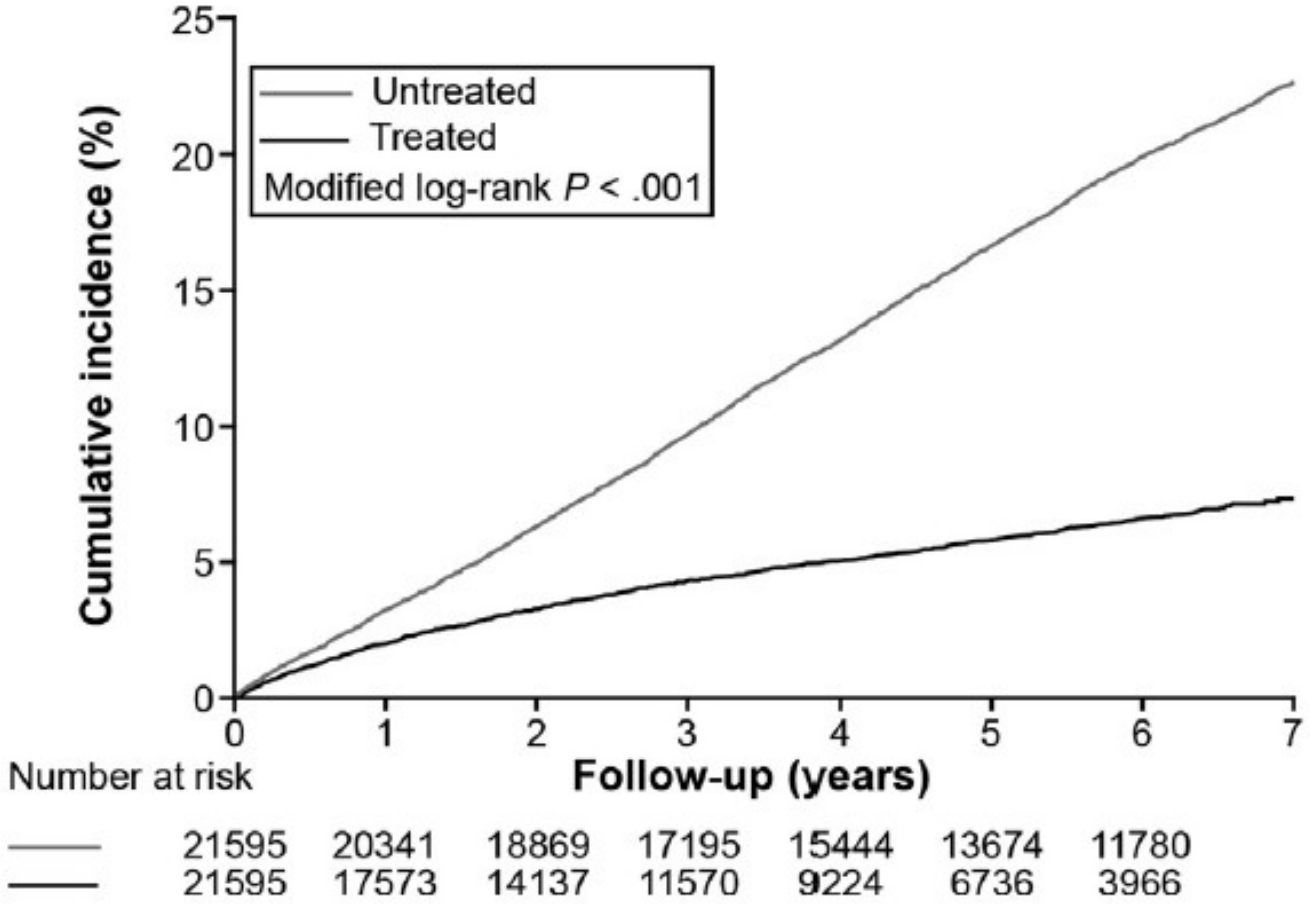
Patient case

- HCC 7mm Seg 3
- Surgery, Fibrosis stage F2



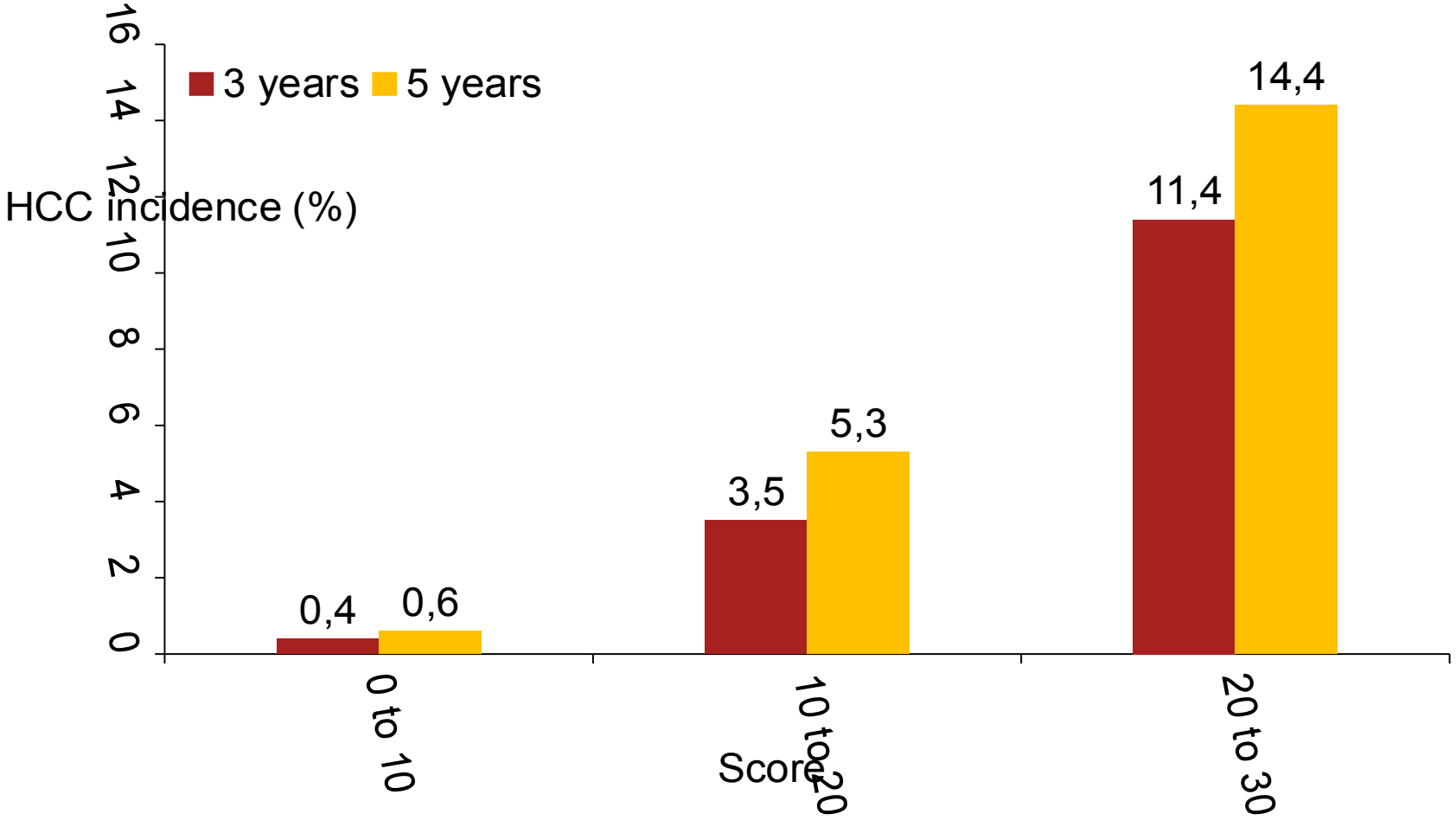
Patients treated by analogs are at lower risk of HCC

21,595 treated HBV(+) patients versus 21,595 matched untreated



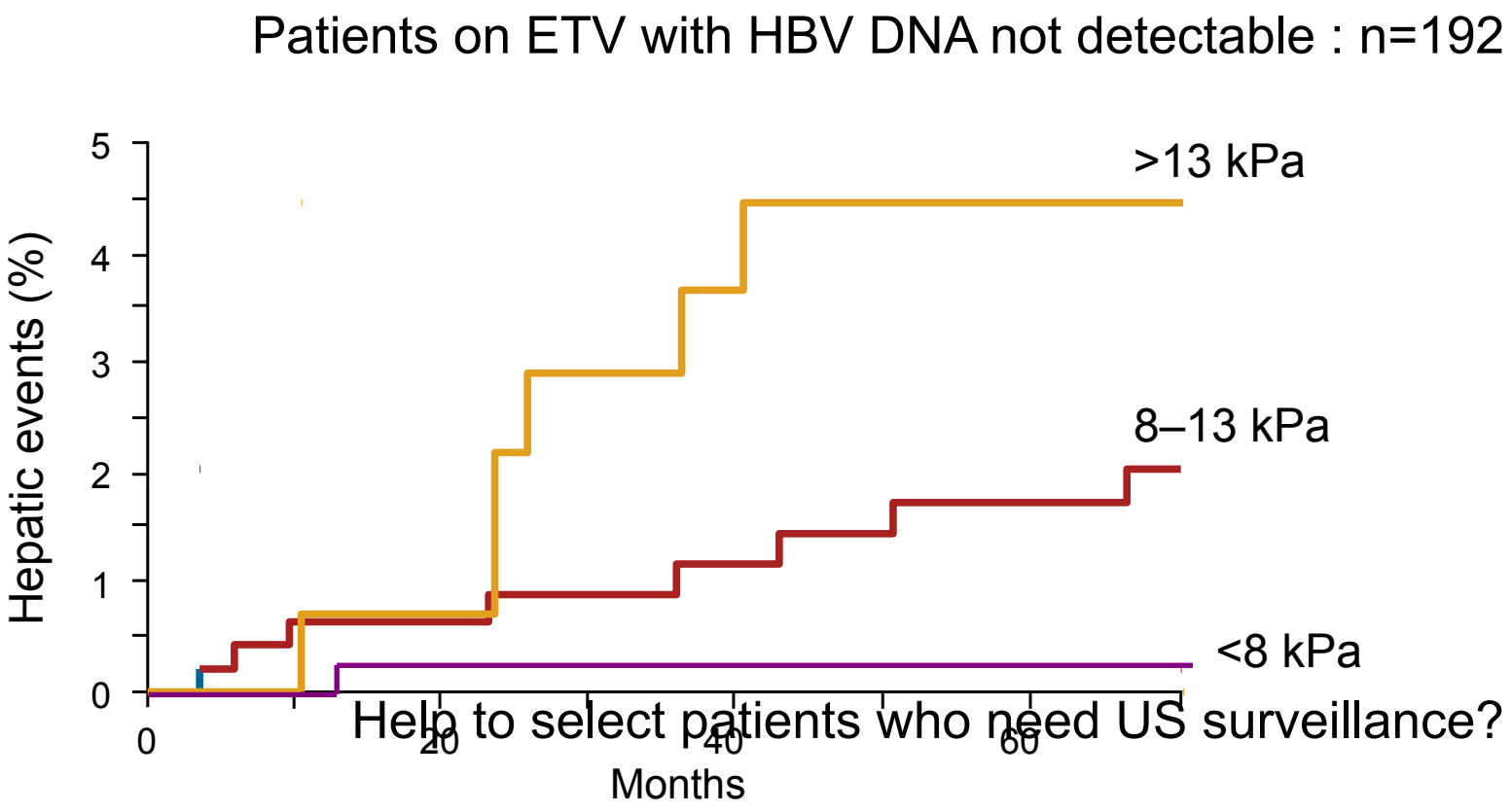
Wu, et al. Gastroenterology 2014

Is transient elastography useful to predict HCC risk?



Wong, et al. J Hepatol 2014

Liver stiffness measured on treatment is predictive of HCC incidence



Lee HW, et al. Am J Gastroenterol 2014;109:1241–9.