LUNCH WORKSHOP
30th January from 12:30 to 14:30

Future therapies for HBV and HDV:
What can we expect?

What can the challenges we face?
HBV: Long term NUC treatment

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Dipartimento di
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Inserm
Institut national
de la santé et de la recherche médicale

CRCL

CASE REPORT 1

55 years old, caucasian
No medical history
2009 : diagnosis of **chronic HBV infection**

Virology :
- HBsAg : + HBs Ab : - HBc Ab : +
- HBe Ag : - HBe Ab : +
- HBV-DNA: 118535 IU/mL
- HDV Ab : - HCV Ab : -

Biochemistry:
- ALT : 86 IU/mL

Disease Evaluation
- Ultrasound: no alterations in liver architecture no focal lesions
- Stiffness: 7,8 kPa

- Treatment with Baraclude 0.5 gr/die started
- HBV-DNA negative at month 7
- ALT normal at month 4
- Follow up: 7 years, persistent negativity of HBV-DNA
  slight (confirmed) rise of ALT (between 0.9x to 1,3x) from 2015
  no AE

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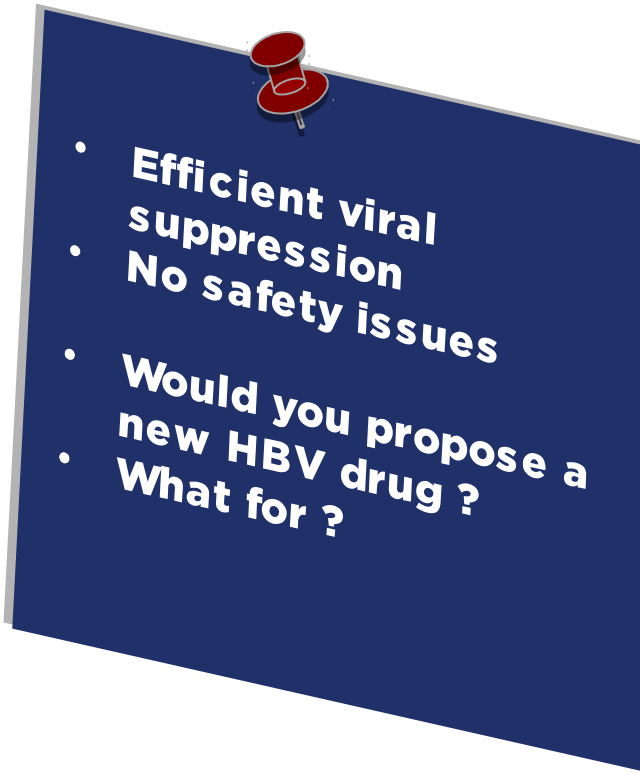

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CASE REPORT 2

43 years old, from CAR, in France from 11.2015
No medical history
Virology :
- HBsAg : + HBs Ab : - HBc Ab : + HDV Ab : -
- HBe Ag : - HBe Ab : + HCV Ab : -

Biochemistry:
- ALT: 86 IU/mL

Ultrasound:
CHB, no focal lesions

After referral (6.2016)
- HBV-DNA: 32395 IU/mL
- qHBsAg: 3235 IU/ml
- Stiffness: 7,8 kPa
- Fibrotest 0,48
- alpha-fetoprotein: 375 ng/ml

- MRI 1.2016: 4.8 cm lesion (VIII segment); CT confirmed

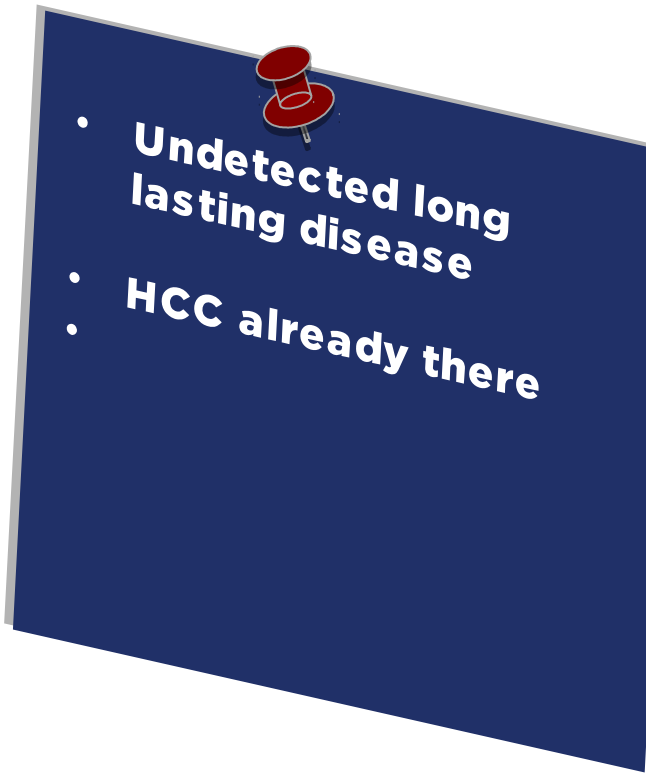
- Laparoscopic resection (7.2016)
- Histology:
  - Nodule: differentiated HCC (G2)
  - Liver: inactive cirrhosis

CASE REPORT 2

43 years old, from CAR, in France from 11.2015
No medical history
Virology :
- HBsAg : + HBs Ab : - HBc Ab : + HDV Ab : -
- HBe Ag : - HBe Ab : + HCV Ab : -

Biochemistry:
- ALT: 86 IU/mL

Ultrasound:
CHB, no focal lesions



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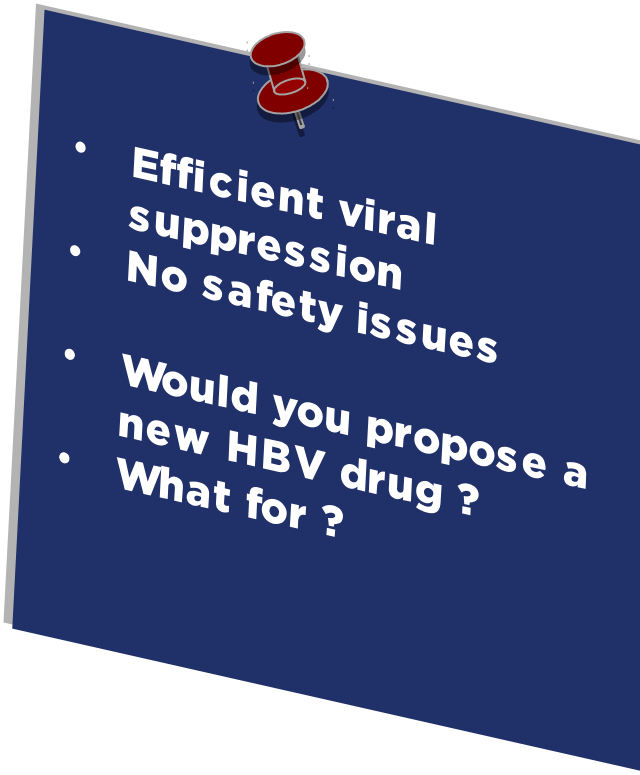

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- Follow up: 7 years, persistent negativity of HBV-DNA
  slight (confirmed) rise of ALT (between 0.9x to 1,3x) from 2015
  no AE

CASE REPORT

Mr G, 48 years old, caucasian
No medical history except a major depression in 1984

Dec-1999 : diagnosis of **chronic hepatitis B**

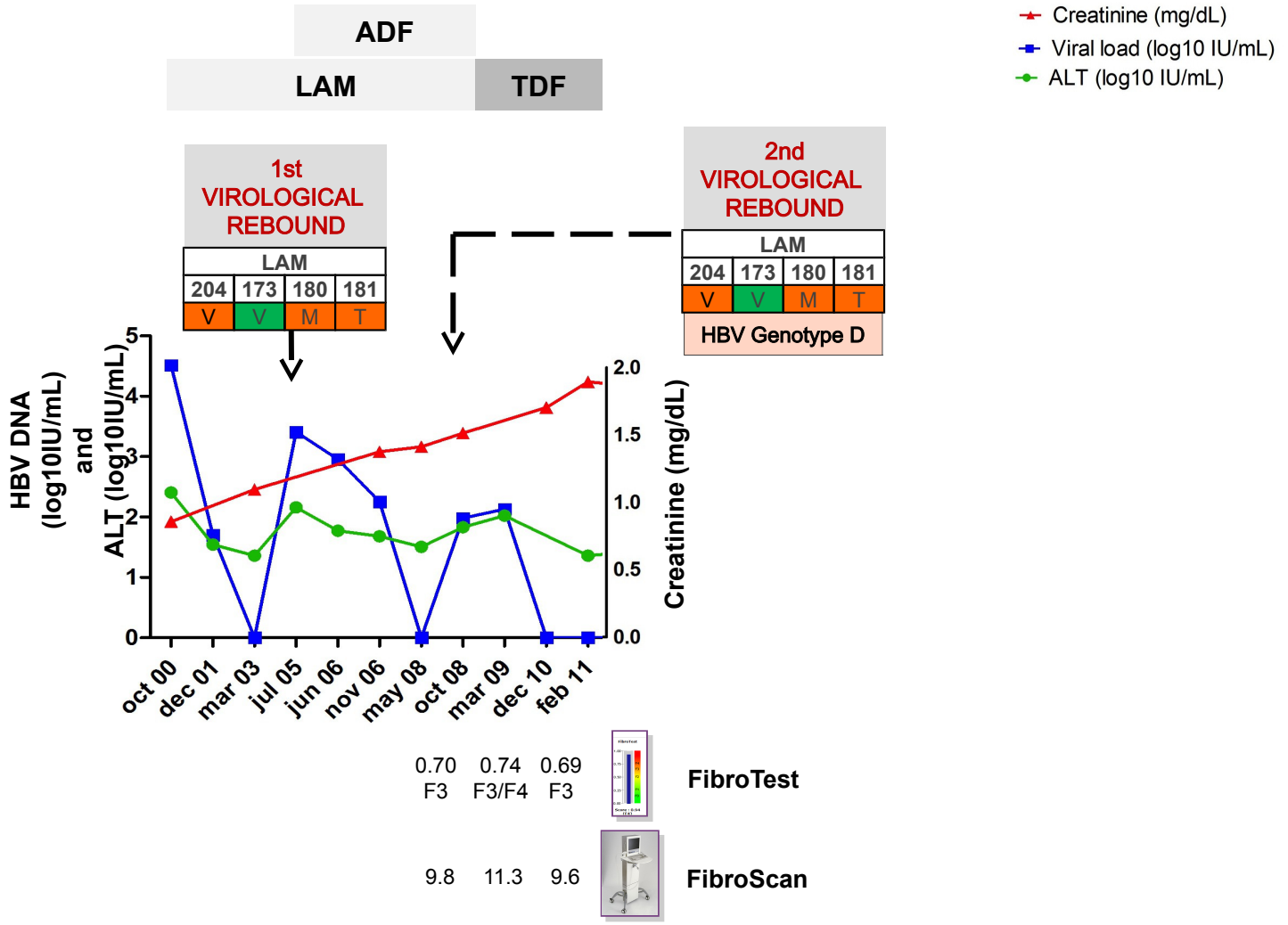
Virology :
- HBsAg : + HBs Ab : - HBc Ab : +
- HBe Ag : - HBe Ab : +
- HBV-DNA: 32569 IU/mL (converted)
- HDV Ab : - HCV Ab : -

Biochemistry:
- ALT : 256 IU/mL

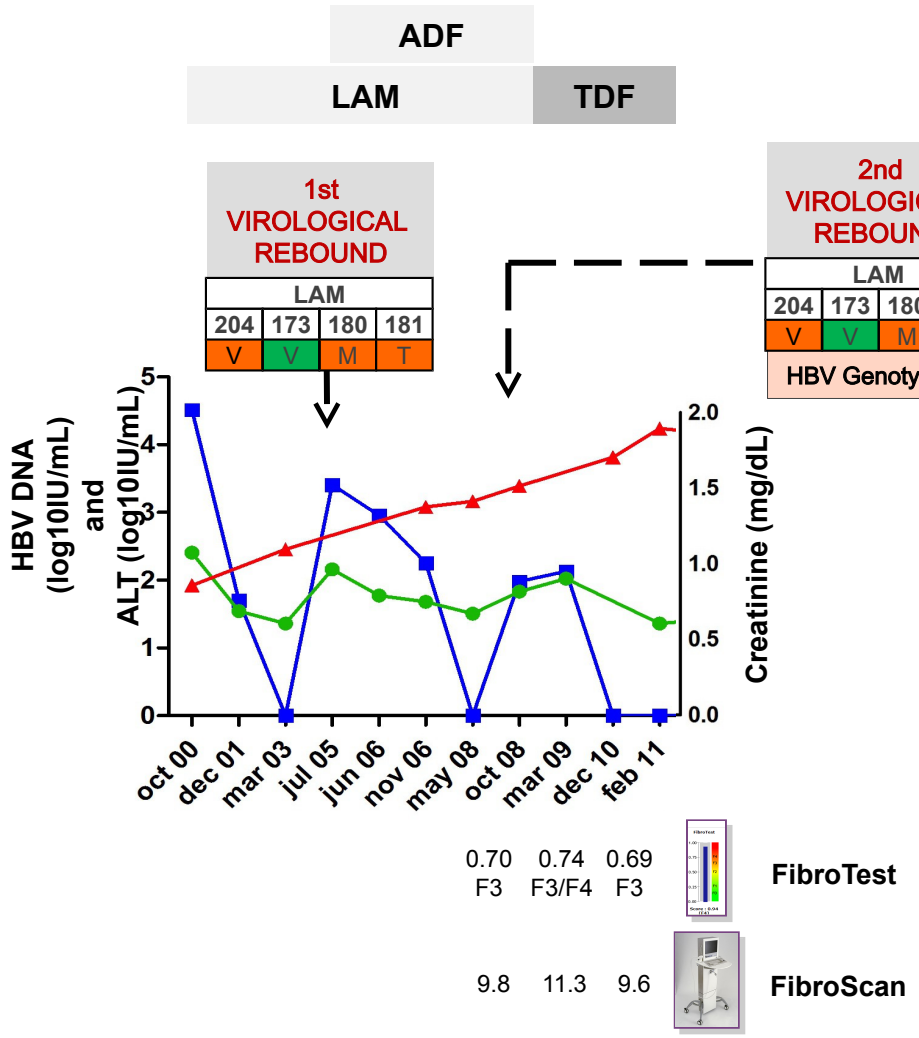
Jan-2000: **Liver biopsy**
Metavir score : stage F3, grade A2

Indication of treatment
Feb-2000 : Start lamivudine

Virological and Biochemical Follow-up:



Virological and Biochemical Follow-up:



- Virological rebounds and treatment adaptation
- Progressive renal insufficiency

Virological and Biochemical Follow-up:

Feb. 2011

- Viral load : < LOD
- ALT : 23 IU/mL
- ↖ Serum creatinine : 1.69 mg/dL (149 µmol/L)
- ↖ Serum phosphate : 2.3 mg/dL (0.74 mmol/L)
- ↖ Glucosuria without history of diabetes mellitus

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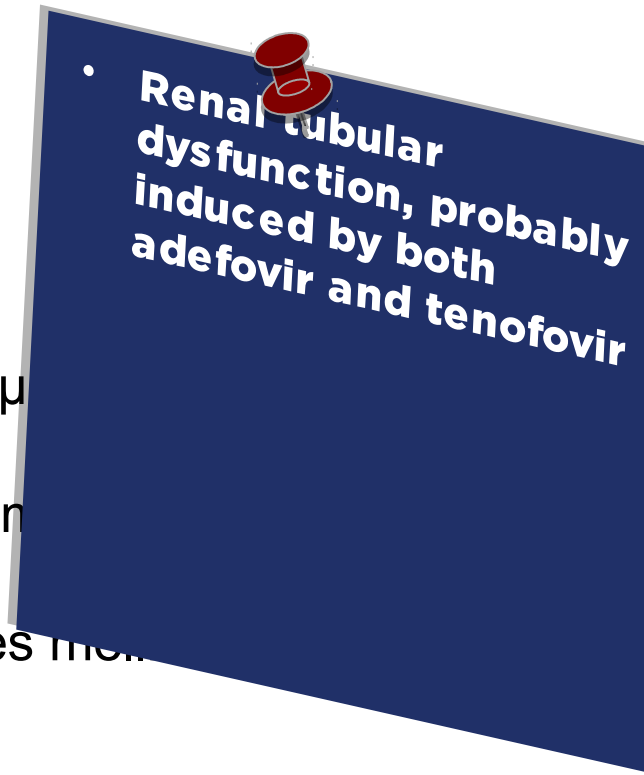

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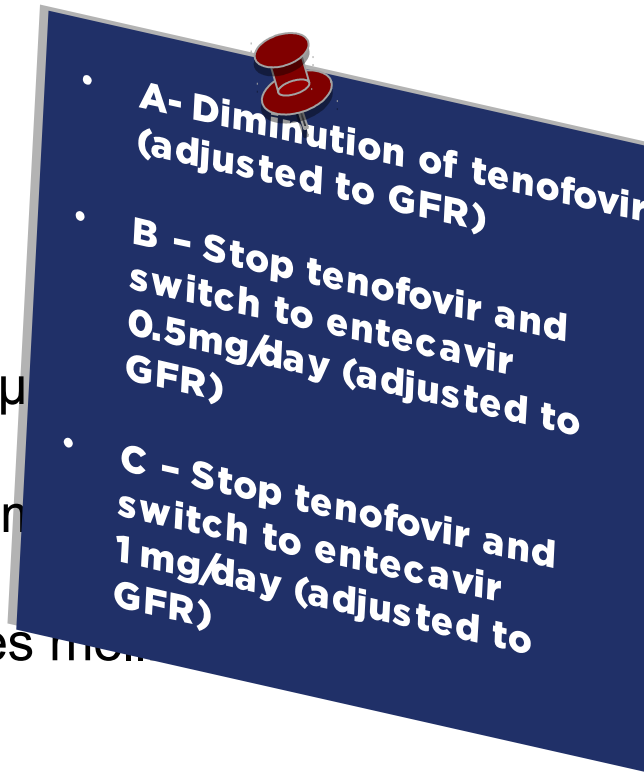


- Renal tubular toxicity ➔ stop TDV and ADV
- LAM-R: high risk of emergence of ETV resistance associated mutation

  [our patient is under TDF and suppressed since 2 years]
  - The only option (at that time) is « double dose » ETV : 1 mg/d

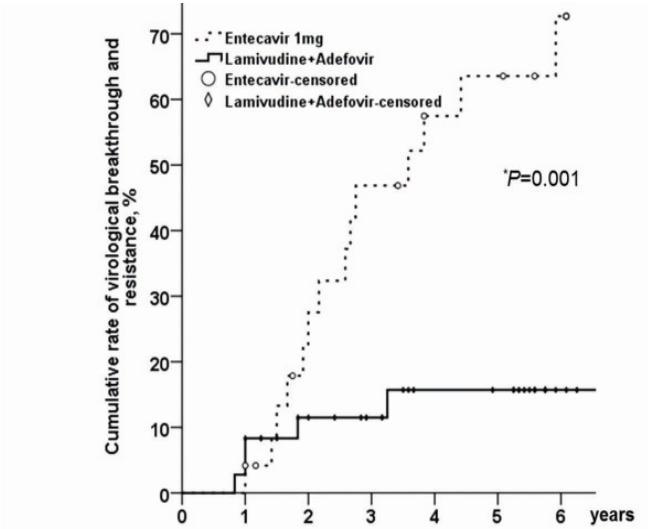
ETV (1 mg) therapy for LAM R patients

- **286 patients treated with ETV 1 mg (n: 141) or continued LAM 100 mg (n:145).**
- **77 ETV patients➔ 96 weeks**
  - **HBV DNA < 300 copies/ml: 40%**
  - **HBe seroconversion: 10%**
  - **ETV resistance: 6/77 patients**

Sherman M. Hepatology 2008; 48: 99-108

Long-term outcomes of two rescue therapies in LAM-R Pts: combined lamivudine and adefovir and 1 mg entecavir

Cumulative rate of virologic breakthrough and resistance



No. ETV 1mg	24	24	21	15	12	7	4
Rate (%)	0	4.2	21.6	40.0	55.6	61.1	71.9
No. LAM+ADV	36	36	34	32	25	22	6
Rate (%)	0	0	9.3	11.1	14.4	14.4	14.4

Ze EY et al; Clinical and Molecular Hepatology 2014; 20:267-73

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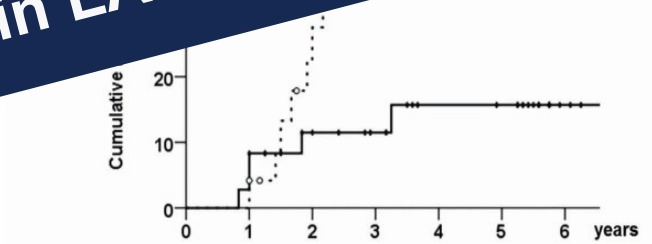
ETV monotherapy improves renal function in patients developing renal side effects during long-term TDF treatment without compromising virological response: a multicenter real-life study in 103 patients

M Vigano' et al. Hepatology 64, S1, 37A

….. but 8% ETV-R in LAM-R group



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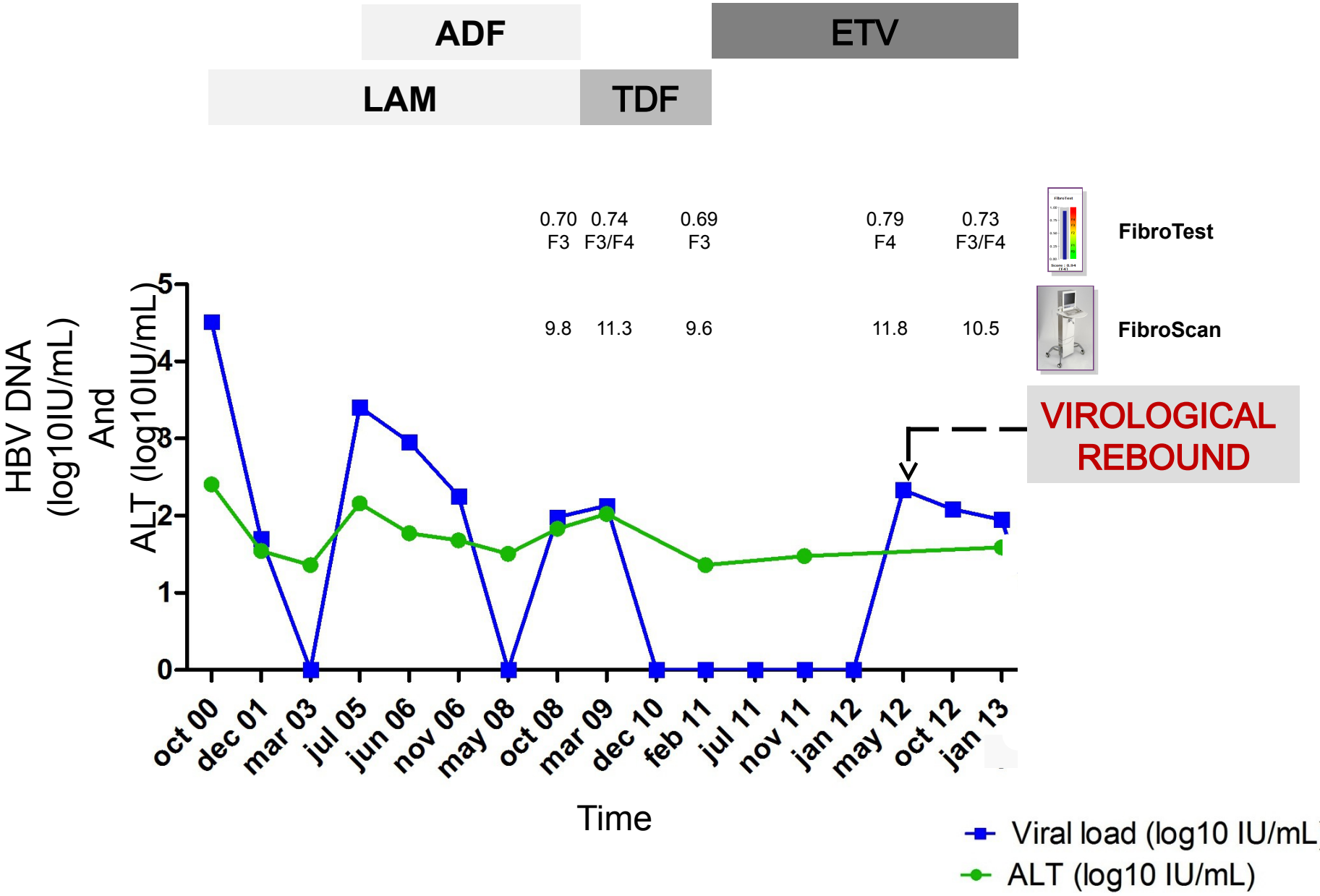
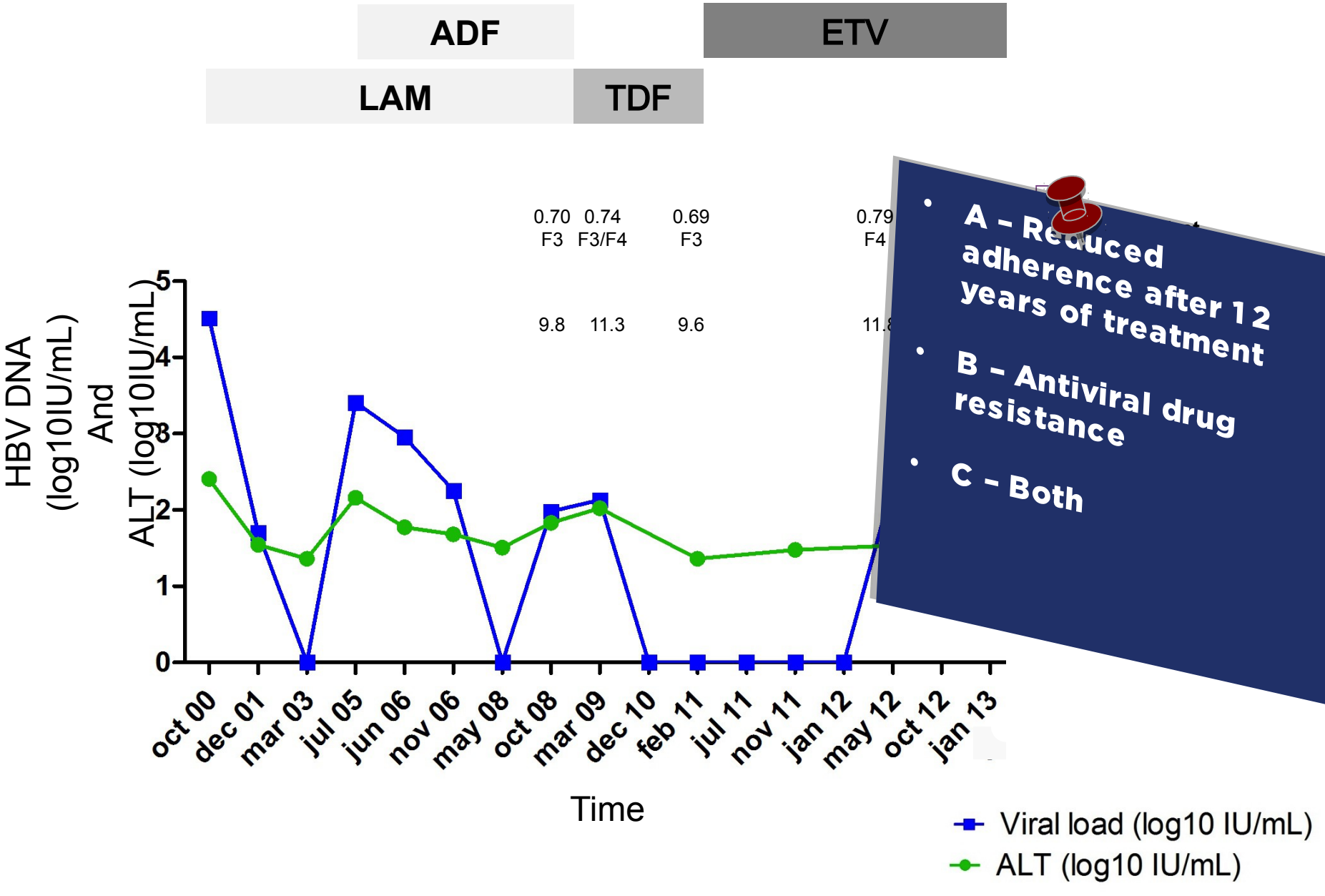
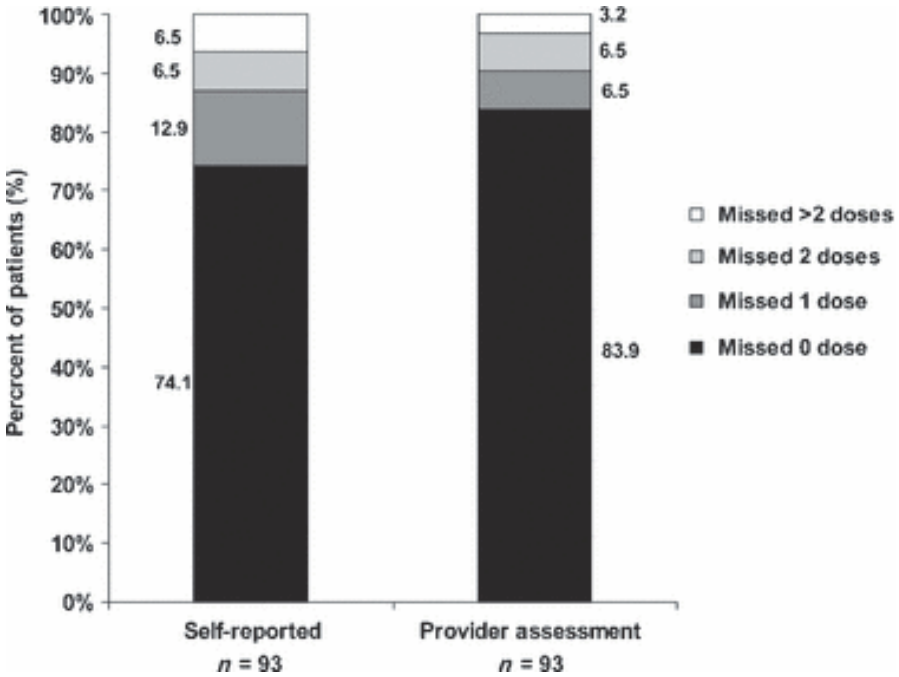
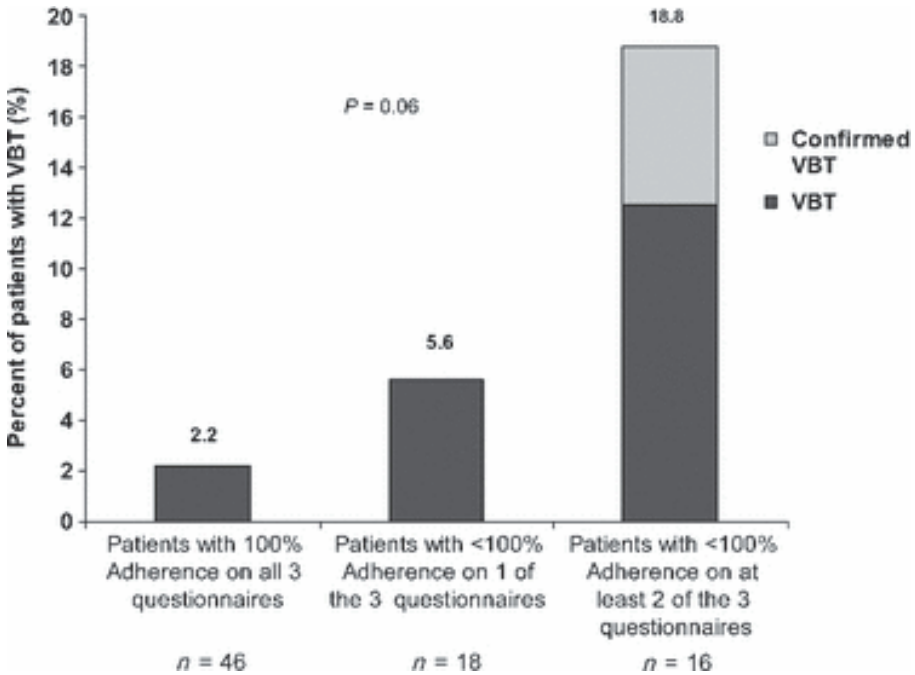


Virological and Biochemical Follow-up



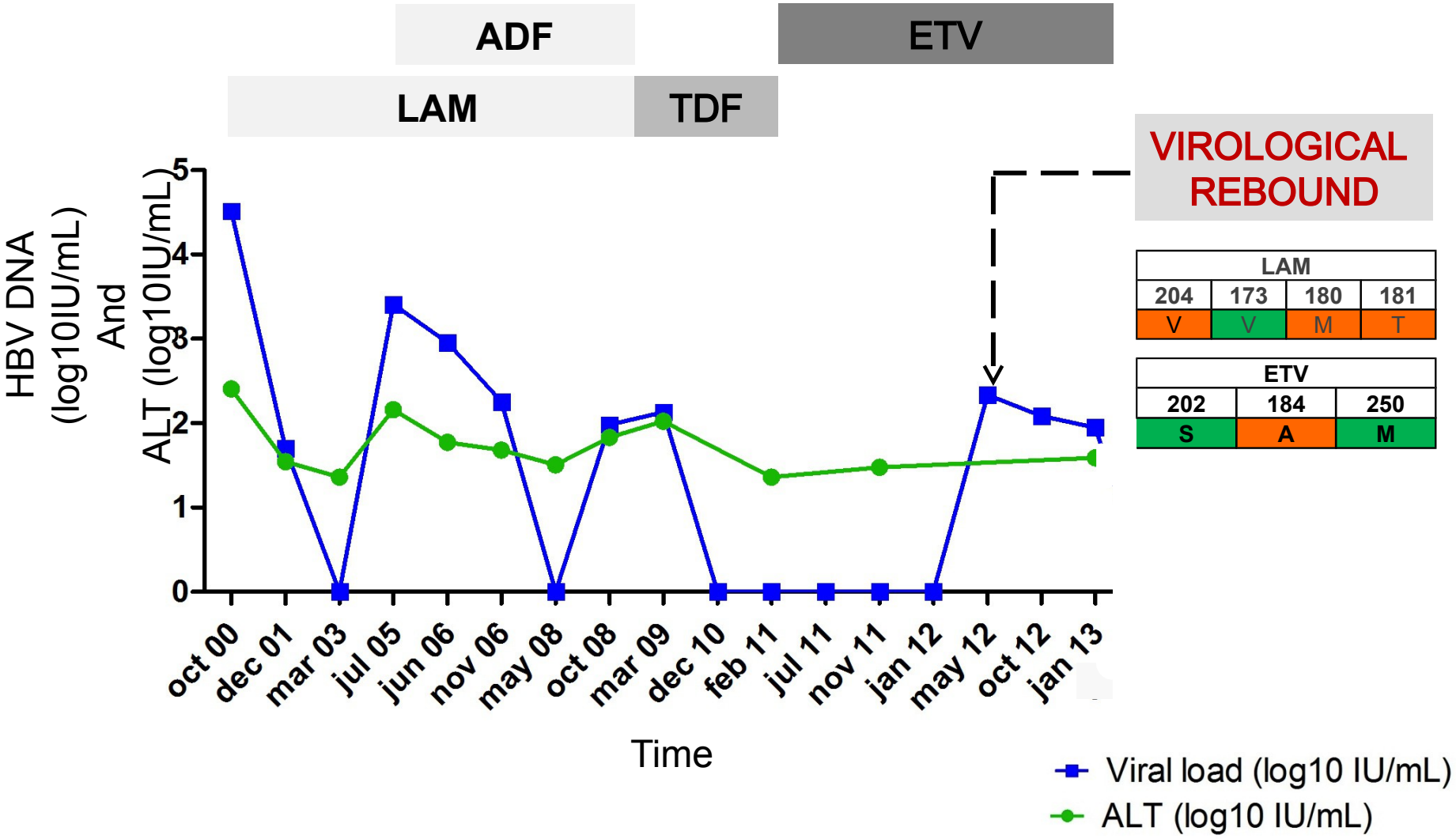
Adherence to nucleos(t)ide analogues for CHB in clinical practice and virological breakthroughs





W. Chotiyaputta et al, Journal of Viral Hepatitis, 19, 3, 205-212

Virological and Biochemical Follow-up



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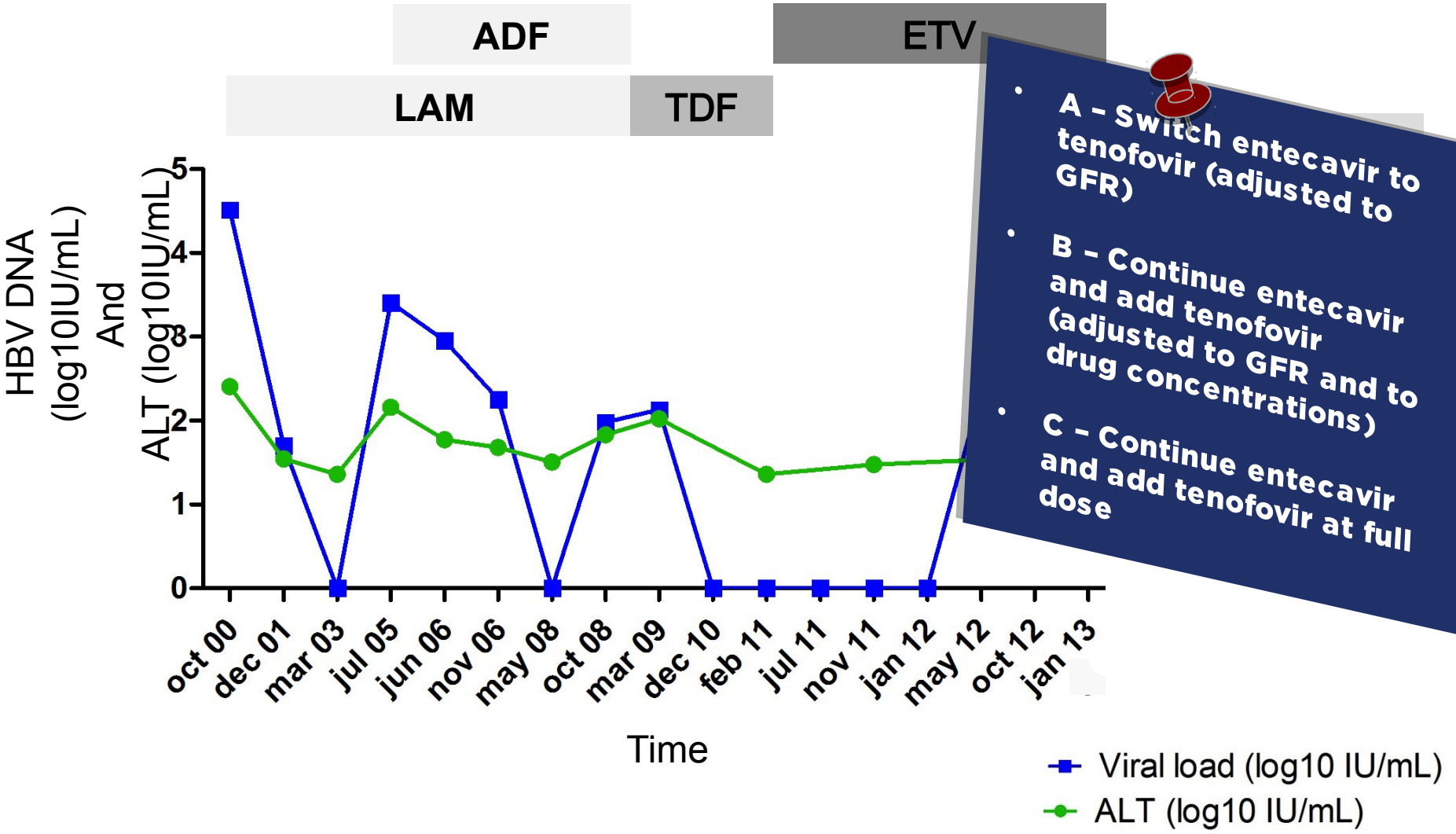
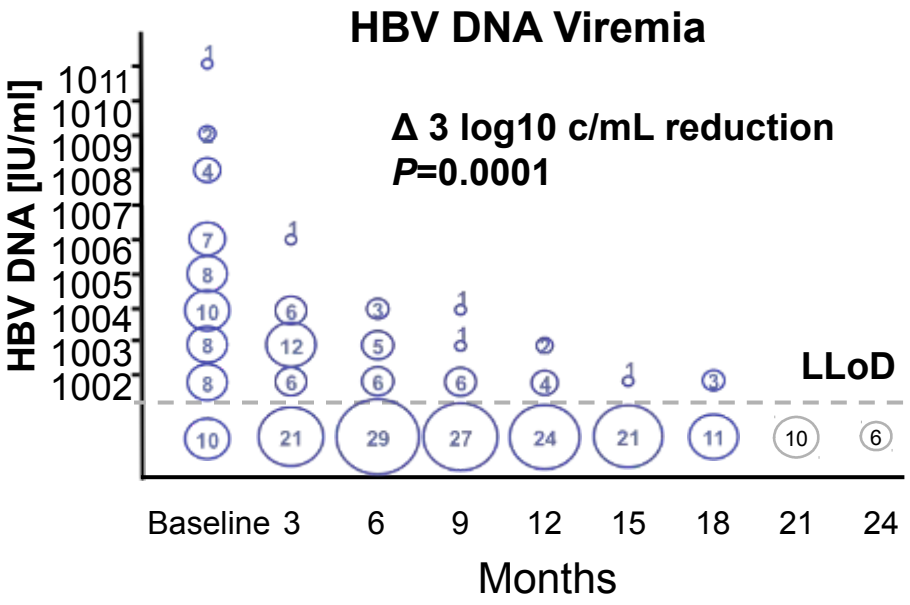
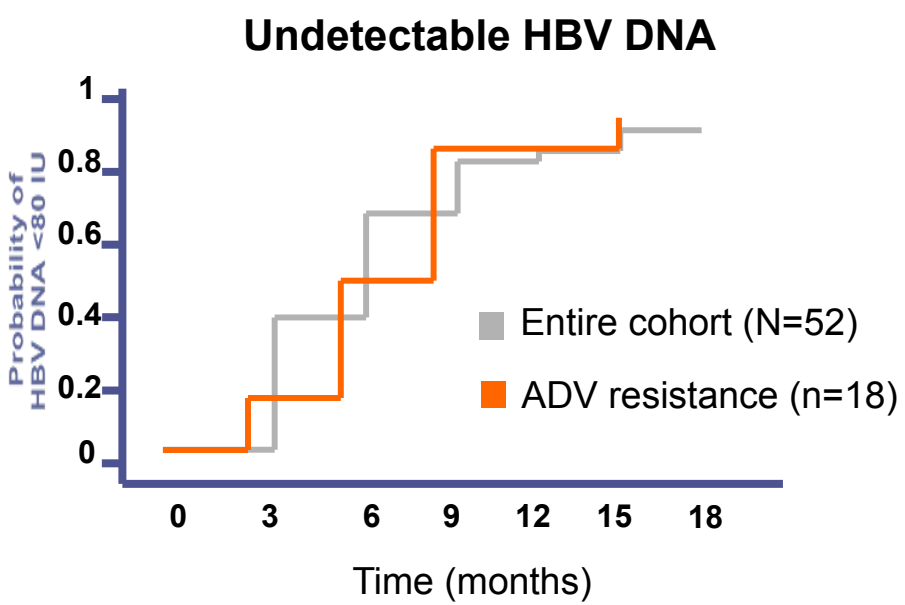


- A – Switch entecavir to tenofovir (adjusted to GFR)
- B – Continue entecavir and add tenofovir (adjusted to GFR and to drug concentrations)
- C – Continue entecavir and add tenofovir at full dose

ETV + TDF combination in patients with treatment failure



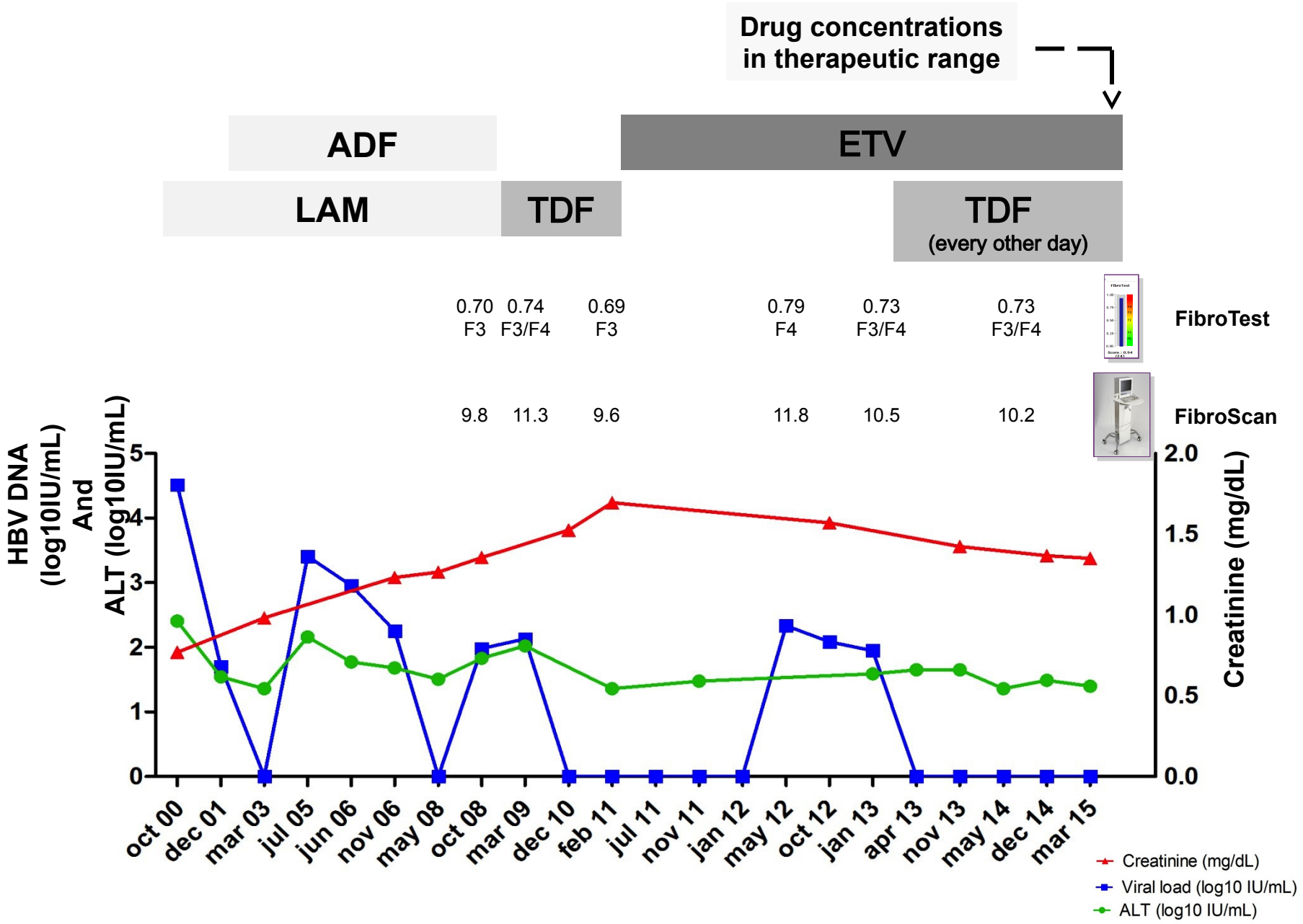


LLoD=Lower Limit of Detection

Rescue therapy with ETV + TDF in CHB patients with advanced liver disease and complex viral resistance patterns or showing partial antiviral responses to preceeding therapies (Virgil Network)

Petersen J, et al. J Hepatol 2012.

Virological and Biochemical Follow-up



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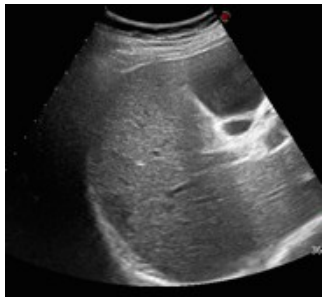


US nodule

ADF

LAM

TDF

ETV

TDF (every other day)

HBV DNA (log10IU/mL) and ALT (log10IU/mL)

Creatinine (mg/dL)

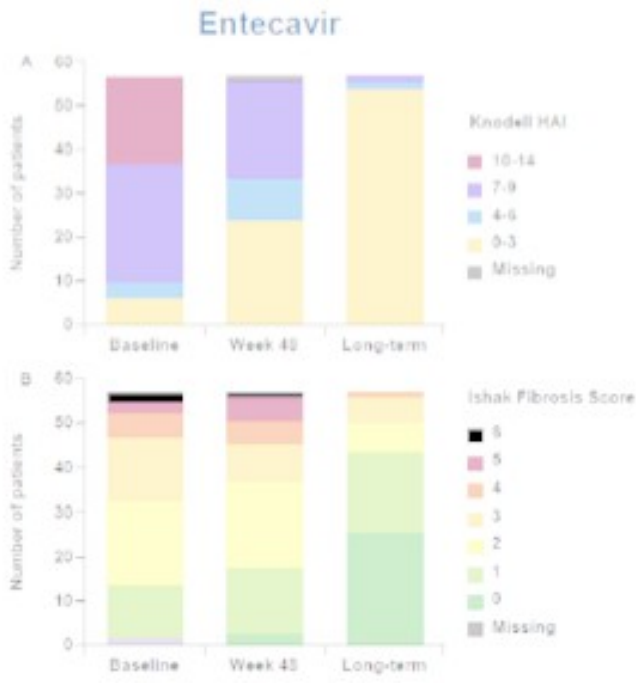
oct 00 dec 01 mar 03 jul 05 jun 06 nov 06 may 08 oct 08 mar 09 dec 10 feb 11 jul 11 nov 11 jan 12 may 12 oct 12 jan 13 apr 13 nov 13 may 14 dec 14 mar 15 aug 15 dec 15 apr 16 oct 16

Creatinine (mg/dL)

Viral load (log10 IU/mL)

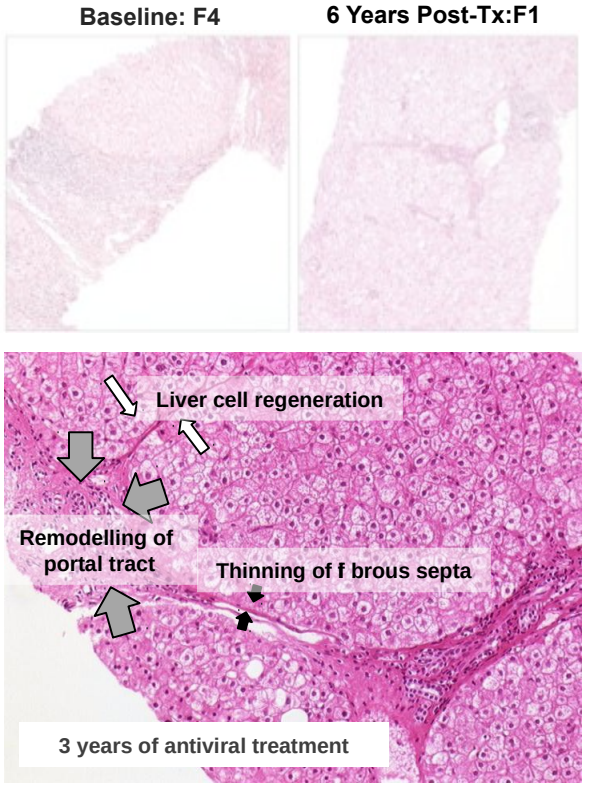
ALT (log10 IU/mL)

Long term viral suppression reduces liver inflammation leading to fibrosis and cirrhosis regression



Chang et al Hepatology 2010

Marcellin et al Lancet 2013



Modified from P. Bedossa (2014)

Long-term NUC and prevention of HCC
Propensity score studies from Asia and US

Author	Patients		Follow-up (yr)		% HCC at 5 yr		RR (95% C.I.)	P-value
	NUC+	NUC-	NUC+	NUC-	NUC+	NUC-		
Wu et al[1] (Taiwan)	21,595	21,595	3.4	5.2	7.3	22.7	0.31 (0.27–0.53)	<.001
Hosaka et al[2] (Japan)	316	316	3.3	7.6	3.7	13.7	0.37 (0.15–0.91)	.03
Kumada et al[3] (Japan)	117	117	12.3	11.6	2.7	11.3	0.28 (0.13–0.62)	.002
Gordon et al[4] (United States)	820	1,851	5.2	5.2	n.a.	n.a.	0.48 (0.27–0.86)	<.01

1. Wu CY et al, Gastroenterology 2014;147:143–151. 2. Hosaka T, Hepatology 2013;58:98–107. 3. Kumada T et al, J Hepatol 2013;58:427–433. 4. Gordon SC et al, Clin Gastroenterol Hepatol 2014;12:885–893.

Long-term NUC and prevention of HCC
Propensity score studies from Asia and US

NUC therapy does not eliminate but significantly reduces the 5-year HCC risk

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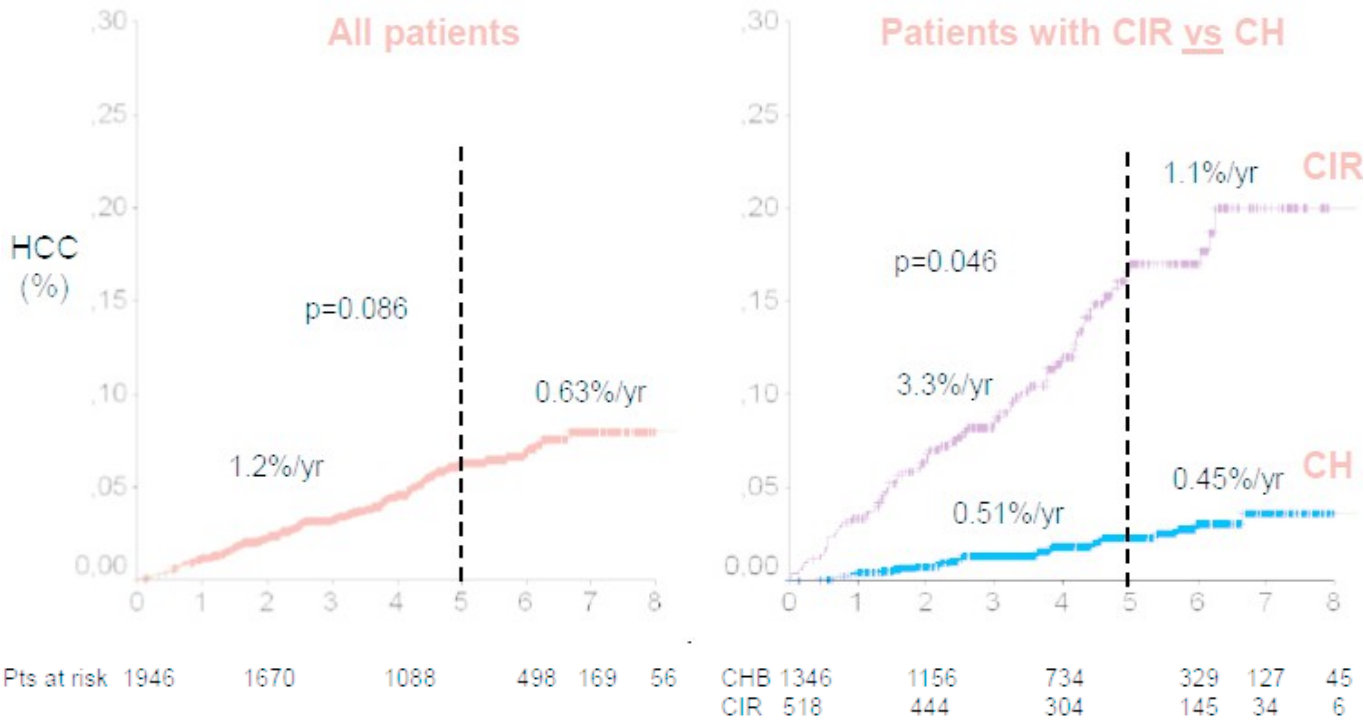
HCC in ETV/TDF treated pts beyond year 5



HCC beyond yr-5 associated only with older age (p=0.062) or age ≥55 at ETV/TDF onset (p=0.02)

Papatheodoridis G, Lampertico P et al. AASLD 2015

Recommendations on HCC surveillance by regional guidelines

AASLD [49]	APASL [50]	EASL-EORTC [51]
• Asian males over age 40 • Asian females over age 50 • Family history of HCC • African/North American blacks • Cirrhosis	• Cirrhosis	• Cirrhosis • Non-cirrhotic HBV carriers with active hepatitis • Family history of HCC

*The recommendations have been modified to focus on patients with chronic hepatitis B.

From: Wong and Janssen, Journal of Hepatology 2015, 63, 722–732

Virological and Biochemical Follow-up:

Aug.2015 - Sep.2015

- US nodule
- CT scan confirmation (single nodule, 2,5 cm)
- HBV DNA blip : 574 IU/ml
- α-feto protein 73 UI/ml
- ALT : 31 IU/mL
- Serum creatinine : 1.32 mg/dL (116 µmol/L)
- Serum phosphate : 2.5 mg/dL (0.81 mmol/L)

Sep. 2015

- Laparoscopic resection
- Histology:
  - Nodule: well differentiated HCC (G2)
  - Liver: inactive cirrhosis

Risk factors of HCC in patients with chronic hepatitis B.

Patient factors	Older age
	Male gender
	Family history of HCC
	Genetic factors
	Cirrhosis
	Smoking
	Alcohol consumption
	Diabetes mellitus
	Obesity
	Exposure to aflatoxin
Viral factors	High HBV DNA level
	Positive hepatitis B e antigen
	HBV genotypes
	HBV mutations
	Hepatitis B surface antigen level
	Co-infection with hepatitis C virus, hepatitis D virus or HIV

HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

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Hepatocellular carcinoma prediction models

	IPM	CU-HCC	GAG-HCC	REACH-B	LSM-HCC	mREACH-B	PAGE-B
Full name	Individual Prediction Model	Chinese University-HCC	Guide with Age, Gender, HBV DNA, Core Promoter Mutations and Cirrhosis-HCC	Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B	Liver Stiffness Measurement-HCC	Modified Risk Estimation for Hepatocellular Carcinoma in Chronic Hepatitis B	
Calculation	Risk Index (RI) for HCC = e^{A}, A = -6.2543 + (1.7219 × liver cirrhosis) + (1.3145 × old age over 40 yr) + (1.2631 × chronic HCV infection) + (0.8257 × AFP > 20 ng/mL) + (0.7754 × chronic HBV infection) + (0.7339 × chronic hepatitis) + (0.5840 × heavy alcoholics) + (0.3 × man) + (0.2830 × ALT > 40 IU/L) + (0.221 × unknown alcohol history)	Age (> 50 yr = 3; ≤ 50 = 0) + albumin (≤ 35 g/L = 20; > 35 = 0) + bilirubin (> 18 μmol/L = 1.5; ≤ 18 = 0) + HBV DNA (< 4 log copies/mL = 0; 4-6 = 1; > 6 = 4) + cirrhosis (yes = 15; no = 0)	14 × sex (male = 1; female = 0) + age (in years) + 3 × HBV DNA (log copies/mL) + 33 × cirrhosis presence = 1; absence = 0)	Male sex: 2 points Age: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points) ALT (IU/L): 15-<45 (1 point), ≥ 45 (2 points) Positive HBeAg: 2 points HBV DNA (log copies/mL): 4-< 5 (3 points), 5-< 6 (5 points), ≥ 6 (4 points)	Age (> 50 yr = 10; ≤ 50 = 0) + albumin (≤ 35 g/L = 1; > 35 = 0) + HBV DNA (> 200000 IU/mL = 5; ≤ 200000 = 0) + liver stiffness (≤ 8.0 kPa = 0; < 8.0-12.0 = 8; > 12.0 = 14)	Male sex: 2 points Age: 1 point for every 5 yr from 35 to 65 yr of age (0-6 points) ALT (IU/L): 15-< 45 (1 point), ≥ 45 (2 points) Positive HBeAg: 2 points Liver stiffness values: < 8.0 kPa (0 point), 8.0-13.0 (2 points), > 13.0 kPa (4 points)	Age; < 30 (-4 points), 30-39 (-2 points), 40-49 (0 point), 50-59 (2 points), 60-69 (4 points), ≥ 70 (6 points) Male sex: 5 points Platelets (mm^3): ≥ 200 × 10^3 (0 point), 100× 10^3-< 200 × 10^3 (6 points), < 100 × 10^3 (11 points)

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

Performance of HCC prediction models

	IPM	CU-HCC	GAG-HCC	REACH-B	LSM-HCC	mREACH-B	PAGE-B
Number of patients	994	1005	820	3584	1035	1308	1325
Place of development	South Korea	Hong Kong	Hong Kong	Taiwan	Hong Kong	South Korea	Europe
Race	Asian	Asian	Asian	Asian	Asian	Asian	Caucasian
Age (yr)		48	40.6	45.7	46	50	52
HBeAg-negative (%)			56.6	84.8	75	60.3	84
Cirrhosis (%)		38.1	15.1	0	32	17.8	20
Follow-up (yr)	2.7	9.94	5.62	12	5.8	6.3	3.6
Antiviral therapy (%)		15.1	0	0	38	64.8	100
HCC (%)	90 (0.1)	105 (10.4)	40 (4.9)	131 (3.7)	38 (3.7)	125 (9.6)	51 (3.8)
Components of the risk scores	Age	Age	Age	Age	Age	Age	Age
	Male	Albumin	Male	Male	Albumin	Male	Male
	Platelet	Bilirubin	BCP mutation	ALT	HBV DNA	ALT	Platelet
	Cirrhosis	Cirrhosis	Cirrhosis	HBeAg-positive	LS value	HBeAg-positive	
	Albumin	HBV DNA	HBV DNA	HBV DNA		LS value	
	AFP						
	Heavy alcoholics						
Risk scores	Low (< 5)	Low (< 5)	Low (< 100)	Low (0-5)	Low (< 11)	Low (< 10)	Low (≤ 9)
	Intermediate (5-15)	Intermediate (5-19)		Intermediate (6-11)			Intermediate (10-17)
	High (> 15)	High (> 19)	High (≥ 100)	High (12-18)	High (≥ 11)	High (≥ 10)	High (≥ 18)
NPV (%)		97% at 10 yr	99% at 10 yr	98% at 10 yr	99.4% at 5 yr	96.8% at 5 yr	100% 5 yr

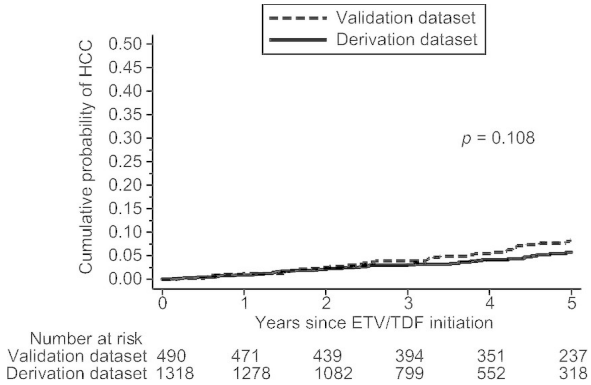
HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; LS: Liver stiffness; AFP: α-fetoprotein; NPV: Negative predictive value.

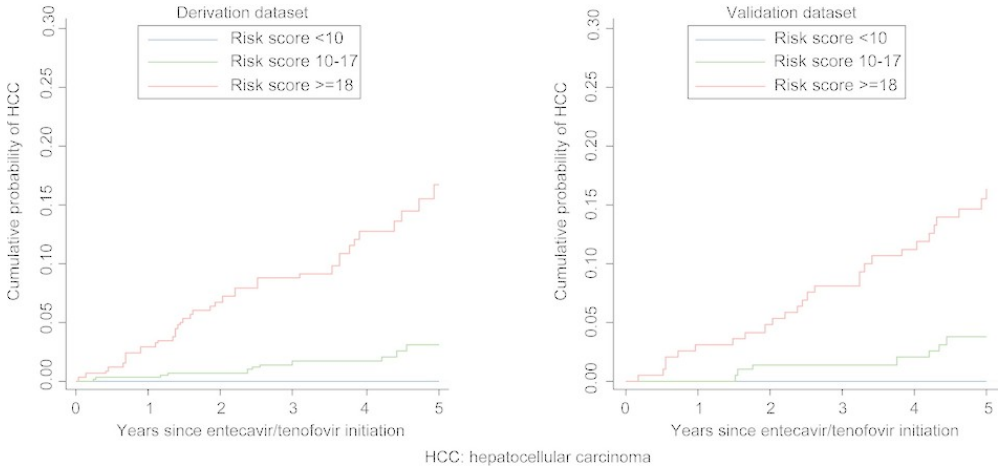
EASL | JOURNAL OF HEPATOLOGY

Journal of Hepatology 2016 vol. 64 | 800–806

PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy

George Papatheodoridis[1,2,*], George Dalekos[3], Vana Sypsa[4], Cihan Yurdaydin[5], Maria Buti[6], John Goulis[7], Jose Luis Calleja[8], Heng Chi[9], Spilios Manolakopoulos[2], Giampaolo Mangia[10], Nikolaos Gatselis[3], Onur Keskin[5], Savvoula Savvidou[7], Juan de la Revilla[8], Bettina E. Hansen[9], Ioannis Vlachogiannakos[1], Kostantinos Galanis[3], Ramazan Idilman[5], Massimo Colombo[10], Rafael Esteban[6], Harry L.A. Janssen[9,11], Pietro Lampertico[10]





HCC: hepatocellular carcinoma

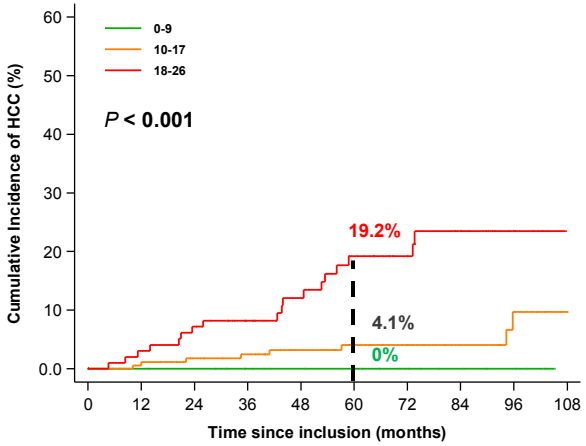
Epidemiological, clinical, biological and virological factors influencing HCC occurrence and validation of predictive scores in 317 HBV-related cirrhotic patients.
Prospective study Cir-B nested in the ANRS CO12 CirVir cohort

HCC predictive factors [multivariate analysis]

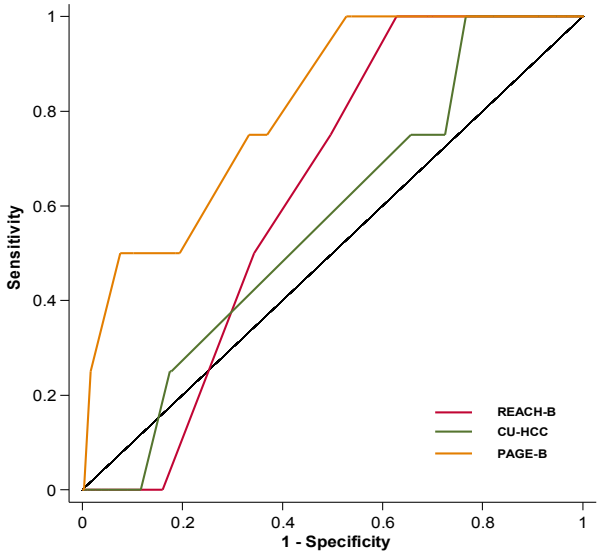
	HR	IC 95	*p*
Age > 50	8.42	[1.97 ; 36.11]	**0.004**
BMI > 30	2.67	[1.03 ; 6.92]	**0.043**
Platelets <150	5.77	[2.15 ; 15.51]	**0.001**

PAGE-B Score	
Platelets	
≥200 000	0
100 000 – 199 999	+6
<100 000	+9
Age	
16-29	0
30-39	+2
40-49	+4
50-59	+6
60-69	+8
≥70	+10
Gender	
F	0
M	+6

Papatheodoridis, J Hepatol 2016



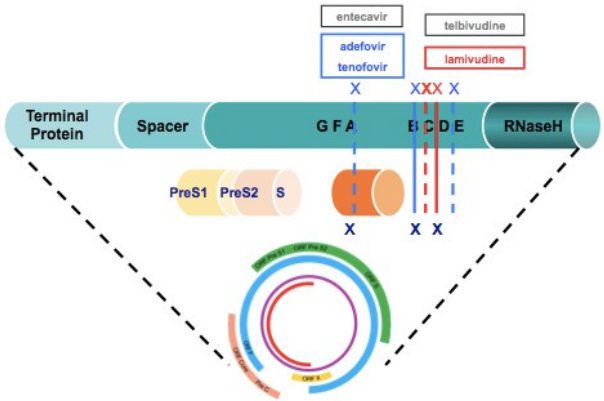
PAGE-B	Number at risk (events)																	
0-9	27	(0)	26	(0)	25	(0)	19	(0)	16	(0)	15	(0)	10	(0)	7	(0)	5	(0)	0
10-17	176	(1)	169	(2)	155	(1)	145	(1)	124	(1)	97	(0)	71	(0)	47	(2)	30	(0)	2
18-26	104	(3)	95	(4)	90	(1)	79	(3)	66	(5)	53	(0)	38	(2)	29	(0)	15	(0)	1

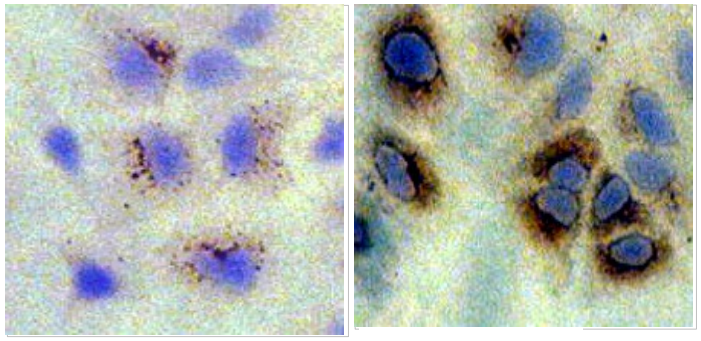


	AUC (1y)	AUC (3 yrs)
REACH-B	0,629	0,694
CU-HCC	0,568	0,617
PAGE-B	0,808*	0,728

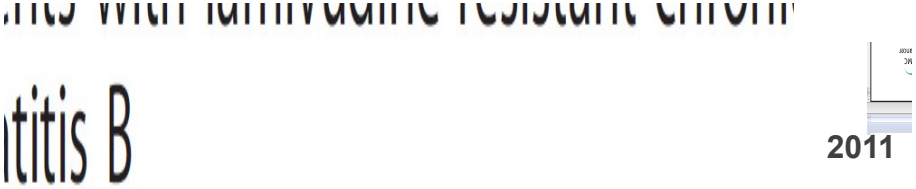
S. Brichler and the ANRS CO12 CirVir cohort. HEPATOLOGY, 64, S1, 897A

The rtA181T / sW172* mutant has a dominant negative secretion defect

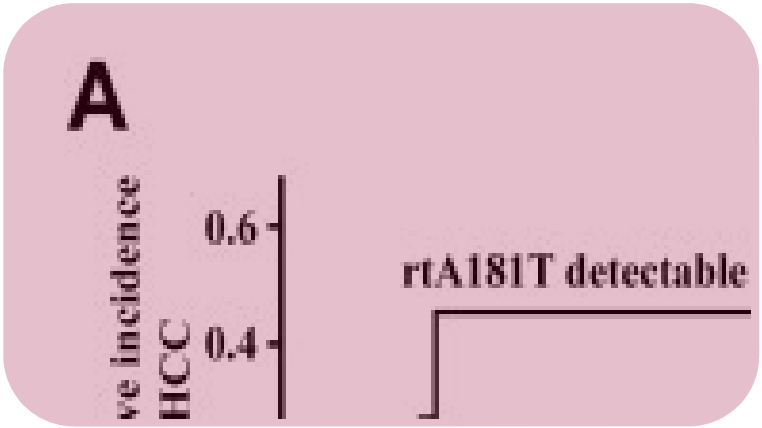




Warner et al, Hepatology 2008



A181T correlates with the onset of HCC in HBV genotype C patients



Virological and Biochemical Follow-up:

Oct. 2016

- HBV DNA : < LOD
- α-feto protein 9 UI/ml
- ALT : 25 IU/mL
- Serum creatinine : 1.18 mg/dL (127 µmol/L)
- Serum phosphate : 2.4 mg/dL (104 mmol/L)

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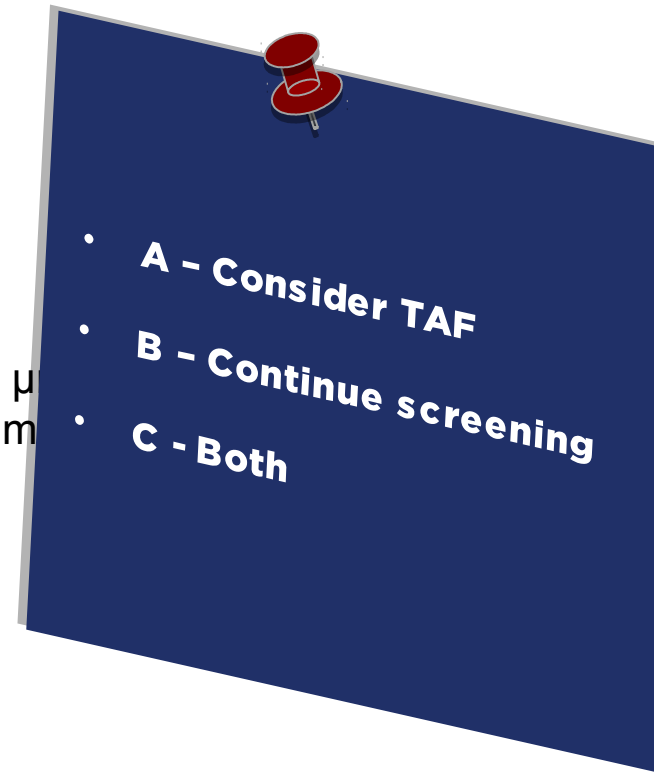
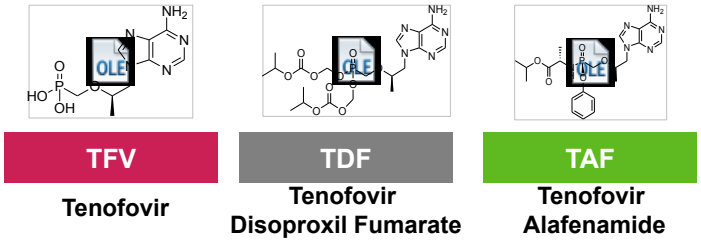
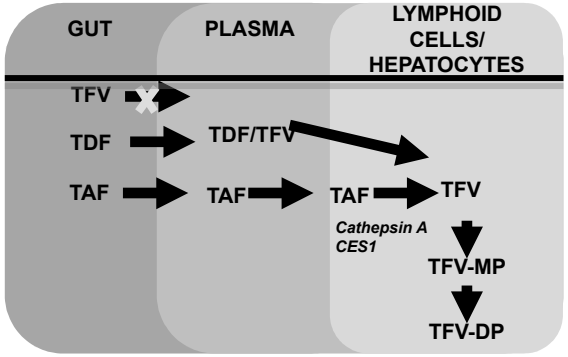


A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-neg CHB: week 48 efficacy and safety results

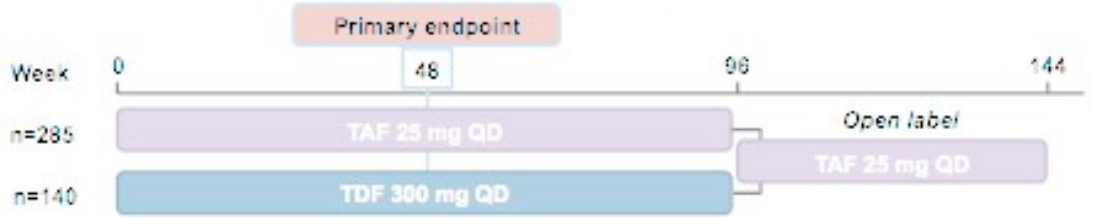




CES1 = carboxylesterase 1; DP= di-phosphate; MP= mono-phosphate.

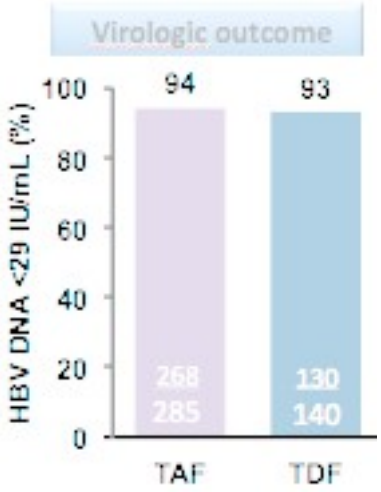
- Improved stability in plasma:
  - Enhanced delivery of active form (TFV-DP) to hepatocytes
  - Lower doses are used; systemic exposures of TFV reduced

Agarwal K et al. AASLD 2013, Poster # 973
Murakami E et al. HepDART 2013, Abstract 104



HBeAg negative

- Mean age ~47 years
- 259 (61%) males
- 306 (72%) Asian
- 91 (21%) treatment-experienced



Buti M, et al. Lancet Gastroenterol Hepatol 2016

A Phase 3 study of tenofovir alafenamide compared with tenofovir disoproxil fumarate in patients with HBeAg-neg CHB: week 48 efficacy and safety results

Renal safety (Wk 48)	TAF n=285	TDF n=140
sCr change, mg/dL	0.012 (0.091)	0.020 (0.103)
$eGFR_{CG}$ change, mL/min	−1.4 (12.7)	−4.7 (12.0)*
No proteinuria, n/n (%)	221/282 (78)	114/140 (81)

Fewer TAF patients had >3% decreases in BMD
Spine: 22% TAF vs 39% TDF**
Hip: 10% TAF vs 33% TDF**

Buti M, et al. Lancet Gastroenterol Hepatol 2016

Conclusion

- Antiviral therapy for CHB can achieve viral suppression in the most difficult to treat patients

- In TDF treated patients, kidney function should be monitored especially in patients previously treated with ADF cirrhotics and in case of co-morbidities

- Surveillance of HCC is mandatory even in case of viral suppression. Predictive scores require further refinement

HBV life cycle and main classes of antivirals in development