Chronic hepatitis B: Long term benefit of treatment

Prof Jean-Pierre Bronowicki

University Hospital Nancy

INSERM U954

Disclosures

Adviser, speaker for:

Abbvie, BMS, Gilead, Janssen, MSD, Bayer,

Patient case

Age / Gender	51-years / male
HBV diagnosis	2006
Route of transmission	No clear risk factor
ALT	111 IU/mL (NV<40 IU/mL)
HBeAg	Negative
HBV DNA	2,000,000 copies/ml (≈350,000 IU/mL)
Liver biopsy	Knodell score 12, fibrosis 4 (Metavir A2F4)
Platelets (G/L)	155
Gastroscopy	No EV
US	No HCC
Liver stiffness (kPa)	17.8 kPa
Comorbidity	No - BMI 25
eGFR (mL/min)	100
Serum Phosphate	0.58 mmol/L (0.81-1.45)

EASL recommandations 2017

At baseline, …kidney function tests (eGFR and serum phosphate levels) should be performed

Patients at risk of renal disease treated with any NA and all patients regardless of renal risk treated with TDF should undergo periodical renal monitoring including eGRF and serum phosphate levels

The frequency of renal monitoring can be every 3 months during the first year and every 6 months thereafter, if no deterioration

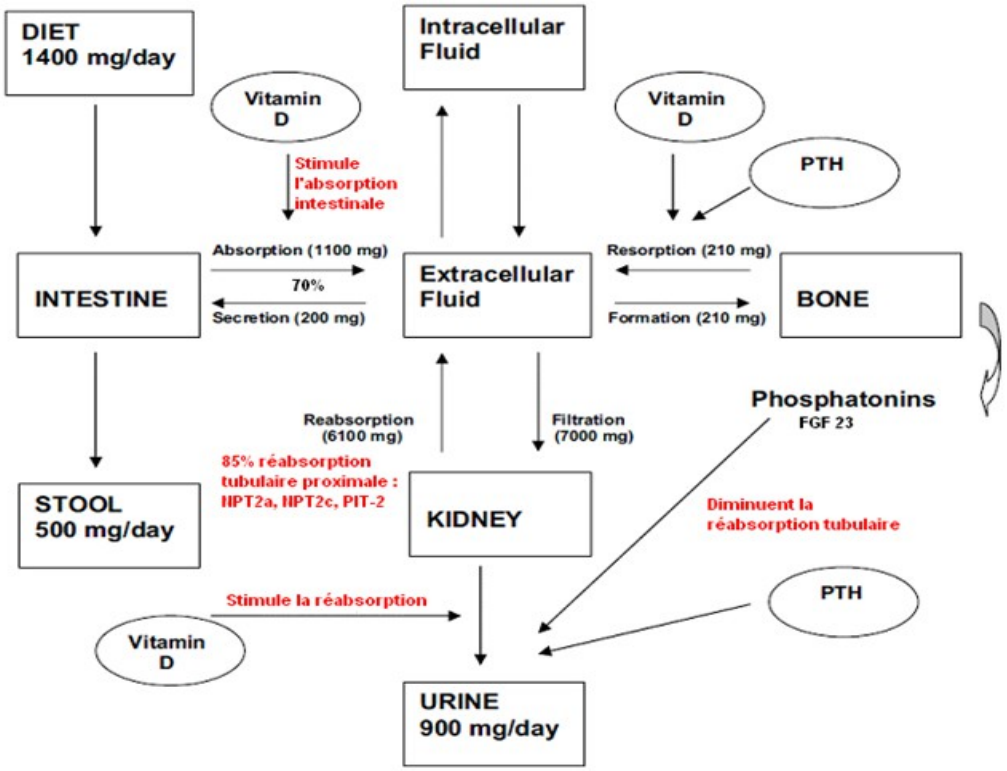
Renal abnormalities in 260 treatment naive patients with chronic HBV infection

Proteinuria (dipstick), n=155	38.1% (59)
Abnormal urinary sediment (dipstick), n=155:	
Haematuria	20.6% (32)
Glycosuria	3.9% (6)
Uninfectious leukocyturia	9% (14)
Hypophosphatemia, n=193	10.9% (21)
Mild (0.6-0.8 mmol/l)	10.5% (20)
Moderate (0.3-0.6 mmol/L)	0.5% (1)
Vitamin D level, n=200	
Hypovitaminosis (<20 mg/L)	64.5% (129)
Vitaminin D deficiency (<5 mg/L)	11.5% (23)
KD patients according to KDOQI/KDIGO classification, n=113	
Stage 1: GFR≥90 + kidney damage*	36.3% (41)
Stage 2: 60-89 (mild decrease in GFR) + kidney damage*	24.8% (28)
Stage 3: 30-59 (moderate decrease in GFR	3.5% (4)
Stage 4-5: 15-29 (severe decrease in GFR) and <15 (dialysis)	0
All stages	64.6% (73)

** Proteinuria (>1+) and/or haematuria (>1+) and/or leukocyturia (<1+ without nitrite)*

Amet S et al. Liver Int 2015;35:148-55

Hypophosphatemia



- Blood : P, Ca, Creatinin, 1-25-OH-vitD, PTH
- Urine : P, Ca, Creatinin
- Phosphaturia:
  - < 5mmol/24h : extra-renal
  - > 5mmol/24h : renal
- Tubular PO4 reabsorption
  - High: extra-renal
  - Low: proximal tubulopathy?

Gaasbeek – Hypophosphatemia : an update of its etiology and treatment AJM 2005

Hypophosphatemia confirmed, Ca N, PTH N, **25-OH-vitD: 5 mg/L**, phosphaturia < 5mmol/24h, TmP/GFR high

→ vitD supplementation → P normalization

Patient case

March 2006: patient started tenofovir in a phase 3 study comparing TDF vs ADF.

Marcellin P et al. N Engl J Med 2008.359:2442-55

What is the risk of HCC under treatment at 5 years in this patient ?

1) Low
2) Intermediate
3) High

Research Article

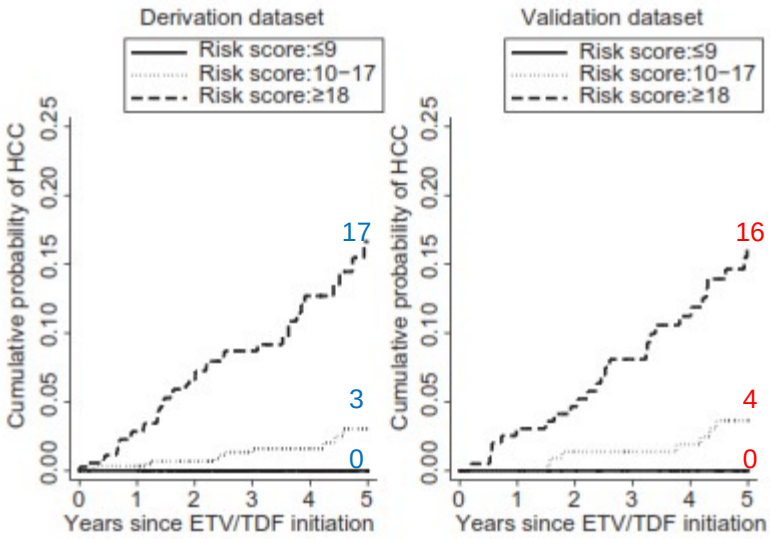
JOURNAL OF HEPATOLOGY

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]

Age (yr)		Gender		Platelets (G/L)	
16-29	0	Female	0	≥200	0
30-39	2	Male	6	100-199	6
40-49	4			<100	9
50-59	6				
60-69	8				
≥70	10				

Page-B score = 18



Patient case

March 2006: patient started TDF in a phase 3 study comparing TDF vs ADF.

	2006 (W24)	2007 (year 1)
ALT (IU/L)	66	55
HBV DNA (copies/mL)	20,000	<400
GFR (mL/min)	>90	>90
Phosphate (mmol/L)	Normal	Normal
Platelets	177	170
LS (kPa)	-	9.1
US	Normal	Normal

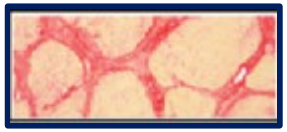
How would you interpret the decrease of liver stiffness from 17.8 to 9.1?

1) **Regression of fibrosis**
2) **Decrease of inflammation**
3) **Probably both**

Patient case

Liver biopsy

2006



Knodell NI score: 12
Ishak fibrosis score: 6

2007

Knodell NI score: 7
Ishak fibrosis score: 3

Would you stop HCC screening ?

1) No
2) Yes

Patient case

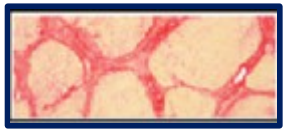
Patient treated with TDF and followed in a open label study with a biopsy at week 240

	2008 (year2)	2009 (year 3)	2010 (year 4)	2011 (year 5)
ALT (IU/L)	41	39	30	28
HBV DNA (IU/mL)	<29	<29	<29	<29
GFR (mL/min)	>90	>90	>90	>90
Phosphate (mmol/L)	Normal	Normal	Normal	Normal
Platelets (G/L)	190	199	191	190
LS (kPa)	8	7.2	6.4	5.7
US	Normal	Normal	Normal	Normal

Patient case

Liver biopsy

2006



Knodell NI score: 12
Ishak fibrosis score: 6

2007

Knodell NI score: 6
Ishak fibrosis score: 3

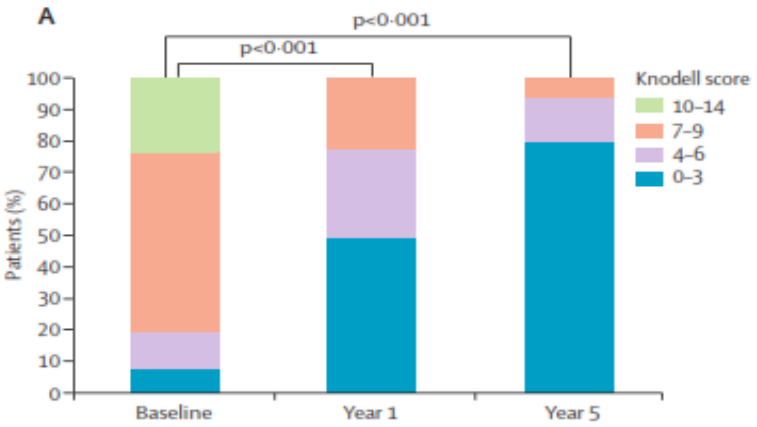
2011

Knodell NI score: 2
Ishak fibrosis score: 2

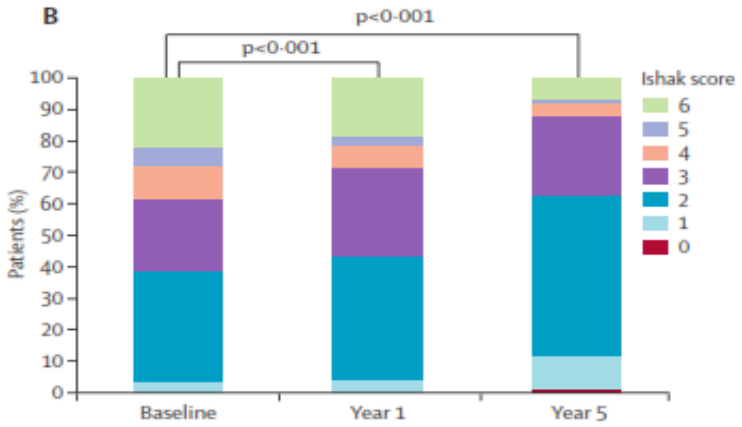
Regression of cirrhosis during treatment with TDF

Histology results over 5-year treatment phase

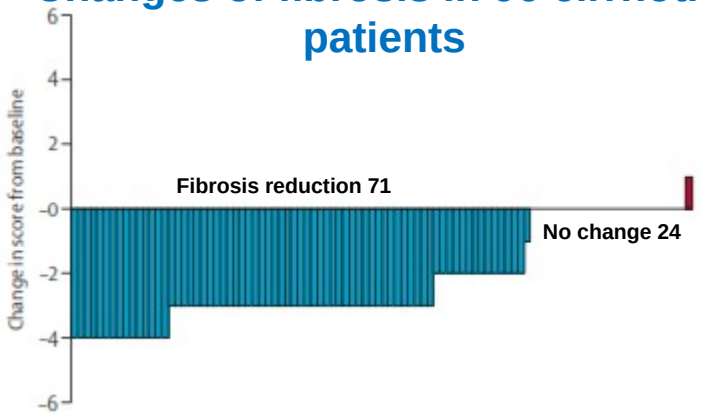
Knodell score



Ishak score



Changes of fibrosis in 96 cirrhotic patients



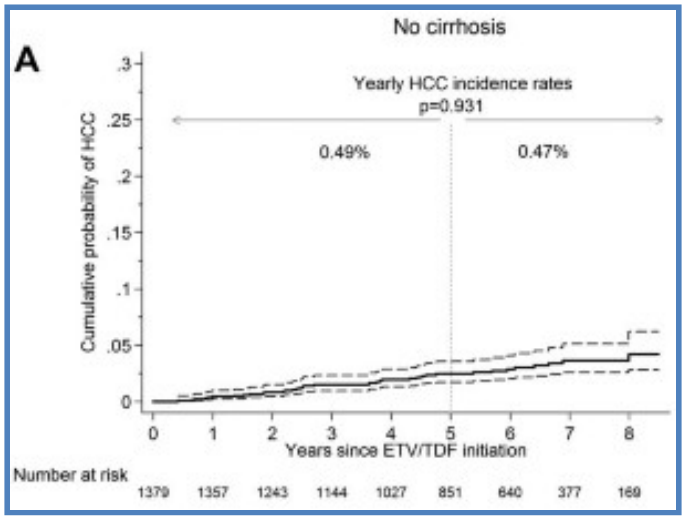
Fibrosis at yr-5	No cirrhosis (n=71)	Cirrhosis (n=25)	
BMI (D1)	25.7	29.0	<0.0007
Diabetes (D1)	1%	24%	0.001
N ALT (yr5)	87%	58%	0.007
Knodell 0-3 (yr5)	83%	52%	0.007
BMI ,OR 7.4, p=0.0044			

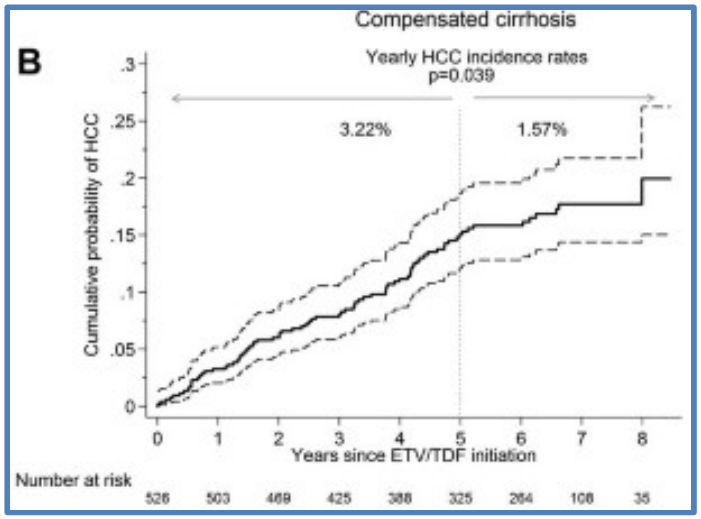
68-75

Would you stop HCC screening ?

1) No
2) Yes

Risk of HCC after the first 5 years of ETV or TDF in caucasian





	Baseline		Year 5	
	HR (95% CI)	p	HR (95% CI)	p
Age (per yr)	1.06 (1.01-1.11)	0.032	1.06 (1.00-1.13)	0.047
Platelets	0.99 (0.98-1.00)	0.021	0.98 (0.97-0.99)	0.004
HBV DNA	0.79 (0.60-1.03)	0.078		
Cirrhosis	1.38 (0.46-4.13)	0.324		

*MV analysis including only cirrhosis at D1 after adjustment for age and platelets at yr 5

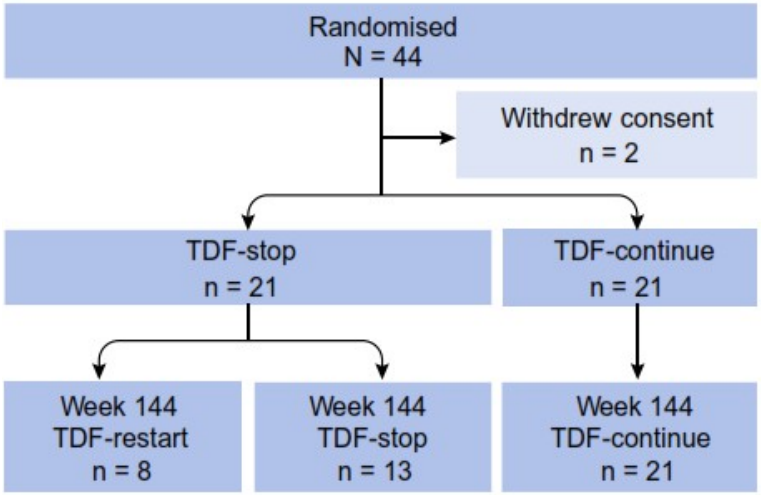
Papatheodoridis G et al. Hepatology 2017.66:1444-5

Would you stop TDF?

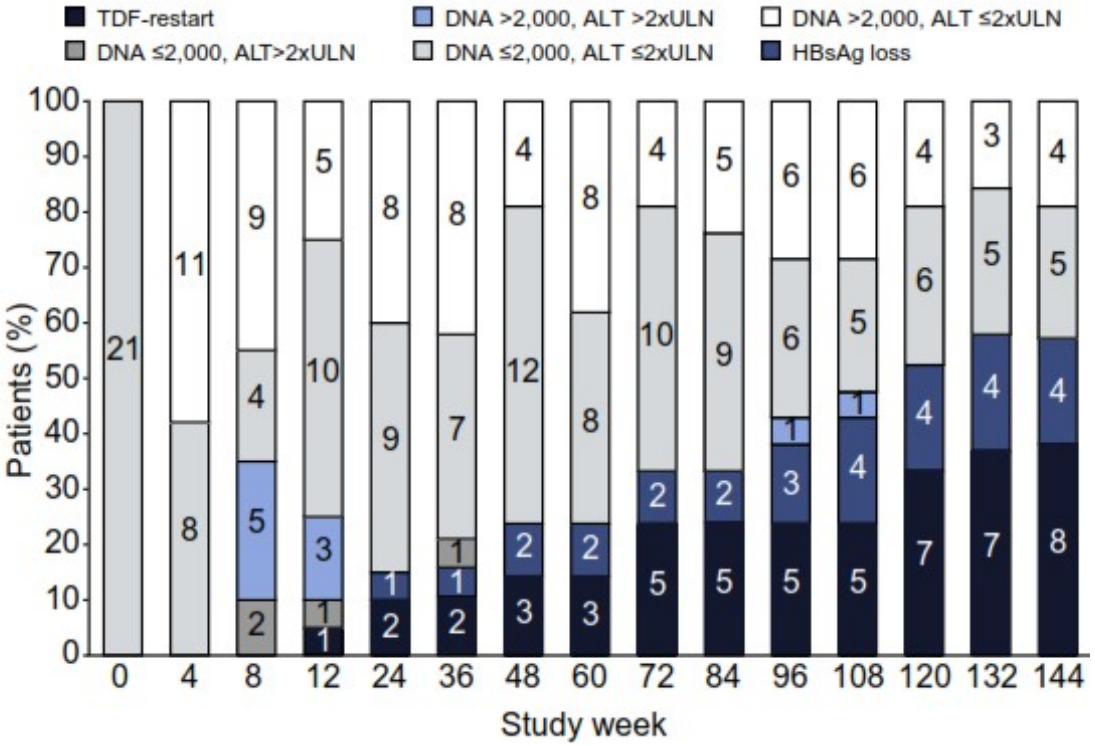
1) No
2) Yes

Long term response after stopping TDF in non cirrhotic HBeAg- patients

HBeAg-, TDF≥4 years,
HBV DNA suppressed 3.5 yr



62%



HBsAg loss: 19 % (n=4)
HBV DNA ≤2000 IU/mL and ALT <2N: 5

Berg T et al. J Hepatol 2017.67:918-24

Patient case

Patient still treated with TDF and screened for HCC by US

	2012 (year 6)	2013 (year 7)	2014 (year 8)	2015 (year 9)	2016 (year 10)
ALT (IU/L)	30	35	36	30	27
HBV DNA (IU/mL)	<29	<29	<29	<29	<29
GFR (mL/min)	88	85	83	80	81
HBsAg (IU/mL)	900	810	660	600	550
Log10 IU/mL	2.95	2.9	2.8	2.78	2.74
Phosphate (mmol/L)	Normal	Normal	Normal	Normal	Normal
Platelets (G/L)	190	199	188	190	192
LS (kPa)	5.5	5.8	5.9	6.1	6.2
US	Normal	Normal	Normal	Normal	Normal

The patient ask you if it is possible to accelerate the HBs clearance ?

1) No
2) May be

HBsAg loss after addition of 48 weeks of PEG-IFN to NUC in HBeAg negative patients

Pegan study

HBeAg - , HBV DNA -, NUC ≥ 1 yr

PEG-IFNα-2a
(180 µg/w.)

NUC (n=90)

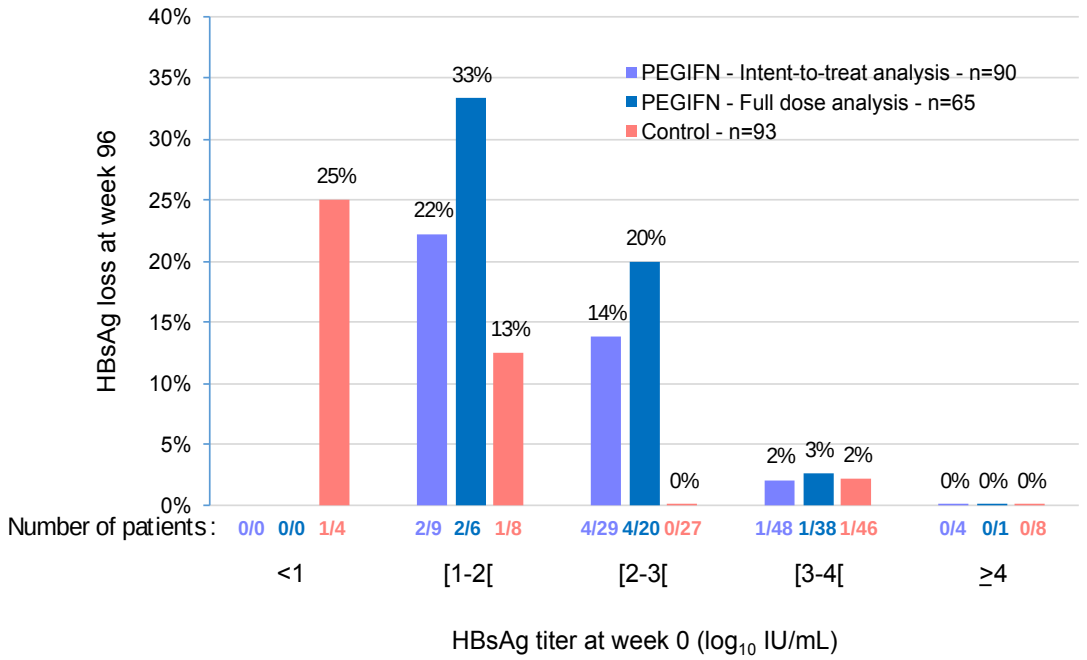
D1 W48 W96

D1 W48 W96

NUC (n=93)

HBsAg loss

Loss of HBsAg at week 96 according to treatment arm stratified by HBsAg titer (in log10 IU/mL) at week 0



HBsAg loss : 6/38 (16%) if HBsAg< 3log10

Bourlière M et al. Lancet Lancet Gastroenterol Hepatol. 2017;2:177-88

Patient case

Patient still HBsAg+ and treated with TDF

(12 years under treatment, cost of TDF 42000 €)

Conclusions

- Renal abnormalities are frequent in HBV+ patients → Renal function tests should be performed before starting NA
- In absence of cirrhosis, HCC surveillance is probably not mandatory if PAGE-B < 9
- Cirrhosis may reverse under NA
- The optimal strategies (HCC surveillance, NA cessation) in patients with cirrhosis reversion remain to be defined