2017

2ème Jeunes Hépatologues Conférence

Du 29 juin au 1er juillet 2017

Saint-Maximin-la-Sainte-Baume

Organisée par
Patrick Marcellin et Lawrence Serfaty

Le Couvent Royal Saint Maximin

www.aphc.info

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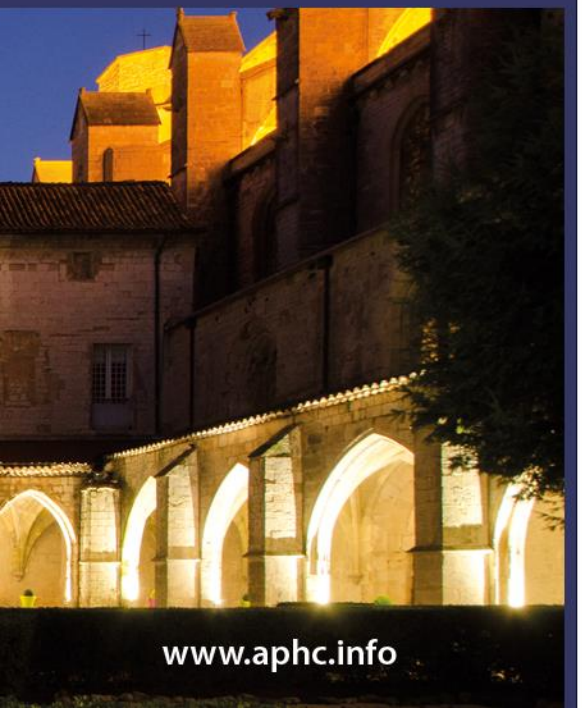

CONTROVERSES
Peut-on arrêter les NUC chez les patients VHB ?

Modérateurs :
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Pr Dominique GUYADER

Pro :
Isaac RUIZ
Cons :
Miroslava SUBIC-LEVRERO

GROUPE HOSPITALIER
HENRI MONDOR
ALBERT CHENEVIER - GEORGES CLEMENCEAU
JOFFRE-DUPUYTREN - EMILE ROUX

Plan général

- Peut-on arrêter les NUC chez les patients VHB ?
- Chez tous les patients?
- Existe-t-il de biomarqueurs?
- Risques d'arrêter le traitement?
- Risques du traitement? (Safety)
- Prix du traitement?
- Patient?

Peut-on arrêter les NUC chez les patients VHB ?

Clinical Practice Guidelines

2012

EASL JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

Clinical Practice Guidelines

2017

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*

Virological responses on NA therapy:

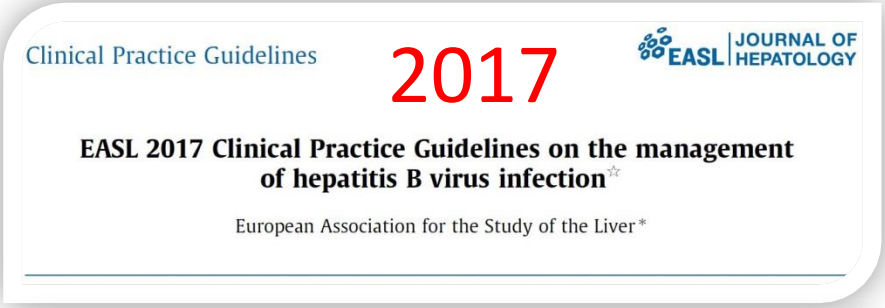
- Primary non-response is defined as less than 1 $\log_{10}$ IU/ml decrease in HBV DNA level from baseline at 3 months of therapy.
- Virological response is defined as undetectable HBV DNA by a sensitive PCR assay. It is usually evaluated every 3–6 months during therapy depending on the severity of liver disease and the type of NA.
- Partial virological response is defined as a decrease in HBV DNA of more than 1 $\log_{10}$ IU/ml but detectable HBV DNA after at least 6 months of therapy in compliant patients.
- Virological breakthrough is defined as a confirmed increase in HBV DNA level of more than 1 $\log_{10}$ IU/ml compared to the nadir (lowest value) HBV DNA level on therapy; it may precede a biochemical breakthrough, characterised by an increase in ALT levels. The main causes of virological breakthrough on NA therapy are poor adherence to therapy and/or selection of drug-resistant HBV variants (resistance) (**A1**).
- HBV resistance to NA(s) is characterised by selection of HBV variants with aminoacid substitutions that confer reduced susceptibility to the administered NA(s). Resistance may result in primary non-response or virological breakthrough on therapy (**A1**).
- NA(s) discontinuation is not common practice to date. However, NA(s) may be discontinued in some patients. Sustained off-treatment virological response may be

NA discontinuation

Recommendations

- NAs should be discontinued after confirmed HBsAg loss, with or without anti-HBs seroconversion (Evidence level II-2, grade of recommendation 1).
- NAs can be discontinued in non-cirrhotic HBeAg-positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy. Close post-NA monitoring is warranted (Evidence level II-2, grade of recommendation 2).
- Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term ($\geqslant$3 years) virological suppression under NA(s) may be considered if close post-NA monitoring can be guaranteed (Evidence level II-2, grade of recommendation 2).

Peut-on arrêter les NUC chez les patients VHB ?



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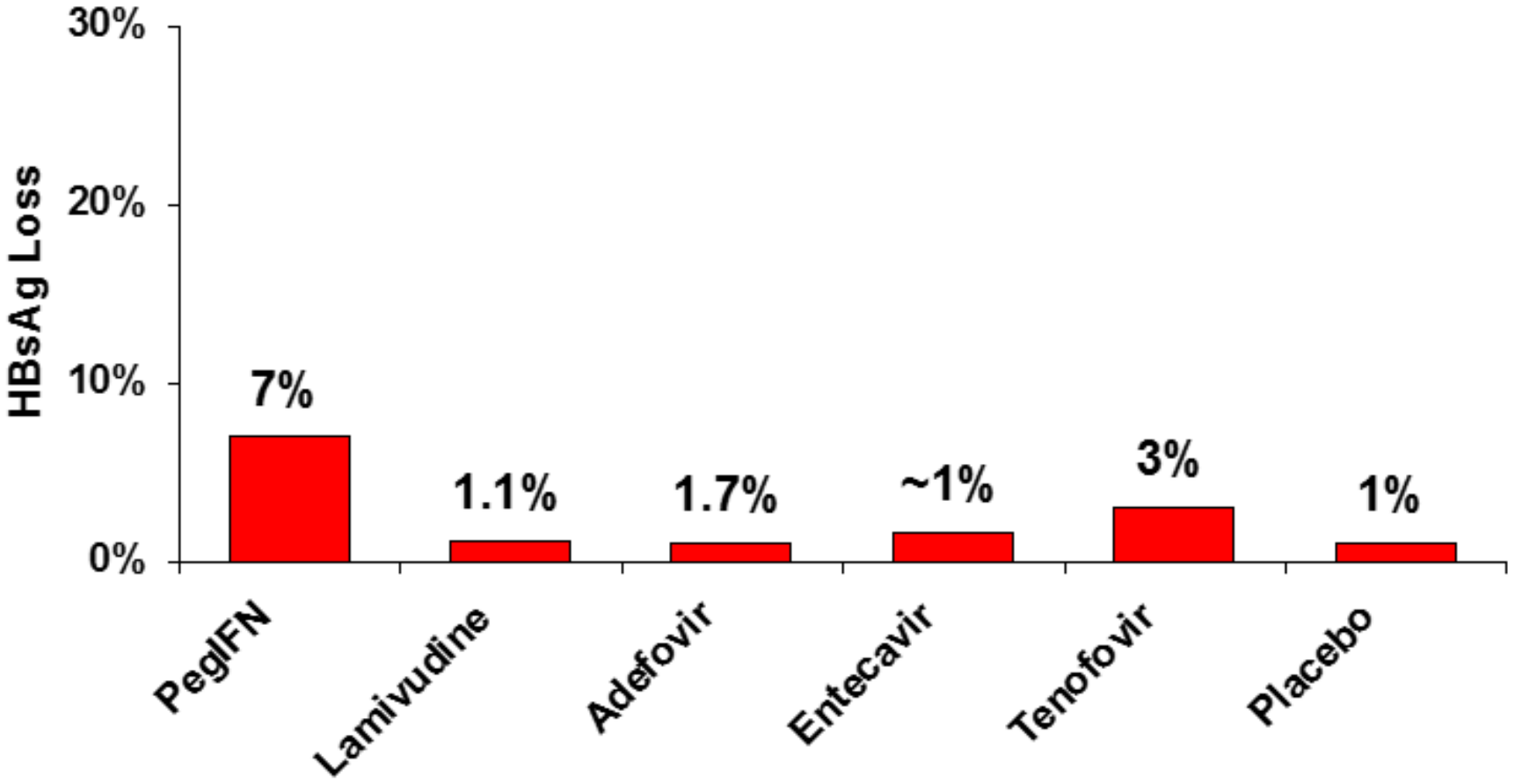
"The ideal end point is HBsAg loss"

= Guerison

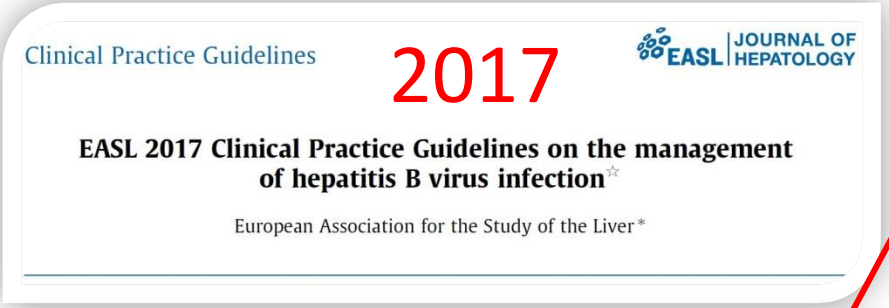
EASL Clinical Practice Guidelines, 2017

% perte de AgHBs sous ttt NA



Chang et al. NEJM 2006,354:1001-10; Lai et al. NEJM 2006,354:1011-20; Liaw et al. GE 2009,136:486-95; Marcellin et al. NEJM 2003,348:808-17; Hadziyannis et al. NEJM 2003,348:800-7; GE 2006,131:1743-51; Lai et al. NEJM 2007,357:2576-88; Heathcote et al. AASLD 2007/2008; Marcellin et al. AASLD 2007/2008/2011

EASL Guidelines 2017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« Selected patients »

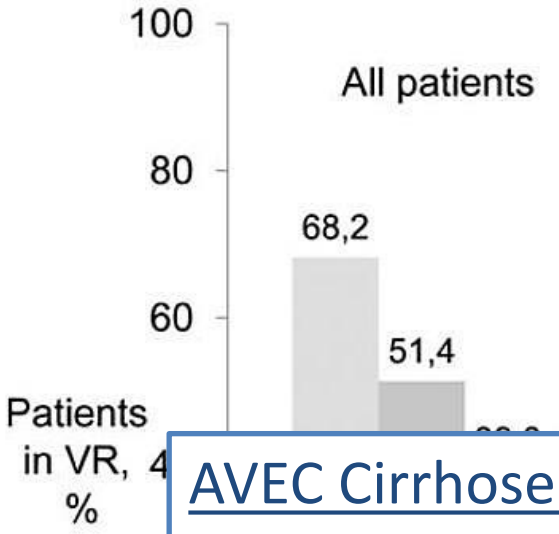
AgHBe-positif

AgHBe-négatif

EASL Clinical Practice Guidelines, 2017

Discontinuation of Oral Antivirals in Chronic Hepatitis B: A Systematic Review

25 études avec 1716 patients



AVEC Cirrhose:

Décompensation hépatique..... 2 (0,8%)
Ictère..... 6 (2,5%)
Retraitement effective 100%
Décès (ins. Hépatique)..... 1 (0,4%)

Papatheodoridis G, Hepatology, 2016

Guidelines EASL, AASLD, APASL

		EASL 2017	AASLD 2015	APASL 2015
HBeAg positif	HBeAg séroconversion	+	+	+
	Cirrhose	SANS		
	ttt consolidation	≥ 12m	≥ 12m	≥ 12m (≥ 3 ans)
	HBV ADN	indétectable		
	Surveillance	+++		
HBeAg négatif	HBsAg perte	<u>SANS cirrhose :</u> Control virologique ≥3a Surveillance après l'arrêt	<u>SANS cirrhose :</u> Recommandation: - ttt à vie <u>AVEC Cirrhose</u> : Pas recommandé	<u>SANS cirrhose :</u> HBsAg perte PLUS anti-HBs séroconversion OU ttt consolidation ≥ 12m <u>AVEC Cirrhose</u> : Seulement si surveillance peut être assurer
	anti-HBs séroconversion			
	Cirrhose			
	ttt consolidation			

EASL. J Hepatol 2017; Sarin SK, et al. Hepatol Int 2016; Terrault NA et al. Hepatology 2016

AgHBe positif

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HBeAg positif	HBeAg séroconversion	+	+	+
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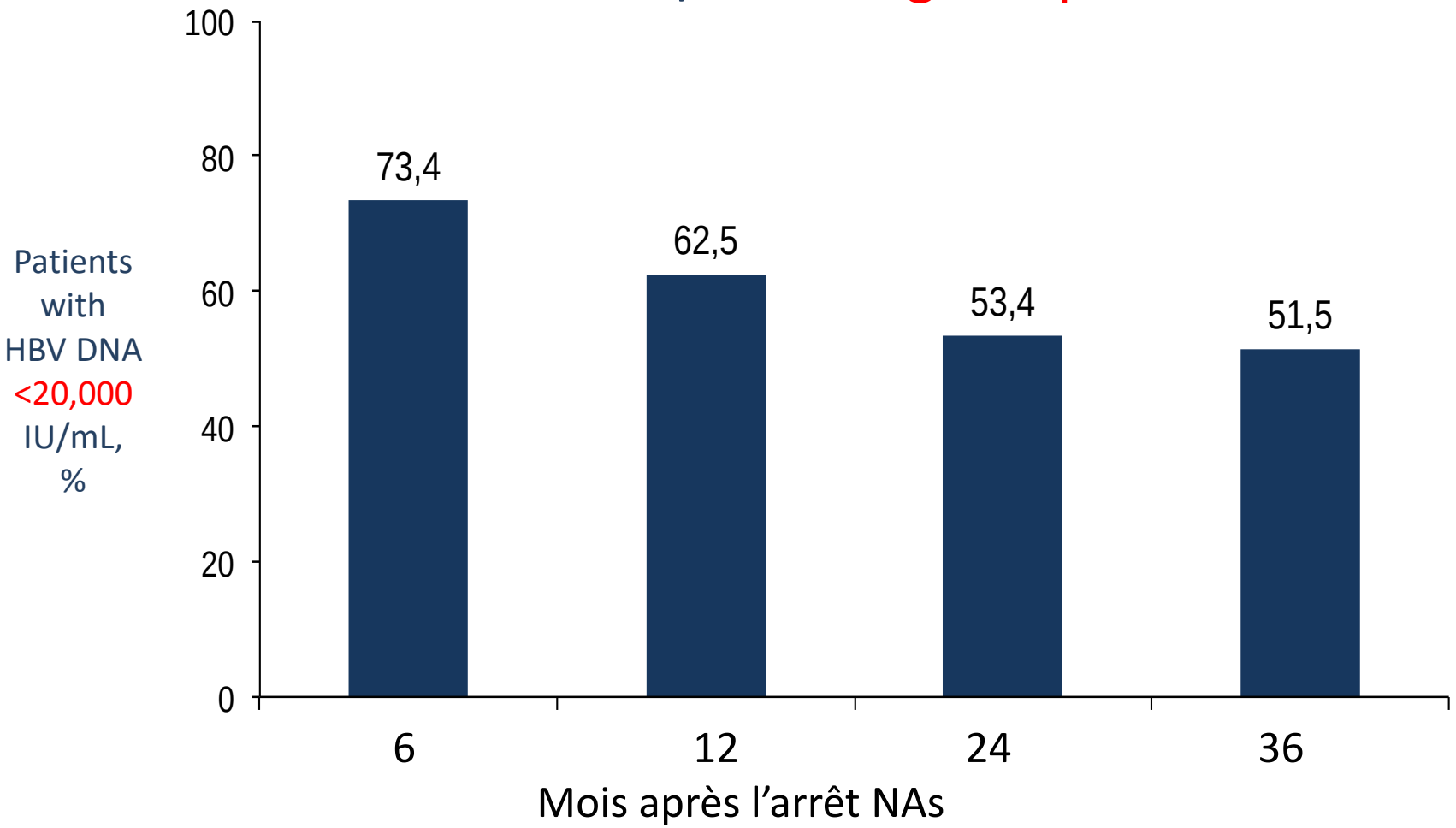
	HBV DNA	indétectable		
	Surveillance	+++		

EASL. J Hepatol 2017; Sarin SK, et al. Hepatol Int 2016; Terrault NA et al. Hepatology 2016

% de RV après l'arrêt des NA

14 études, 733 patients AgHBe positif

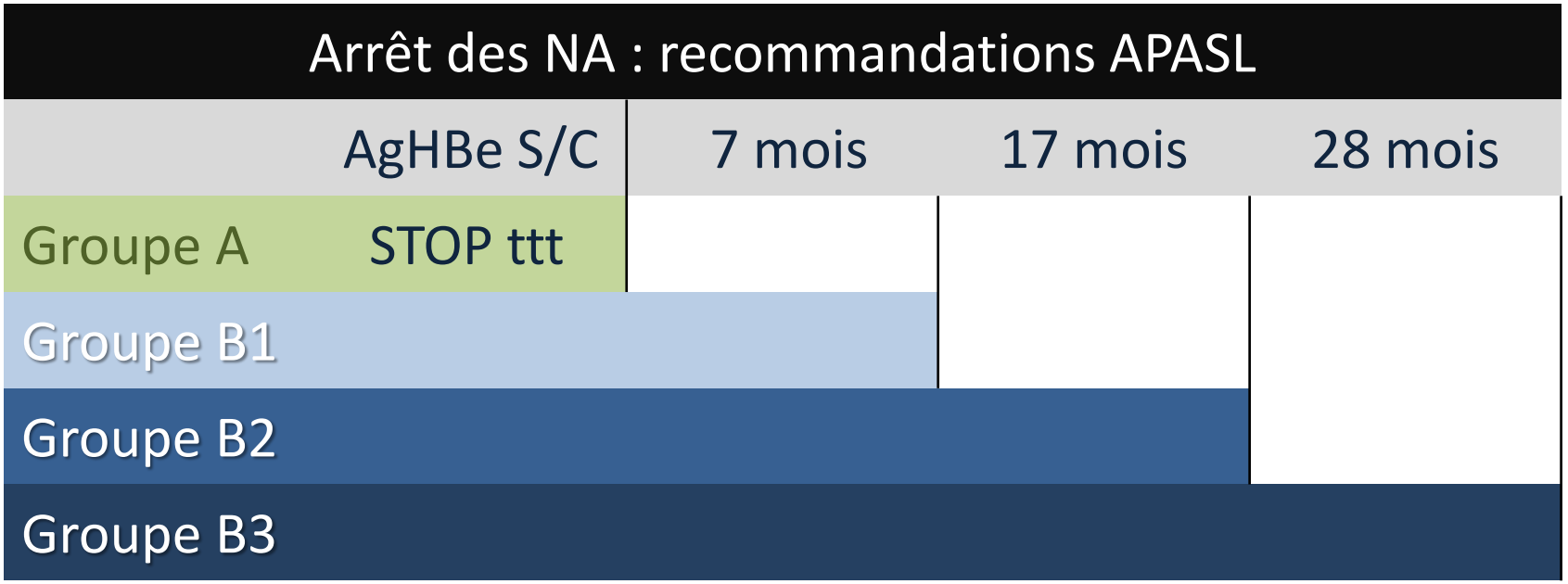


Pooled AgHBs loss: 1%; Durable biochemical remission: 76%

Papatheodoridis G et al. Hepatology 2016

Traitement de consolidation

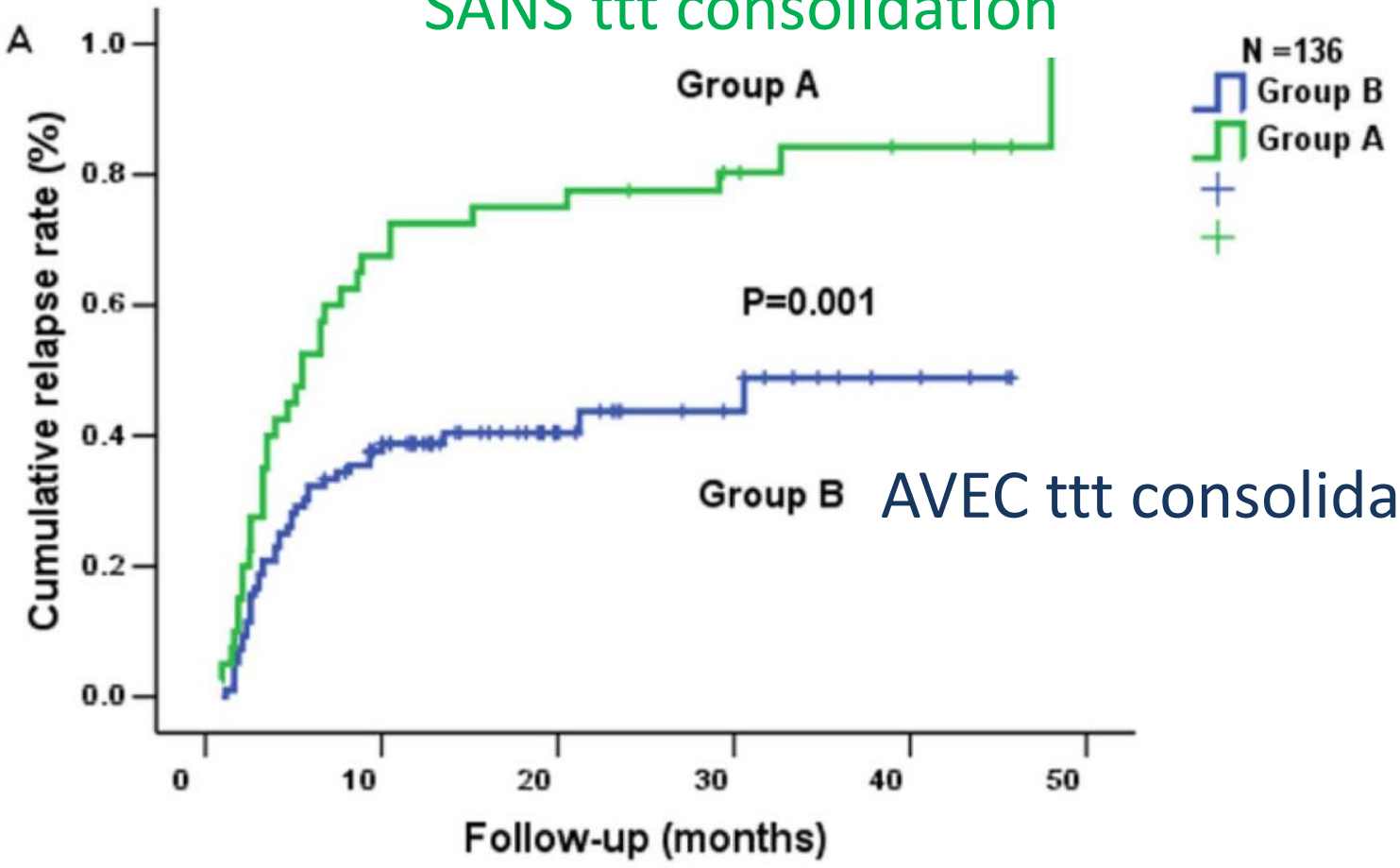
162 patients AgHBe positive, avec une hépatite chronique B
Rechute virologique = augmentation ADN HBV >10^3copies/ml.



Xingfei Pan, PLOS One 2013

Traitement de consolidation

SANS ttt consolidation

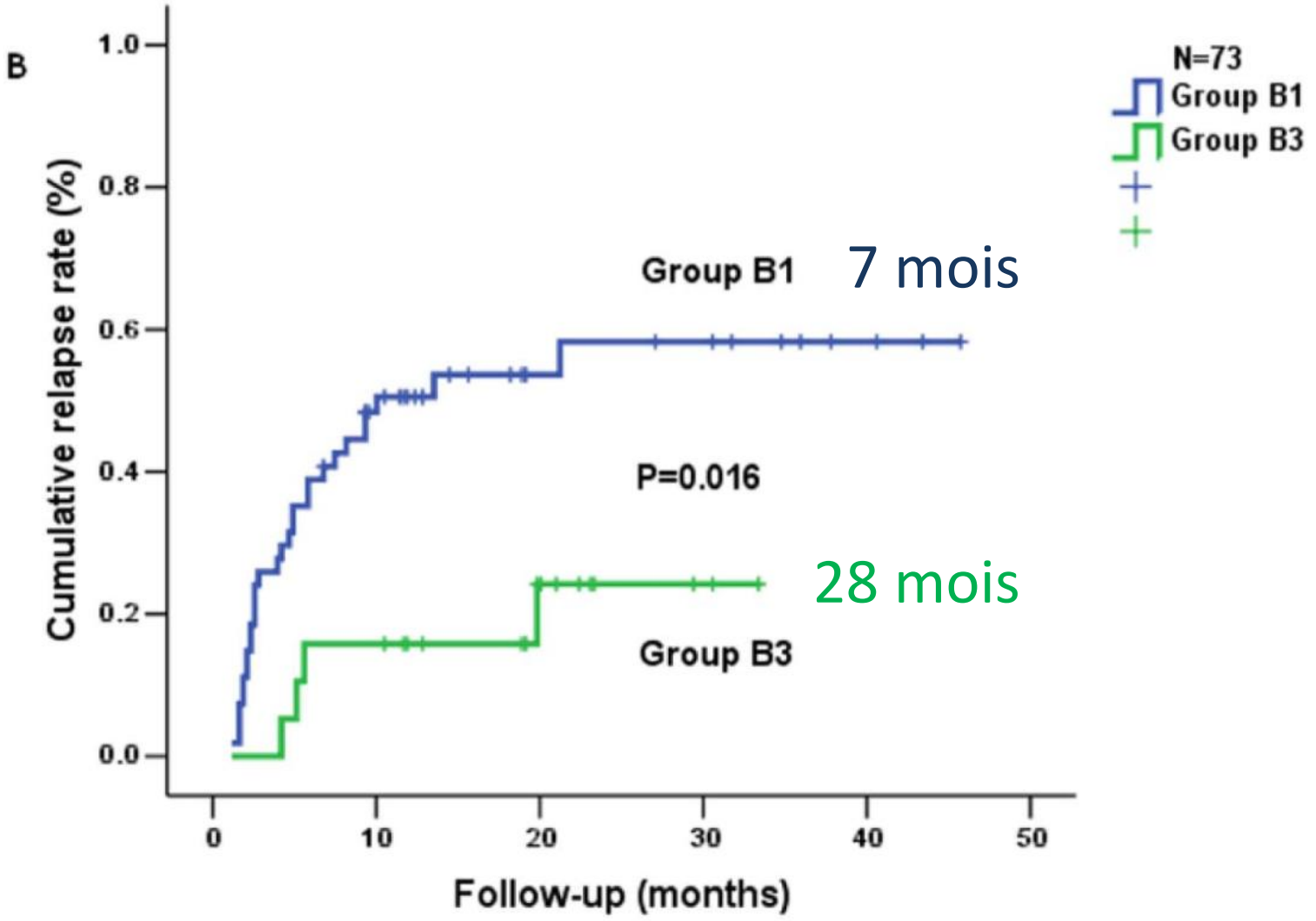


AVEC ttt consolidation

L'importance du traitement de consolidation

Xingfei Pan, PLOS One 2013

Traitement de consolidation



Xingfei Pan, PLOS One 2013

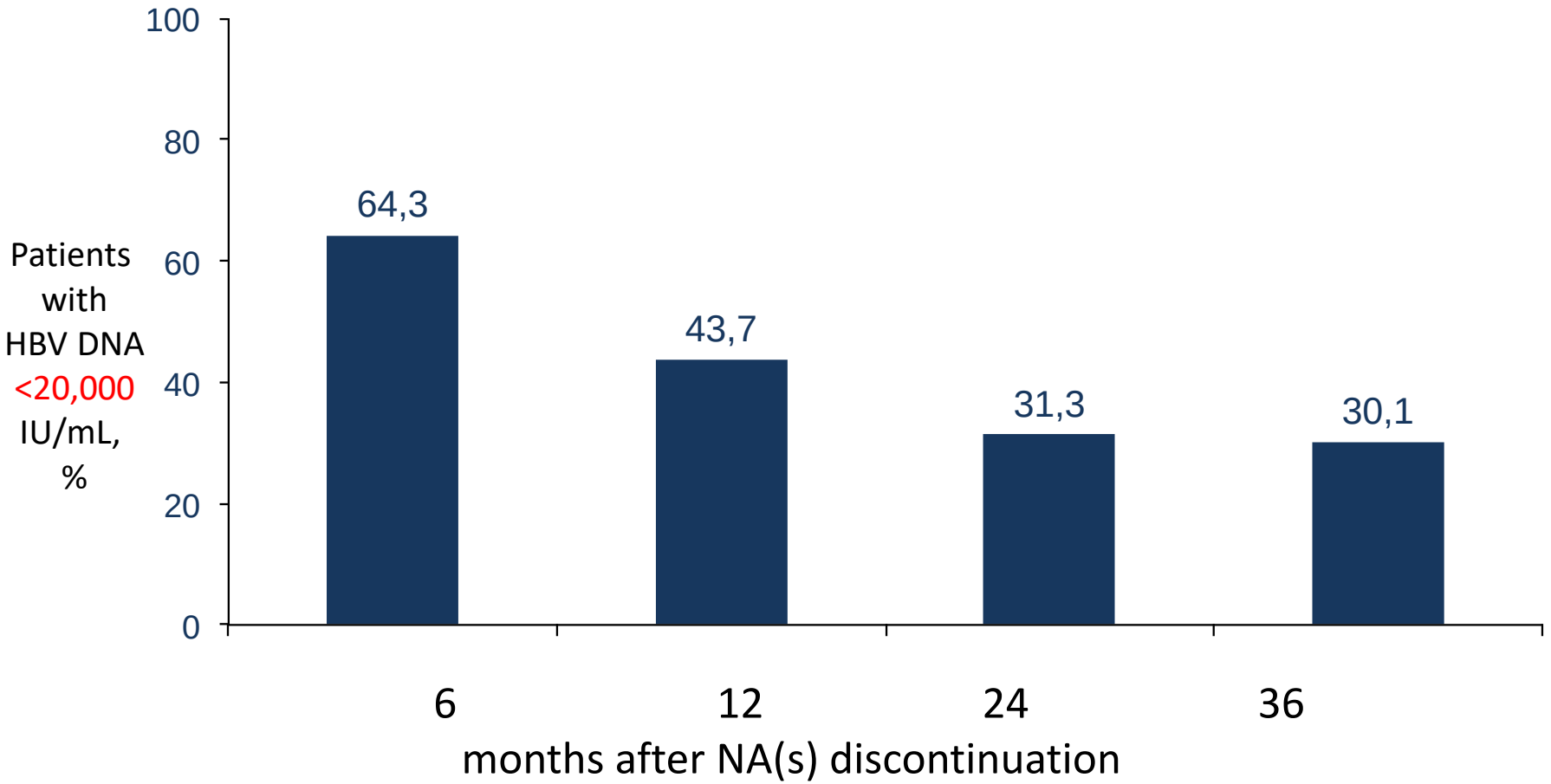
AgHBe négatif

		EASL 2017	AASLD 2015	APASL 2015
AgHBe négatif	HBsAg perte	<u>SANS cirrhose :</u> Control virologique ≥3a Surveillance après l'arrêt	<u>SANS cirrhose :</u> Recommandation: - ttt à vie <u>AVEC Cirrhose</u> : Pas recommandé	<u>SANS cirrhose :</u> HBsAg perte PLUS anti-HBs séroconversion OU ttt consolidation ≥ 12m <u>AVEC Cirrhose</u> : Seulement si surveillance peut être assurer
	anti-HBs séroconversion			
	Cirrhose			
	ttt consolidation			

EASL. J Hepatol 2017; Sarin SK, et al. Hepatol Int 2016; Terrault NA et al. Hepatology 2016

% de RV après l' arrêt des NA

17 études, 967 patients **AgHBe négatif**



Pooled HBsAg loss: 1.7%; Durable biochemical remission: 57%

Papatheodoridis G et al. Hepatology 2016

Patients AgHBe négatif, sans cirrhose

- 60 patients non cirrhotiques avec hépatite chronique B AgHBe négatif
- Arrêt du traitement par analogue (ETV/TDF)

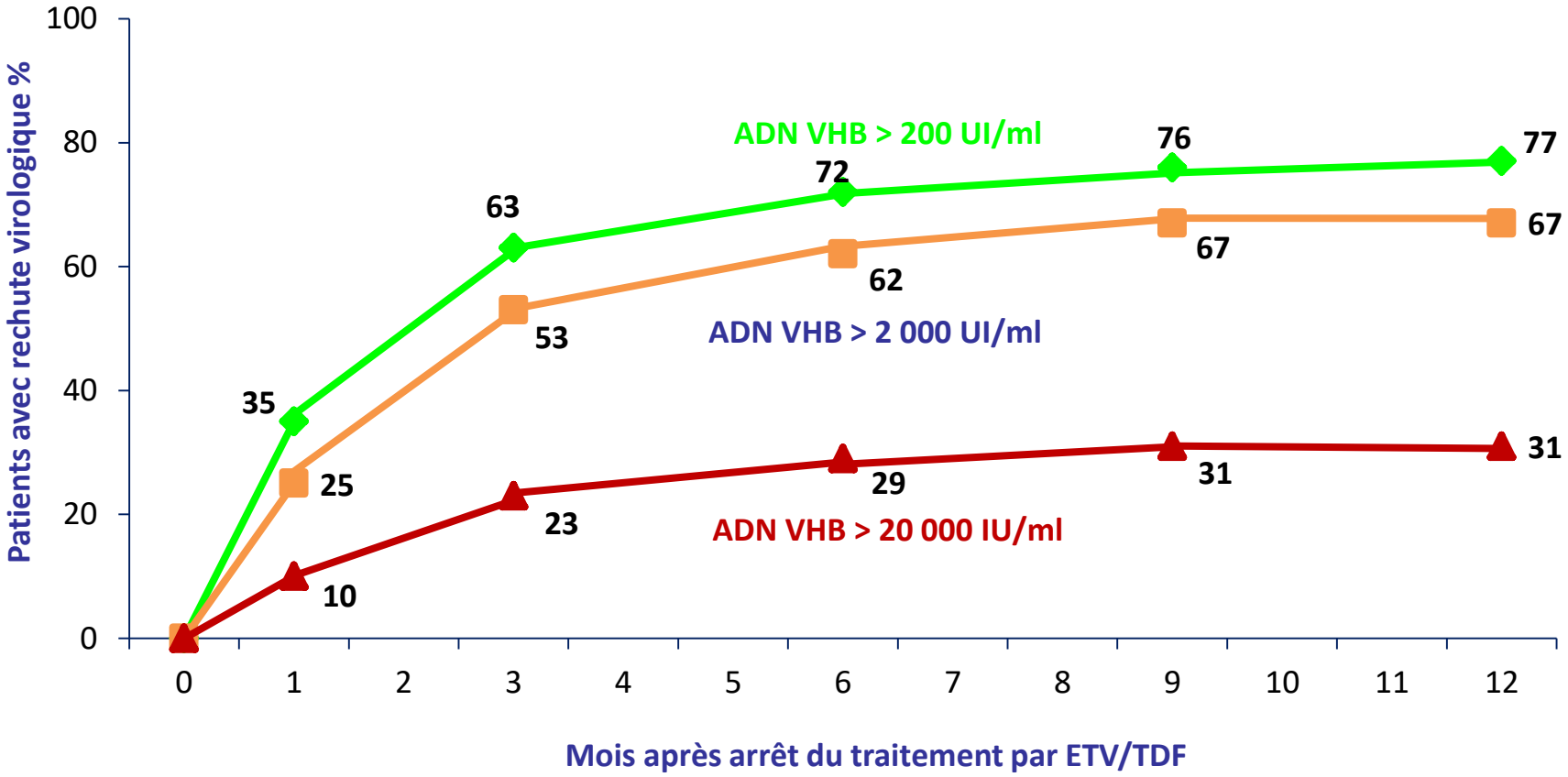
- Evaluation prospective à 1 an :
  - Proportion de patients en rémission sans traitement antiviral
  - Proportion de patients avec reprise du traitement antiviral

- Les critères de proposition de retraitement étaient :
  - ALAT > 10N (n=3)
  - ALT > 5N et bilirubine > 2 mg/dl (34 µmol/l)
  - ALT > 3N et ADN VHB > 100 000 UI/ml (n=6)
  - ALT > N et ADN VHB > 2 000 /ml à 3 dosages consécutifs (n=2)

Papatheodoridis G, Grèce, EASL 2017

Patients AgHBe négatif, sans cirrhose

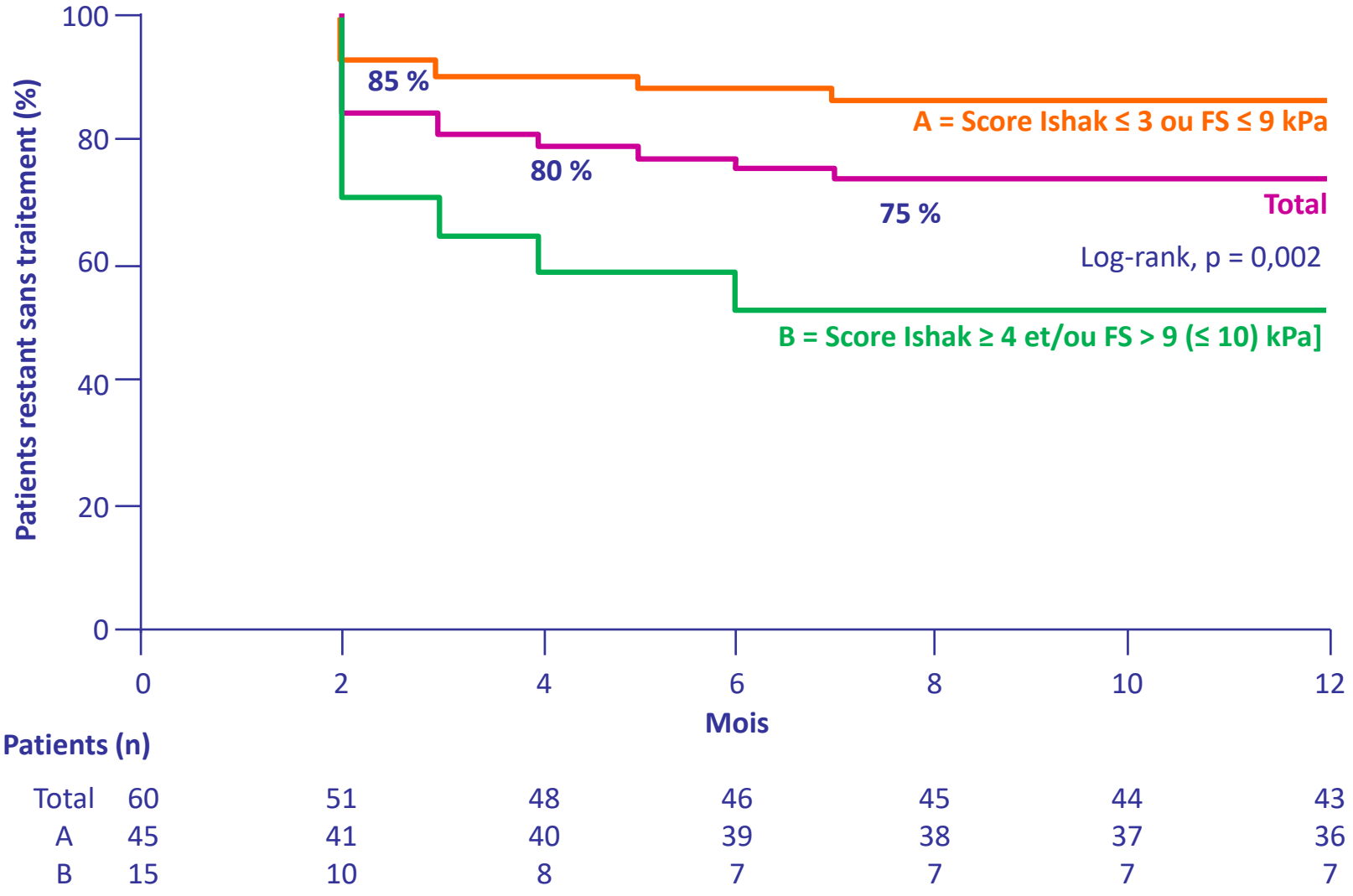
Rechute virologique



Papatheodoridis G, Grèce, EASL 2017

Patients AgHBe négatif, sans cirrhose

Probabilité d'absence de retraitement



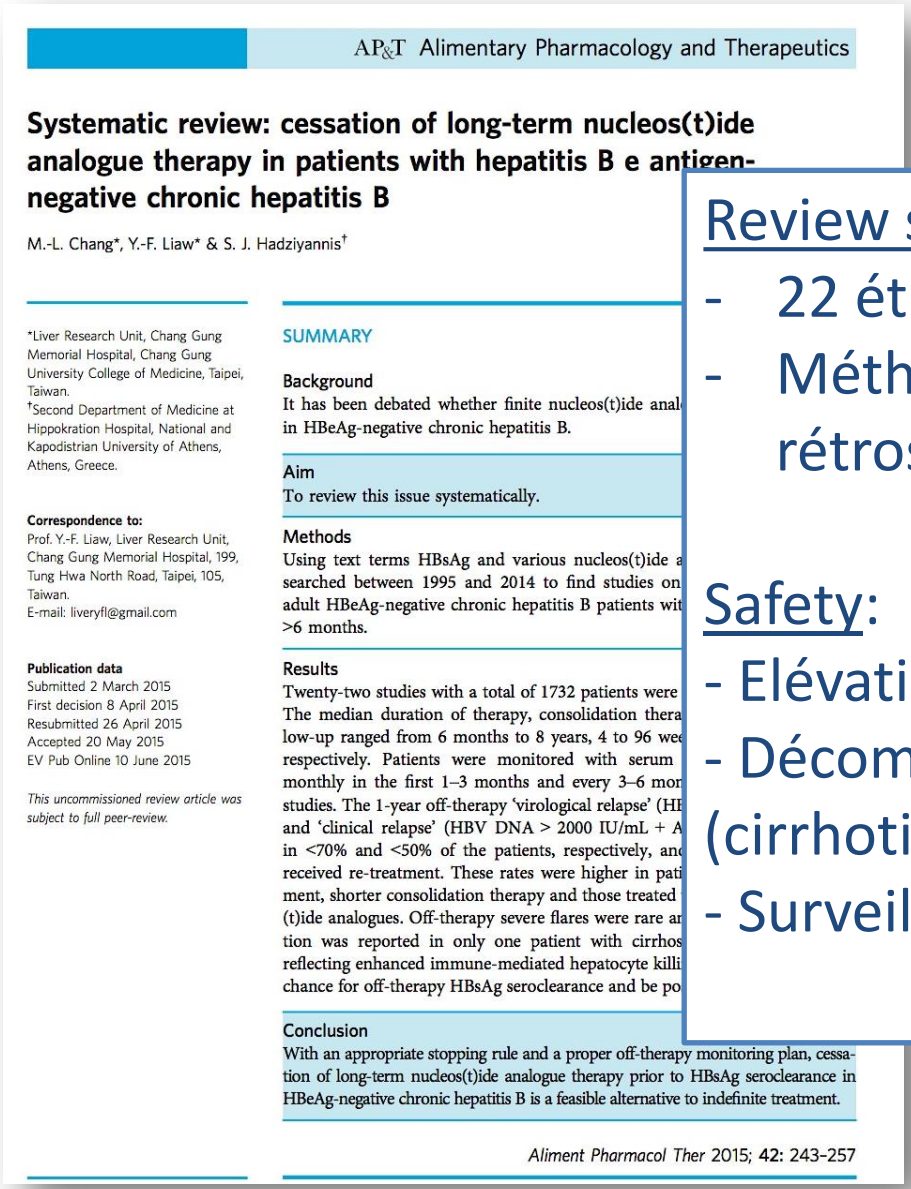
Patients (n)

Total	60	51	48	46	45	44	43
A	45	41	40	39	38	37	36
B	15	10	8	7	7	7	7

Papatheodoridis G, Grèce, EASL 2017

Risques d’arrêter le traitement?

Risques d'arrêter le traitement?



AP&T Alimentary Pharmacology and Therapeutics

Systematic review: cessation of long-term nucleos(t)ide analogue therapy in patients with hepatitis B e antigen-negative chronic hepatitis B

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First decision 8 April 2015
Resubmitted 26 April 2015
Accepted 20 May 2015
EV Pub Online 10 June 2015

This uncommissioned review article was subject to full peer-review.

SUMMARY

Background
It has been debated whether finite nucleos(t)ide anal
in HBeAg-negative chronic hepatitis B.

Aim
To review this issue systematically.

Methods
Using text terms HBsAg and various nucleos(t)ide a
searched between 1995 and 2014 to find studies on
adult HBeAg-negative chronic hepatitis B patients wit
>6 months.

Results
Twenty-two studies with a total of 1732 patients were
The median duration of therapy, consolidation thera
low-up ranged from 6 months to 8 years, 4 to 96 we
respectively. Patients were monitored with serum
monthly in the first 1–3 months and every 3–6 mor
studies. The 1-year off-therapy 'virological relapse' (HI
and 'clinical relapse' (HBV DNA > 2000 IU/mL + A
in <70% and <50% of the patients, respectively, and
received re-treatment. These rates were higher in pati
ment, shorter consolidation therapy and those treated
(t)ide analogues. Off-therapy severe flares were rare ar
tion was reported in only one patient with cirrhos
reflecting enhanced immune-mediated hepatocyte killi
chance for off-therapy HBsAg seroclearance and be po

Conclusion
With an appropriate stopping rule and a proper off-therapy monitoring plan, cessation of long-term nucleos(t)ide analogue therapy prior to HBsAg seroclearance in HBeAg-negative chronic hepatitis B is a feasible alternative to indefinite treatment.

Aliment Pharmacol Ther 2015; **42:** 243–257

The STOP strategy

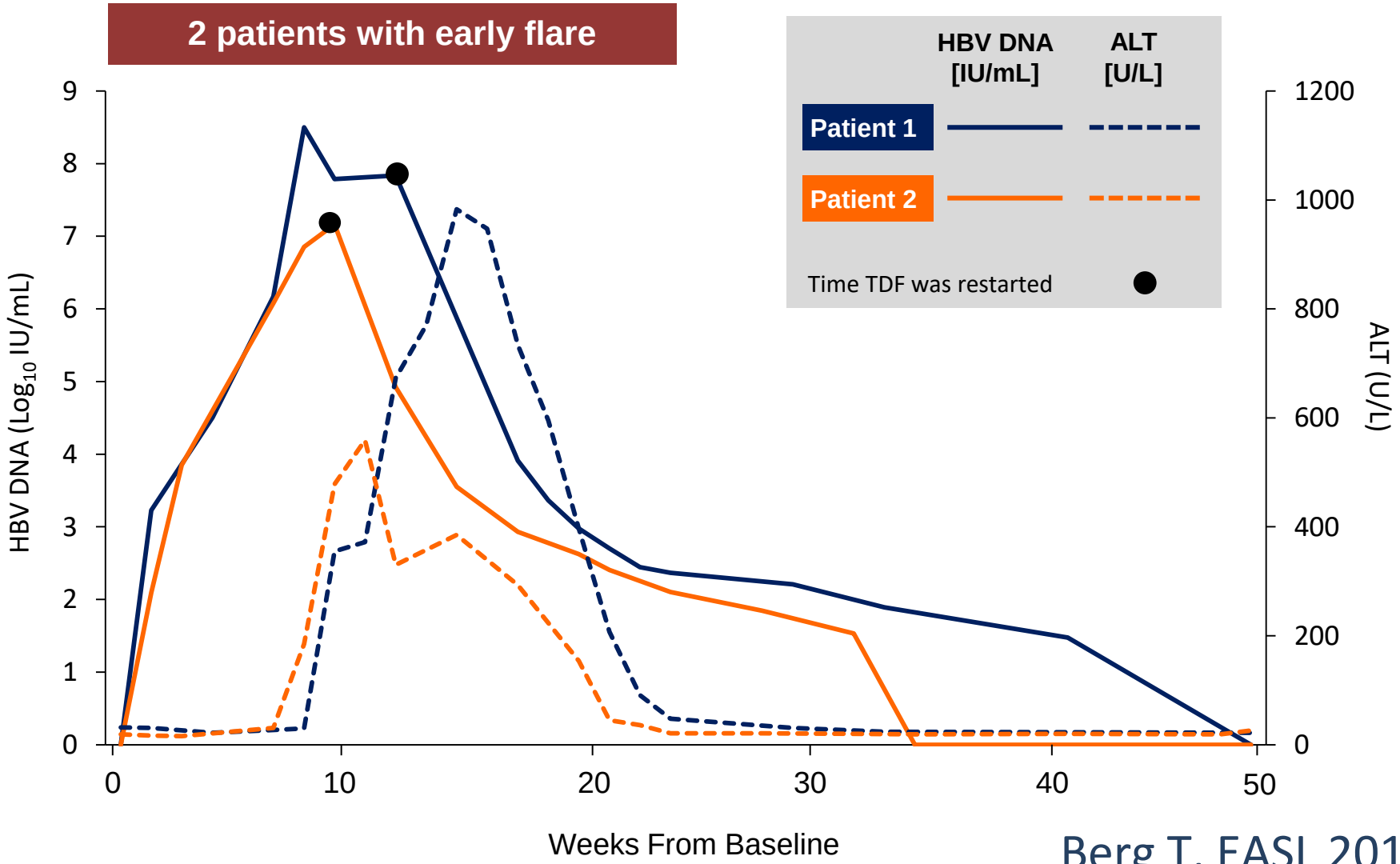
Review systématique:
- 22 études, 1732 patients
- Méthodologie hétérogène, études rétrospectives et série de cas

Safety:
- Elévation ALAT = RARE
- Décompensation hépatique = 1/1732 (cirrhotique, répondu ttt sauvetage)
- Surveillance est nécessaire

M.-L. Chang , Aliment Pharmacol Ther 2015

Traitement des rechutes?

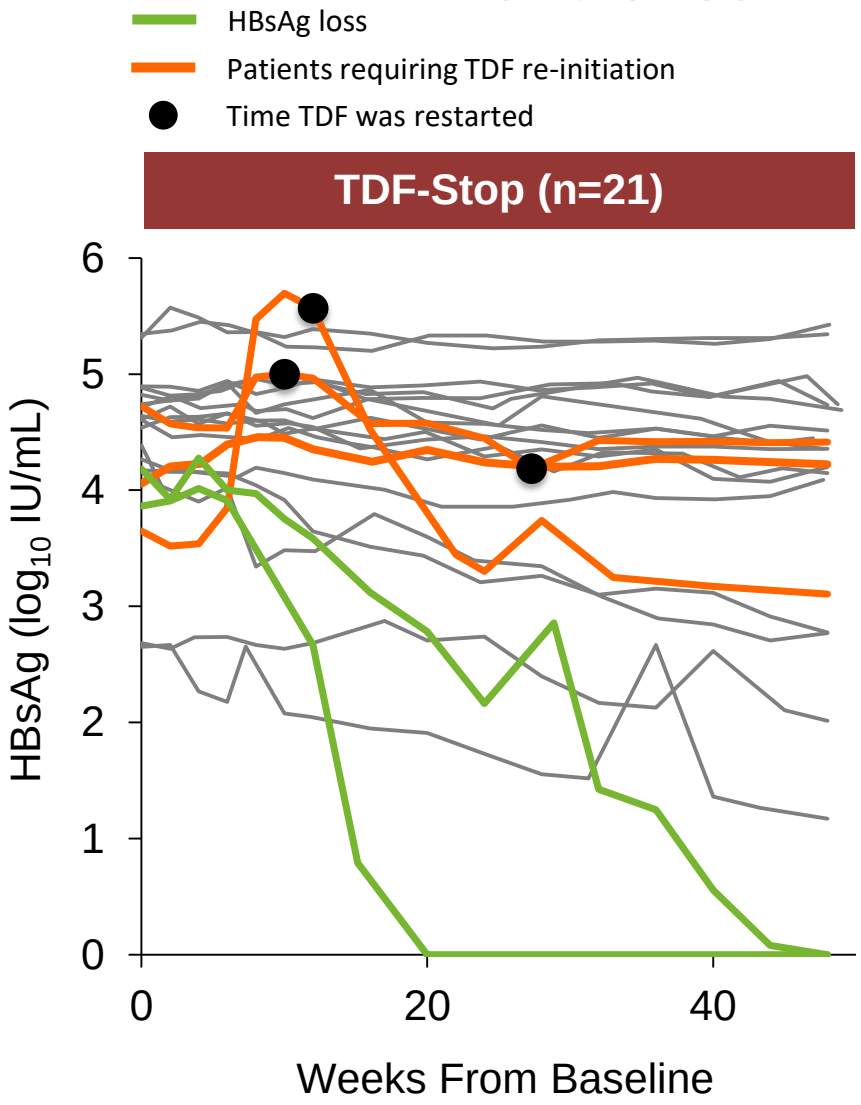
Controlled Trial ("FINITE CHB")



Berg T, EASL 2015

Bénéfices de l'arrêt = "therapeutic" flare

Controlled Trial ("FINITE CHB")



Arrêt NA

Rechute virologique

↓

« therapeutic hepatitis flare »

↓

Réponse Virologique

↓

Réponse immunitaire

↓

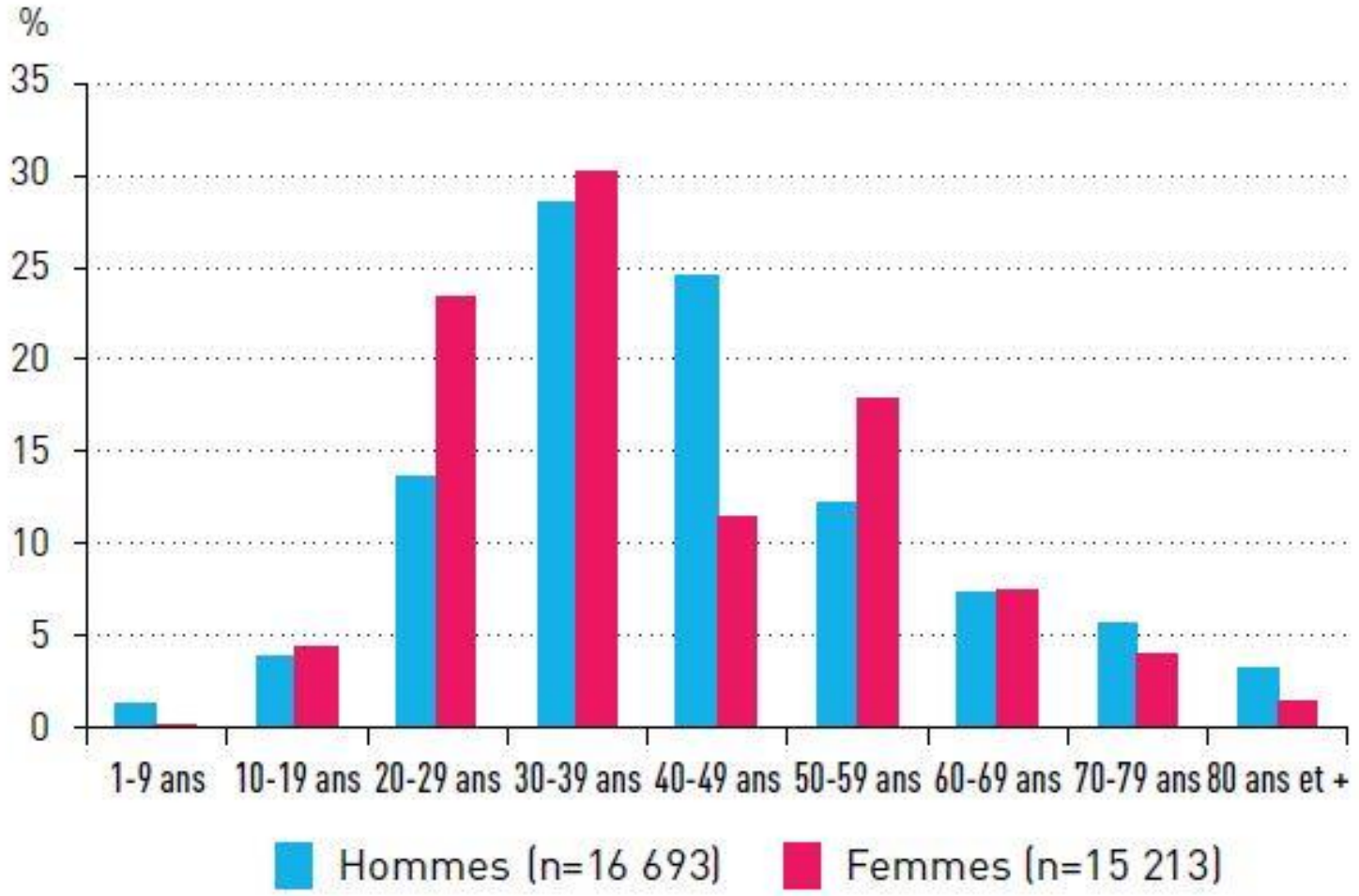
Perte AgHBs

Berg T, EASL 2015

- Risques du traitement? (Safety)

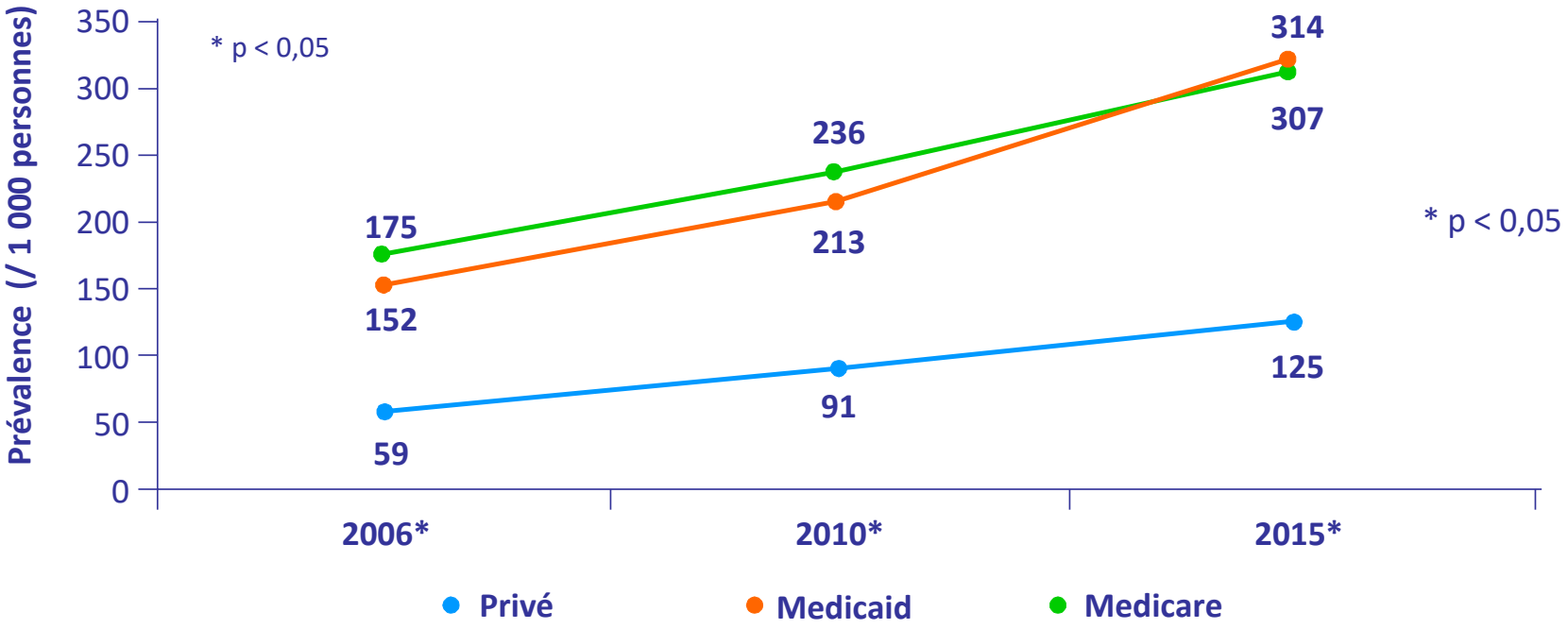
Épidémiologie

Distribution par sexe et âge des personnes confirmées positives pour l'AgHBs, 2013, France



Risques du traitement? (Safety)

- Etude rétrospective nord américaine
- 44 026 VHB+ comparés à 121 568 VHB-



Prévalence de l'ostéoporose varie de 10 à 60 %

Gordon SC, Etats-Unis, EASL 2017

Effets indésirables: Syndrome de Fanconi

Table 1. Review of characteristics of patients developed TDF-induced Fanconi syndrome.

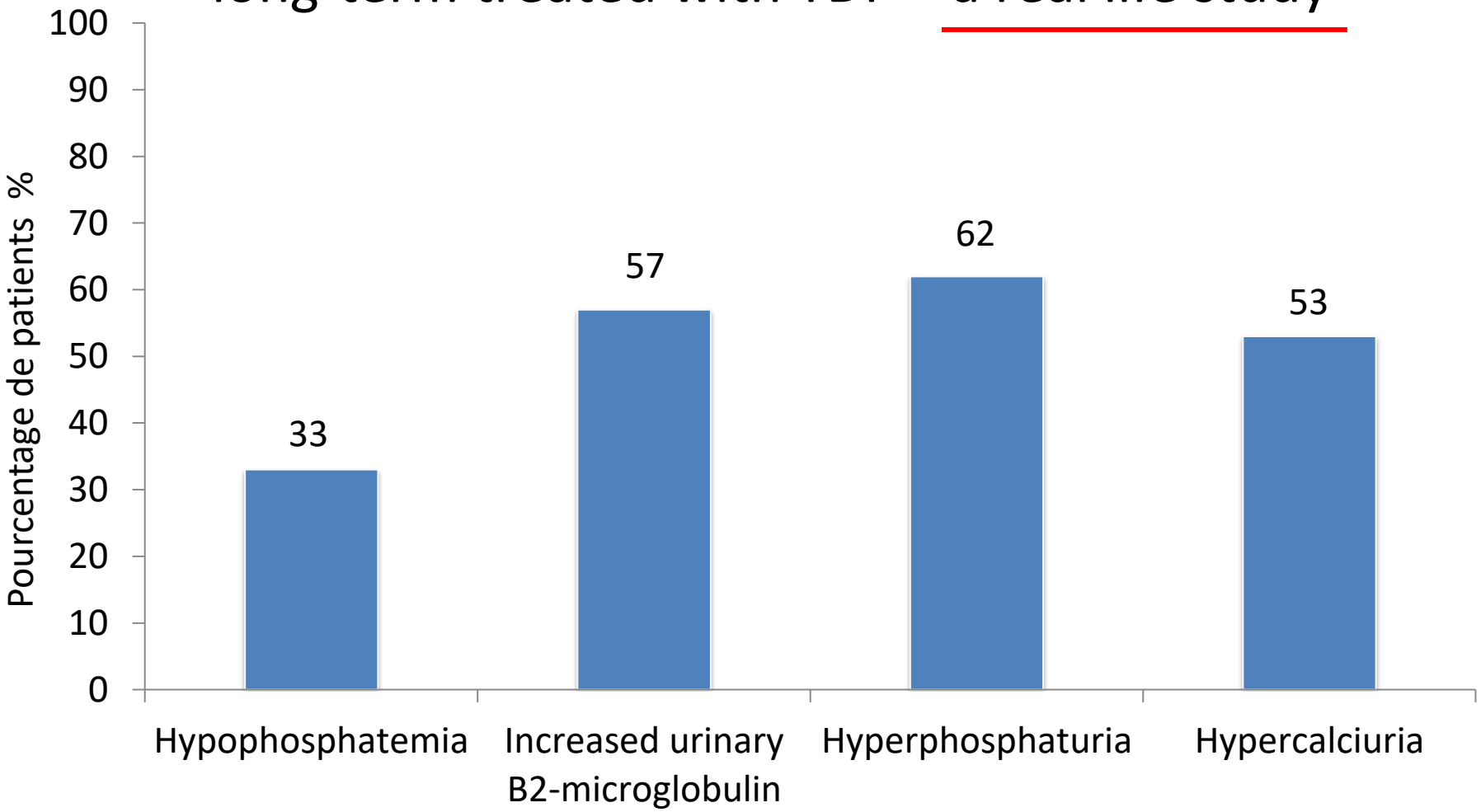
	Sex	Age (years)	Treatment before start of TDF*	Arterial hypertension	Diabetes	Time from start of TDF (months)	Switch to	eGFR after switch to ETV
Samarkos, *et al.*[8]	M	82	ADV	No	Yes	6	ETV	Death for sepsis (2 months after)
Gracey, *et al.*[9]	M	39	ADV	Yes	No	48	ETV	Improved (24 months after)
Gracey, *et al.*[9]	M	54	naive	Yes	No	21	ETV	Improved (18 months after)
Viganò, *et al.*[10]	M	58	ADV	Yes	No	9	ETV	Improved (15 months after)
Viganò, *et al.*[10]	M	62	naive	Yes	No	31	ETV	Improved (12 months after)
Hwang, *et al.*[11]	F	44	naive	No	Yes	3	ETV	Improved (3 months after)
This case report	**M**	**58**	**ADV**	**Yes**	**No**	**12**	**ETV**	Improved (12 months after)

* *Time between diagnosis of Fanconi syndrome and start of TDF. M: male. F: female. ADV: adefovir. ETV: entecavir. eGFR: estimated glomerular filtration rate.*

Moyenne: 18,6 mois

Effets indésirables

High rates of renal tubular damage in 281 HBV patients long-term treated with TDF – a real life study



Lampertico, manuscript in preparation, 2017

Effets indésirables

Clinical Practice Guidelines

2017

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

European Association for the Study of the Liver*

Table 5. Indications for selecting ETV or TAF over TDF.*

1. Age >60 year
2. Bone disease
Chronic steroid use or use of other medications that worsen bone density
History of fragility fracture
Osteoporosis
3. Renal alteration**
eGFR <60 min/ml/1.73 m^2
Albuminuria >30 mg or moderate dipstick proteinuria
Low phosphate (<2.5 mg/dl)
Hemodialysis

* TAF should be preferred to ETV in patients with previous exposure to nucleoside analogues.

** ETV dose needs to be adjusted if 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.

Notre sauveur!!

Ténofovir Alafenamide chez les patients AgHBe +

Tolérance

Effets indésirables EI (%)	TAF (n = 581)	TDF (n = 292)
Au moins un EI	399 (69)	192 (66)
EI grade 3-4	27 (5)	11 (4)
Arrêt pour EI	6 (1)	3 (1)
Décès	1	0

Tolérance rénale

Paramètres	TAF	TDF	p
Evolution Créatinine (mg/dl)	0,009 (0,124)	0,026 (0,095)	0,02
Evolution eFGR (ml/mn)	-0,3 (14,5)	-4,7 (13,5)	<0,001
Absence de protéinurie (%)	73	77	0,21

- Tolérance osseuse
  - Diminution de plus de 3 % de la densité osseuse à la semaine 48 :
  - Rachis : 18 % (TAF) versus 38 % (TDF), p < 0,001
  - Hanches : 8 % (TAF) versus 24 % (TDF), p < 0,001

Chan HL, Chine, EASL 2016, Abs. GS12 actualisé

Ténofovir Alafenamide chez les patients AgHBe-

Tolérance générale

Effets indésirables EI (%)	TAF n = 285	TDF n = 140
Au moins un EI	210 (74)	99 (71)
EI grade 3-4	12 (4)	6 (4)
EI sévère	14 (5)	9 (6)
Arrêt pour EI	3 (1)	2 (1)
Décès	0	1

Tolérance rénale

Paramètres	TAF	TDF	p
Modification de la Créatinine (mg/dl)	0,012 (0,09)	0,02 (0,1)	0,32
ΔFGR (ml/mn)	-1,4 (12,7)	-4,7 (12)	0,004
Absence de protéinurie (%)	81	81	0,9

Tolérance osseuse

- Diminution de plus de 3 % de la densité osseuse à la semaine 48 :
- Rachis : 22 % (TAF) versus 39 % (TDF), $p < 0,001$
- Hanches : 10 % (TAF) versus 33 % (TDF), $p < 0,001$

Buti M, Espagne, EASL 2016

Prix

Table 1. Expiry dates for basic patents, and global price overview for HBV drugs

Drug	Expiry dates[a]		US lowest price[b]	Global lowest price (US$ pppy)
	USA	EU		
Entecavir (ETV)	2015 (invalidated 2014)	2017	$15,111** originator $6,127** generic	$427[c]
Adefovir (ADV)	2014	2016	$13,480** originator	$133[c]
Emtricitabine (FTC)	2021	2016	$6,203** originator	$62[d]*
Tenofovir disoproxil fumarate (TDF)	2018	2018	$10,718** originator	$38[e]***
Lamivudine (3TC)	2010	2010	$2,627** originator $1,047** generic	$10[e]*

For lamivudine, all prices are reported for doses used in treating HIV, as comparable information is only available for this dose – 150mg. For adefovir, no global price overview exists, but the lowest price of generic adefovir in India is shown to give an impression

[a] All patent dates from Gilead 2012 Form 10-K Annual Report [48]; [b] goodrx.com lowest price of authorized pharmacy, including coupon discount [55]
[c] drugsupdate.com [56]; [d] Lowest price as reported by MSF[35]; [e] Lowest 'incoterms' price as reported in the WHO's Global Price Reporting Mechanism in 2014 [33]
* WHO prequalified; ** USFDA approved; *** WHO prequalified and USFDA approved; pppy: per person per year

Hill A, J Virus Eradication 2015

L'accès au traitement

Monde

Drugs for treating hepatitis B	% of Member States reporting its inclusion (*N*=126)
Lamivudine	66.7
Interferon alpha	54.0
Pegylated interferon	50.8
Tenofovir	48.4
Entecavir	34.9
Adefovir dipivoxil	34.1
Telbivudine	23.8

Europe

Drugs for treating hepatitis B	% of Member States reporting its inclusion (*N*=12)
Lamivudine	84.1
Interferon alpha	77.3
Tenofovir	75.0
Pegylated interferon	61.4
Entecavir	54.5
Adefovir dipivoxil	50.0
Telbivudine	38.6

Global policy report on the prevention and control of viral hepatitis in WHO, 2013

La dernière raison…

Les patients demandent TOUT le temps!!

Conclusions

- Peut-on arrêter les NUC chez les patients VHB ? OUI
- Chez tous les patients? Patients SELECTIONES
  - AgHBe positive SANS cirrhose:

    AgHBe S/C, ttt consolidation ≥12m, ADN HBV indétectable

  - AgHBe négative SANS cirrhose:

    Control virologique ≥3a, surveillance après l'arrêt

- Surveillance:
  - c/3 mois pendant 1e année, après chaque 6 mois

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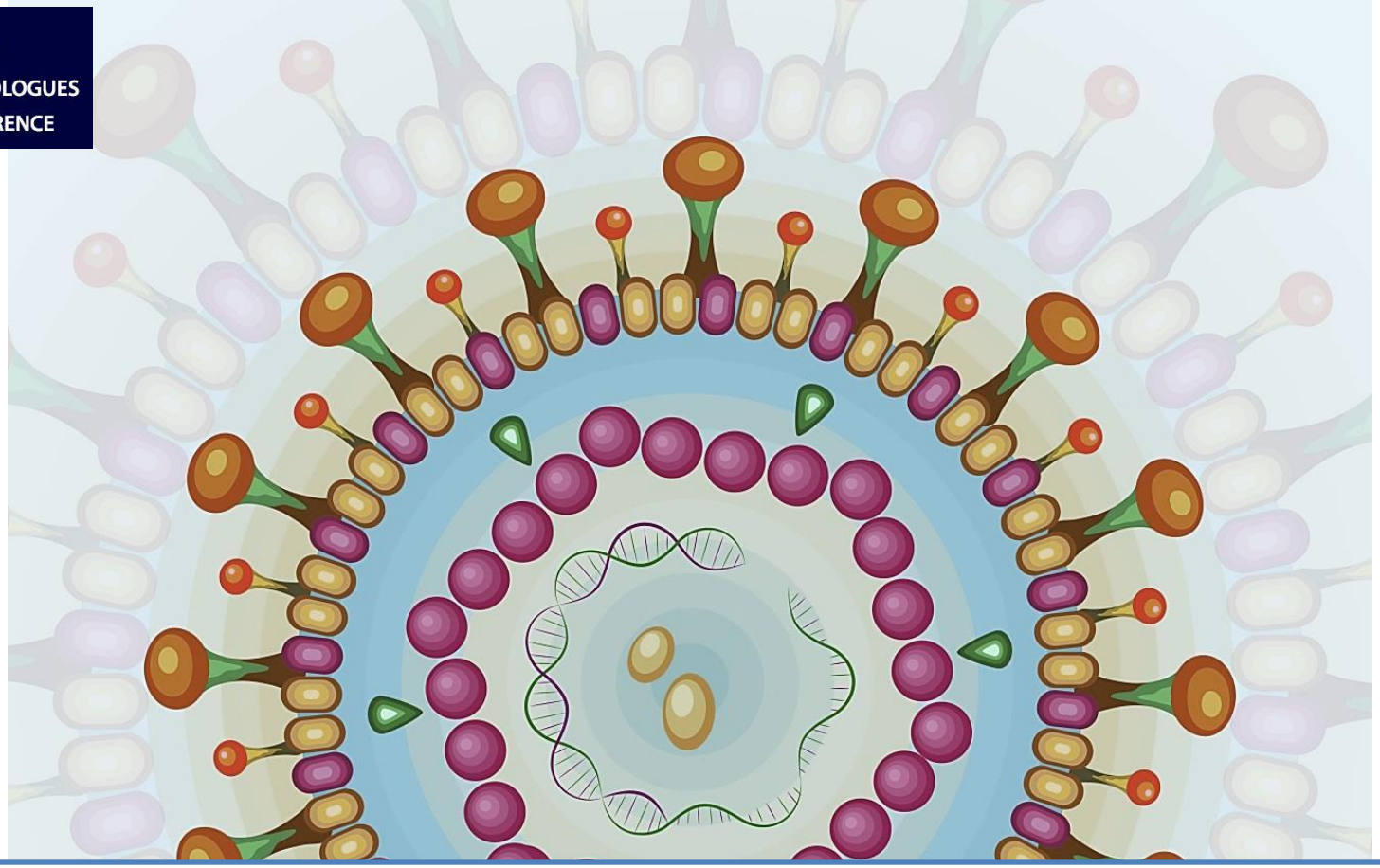

Therefore your honor…

I rest my case!