How to manage HBV patients in 2017?

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Whom to treat and with what?

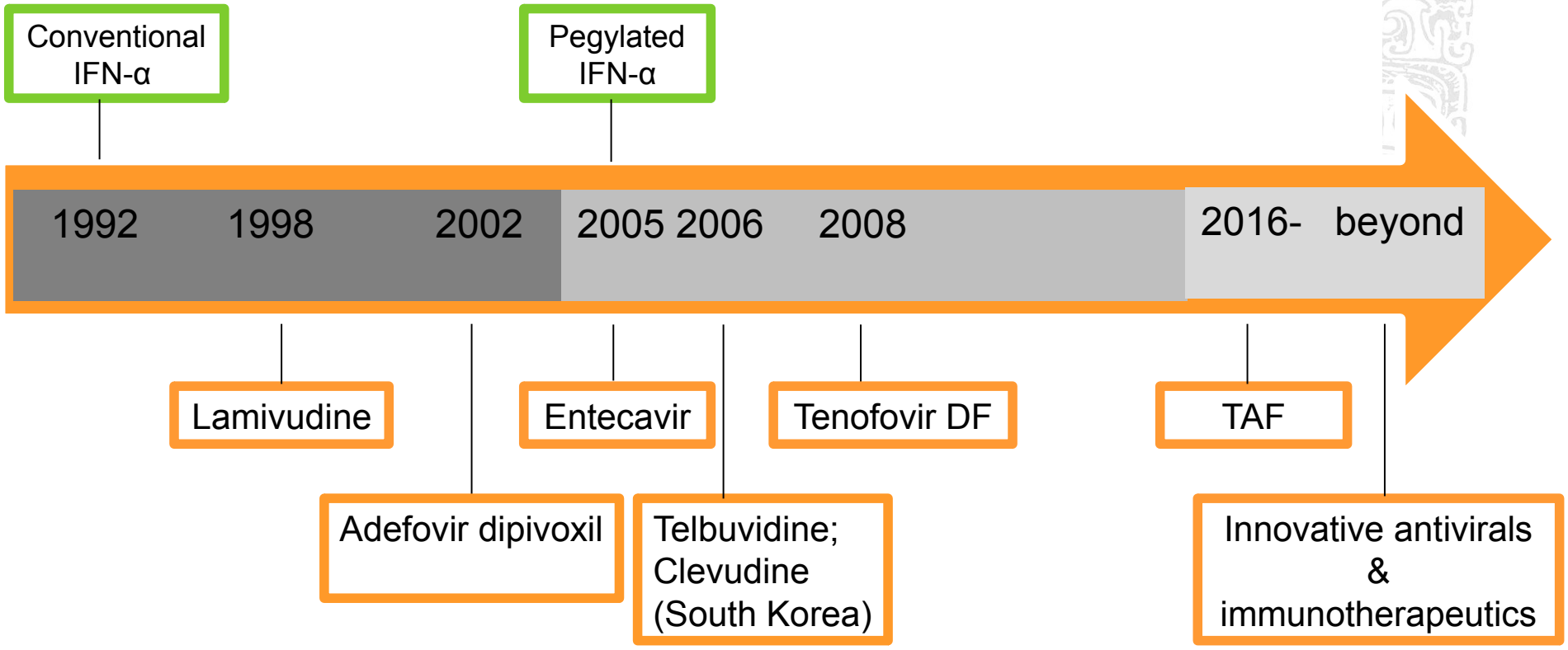
Can we stop treatment with NUCs?

HBV reactivation

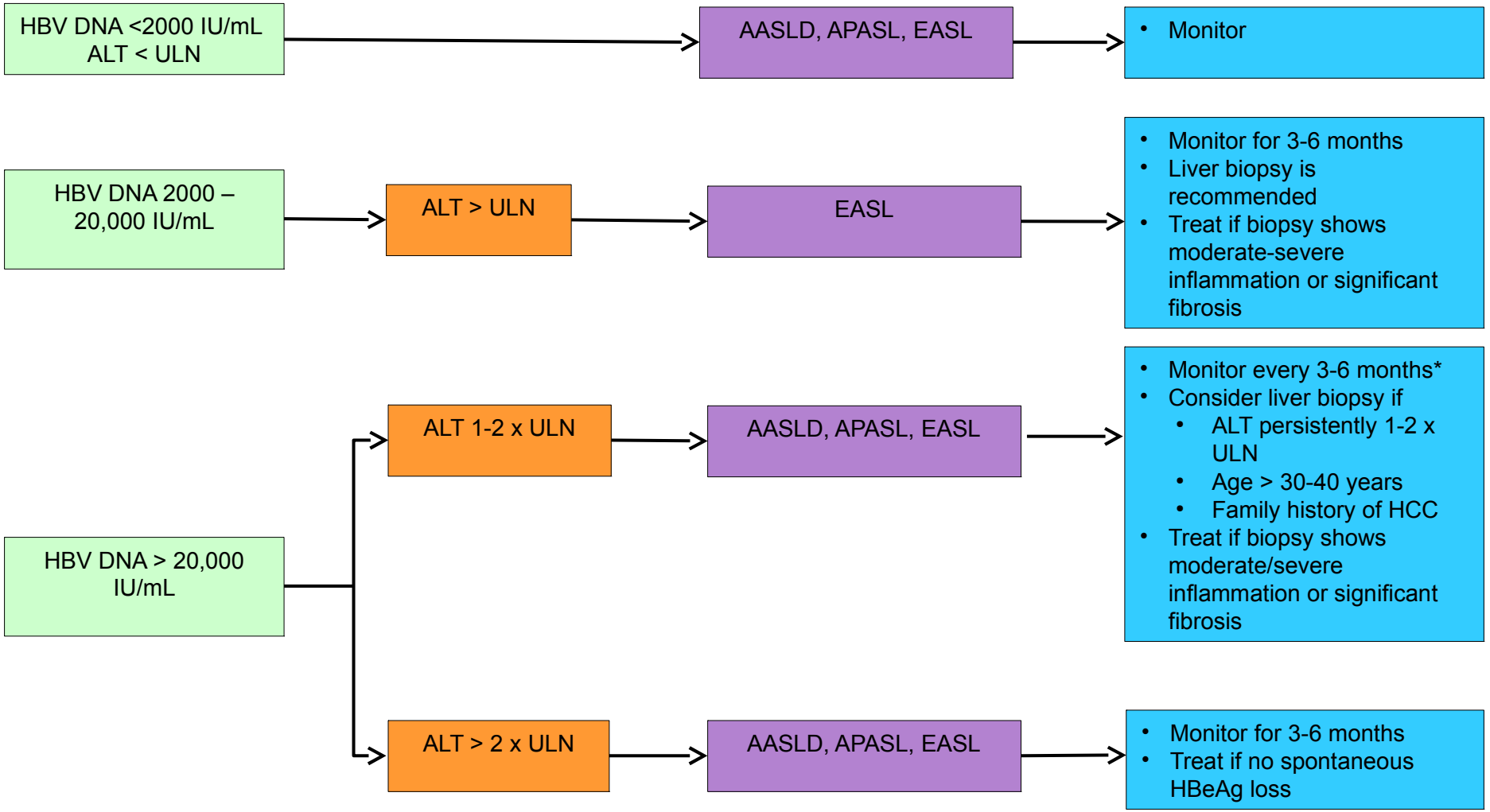
New therapy in the pipeline

Whom will I treat and with what?

Registered Treatments of CHB



Algorithm showing guideline recommendations for the treatment of patients with HBeAg-positive CHB



Chen GF, Wang C, Lau G. Liv Intern 2017; 37 (Suppl 1) :59-66

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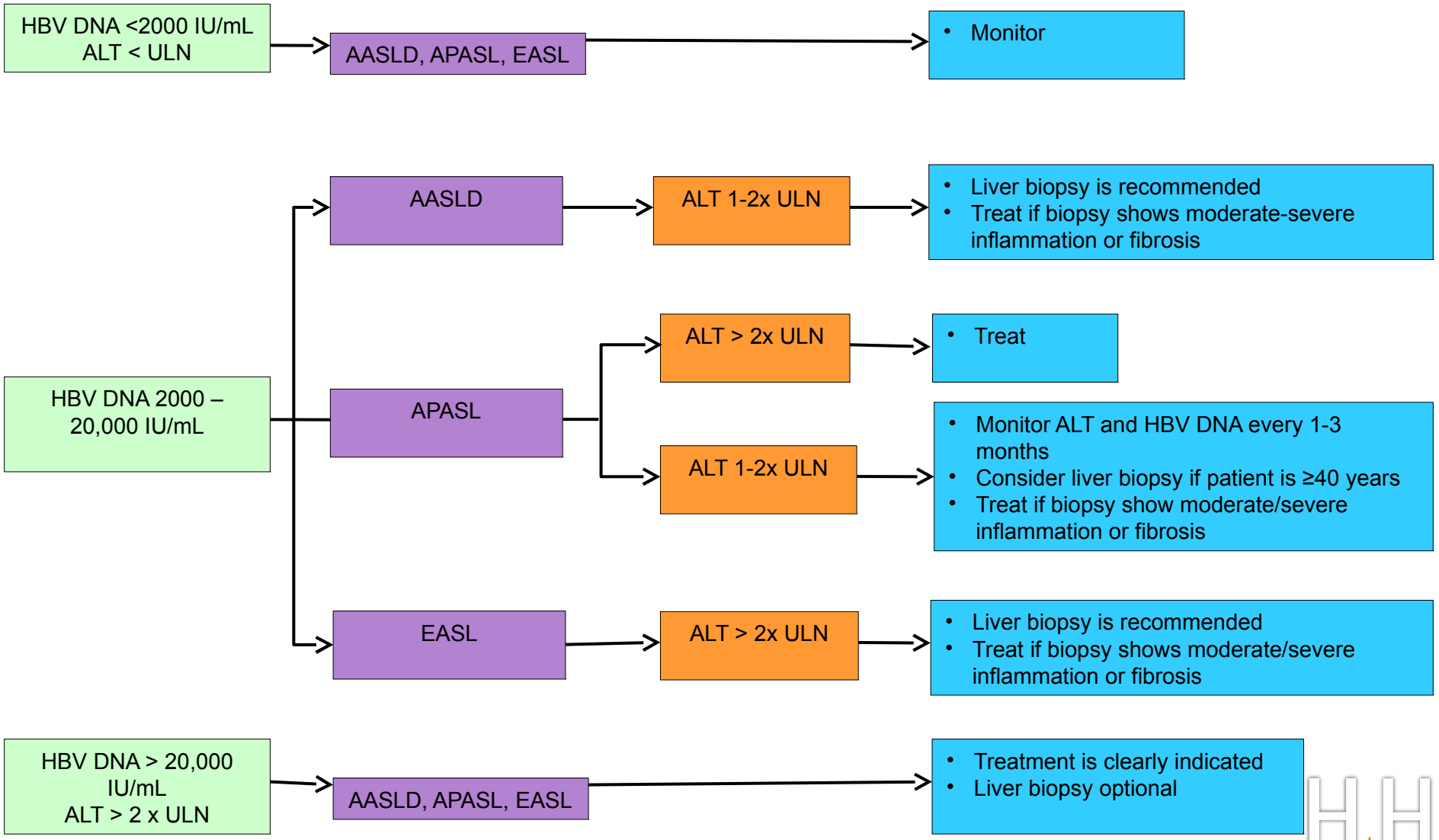
Algorithm showing guideline recommendations for the treatment of patients with HBeAg-negative CHB



Chen GF, Wang C, Lau G. Liv Intern 2017; 37 (Suppl 1) :59-66

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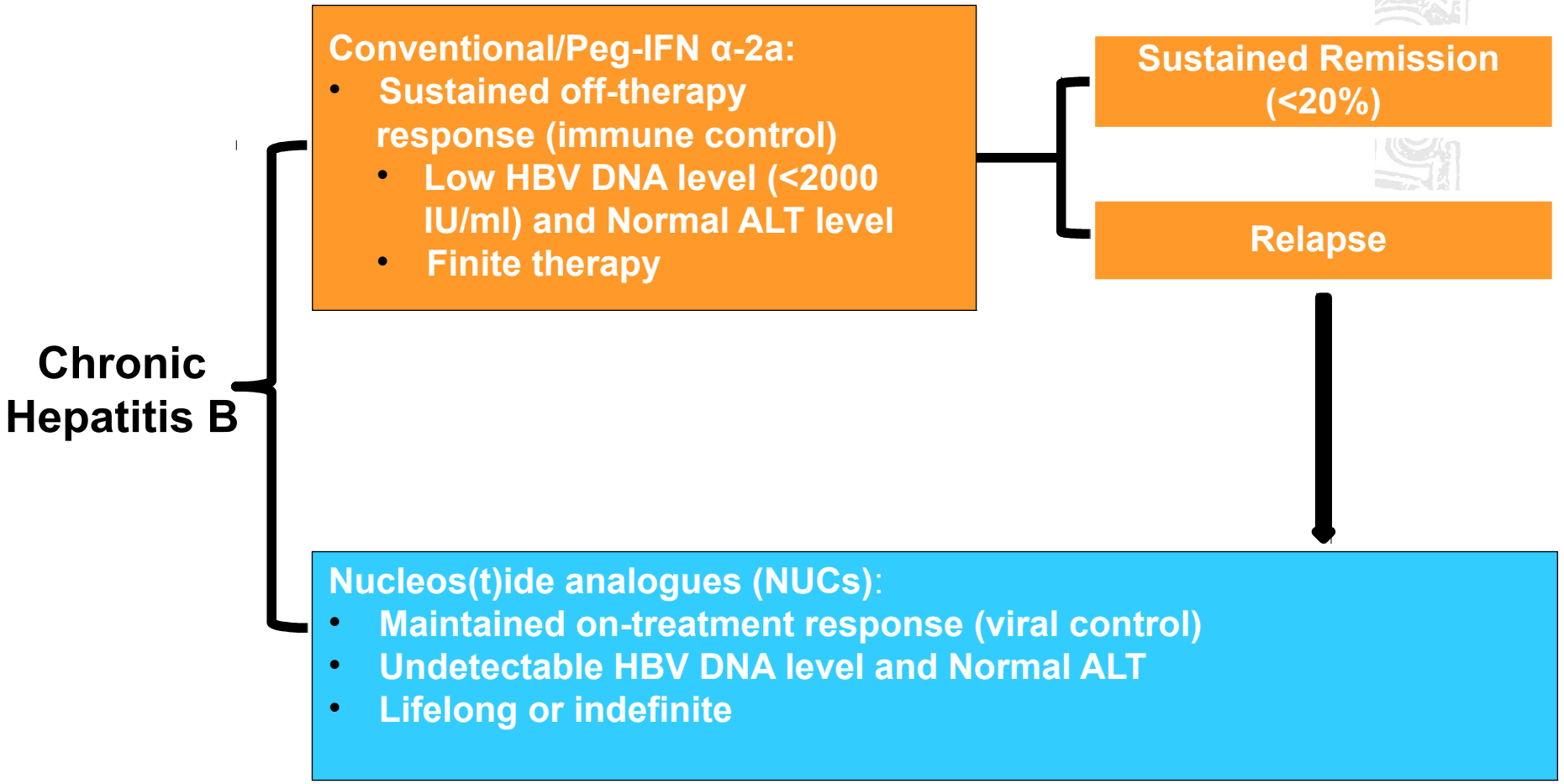
Therapies for chronic hepatitis B in real world



Guideline recommendations regarding when to stop NUCs

Status	Stopping rules	AASLD 2016	APASL 2016	EASL 2012
HBeAg+	HBeAg seroconversion	✔	✔	✔
	Undetectable HBV DNA		✔	✗
	Persistently normal ALT	✔	✔	✗
	≥12 mo consolidation	✔	✔	✔
HBeAg-	HBsAg loss following either anti-HBs seroconversion or ≥12 mo of a post-HBsAg clearance consolidation period	??	✔	??
	≥2 years with undetectable HBV DNA on three separate occasions, 6 mo apart	✗	✔	✗
Cirrhosis	INDEFINITELY	✔	✗	✔
	May be considered with a careful off-therapy monitoring plan	✗	✔	✗

Terrault NA et al, APASL, AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-283.
Sarin SK et al, Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
EASL, EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-185.

HBsAg loss to approved therapies in HBeAg-positive and HBeAg-negative patients

Treatment response parameters	Approved therapies						
	LAM	ADV	ETV	LdT	TDF	PEG-IFN	PEG-IFN plus LAM
HBeAg-positive patients							
At week 48 or 52							
HBsAg loss, %	<1	0	2	0	3	3	3-7
During extended treatment							
HBsAg loss, % (years)	0-3(2-3)	2 (5)	5 (2)	1.3(2)	10 (5)	11 (3.5)	15 (3.0）
HBeAg-negative patients							
At week 48 or 52							
HBsAg loss, %	<1	0	<1	<1	0	4	3
During extended treatment							
HBsAg loss, % (years)	<1 (4)	5 (5)	NA	<1 (2)	0.3 (5)	8 (3)	8 (3)

Yapali, S., et al. Clin Gastroenterol Hepatol 2014; Chang TT, et al. N Engl J Med. 2006;354:1001-1010. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Buster EH, et al. Gastroenterology. 2008;135;459-467. Gish R, et al. Gastroenterology. 2007;133:1437-1444. Heathcote J. AASLD 2008. Abstract 158. Heathcote J, et al. AASLD 2009. Abstract 483. Janssen HL, et al. Lancet. 2005;365:123-129
Lai CL, et al. N Engl J Med. 2006;354:1011-1020. Marcellin P, et al. N Engl J Med. 2008;359:2442-2455. Marcellin P, et al. AASLD 2008. Abstract 146. Shouval D, et al. J Hepatol. 2009;50:289-295. Marcellin P, et al. AASLD 2009. Abstract 481. Brunetto M, et al. EASL 2008. Abstract 683.

Addition of a 48 wk pIFN to NUCs in HBeAg-neg CHB with undetectable HBV DNA for a least 1 year was poorly tolerated and did not result in a significant increase of HBsAg clearance

	PEG-IFN + NUCs	NUCs	
	n=92	n=93	p value
Loss of HBsAg, n (%)	7 (7.8)	3 (3.2%)	0.15
Adverse event			
Discontinuation of PEG-IFN, n(%)	17 (20)	n/a	
Grade 3, n(%)	26 (29)	3 (3)	
Grade 4, n(%)	19 (21)	6 (6)	

Marc Bourlière et al, Lancet GH, 2017, DOI: http://dx.doi.org/10.1016/S2468-1253(16)30189-3

Safety summary of Tenofovir alafenamide (TAF) for treatment of CHB

	Study 110 HBeAg +			Study 108 HBeAg -		
	TAF 25mg	**TDF 300mg**		**TAF 25mg**	**TDF 300mg**	
Changes in	**n=581**	**n=292**	**P value**	**n=285**	**n=140**	**P value**
Bone mineral density (Hip)	-0.1%	1.72%	<0.001	-0.29%	-2.16%	<0.001
Bone mineral density (Spine)	-0.42%	-2.29%	<0.001	-0.88%	-2.51%	<0.001
Serum creatinine	0.01 mg/dL	0.03 mg/dL	0.02	0.01 mg/dL	0.02 mg/dL	0.32
AEs leading to study drug discontinuation, % (n)	1.0% (n=6)	1.0% (n=3)	ns	1.0% (n=3)	1.0% (n=2)	ns
The most commonly reported AEs	• Headache • URI • Nasopharyngitis • Cough		Occurred at similar rates among TAF vs TDF			

Buti M et al Lancet GH 2016, Chan HL et al Lancet GH 2016

Review article: long-term safety of nucleoside and nucleotide analogues in HBV-monoinfected patients

P. Lampertico*, H. L. Y. Chan†, H. L. A. Janssen‡, S. I. Strasser§, R. Schindler¶ & T. Berg**

- In selected populations (registration studies)
  - Both ETV and TDF were well tolerated with no clinically significant renal toxicity or lactic acidosis
- 'Real-world' clinical experience-conflicting
  - ETV-associated lactic acidosis
  - TDF-associated renal impairment

Aliment Pharmacol Ther 2016; 44: 16–34

Life long treatment for patients receiving NUCs

- Potent suppression of HBV replication
  - Reverse liver fibrosis and cirrhosis
  - Halt progression to liver failure

- BUT
  - Rarely lead to HBsAg loss
  - Decrease but not eliminate incidence of HCC
  - Probably life long treatment-cost,compliance,safety

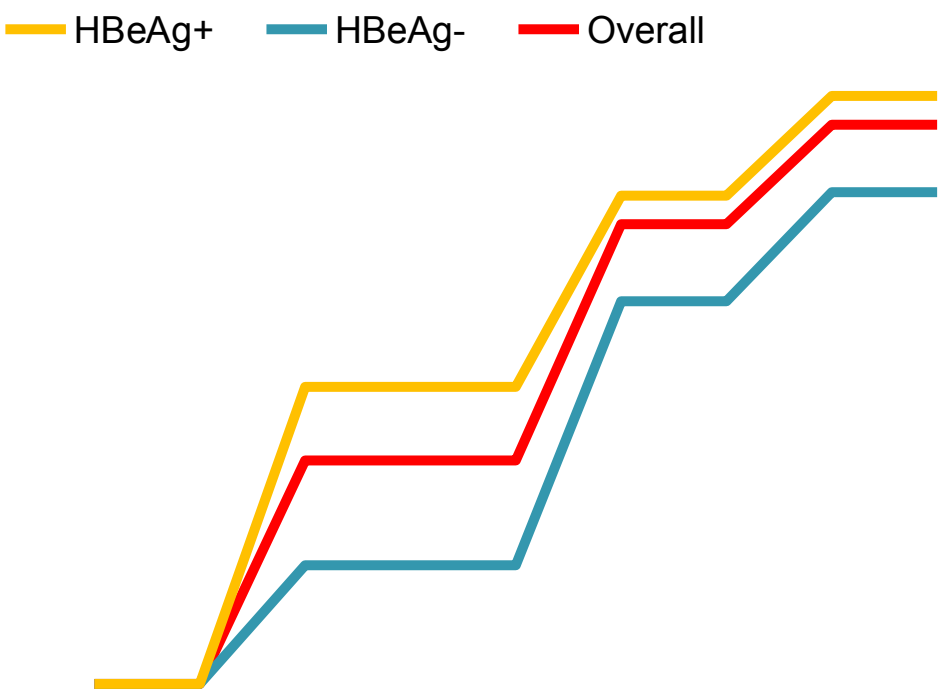
Predictors of virological remission after stopping NUCs

Factors associated with virological remission after discontinuation of NUCs

	Probability of Durable VR, % (95% CI)	Odds Ratio (95% CI)	P
All patients			
VR defined by HBV DNA			0.180
<200 IU/mL	34.1 (17.4-56.0)	1	
<2000 IU/mL	54.7 (41.9-66.8)	2.33 (0.83-6.57)	
<20,000 IU/mL	62.0 (38.3-80.9)	3.14 (0.84-11.71)	
Duration of on-NAs VR			0.616
<12 months	52.5 (28.1-75.8)	1	
12-24 months	48.1 (34.9-61.5)	0.84 (0.26-2.71)	
>24 months	61.1 (39.0-79.4)	1.42 (0.36-5.62)	
HBeAg-positive patients			
VR defined by HBV DNA			0.289
<200 IU/mL	42.0 (16.6-72.4)	1	
<2000 IU/mL	71.2 (52.2-84.8)	3.41 (0.74-15.71)	
<20,000 IU/mL	63.1 (32.8-85.7)	2.37 (0.39-14.33)	
Duration of on-NA VR			0.544
<12 months	53.2 (27.4-77.4)	1	
12-24 months	72.0 (49.2-87.2)	2.26 (0.52-9.84)	
>24 months	60.3 (27.1-86.1)	1.33 (0.22-7.98)	
Duration of consolidation therapy after HBeAg seroconversion			0.928
<12 months	62.6 (38.5-81.8)	1	
≥12 months	64.1 (42.2-81.3)	1.06 (0.28-4.02)	
HBeAg-negative patients			
VR defined by HBV DNA			0.513
<200 IU/mL	29.3 (10.8-58.7)	1	
<2000 IU/mL	48.0 (30.6-65.9)	2.24 (0.53-9.41)	
<20,000 IU/mL	51.4 (15.4-86.1)	2.56 (0.30-22.03)	
Duration of on-NA VR			0.017
<12 months	50.0 (14.9-85.1)	1	
12-24 months	34.1 (22.8-47.6)	0.52 (0.08-3.24)	
>24 months	75.0 (50.5-89.8)	3.00 (0.39-23.30)	

Papatheodoridis et al, HEPATOLOGY, VOL. 63, NO. 5, 2016

Virological relapse after discontinuation of nucleos(t)ide analogues (ETV & TDF)

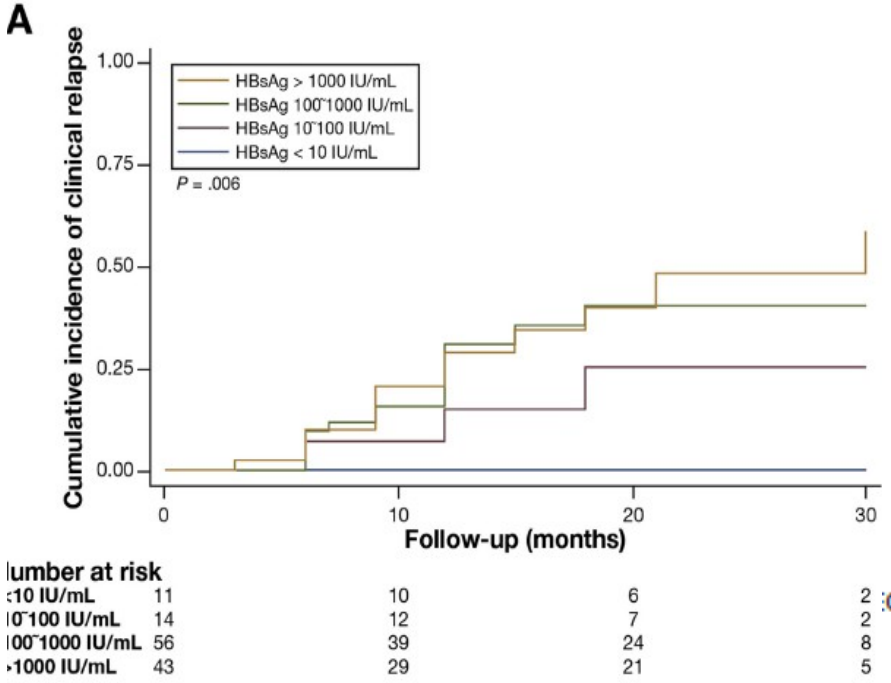


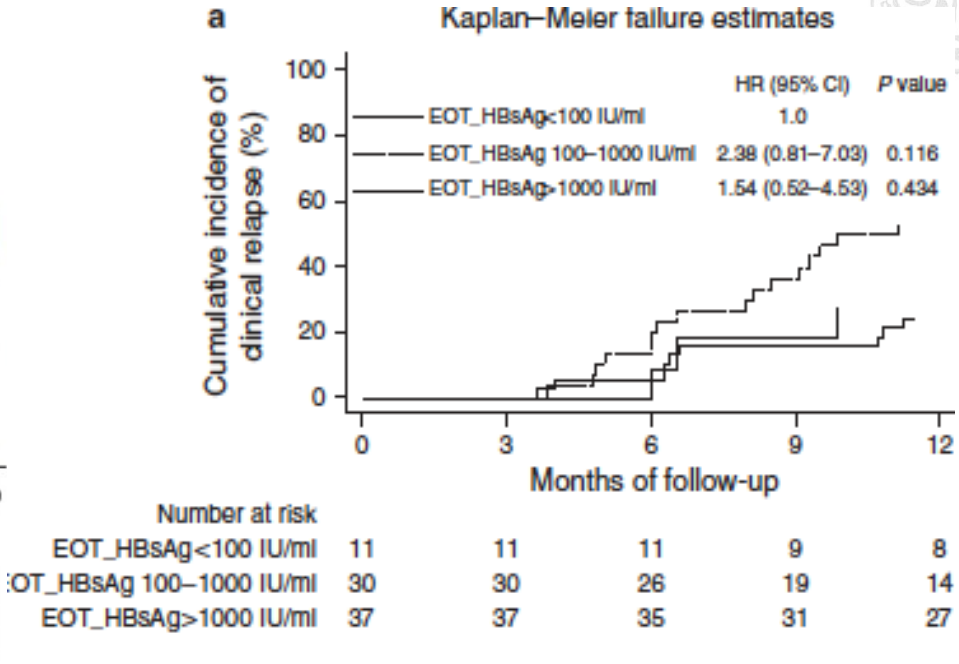
Virologic relapse rate increased over the follow-up time

Chen GF, Wang C, Shao Q et al, APASL 2017, Poster presentation

Clinical relapse after discontinuation of nucleos(t)ide analogues - qHBsAg

Significant dose-response association between EOT HBsAg level and clinical relapse in patients with negative HBeAg at the end of treatment





Hsu et al, Clin Gastroentrol Hepatol 2016;14:1490–1498

Wang et al, Am J Gastroenterol 2016; 111:1286–1294

The association of HBV RNA levels and viral rebound after the discontinuation of NUCs

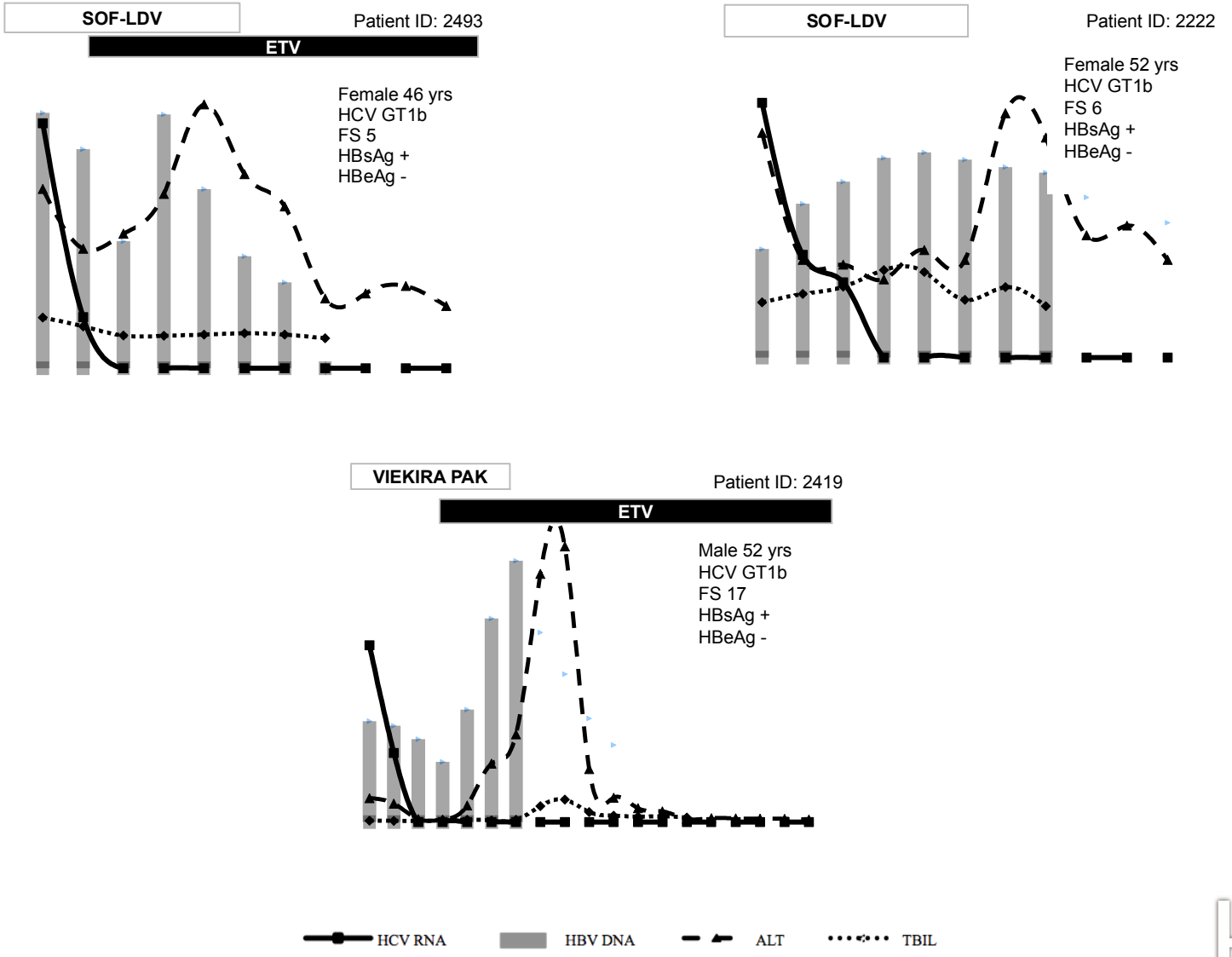
HBV RNA	Viral rebound (n)	No viral rebound (n)	Total (n)	*p* value*
Positive	21 (100%)	0 (0)	21	
Below the LOQ	3 (25%)	9 (75%)	12	0.001
Total	24 (73%)	9 (27%)	33	

*Chi-square test; n, number of CHB patient.

Wang et al, Journal of Hepatology 2016 vol. 65: 700–710

HBV reactivation-new concern

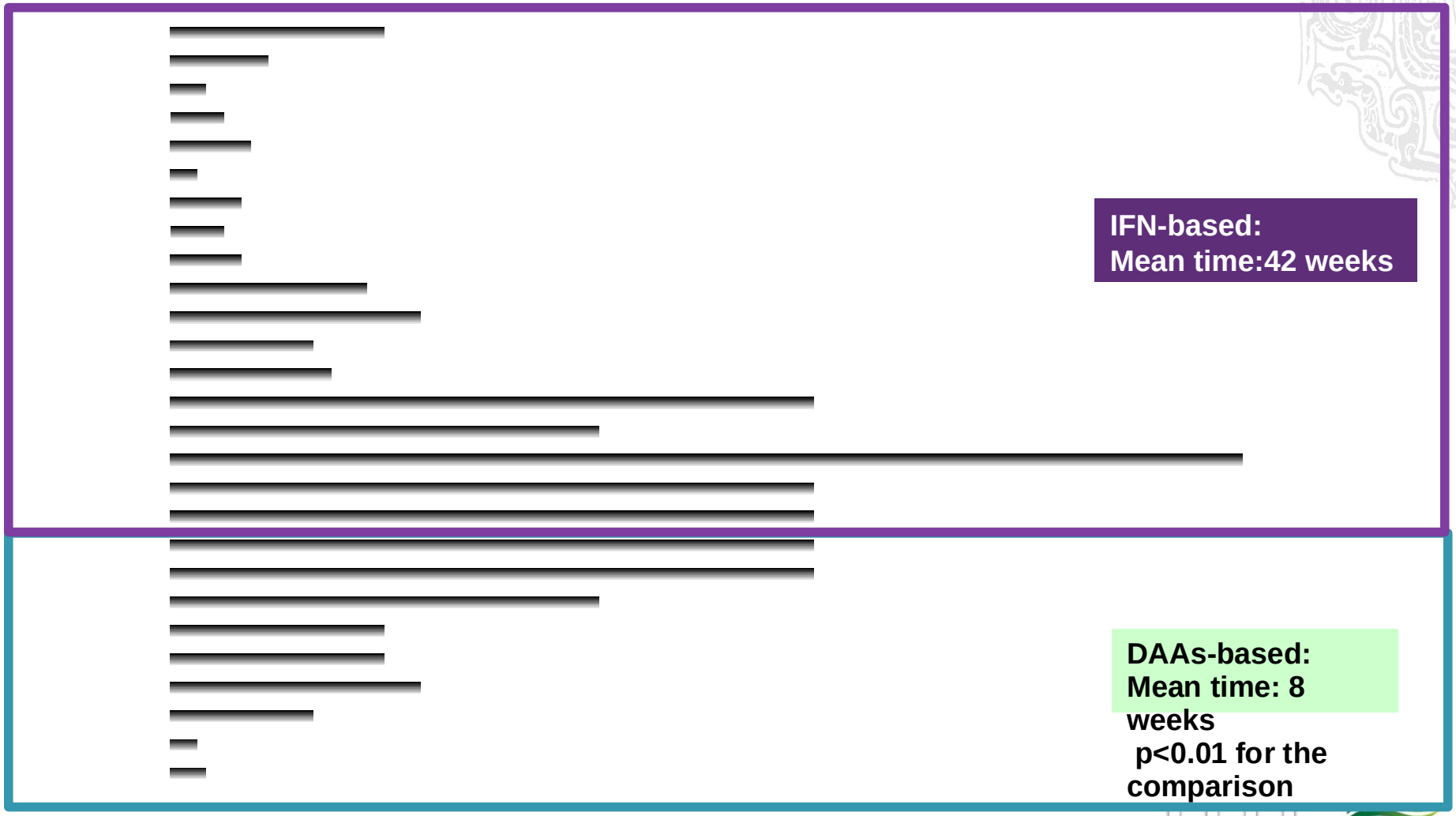
Hepatitis due to HBV reactivation in HBsAg+ CHC Chinese



Wang C et al. Clin Gastroentrol Hepatol 2017;15: 132-136

Time to HBV reactivation was significantly shorter with DAAs Vs IFN

Time to HBV reactivation after initiation of anti-HCV treatment (Weeks)



Chen et al, APASL (Oral presentation) Shanghai 2017

Current recommendations

	AASLD1	EASL2	US FDA3	PRAC4
Screening for HBV serology				
Preemptive NUCs	Only active CHB	ALL HBsAg+ or OBI	Consult Hepatologist	According to guidelines
				According to guidelines
Monitoring				

1. AASLD/ISDA. HCV guidance: recommendations for testing, managing, and treating hepatitis C. Updated September 16, 2016. Pawlotsky JM et al.
2. EASL recommendations on treatment of hepatitis C 2016. Journal of Hepatology, in press, 2016.
3. The U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct-acting antivirals for hepatitis C. 2016 [Nov, 2016]. http://www.fda.gov/Drugs/DrugSafety/ucm522932.htm.
4. PRAC Warns Of Risk Of Hepatitis B Re-activation With Direct-acting Antivirals For Hepatitis C. http://www.benzinga.com/news/16/12/8764261/prac-warns-of-risk-of-hepatitis-b-re-activation-with-direct-acting-antivirals

What we really need?

“CURE”

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Types of HBV cure

Functional Cure- clinical resolution

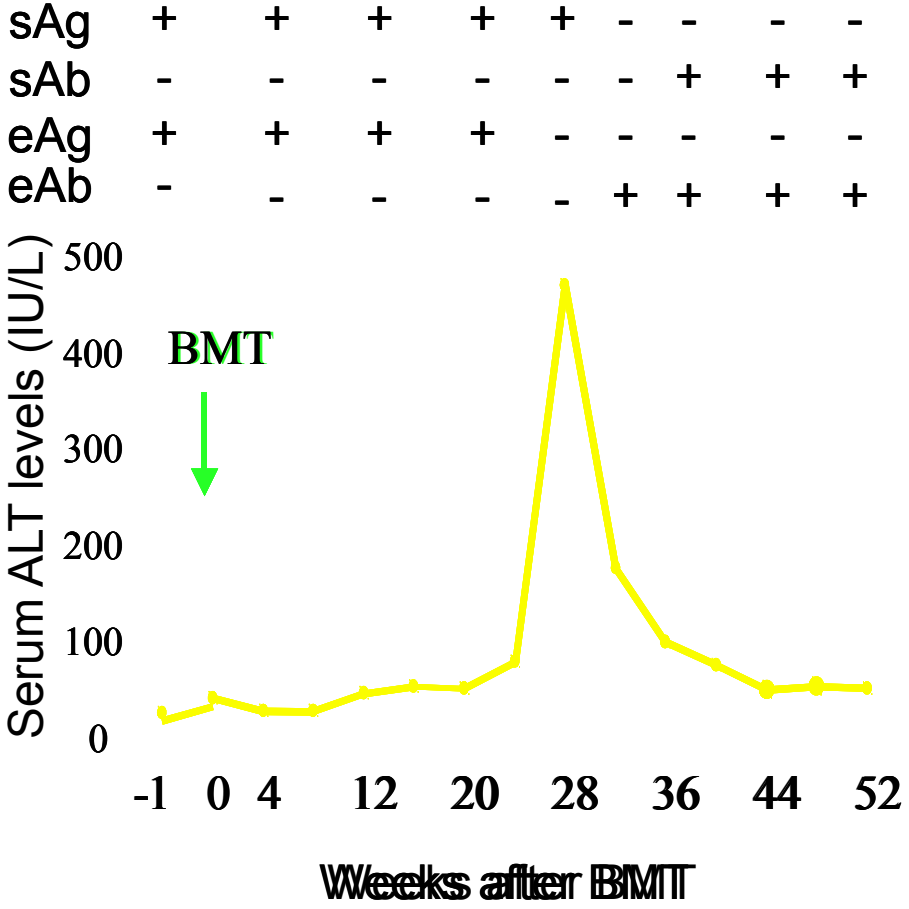
Sustained, off drug:

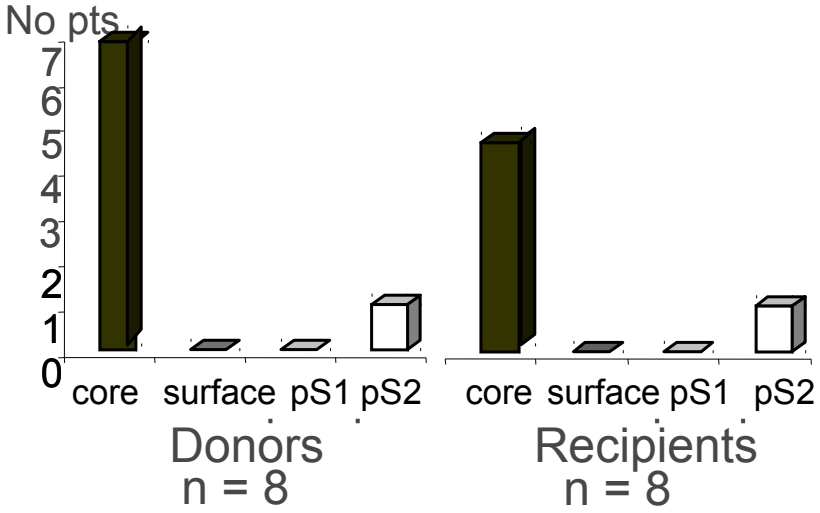
- No inflammation: ALT and liver biopsy
- HBsAg loss
- HBsAb gain

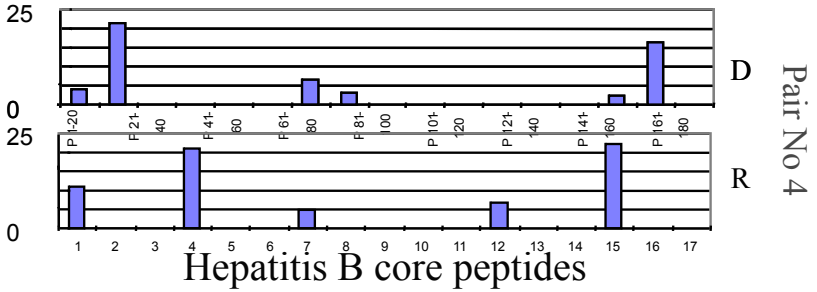
Complete cure- virological cure

- All of above plus
- Loss of cccDNA

Resolution of CHB in Man by Adoptive Transfer of Immunity to HBcAg







Lau GK et al. Gastroenterology 2002;122: 614-624.

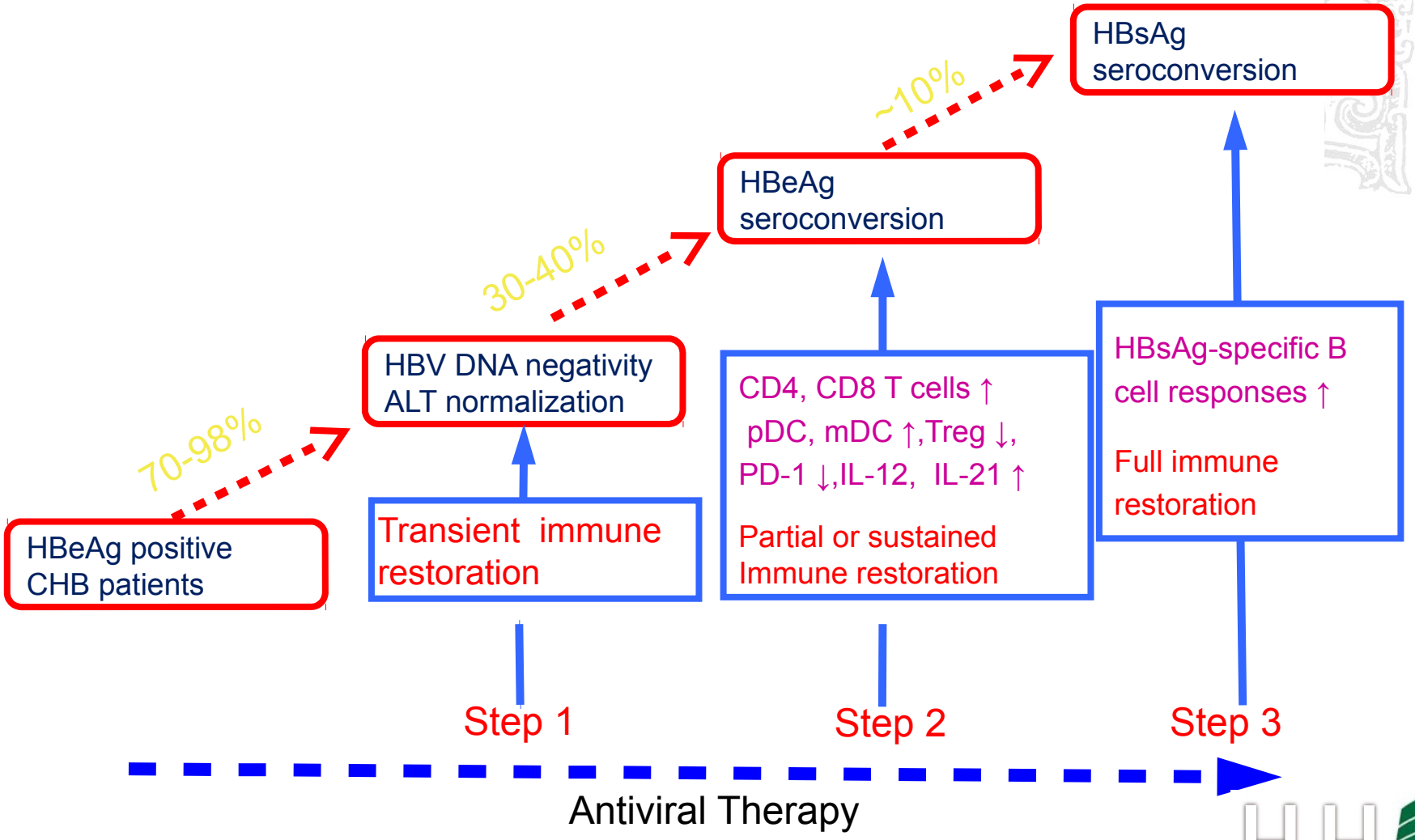
New therapy in the pipeline

Experimental Therapeutics for HBV in the pipeline

Compound	General Mechanism	Intended target	Clinical Stage	Sponsor	References
GS9620	IDA-I	Toll 7R agonist	Phase II	Gilead Sci	Lanford 2013
GS7340	DAA	Prodrug-tenofovir	Phase II/III	Gilead Sci	Menandex 2014
GS4774	IDA-I	Rx vaccine	Phase II/III	Gilead Sci	Mohommed 2013
RepA9	DAA	HBsAg	Phase I/II	Replicor	Nordeen 2007
ARC520	DAA	RNAi	Phase I/II	Arrowhead	Arrowhead web site
MycB	DAA	HBV receptor	Phase I/II	Myr-GmbH	Urban 2014
NVR1221/3778	DAA	Capsid	Phase I/II	Noviro	Gane 2014
Heplisav B	IDA-I	Rx Vaccine	Phase I	Dynavax	Halperin 2012
Briniprint	IDA-H	SMAC	Phase I	Tetralogic	Tertalogic Website
ISIS HBV	DAA	Antisense	Phase I	Isis	Isis web site
Bay41109	DAA	Capsid	Phase I	AiCuris	Res 2007

Direct Acting Antiviral (DAA)-action against a virus specified gene product
Indirect Acting Immunological (IDA-I) or Indirect Acting Host (IDA-H)- targets a host function

Antiviral treatment reduce/block hepatic inflammation through HBV replication suppression



Lau GK, Wang FS. J Hepatol . 2012

Research platform

Our team

- **Liver Cirrhosis Diagnosis and Treatment Center, 302 Military Hospital**
- **Beijing 302- Hong Kong H & H Liver**

Institute of Translational Hepatology (Beijing)

H & H Medical Group (Hong Kong)

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