



2 0 1 7  
2<sup>ème</sup>  
**JEUNES  
HÉPATOLOGUES  
CONFÉRENCE**

**Du 29 juin au 1<sup>er</sup> juillet 2017**  
Saint-Maximin-la-Sainte-Baume

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Organisée par  
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**Modérateurs : Dominique GUYADER Didier SAMUEL**

**CONTROVERSE**

**Peut-on arrêter les NUC chez les patients VHB ? Pro and Cons.**

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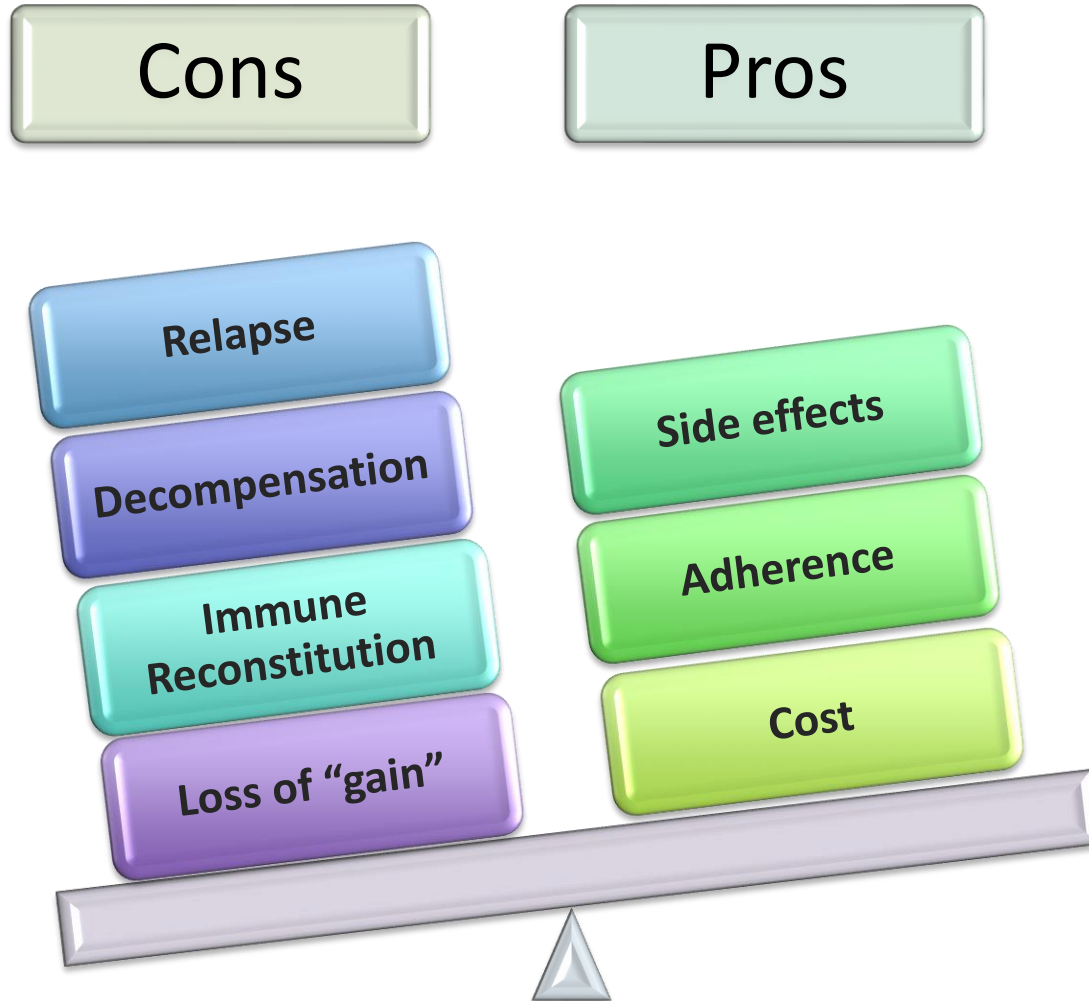


Institut national  
de la santé et de la recherche médicale



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# Why we do not want to stop NA?

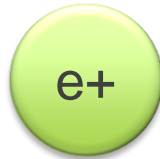




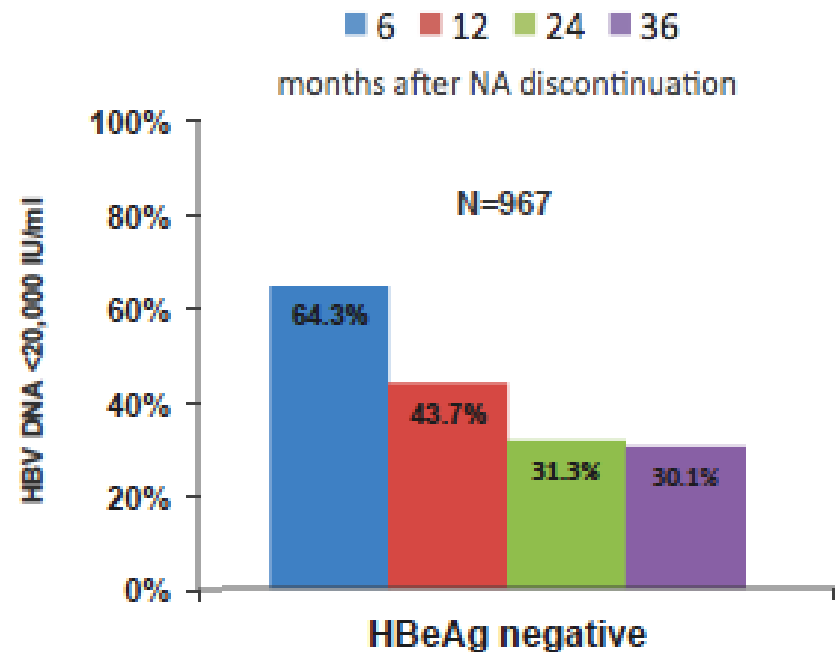
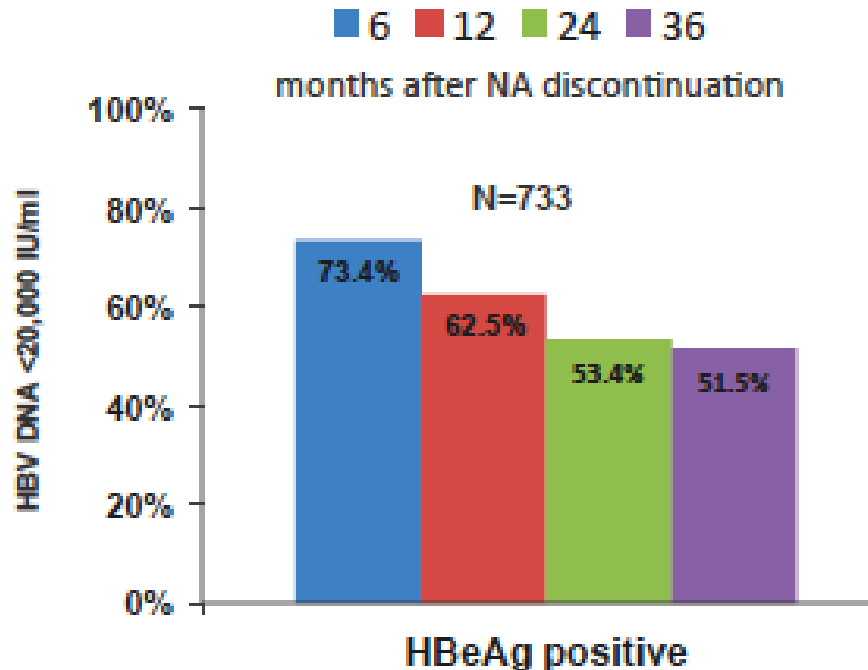
# Stop-NUCs. Cons

Relapse

14 studies  
Pooled HBs loss 1 %  
Durable biochemical remission 76 %



17 studies  
Pooled HBs loss 1,7 %  
Durable biochemical remission 57 %



# Stop-NUCs. Cons

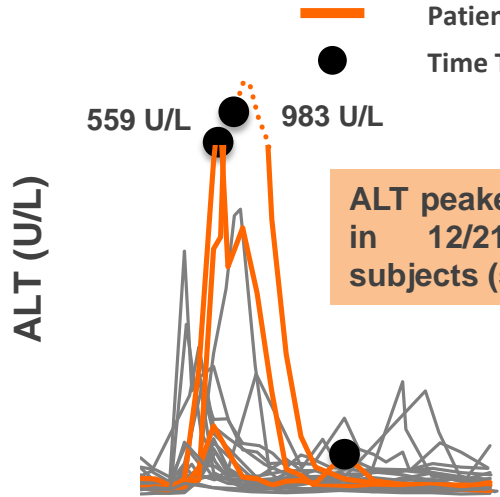
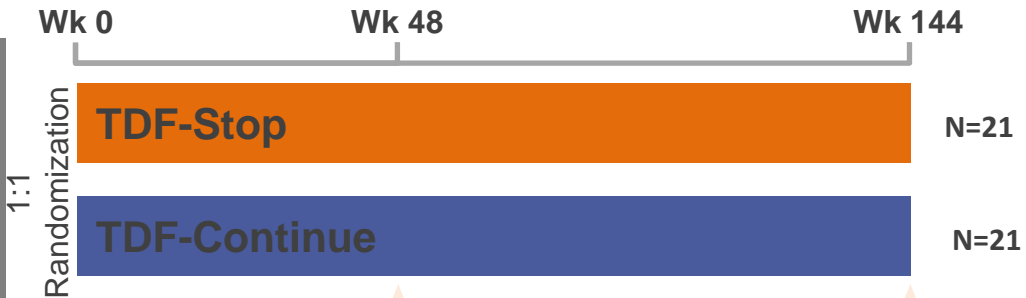
Relapse



## “FINITE CHB” : Stopping Tenofovir Disoproxil Fumarate Treatment After Long-Term Virologic Suppression in HBeAg-Negative CHB

**CHB patients**

- HBeAg-negative
- ≥4 years TDF therapy
- HBV DNA UD >3.5 yrs
- No cirrhosis

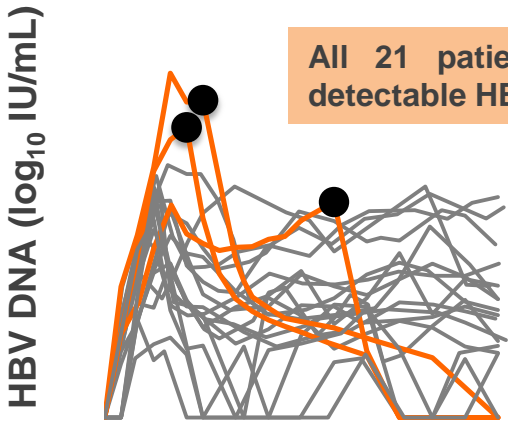


ALT peaked at >2xULN in 12/21 TDF-Stop subjects (57%)

Weeks From Baseline

Patients requiring TDF re-initiation (n=3)

Time TDF was restarted



All 21 patients had detectable HBV DNA

Weeks From Baseline

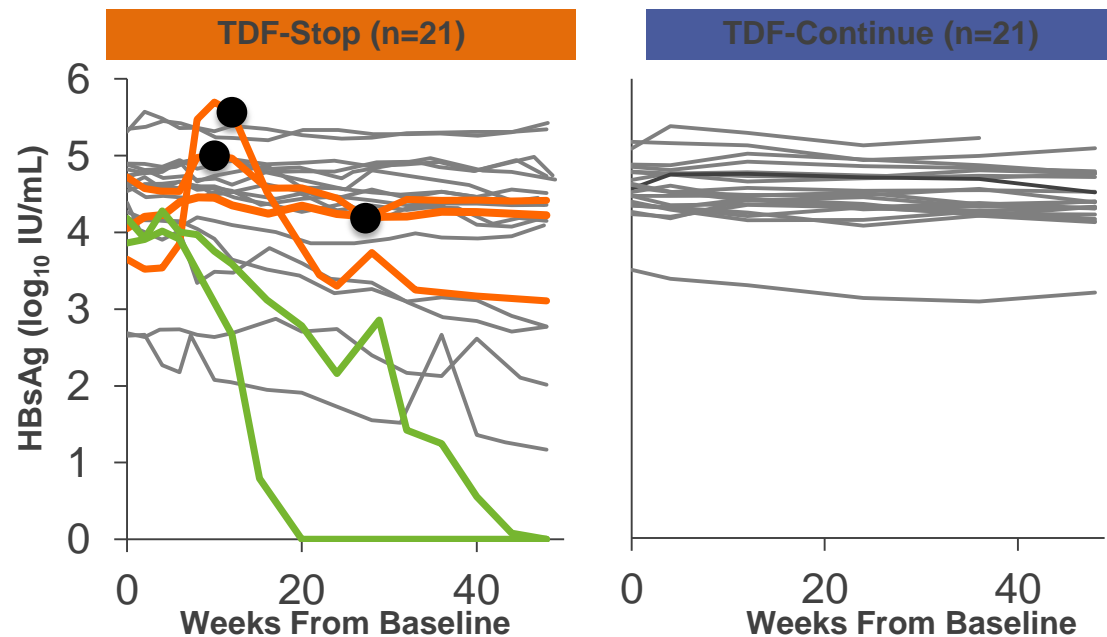
# Stop-NUCs. Cons

e-

Relapse

## “FINITE CHB” : Stopping Tenofovir Disoproxil Fumarate Treatment After Long-Term Virologic Suppression in HBeAg-Negative CHB

- HBsAg loss
- Patients requiring TDF re-initiation
- Time TDF was restarted



Profound HBsAg decline  
in TDF stop group



# Stop-NUCs. Cons

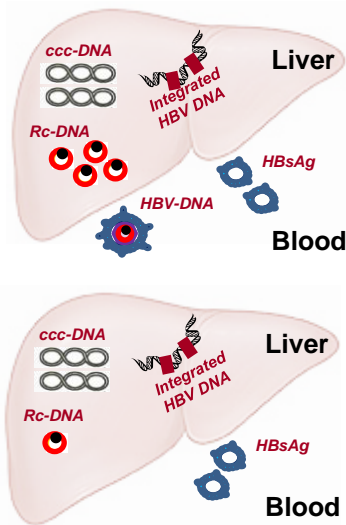
Decompensation

- **Risk of decompensation in cirrhotic patients (0.8 %)**
- **Stop-NUC in cirrhotic patients after HBsAg loss is safe (no relapse)**
- **Risk of decompensation is minimal if patients are not cirrhotics**

# Stop-NUCs. Cons

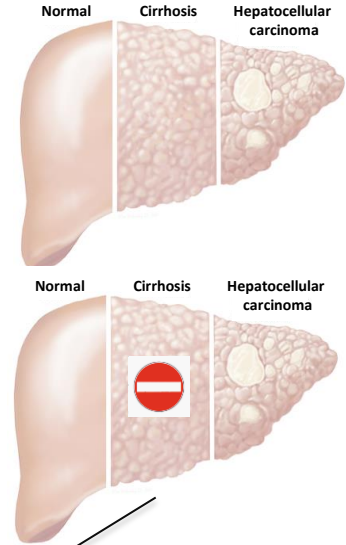


Loss of "gain"

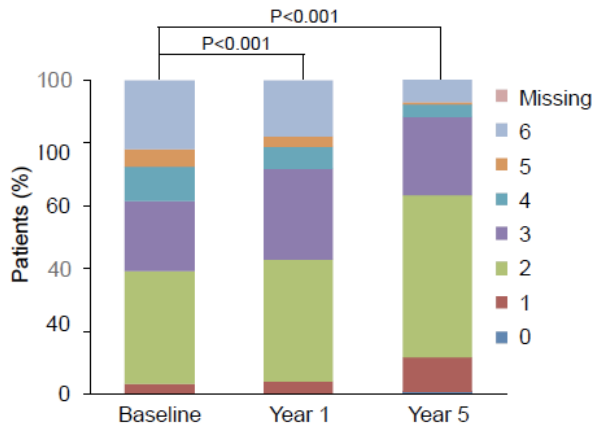


UNTREATED

NUCs



Ishak fibrosis score



Marcellin P., Lancet 2013

**Decompensation is fully prevented in ETV or TDF treated compensated cirrhotics (if HBV is the only aetiology !)**

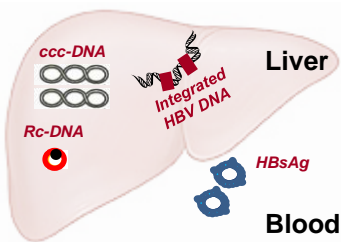
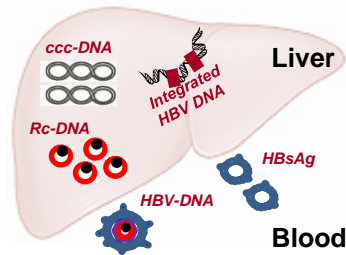
- ▶ ETV: 3-5 years real life cohort studies in Europe and Asia (1-4)
- ▶ TDF: 3-4 years real life cohort studies in Europe (5-6)

1. Wong GL, et al, Hepatology 2013; 2. Zoutendijk R, et al, Gut 2013; 3. Lampertico P, et al, EASL 2013; 4. Lim et al, Gastroenterology 2014; 5. Lampertico P, et al, AASLD 2013; 6. Papatheodoridis G et al, AASLD 2013

# Stop-NUCs. Cons

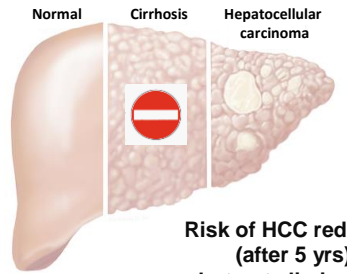
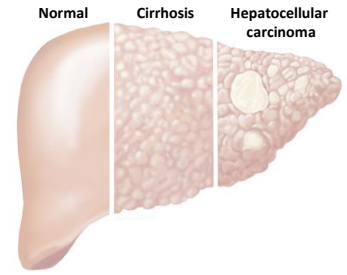


Loss of "gain"



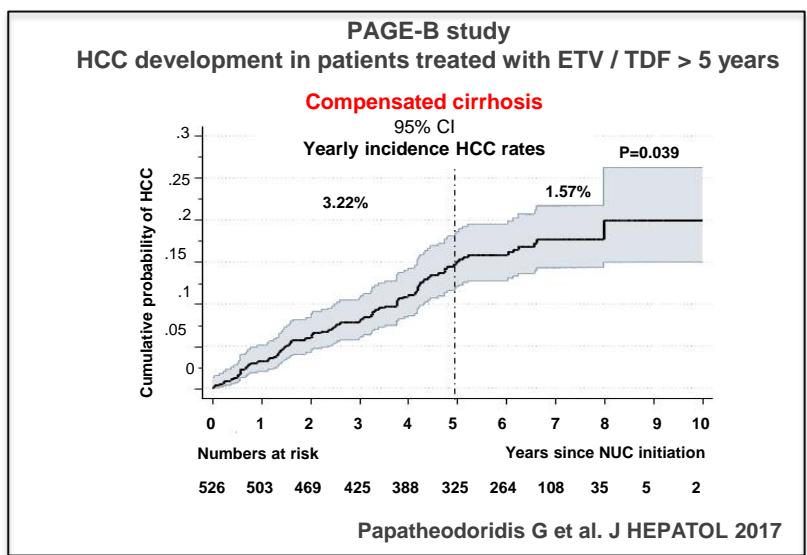
UNTREATED

NUCs



Risk of HCC reduced (after 5 yrs) but not eliminated

- cccDNA persists in the liver
  - HBV DNA blips in NA suppressed pts
  - Ongoing intrahepatic replication
- Boyd et al. J Hepatol 2016





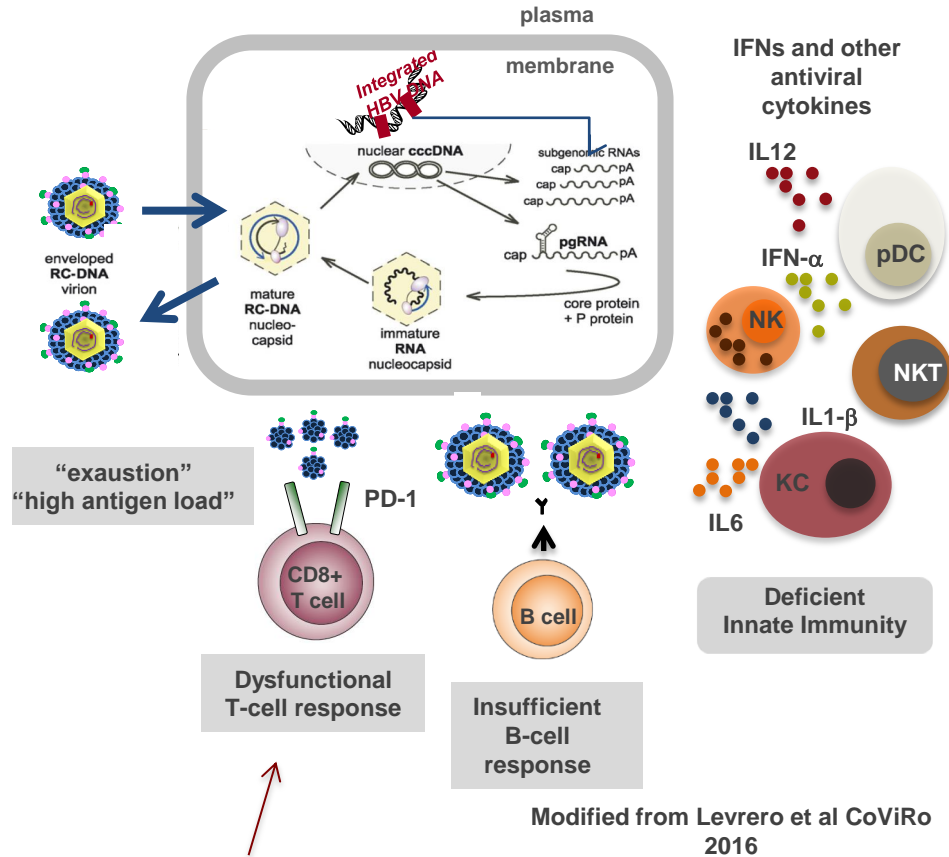


# Stop-NUCs. Pros

## *Can we agree with the Procurator ?*

Loss of "gain"

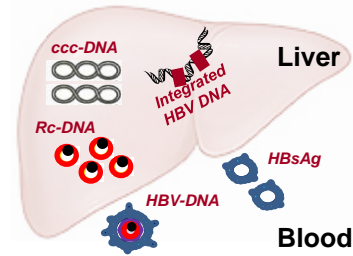
Immune Reconstitution



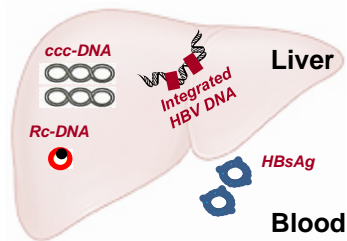
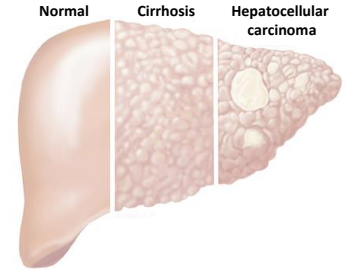
- NAs treatment partially restores HBV specific CD8 T cells responses (Boni, 2007; Fiscaro, 2012)
- Is restoration maintained or even boosted after Stop-NUCs ???



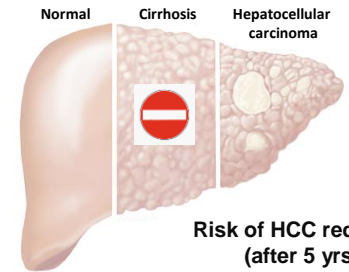
# Stop-NUCs. Cons



UNTREATED



NUCs



Risk of HCC reduced (after 5 yrs) but not eliminated

Loss of "gain"

**Do we lose the gains ?**  
[fibrosis, liver function, HCC risk]

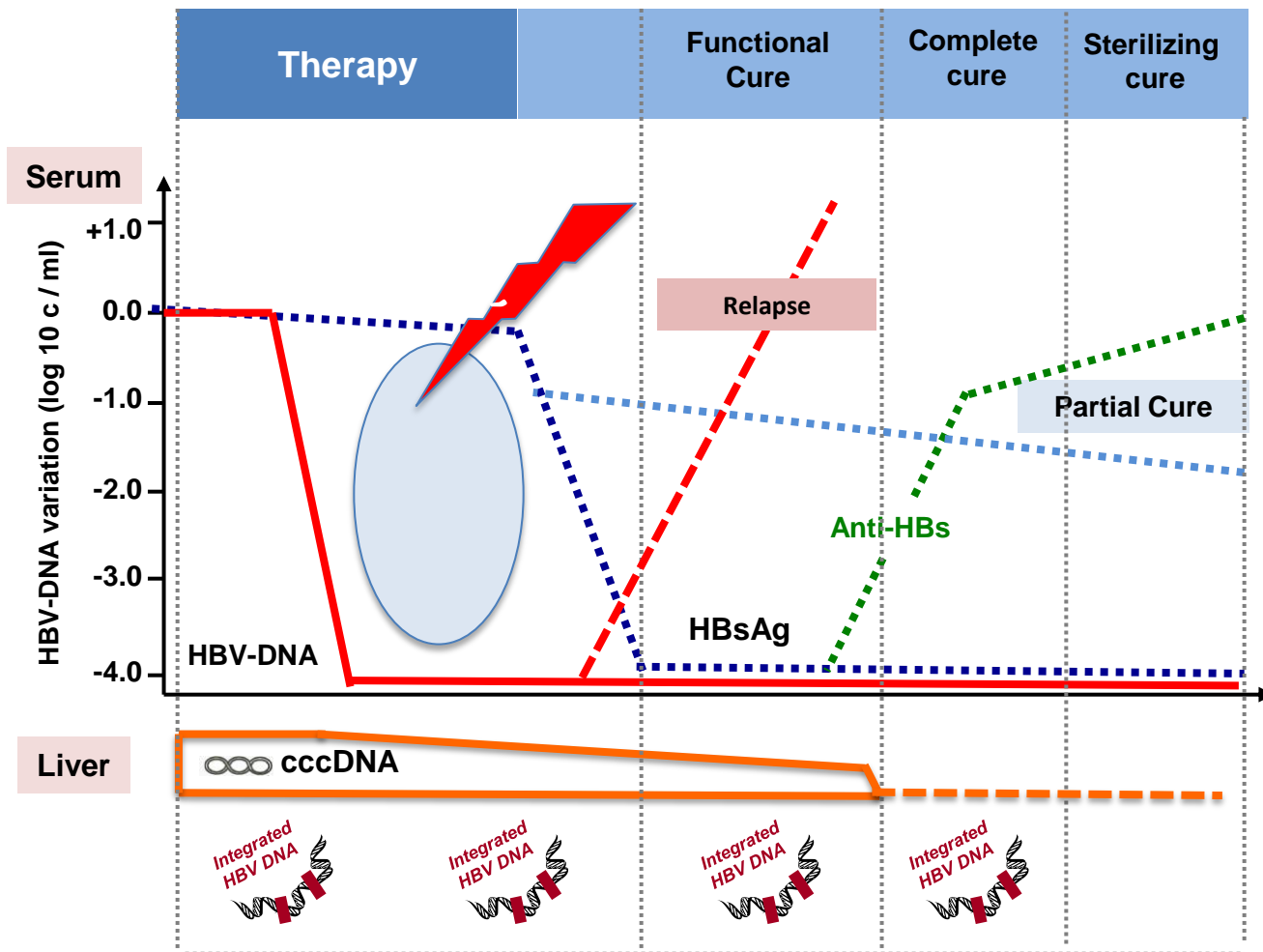
**We simply do not know !**  
**Studies are needed**



# Stop-NUCs

DO WE HAVE A BIOMARKER ?

No relapse  
HBsAg loss

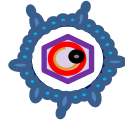


# Stop-NUCs

DO WE HAVE A BIOMARKER ?

No relapse  
HBsAg loss

HBV-DNA



- No/Low correlation with cccDNA activity
- Does not predict “HBs loss / cure”

**To be confirmed:**

- HBV DNA  $\leq 20000$  IU/ml at baseline is associated with fewer clinical relapse  
(Jeng WJ, et al. Hepatology 2013)
- 3 – 4.5 years suppression in anti-HBe CHB ???

qHBsAg



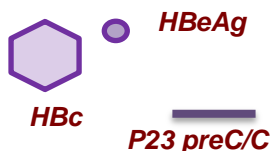
- No/Low correlation with cccDNA activity
- Does not predict “HBs loss / cure”
- Low qHBs may predict “no relapse” and HBs loss after Stop-NUCs but cut-off not well established

# Stop-NUCs

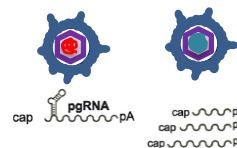
DO WE HAVE A BIOMARKER ?

No relapse  
HBsAg loss

## HBcrAg



## circulating HBV-RNAs



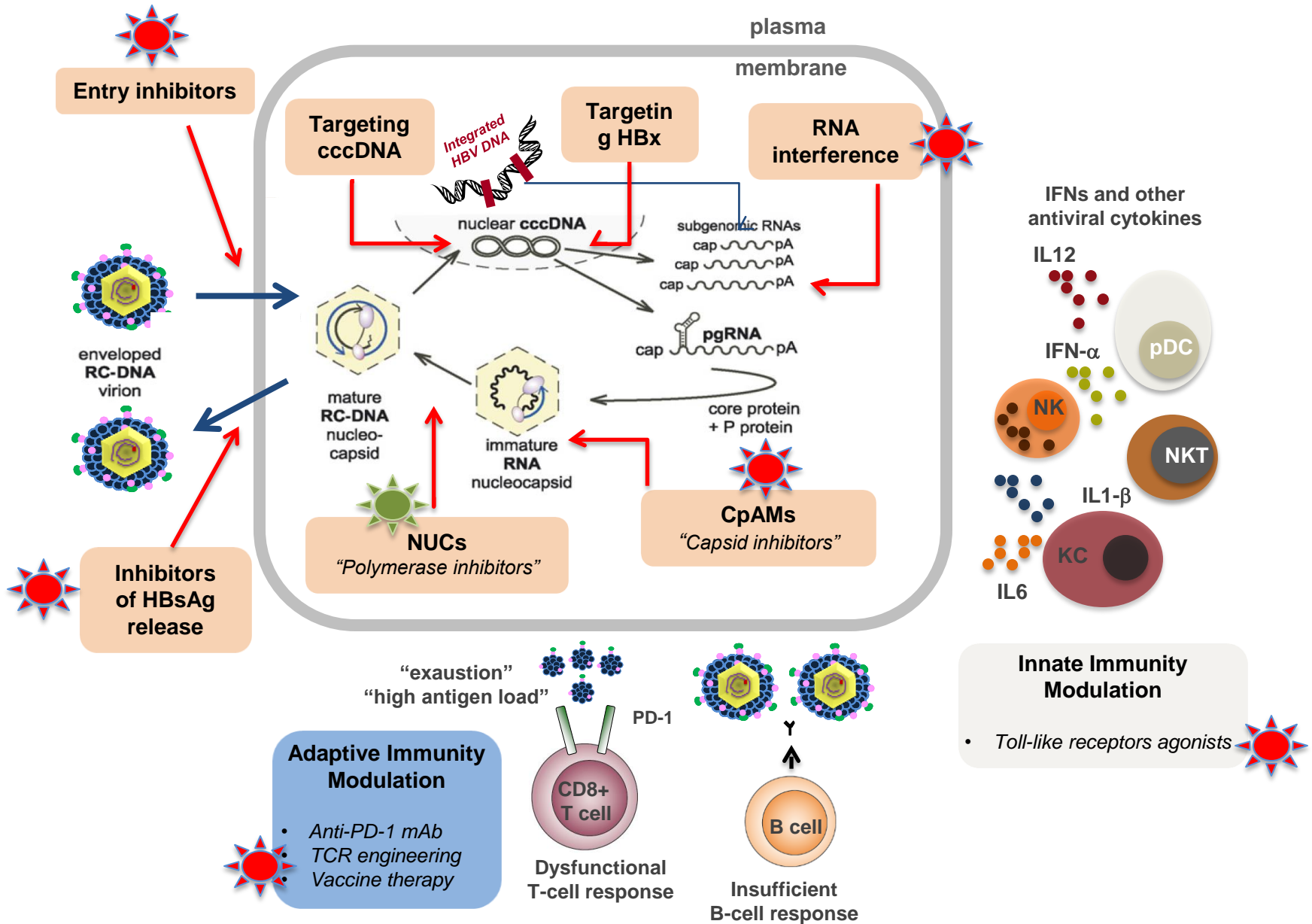
- **Good correlation with cccDNA activity (Testoni et al, submitted 2017)**
- **Composite biomarker**
- **Low sensitivity [negative in 50 to 70% of anti-HBe CHB and most NUC treated anti-HBe CHB]**

- **Literature and preliminary data support correlates with cccDNA activity**
- **RT-PCR assay [high sensitivity and specificity]**
- **HBV-RNA positivity is associated with viral rebound after stop-NUCs (Wang et al J Hepatol 2016)**

HBV RNA	Viral rebound (n)	No viral rebound (n)	Total (n)	*p value
Positive	21	0	21	
Below the LoQ	3	9	12	0.001
Total (n)	24	9	33	

\*Chi-Square test; n, number of CHB patients.

# Therapeutic targets





# Stopping NA - conclusion

- **HBeAg positive CHB**

Stopping NA after HBeAg seroconversion or HBV undetectable according to clinical guidelines is associated with significant risk of hepatitis relapse

- **HBeAg negative CHB**

Stopping NA is associated with higher risk of hepatitis relapse

- Risk of decompensation low in non cirrhotic patients but close monitoring is mandatory and treatment must be restarted in the case of severe flares
- New regimens with the New molecular entities (NMEs) will likely include NUCs
- Do we lose NA treatment benefits ?
- Better predictors (biomarkers ?) needed

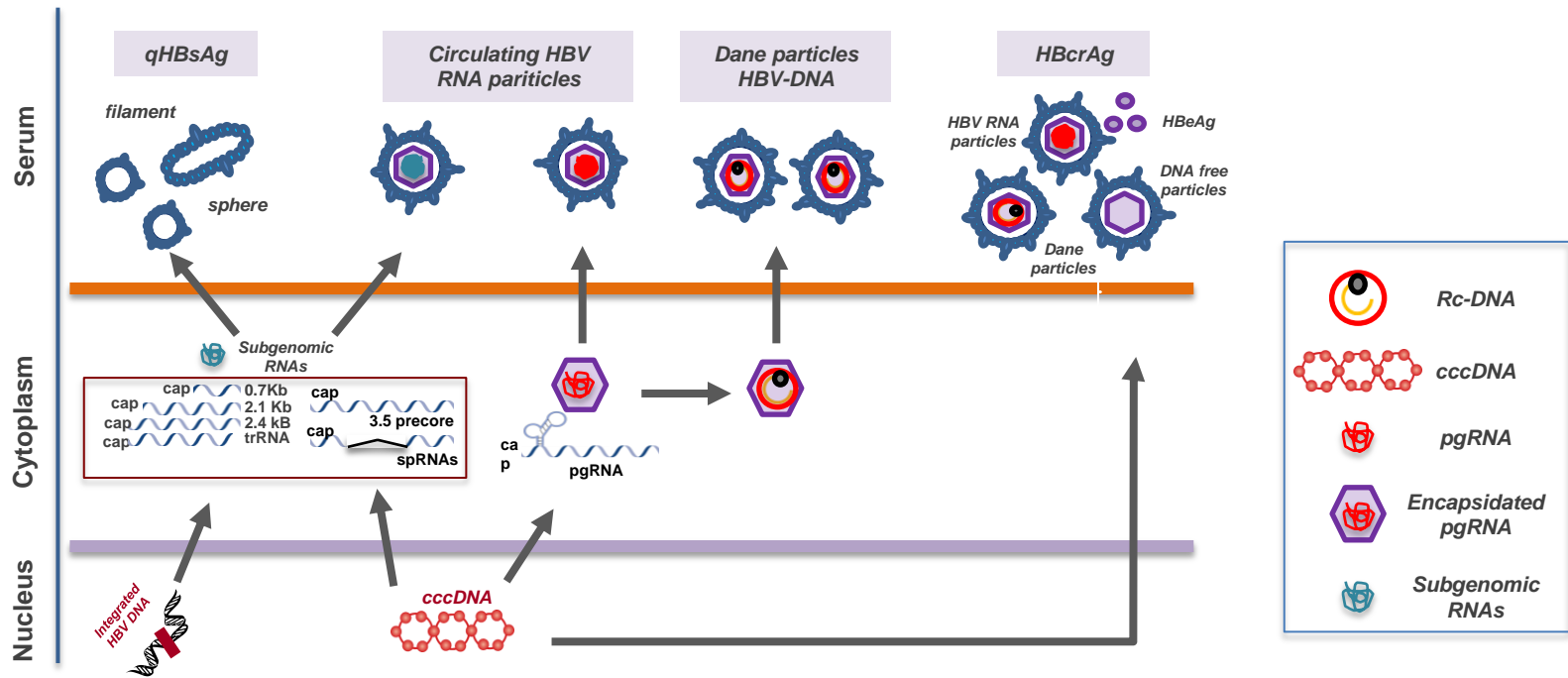
**Can we stop-NUCs ? YES**

**Should we stop NUCs ? NO**

**Will I stop-NUCs ? NO**

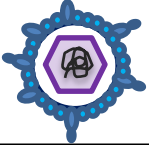
















# HBV-RNA containing circulating particles

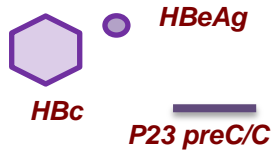
## Compartmentalization

		Literature	Consortium
	RNA containing viral particles	+	+
	RNA containing capsids	?	?
	Exosomes	-	+/?
	Free RNAs	-	?

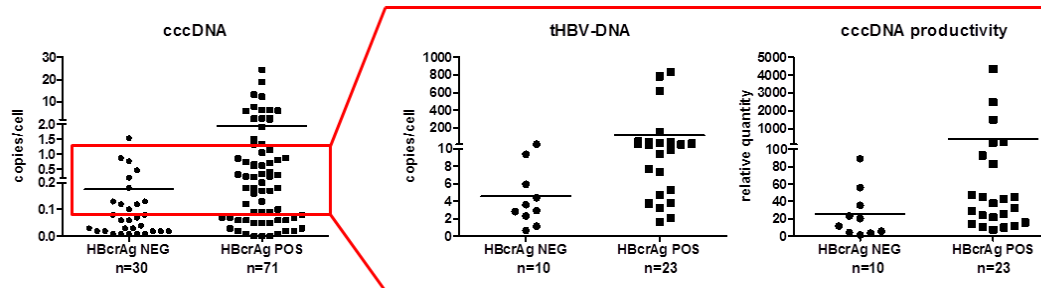
## RNA species

		Source	Literature	Consortium
 cap	3.5 kb pgRNA	cccDNA	+	+
 cap	3.5 Kb PreC RNA	cccDNA	?	?
 cap	Spliced RNAs	cccDNA [integrated]	+	+
 cap	0.7 Kb HBx	Incoming virions / cccDNA	+	?
 cap	2.1 Kb HBs	cccDNA / [integrated]	?	?
 cap	2.4 Kb HBs	cccDNA / [integrated]	?	?
 cap	2.1/2.4 Kb trRNAs	Integrated	+	+

# HBcrAg



• Good correlation with cccDNA activity



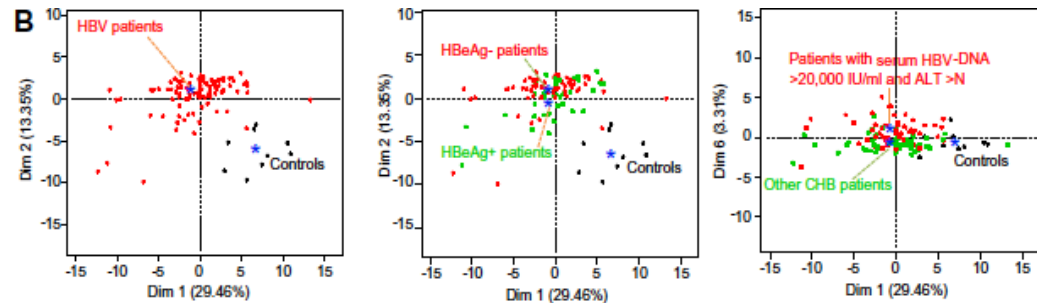
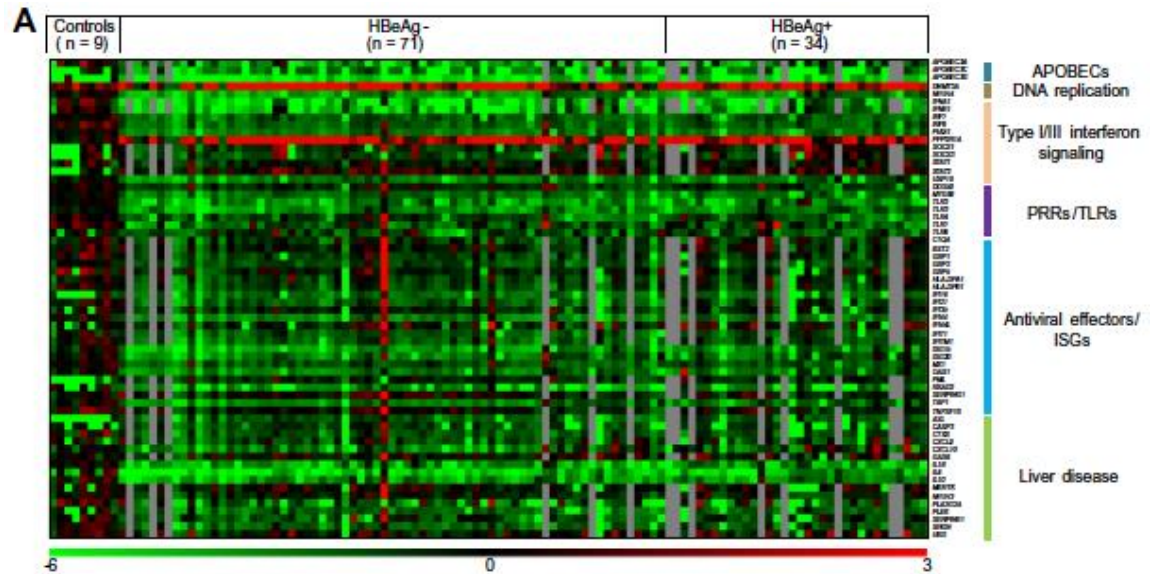
Testoni et al, manuscript in preparation

	IA+ENEG (n=130)	
	HBcrAg	qHBsAg
tHBV-DNA	R= 0.78; p<0.0001	R= 0.38; p=0.001
cccDNA	R= 0.62; p<0.0001	R= 0.17; p=ns
pgRNA	R= 0.75; p<0.0001	R= 0.35; p=0.001
cccDNA transcriptional activity [pgRNA/cccDNA]	R= 0.59; p<0.0001	R= 0.35; p=0.002

# Stop-NUCs. Pros

Intrahepatic innate immune response pathways are downregulated in untreated chronic hepatitis B patients

- Immune Reconstitution
- Side effects
- Adherence
- Cost



# Stop-NUCs. Pros

## Can we agree with the Procurator ?

The Journal of Infectious Diseases

**BRIEF REPORT**

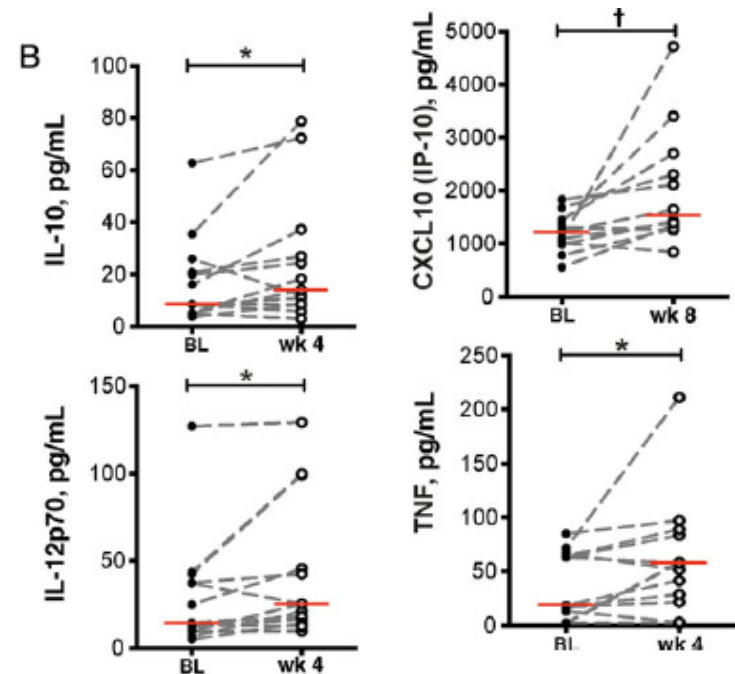
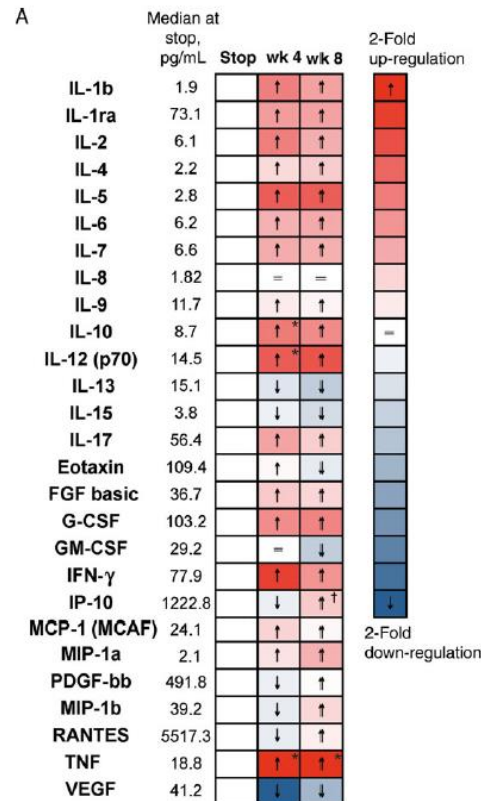
### Viral and Host Responses After Stopping Long-term Nucleos(t)ide Analogue Therapy in HBeAg-Negative Chronic Hepatitis B

Immune Reconstitution

Side effects

Adherence

Cost



Induction of soluble immune mediators (SIMs) after nucleos(t)ide analogue (NA) treatment cessation

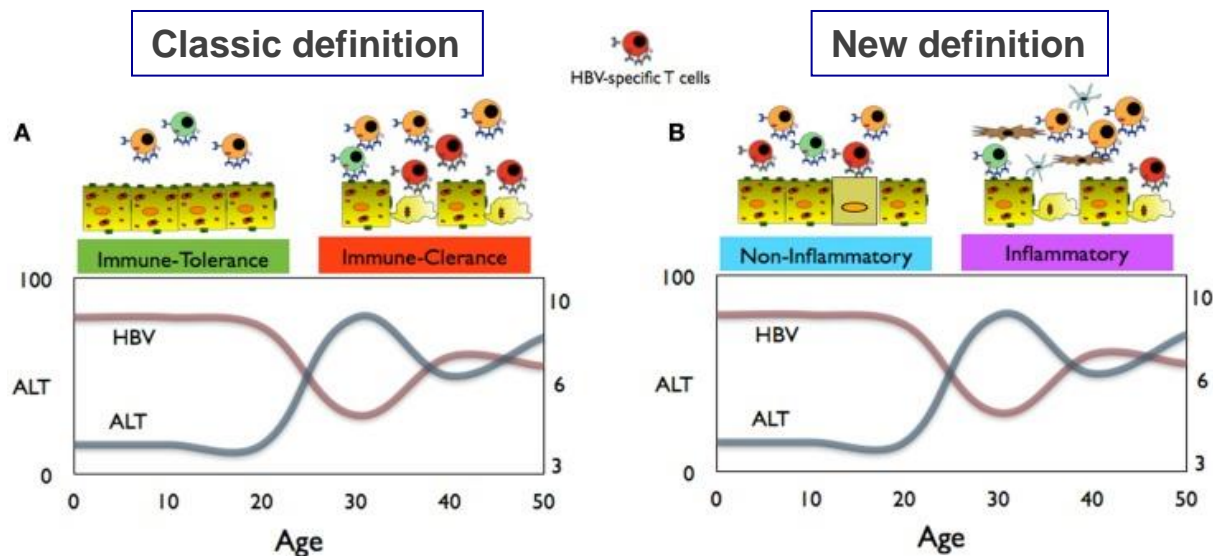
# Natural history of HBV - New nomenclature

	HBeAg positive Chronic <i>infection</i>	HBeAg positive Chronic <i>hepatitis</i>	HBeAg negative Chronic <i>infection</i>	HBeAg negative Chronic <i>hepatitis</i>
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL <sup>oo</sup>	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated*
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative Chronic hepatitis

\*Persistently or intermittently

<sup>oo</sup> HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis

EASL 2017 CPG HBV, J Hepatol 2017



Kennedy et al, Gastroenterology 2012; Hong, Bertoletti et al, Nature Com, 2015