Update HBV

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DISCLOSURES

Advisory board member for Gilead, MSD, Abbvie, BMS, Transgene, Inovio

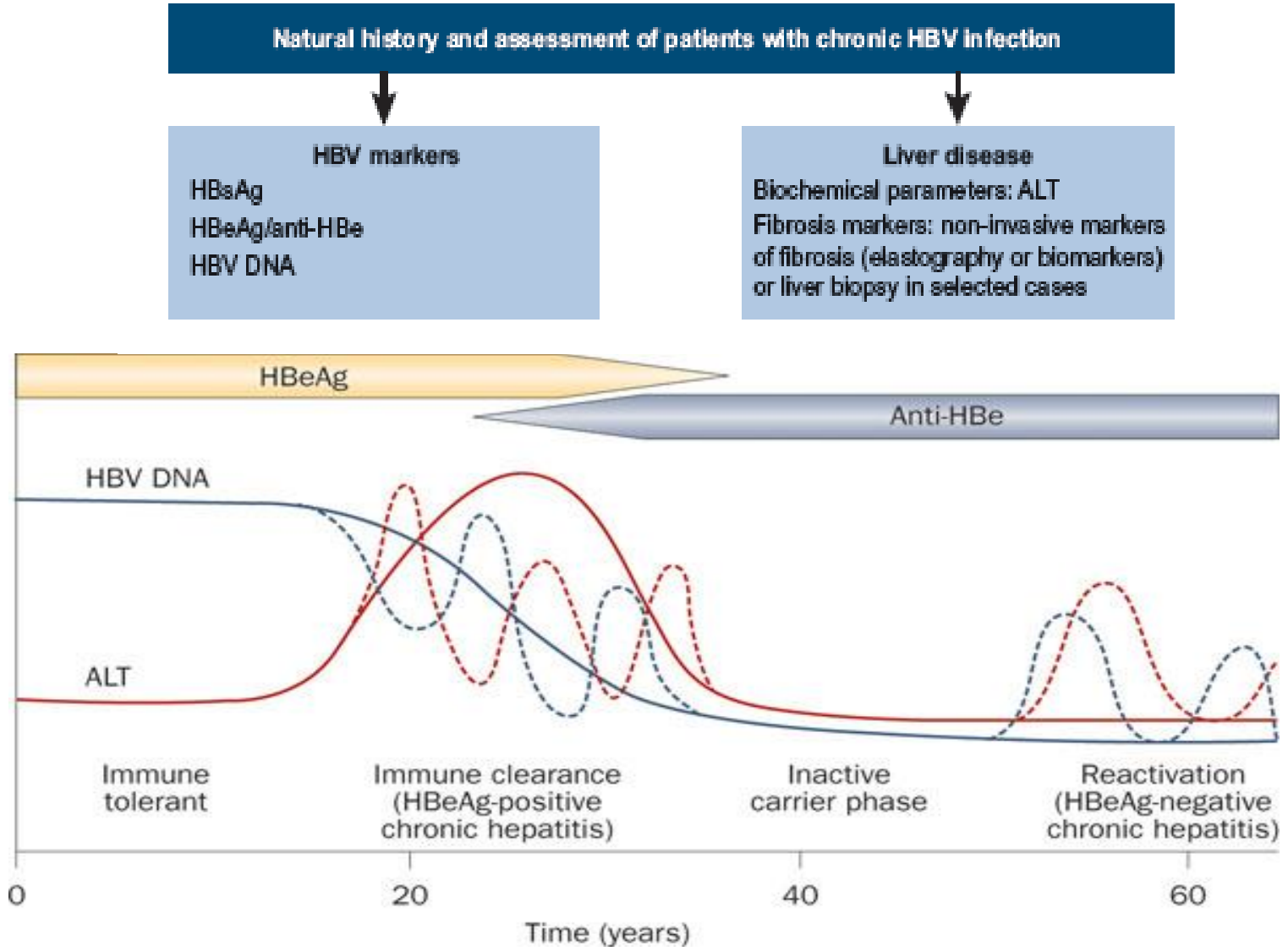
Consultant for Gilead, Arrowhead

Research grants from Gilead, Abbvie, BMS

List of topics

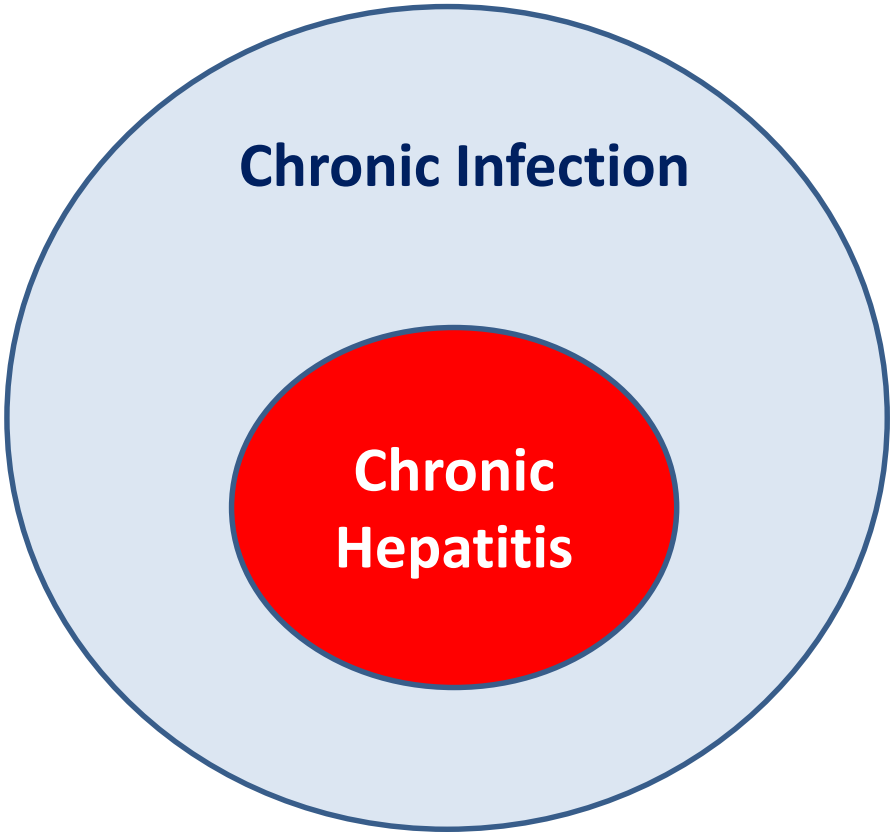
- Reclassification of the HBV infection phases and implications for therapy
- NUC withdrawal before HBsAg loss
- Novel diagnostic tools

Natural course of chronic HBV infection



Kwon, H. & Lok, A. S. *Nat. Rev. Gastroenterol. Hepatol.* 2011

Natural history of HBV - New nomenclature



EASL 2017 CPG HBV, J Hepatol 2017, epub April

Natural history of HBV and treatment indications

PHASE	1	2	3	4
New terminology	HBeAg positive Chronic *infection*	HBeAg positive Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis
Old terminology	*Immune tolerant*	*HBeAg-positive CHB*	*Inactive carrier*	*HBeAg-negative CHB*
HBsAg	High	High/Intermediate	Low	Intermediate
HBeAg	Positive	Positive	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4-10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL
ALT	Normal	Elevated	Normal	Elevated**
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe
Disease progression	Low	**Moderate to high**	No, very low	**Moderate to high**
Treatment	Not indicated***	**Indicated**	Not indicated	**Indicated**

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

** Persistently or intermittently

*** Treatment is indicated in some patients

EASL 2017 CPG HBV, J Hepatol 2017

Natural history of HBV and treatment indications

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EASL 2017 CPG HBV, J Hepatol 2017

Natural history of HBV and treatment indications

PHASE	1	2	3	4	5
New Terminology	HBeAg positive Chronic *infection*	HBeAg positive Chronic hepatitis	HBeAg negative Chronic *infection*	HBeAg negative Chronic hepatitis	Resolved HBV infection
Old terminology	*Immune tolerant*	*HBeAg-positive CHB*	*Inactive carrier*	*HBeAg-negative CHB*	HBsAg negative/anti-HBcore positive
HBsAg	High	High/Intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10E7 IU/mL	10E4-10E7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL[a]
ALT	Normal	Elevated	Normal	Elevated**	Normal
Liver disease	None/minimal	Moderate/severe	None	Moderate/severe	None[b]
Disease progression					None[b]
Treatment					Not indicated but prophylaxis for selected cases

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

** Persistently or intermittently; [a] in >95% of patients but HBV-DNA frequently detectable in the liver; [b] residual HCC risk only if cirrhosis has developed before HBsAg loss

EASL CPG HBV, J Hepatol 2017

Natural history of HBV and treatment indications

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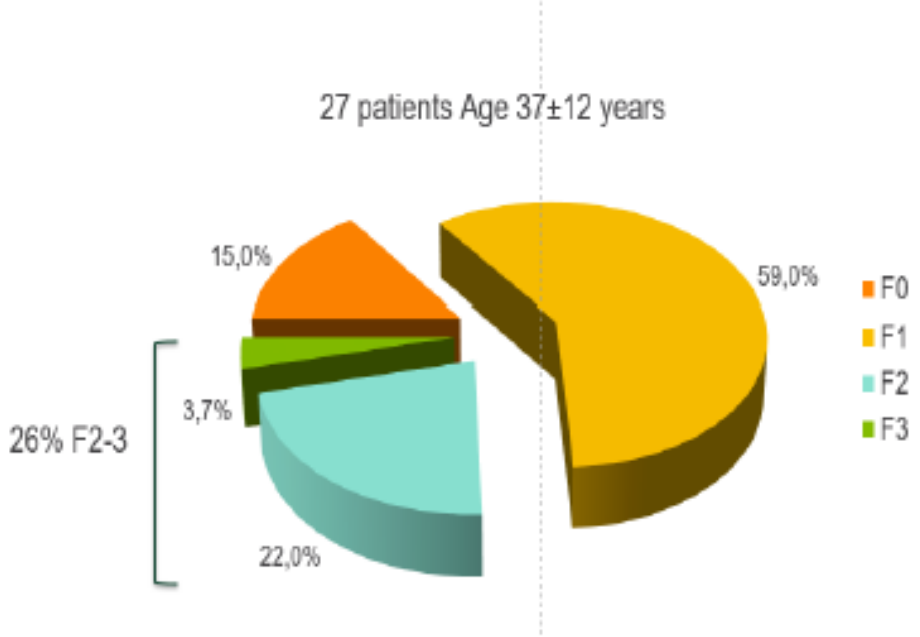
* HBV-DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis
** Persistently or intermittently; *** Treatment is indicated in some patients

EASL HBV CPG, J Hepatol 2017

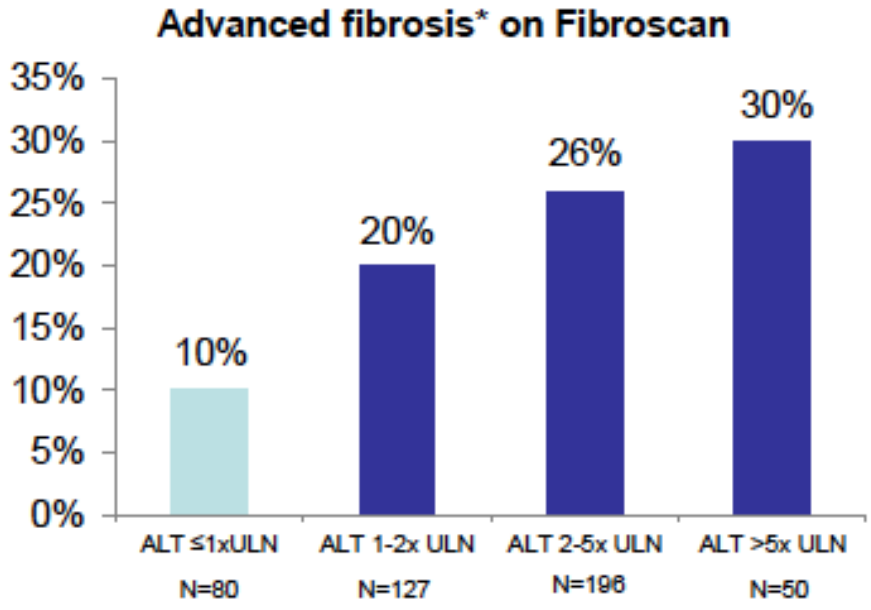
Fibrosis among HBeAg positive CHB patients with normal ALT levels (AASLD criteria) and high HBV DNA levels

Histology series in Asian-Americans with positive HBeAg, normal ALT (AASLD criteria) and high HBV DNA



Nguyen MH, et al. Am J Gastroenterol 2009;104:2206-13

Advanced fibrosis by Fibroscan in HBeAg pos patients with normal ALT (AASLD criteria)

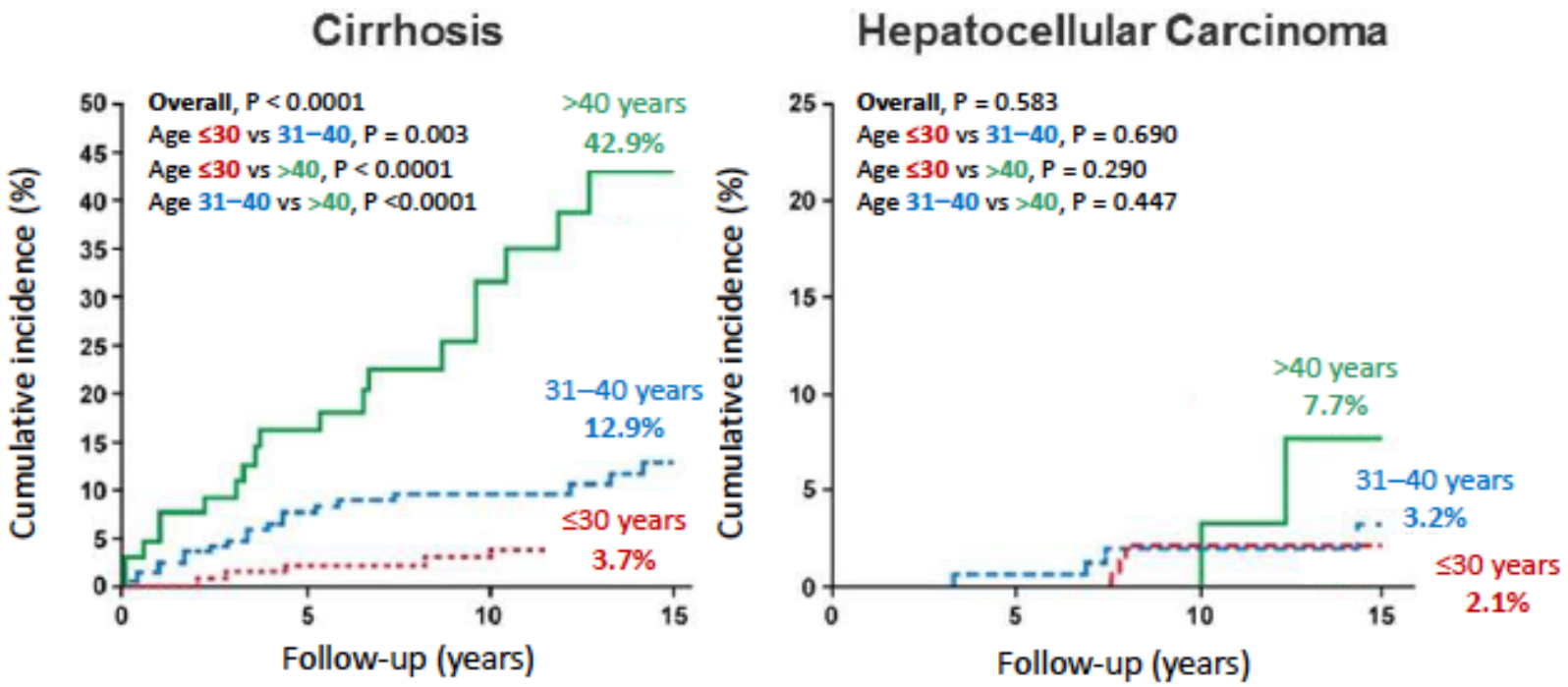


*LSM >9kPa (normal ALT) or >12 kPa (elevated ALT)

Wong GL, et al. Clin Gastroenterol Hepatol 2009;7:227-233

Age at HBeAg seroconversion correlates with risk of liver complications – A Taiwan study

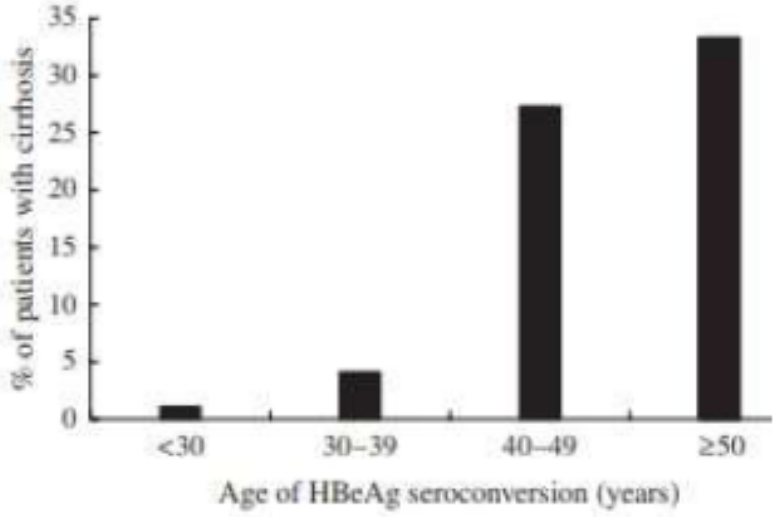
N = 483 CHB patients



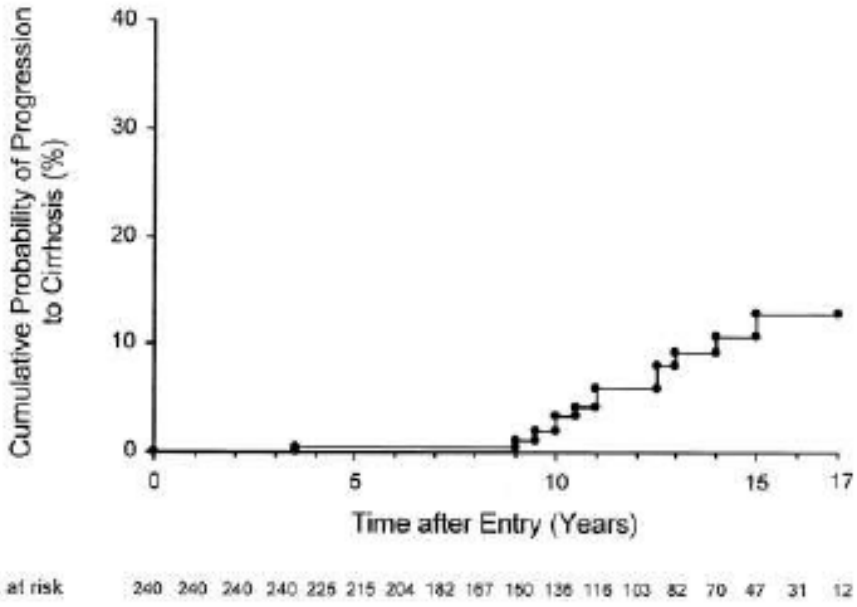
Chen YC, et al. Hepatology 2010;51:434–44

Probability of progression to cirrhosis in HBeAg positive patients with normal ALT levels at baseline

Progression to cirrhosis by age

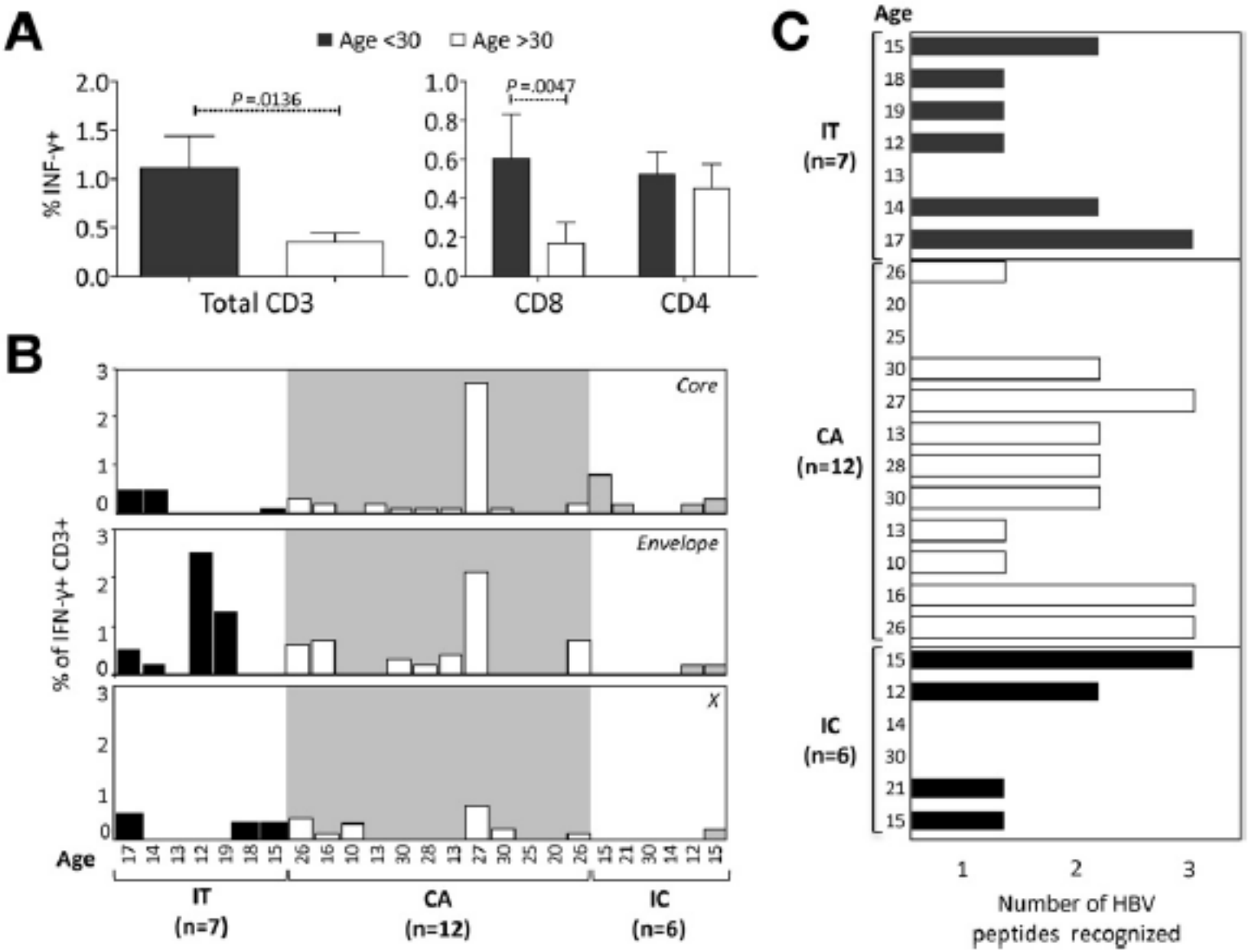


Progression to cirrhosis by time

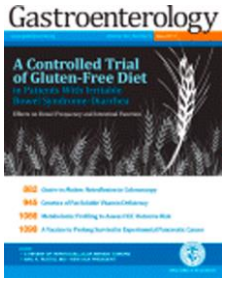


Chu CM, Liaw YF. J Viral Hepat 2007;14(3):147-52; Chu CM et al. Am J Med 2004;116:829 – 834

Evidence of immune activity in HBeAg positive chronic infection



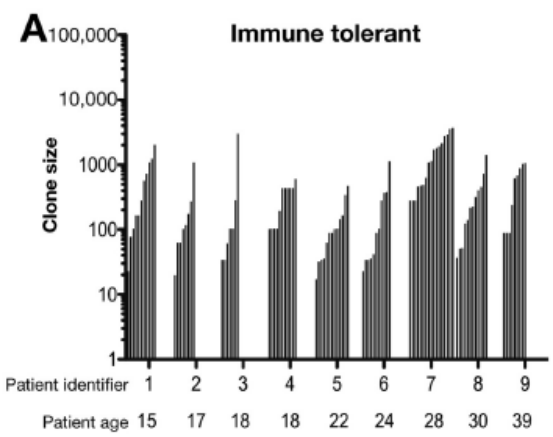
Kennedy PT et al Gastroenterology 2012

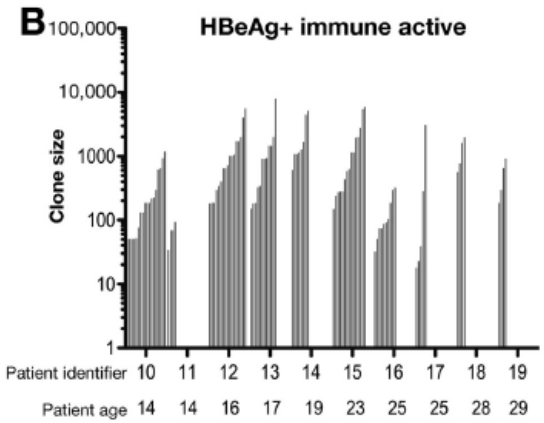


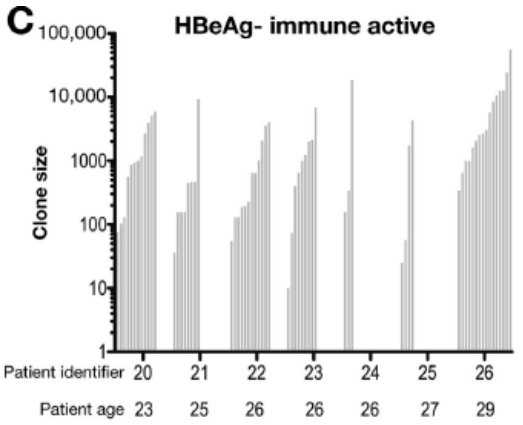
HBV DNA Integration and Clonal Hepatocyte Expansion in Chronic Hepatitis B Patients Considered Immune Tolerant

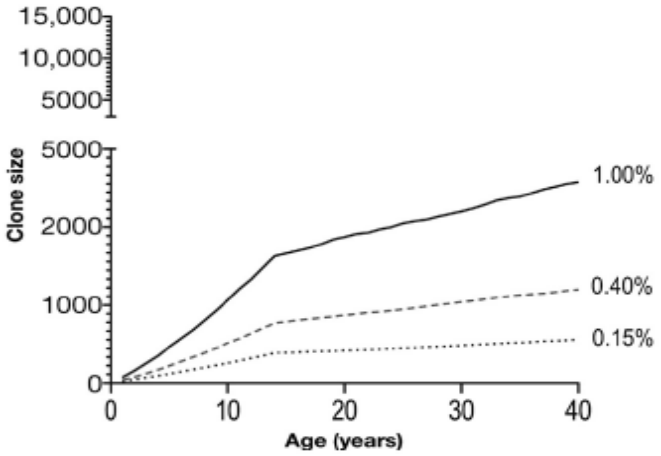
William S. Mason,[1] Upkar S. Gill,[2] Samuel Litwin,[1] Yan Zhou,[1] Suraj Peri,[1] Oltin Pop,[3] Michelle L. W. Hong,[4] Sandhia Naik,[5] Alberto Quaglia,[3] Antonio Bertoletti,[4] and Patrick T. F. Kennedy[2]

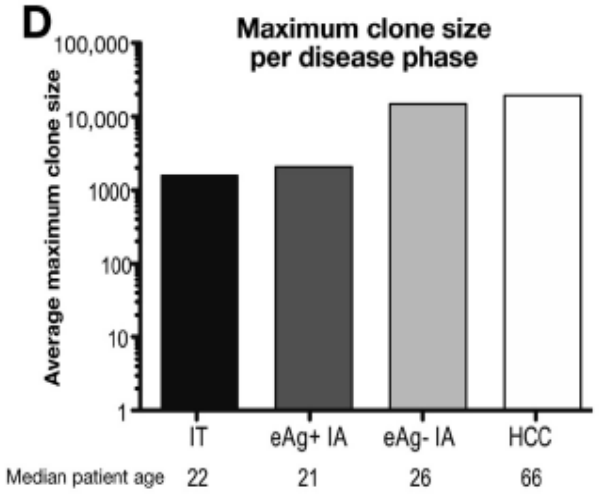
Gastroenterology 2016;151:986–998

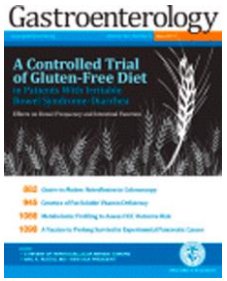












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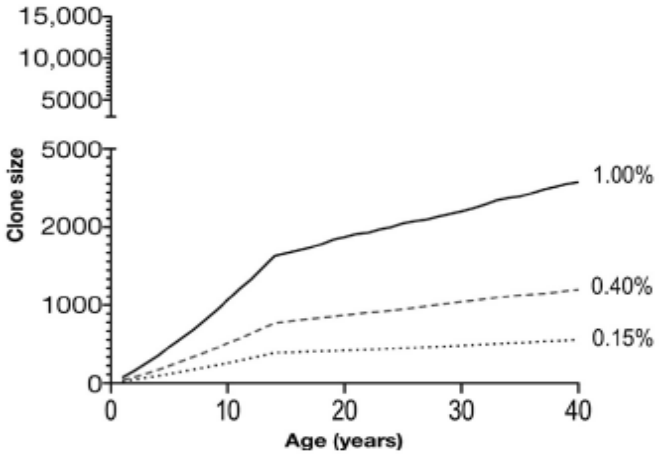
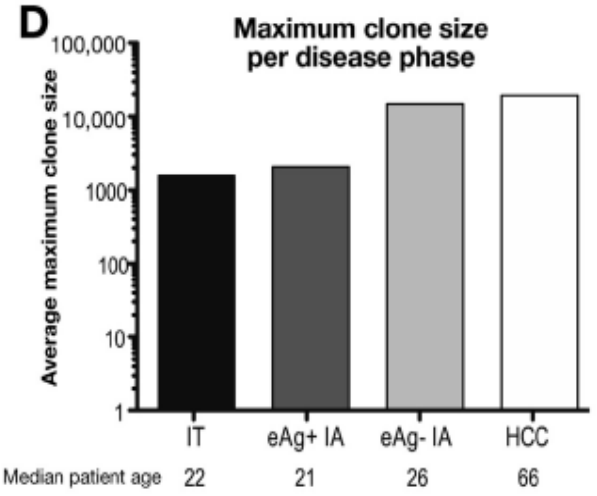
The study confirms the presence of HBV-specific T cell responses and the significant extent of HBV-DNA integration/cell mutagenesis along with clonal hepatocyte expansion in the IT phase and accross the different disease phases.

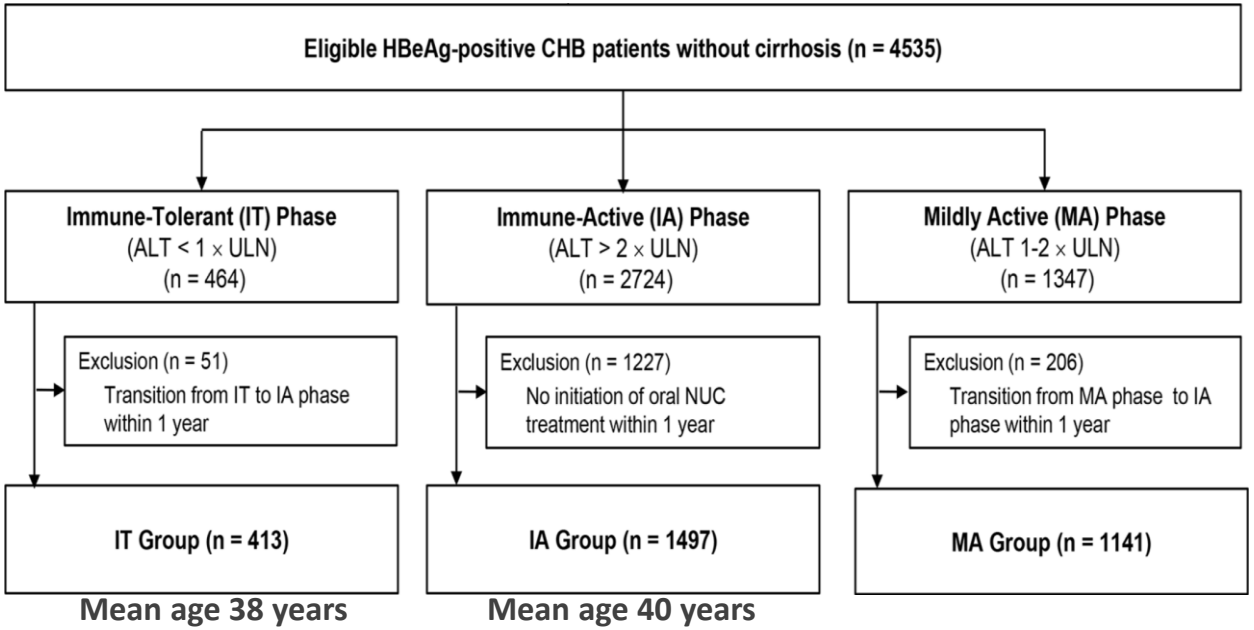
These findings challenge the notion of an IT phase without disease progression and raise questions about the timing of therapeutic intervention to minimize genetic damage to the hepatocyte population and to reduce the carcinogenesis promoting effect of increased hepatocyte tournover.

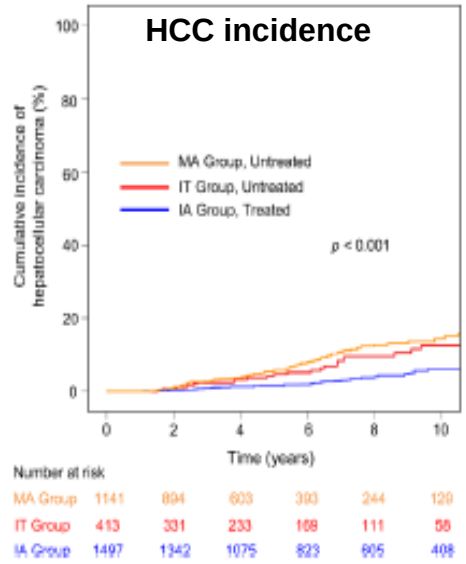
Patient age 15 17 18 18 22 24 28 30 39

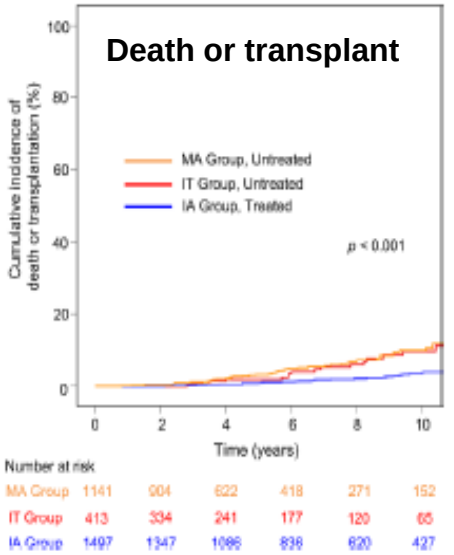




HCC risk and mortality in *immune-tolerant* HBV infection

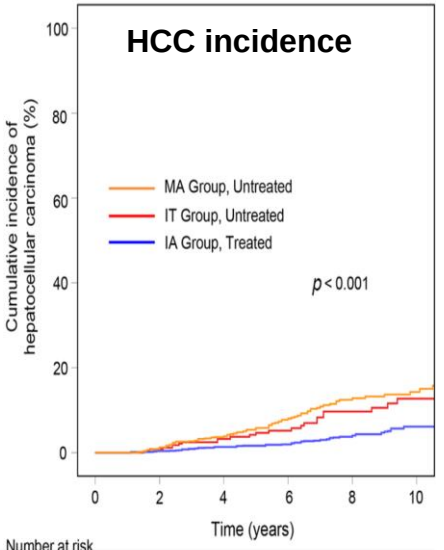


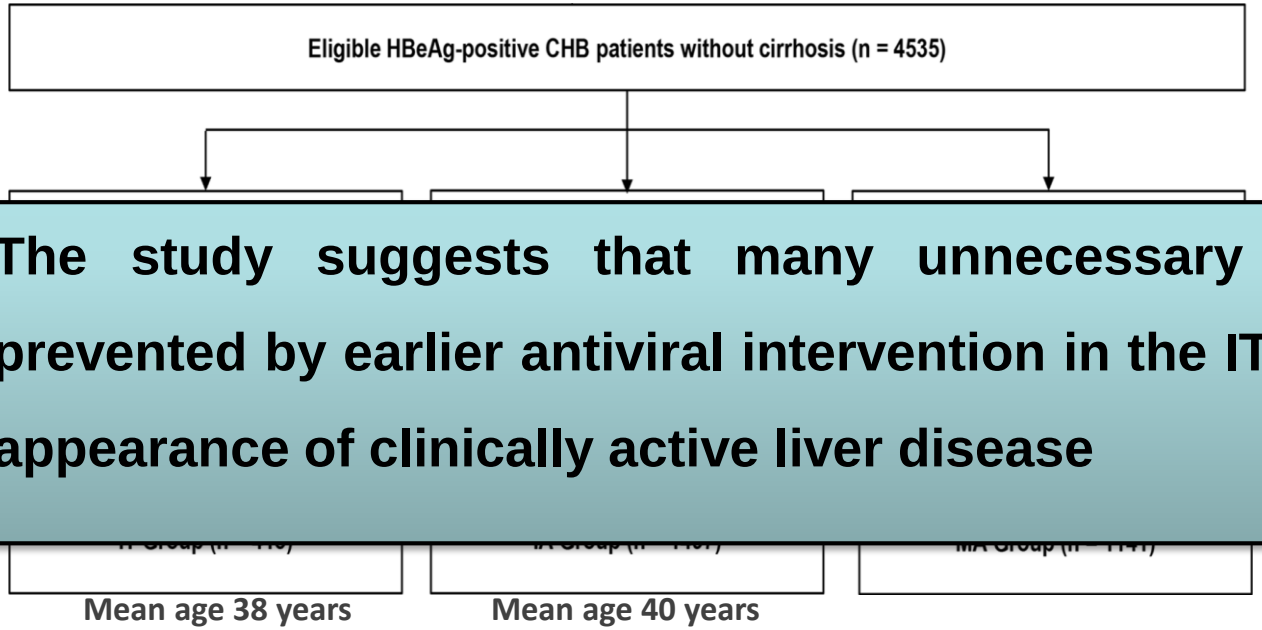




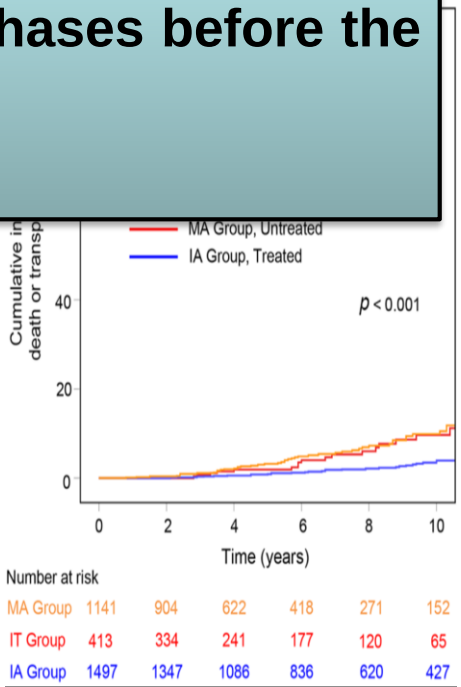
Kim et al., Gut 2018

HCC risk and mortality in *immune-tolerant* HBV infection





The study suggests that many unnecessary deaths could be prevented by earlier antiviral intervention in the IT phases before the appearance of clinically active liver disease



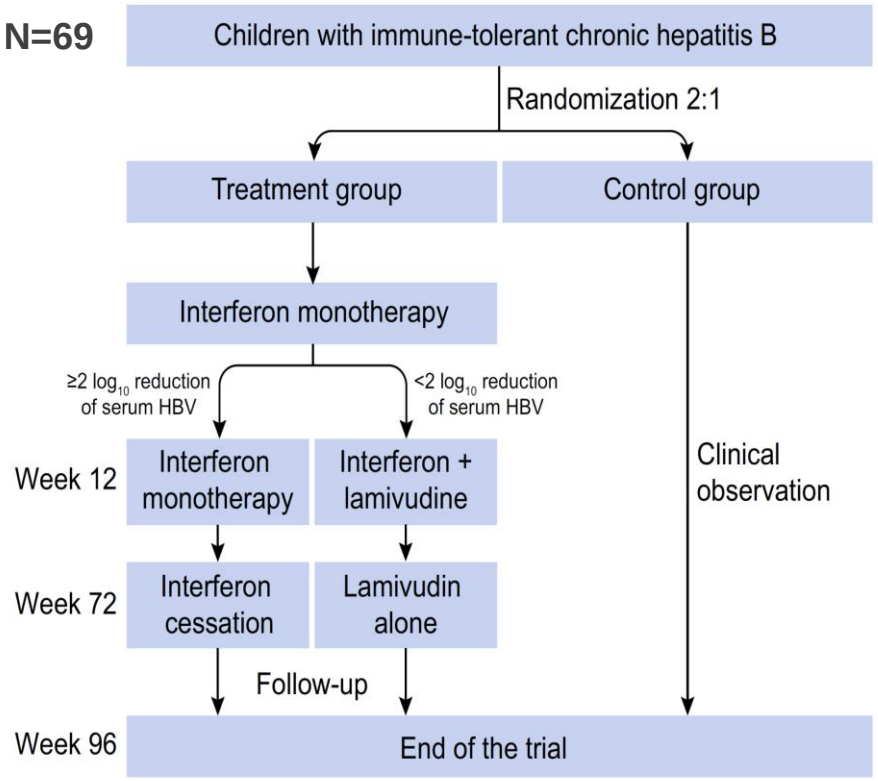
Kim et al., Gut 2018

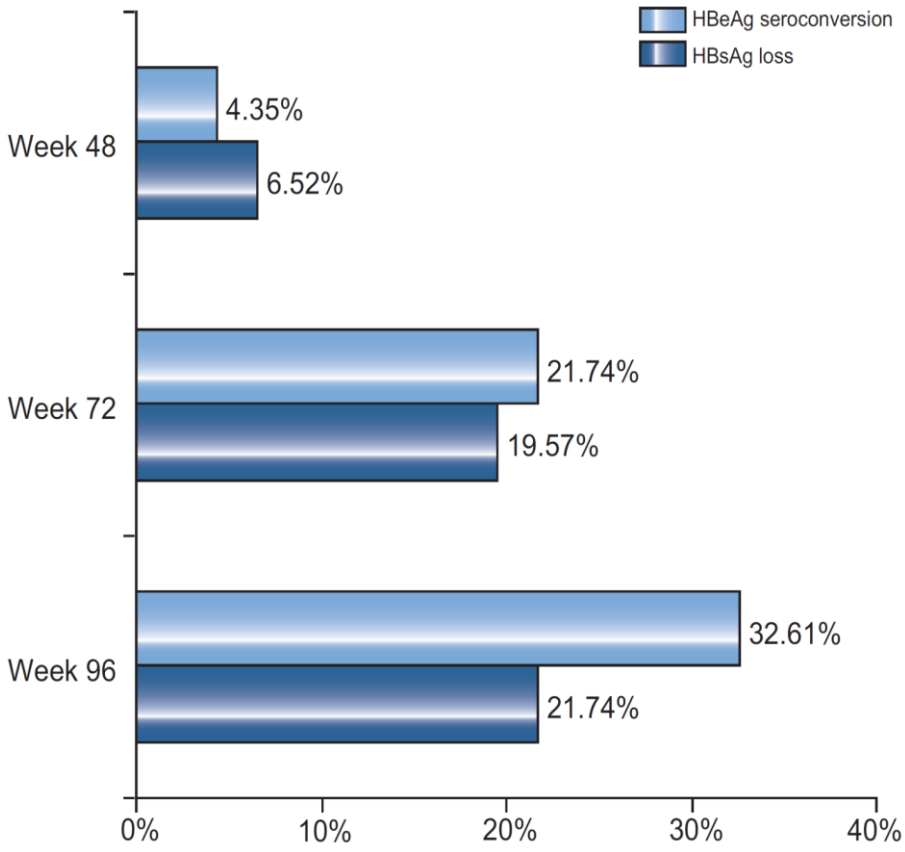
Indications for treatment

EASL 2017

- All patients with HBeAg-positive or -negative chronic hepatitis B, defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis, should be treated (Evidence level I, grade of recommendation 1).
- Patients with compensated or decompensated cirrhosis need treatment, with any detectable HBV DNA level and regardless of ALT levels (Evidence level I, grade of recommendation 1).
- Patients with HBV DNA >20,000 IU/ml and ALT >2xULN should start treatment regardless of the degree of fibrosis (Evidence level II-2, grade of recommendation 1).
- Patients with HBeAg-positive chronic HBV infection, defined by persistently normal ALT and high HBV DNA levels, may be treated if they are older than 30 years regardless of the severity of liver histological lesions (Evidence level III, grade of recommendation 2).
- Patients with HBeAg-positive or HBeAg-negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations can be treated even if typical treatment indications are not fulfilled (Evidence level III, grade of recommendation 2).

Early treatment in the HBeAg-positive chronic infection (immune-tolerant) phase?





HBV-DNA negative patients

55% at week 72
74% at week 96

Control Group
HBeAg seroconversion: 4.35%
HBsAg loss: 0%

Zhu S et al. J Hepatol 2018

Discontinuation of NUC therapy

- After HBsAg loss / anti-HBs seroconversion
- Before HBsAg loss

Discontinuation of NUC therapy

- After HBsAg loss /anti-HBs seroconversion
- Before HBsAg loss

NA discontinuation

Recommendations:

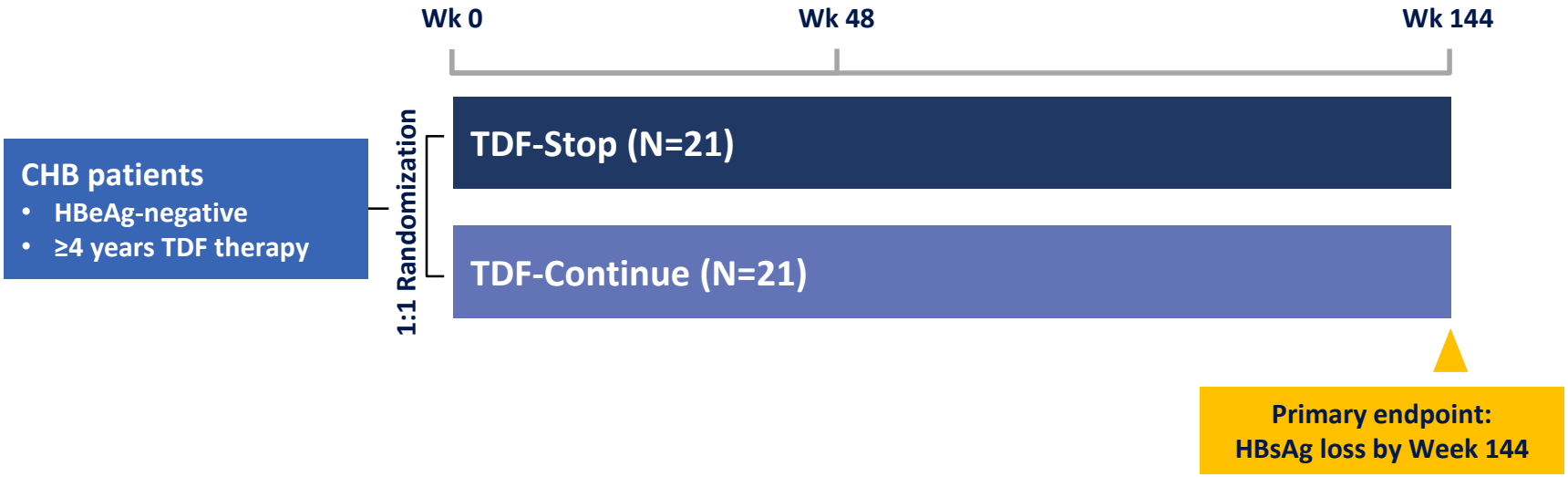
1) NAs **should be discontinued after confirmed HBsAg loss**, with or without anti-HBs seroconversion. (Evidence level II-2, grade of recommendation 1).

2) 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)

3) Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term (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)

EASL 2017 CPG HBV, J Hepatol 2017

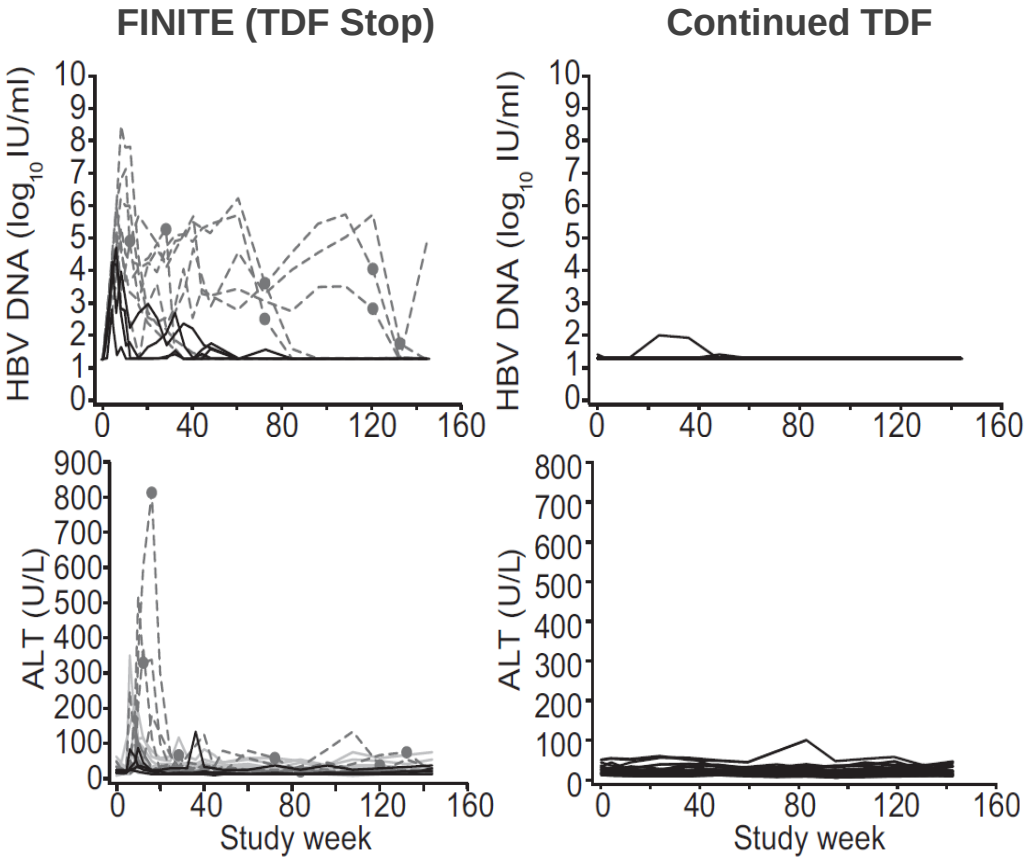
FINITE treatment duration for HBeAg negative chronic Hepatitis B? The first prospective randomized trial (FINITE study)



- Open-label, multicenter, randomized, controlled trial
- HBeAg-negative at TDF initiation and randomization
- HBV DNA <400 copies/mL for ≥3.5 years before randomization
- No cirrhosis (Fibroscan 10 kPa), normal ALT, HBeAg-, anti-HBe+, HBsAg+
- No history of decompensated liver disease

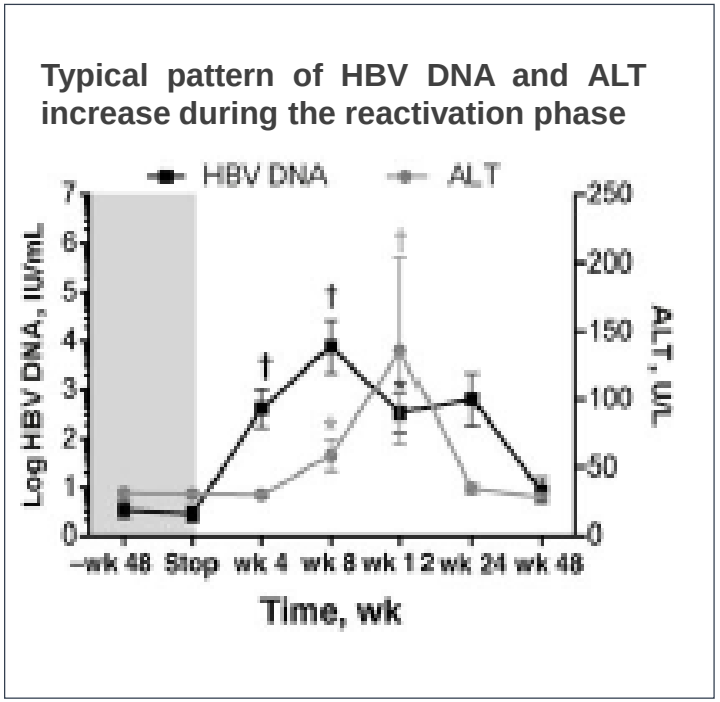
Berg T et al. J Hepatol 2017, 67(5):918-924

ALT and HBV DNA after stopping NAs in the FINITE study



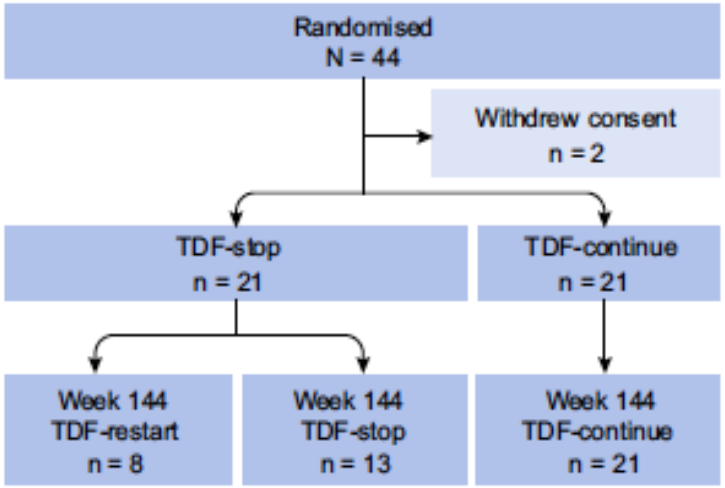
Week 144
69% HBV-DNA < 2,000 IU/ml
47% HBV-DNA < 29 IU/ml

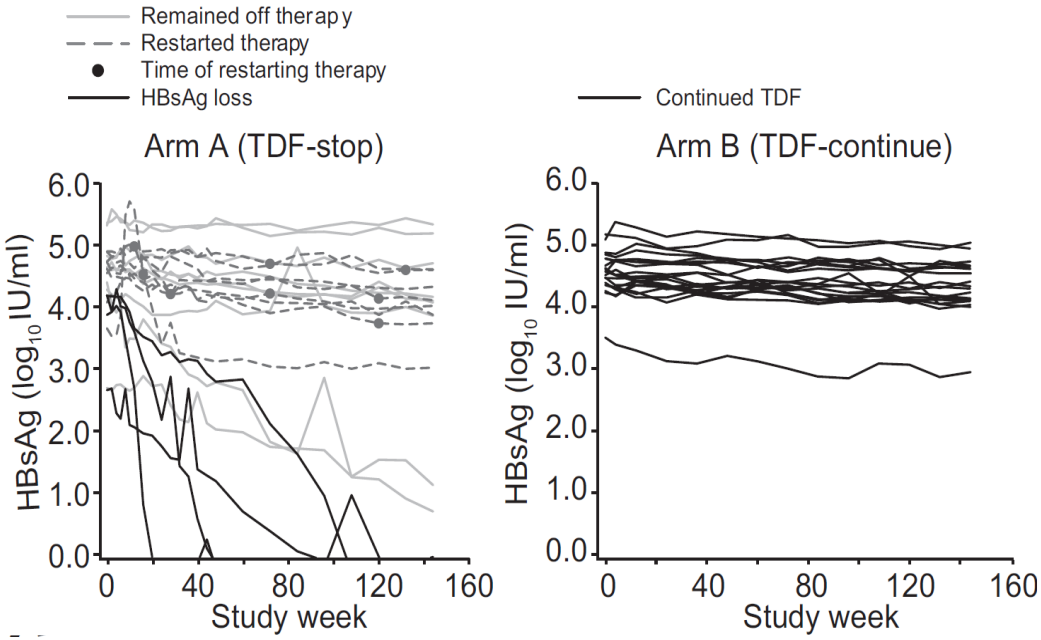
Berg T et al. J Hepatol 2017, 67(5):918-924



Höner zu Siederdissen et al.
J Infect Dis 2016; 214: 1492

FINITE treatment duration for HBeAg negative CHB
The first prospective randomized trial (FINITE study)





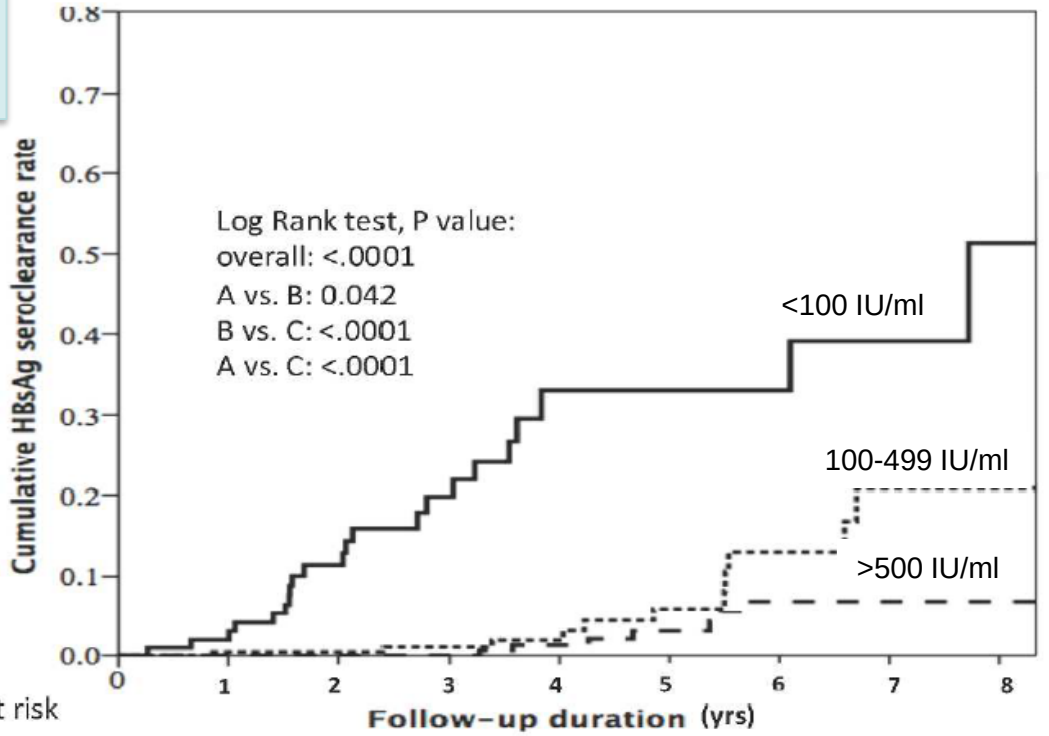
- **62% remained without treatment 3 years**
- **19% lost HBsAg**

Berg T et al. J Hepatol 2017, 67(5):918-924

NUC discontinuation before HBsAg loss in HBeAg negative CHB from Taiwan

Probability of off-therapy HBsAg loss according to HBsAg levels at EOT

HBsAg loss
1.78% a year after suspension
0.15% a year under therapy



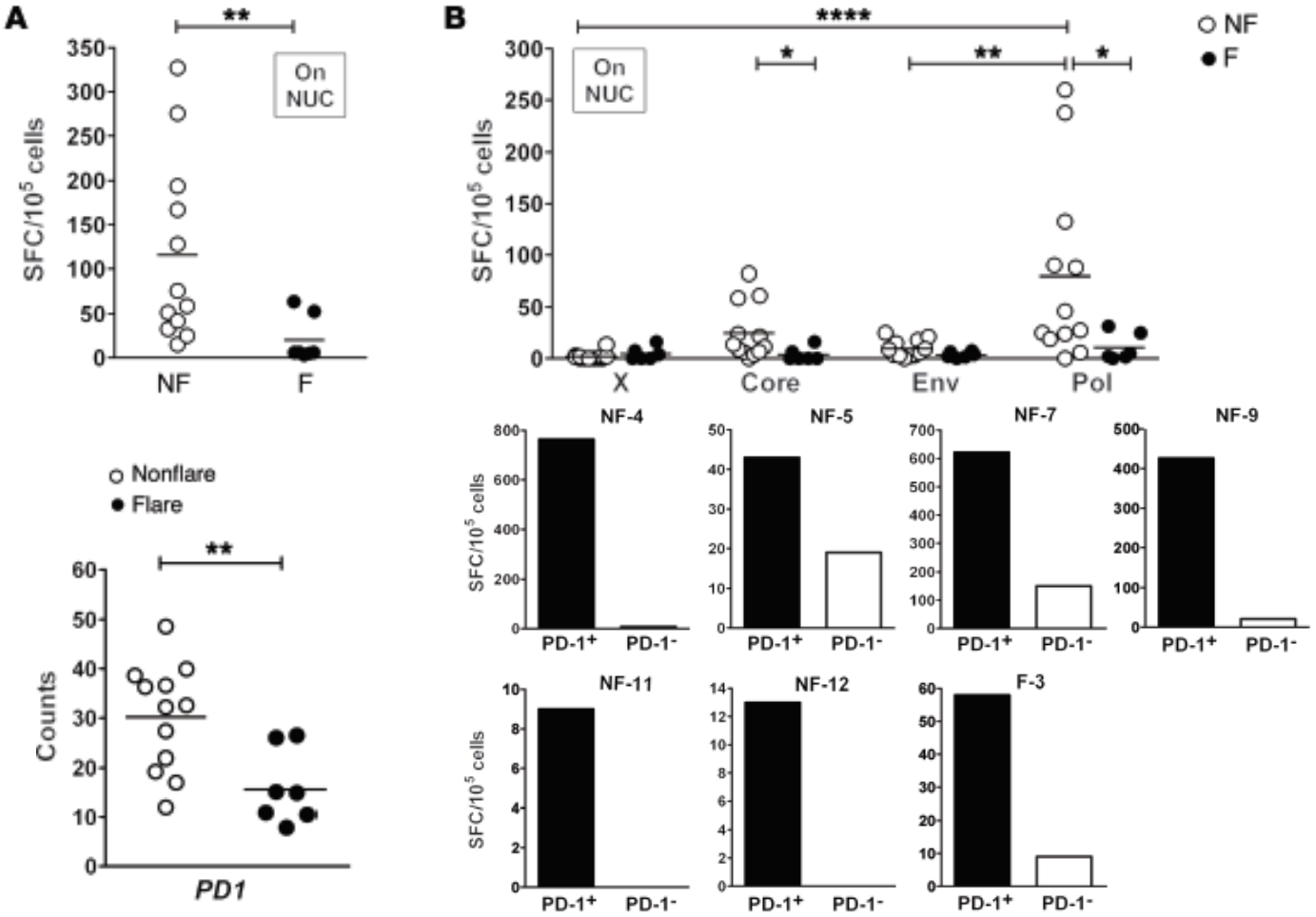
Patient at risk

EOT HBsAg (IU/ml)									
>=500	303	92	61	39	17	14	12	8	4
100-499	274	232	185	129	86	52	30	18	8
<100	114	92	61	39	17	13	12	8	4

Jeng WJ et al, Hepatology 2018

Hepatitis B virus–specific T cells associate with viral control upon nucleos(t)ide-analogue therapy discontinuation

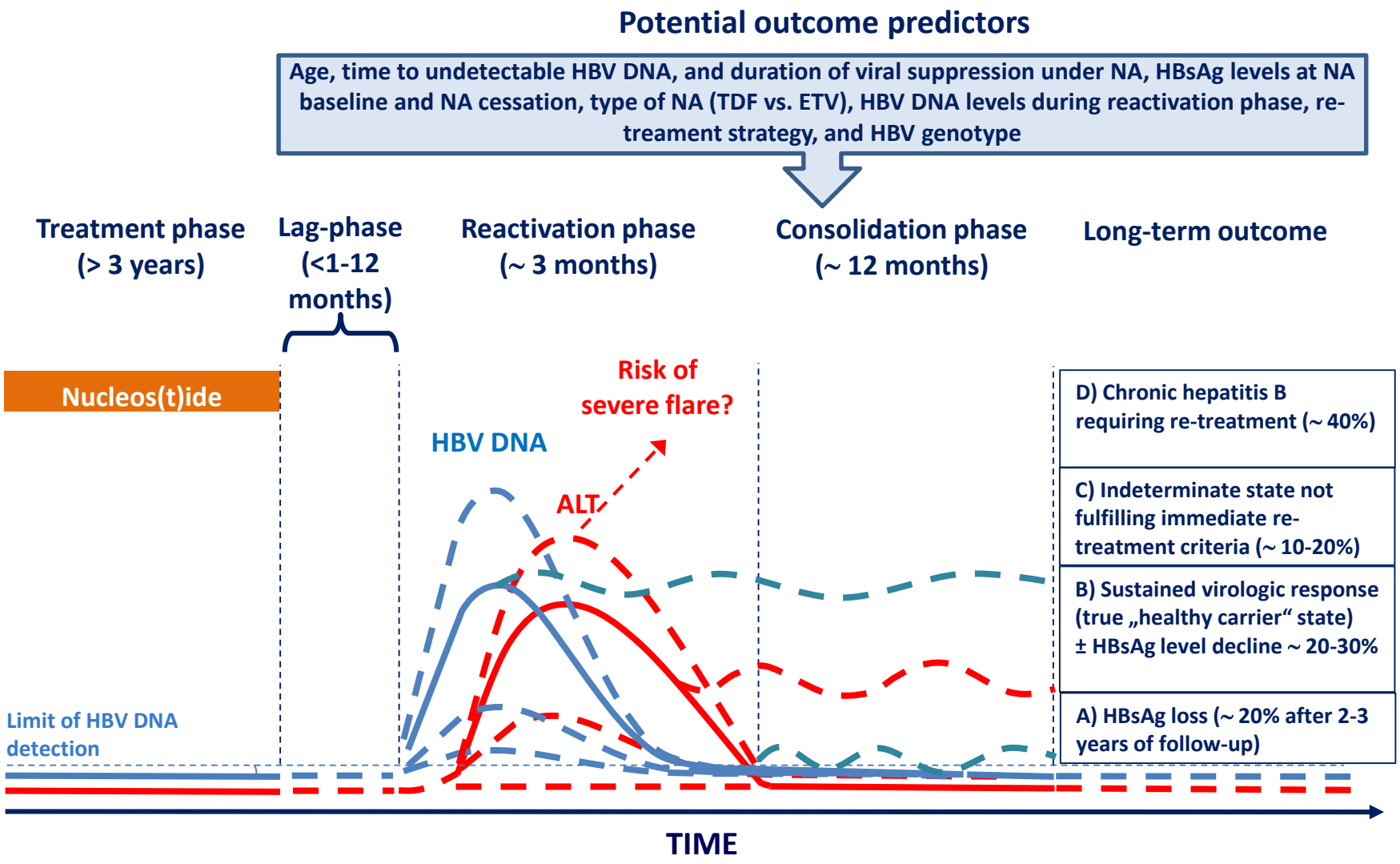
Laura Rivino,[1] Nina Le Bert,[1,2] Upkar S. Gill,[1,2] Kamini Kunasegaran,[1] Yang Cheng,[4] Damien Z.M. Tan,[2] Etienne Becht,[4] Navjyot K. Hansi,[2] Graham R. Foster,[3] Tung-Hung Su,[5] Tai-Chung Tseng,[5] Seng Gee Lim,[6] Jia-Horng Kao,[5] Evan W. Newell,[4] Patrick T.F. Kennedy,[3] and Antonio Bertoletti[1,2,4]



Effect of NA withdrawal

Category	Type of therapy	Therapy duration	Patient number	Follow-up duration	Virologic relapse rates	Clinical relapses	Authors	Journal	HBsAg loss
HBeAg-	Entecavir	2 years	95	1 year	58%	45%	Jeng WJ et al.	Hepatology 2013	none
HBeAg-	Entecavir	3 years	184	1 year	91%	11.7%	Seto W-K et al	Gut 2015	none
HBeAg-	Adefovir	4-5 years	33	6 years	45%	45%	Hadziyannis S et al	Gastroenterology 2012	39%
HBeAg-	Lamivudine adefovir, entecavir	160 weeks	66	72 weeks	30%	10%	He D et al	BMC Infectious Diseases 2013	3%
HBeAg-	Entecavir Tenofovir	$\geq$ 4 years	57	18 months	72%		Papatheodoridis GV et al	Antivir. Ther. 2018	25%

NUC discontinuation in HBeAg negative CHB before HBsAg loss



Lampertico P and Berg T, Hepatology 2018

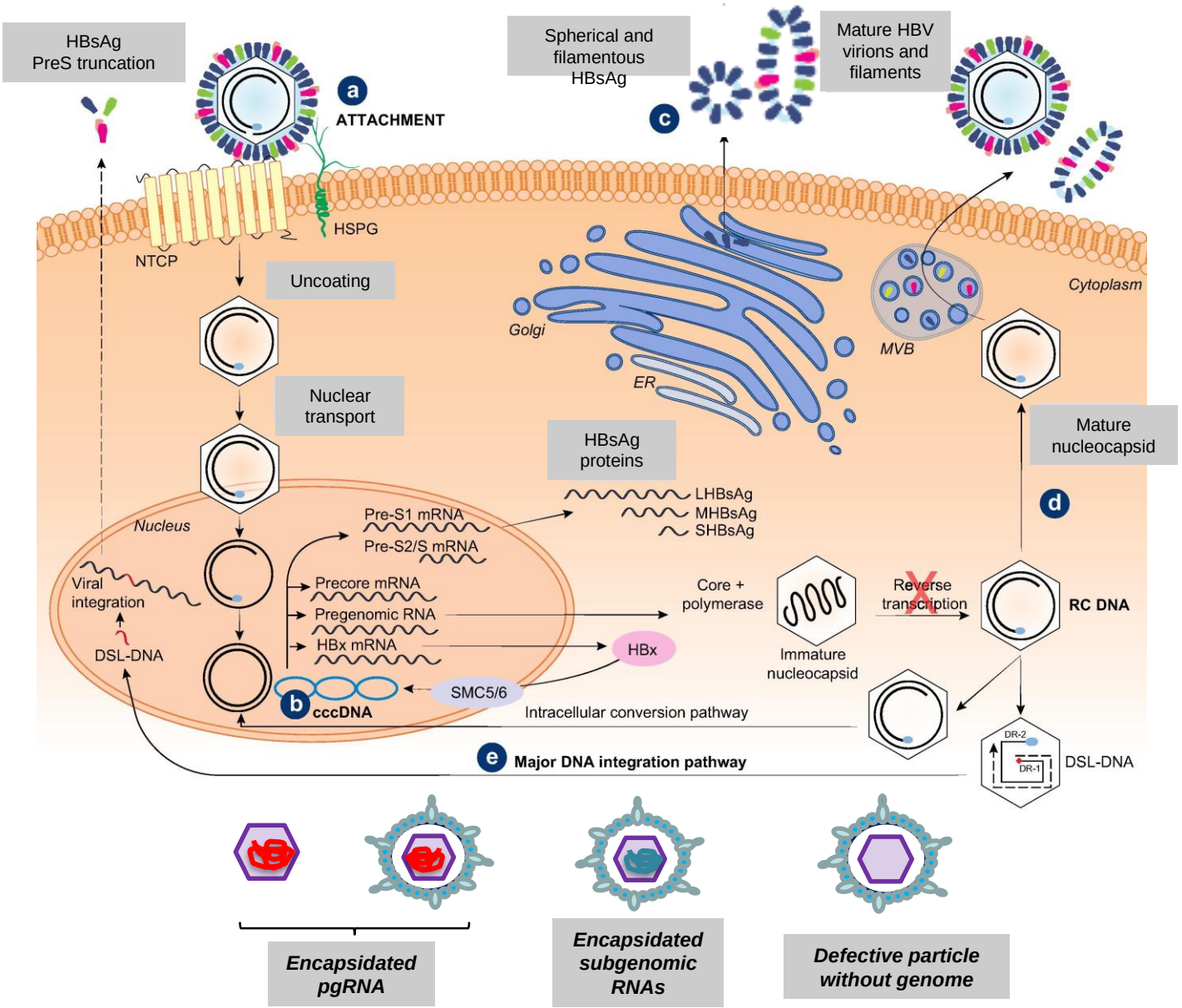
NA DISCONTINUATION IN HBe NEGATIVE CHB
TAKE-HOME MESSAGES

- NA discontinuation frequently results in a virologic/biochemical relapse that runs through different phases (lag, reactivation and consolidation phases)
- The flares observed during the reactivation phase are often transient and likely represent the trigger for a long-term HBV-specific immune control and do not need immediate interventions but close follow-up evaluations
- To guarantee a safe and effective outcome of NA treatment discontinuation, the NA re-treatment should be initiated timely enough to prevent harm for the patient, but virologic and biochemical flares should be tolerated to some extent to allow the establishment of a “functional cure“

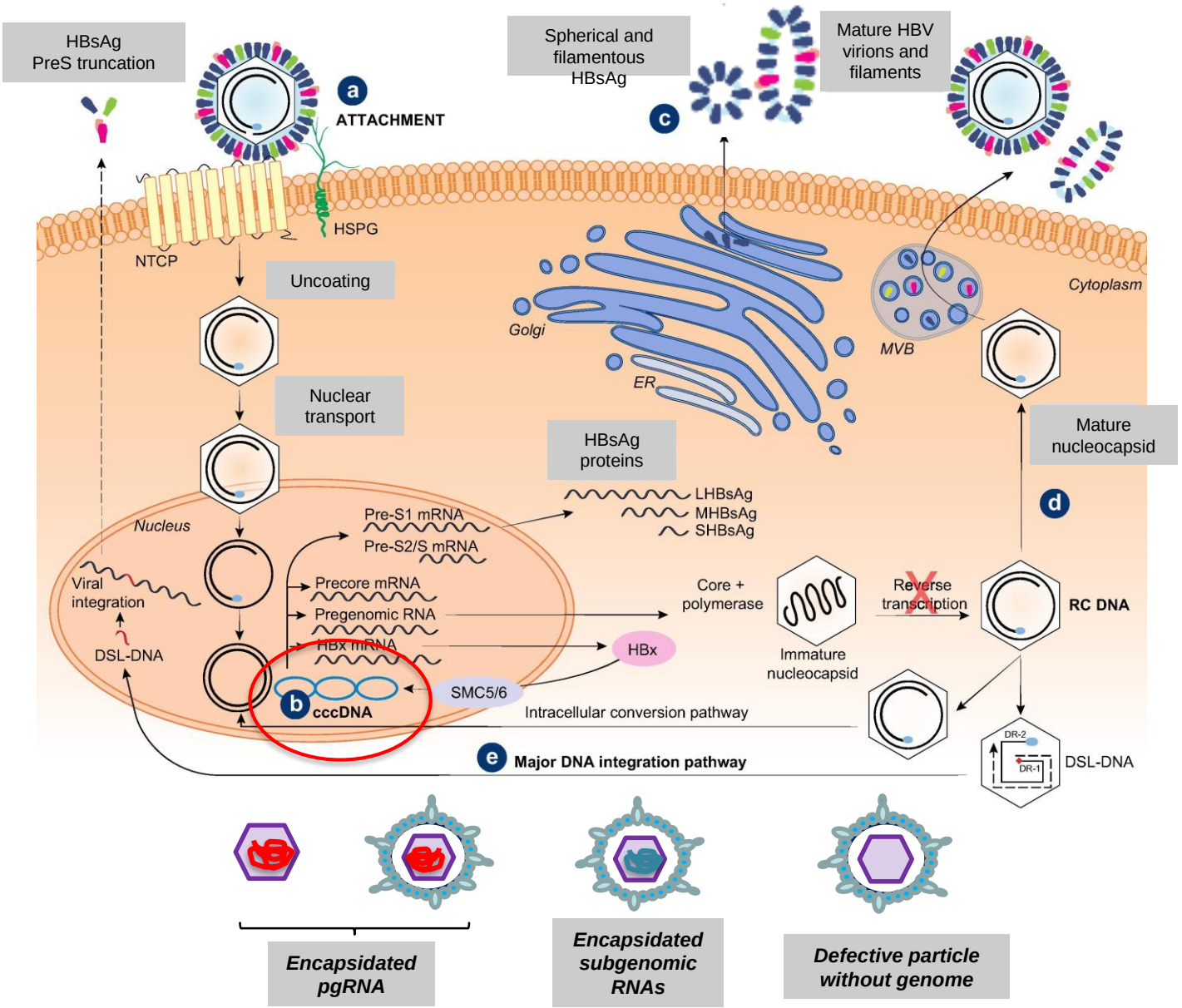
Novel diagnostic tools

Is HBsAg loss an adequate endpoint for new treatment strategies?

Potential biomarkers for assessing endpoints



Potential biomarkers for assessing endpoints



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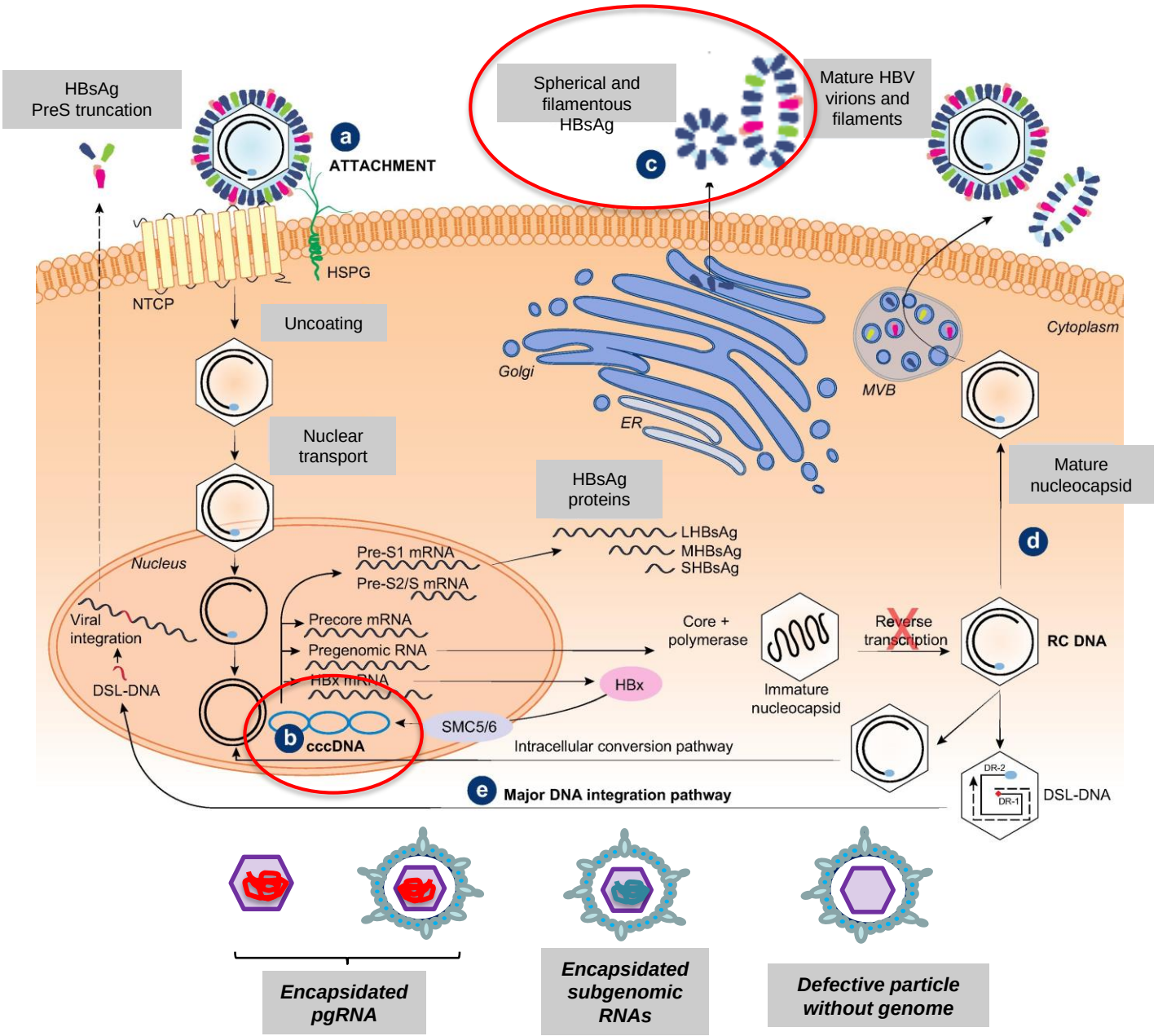

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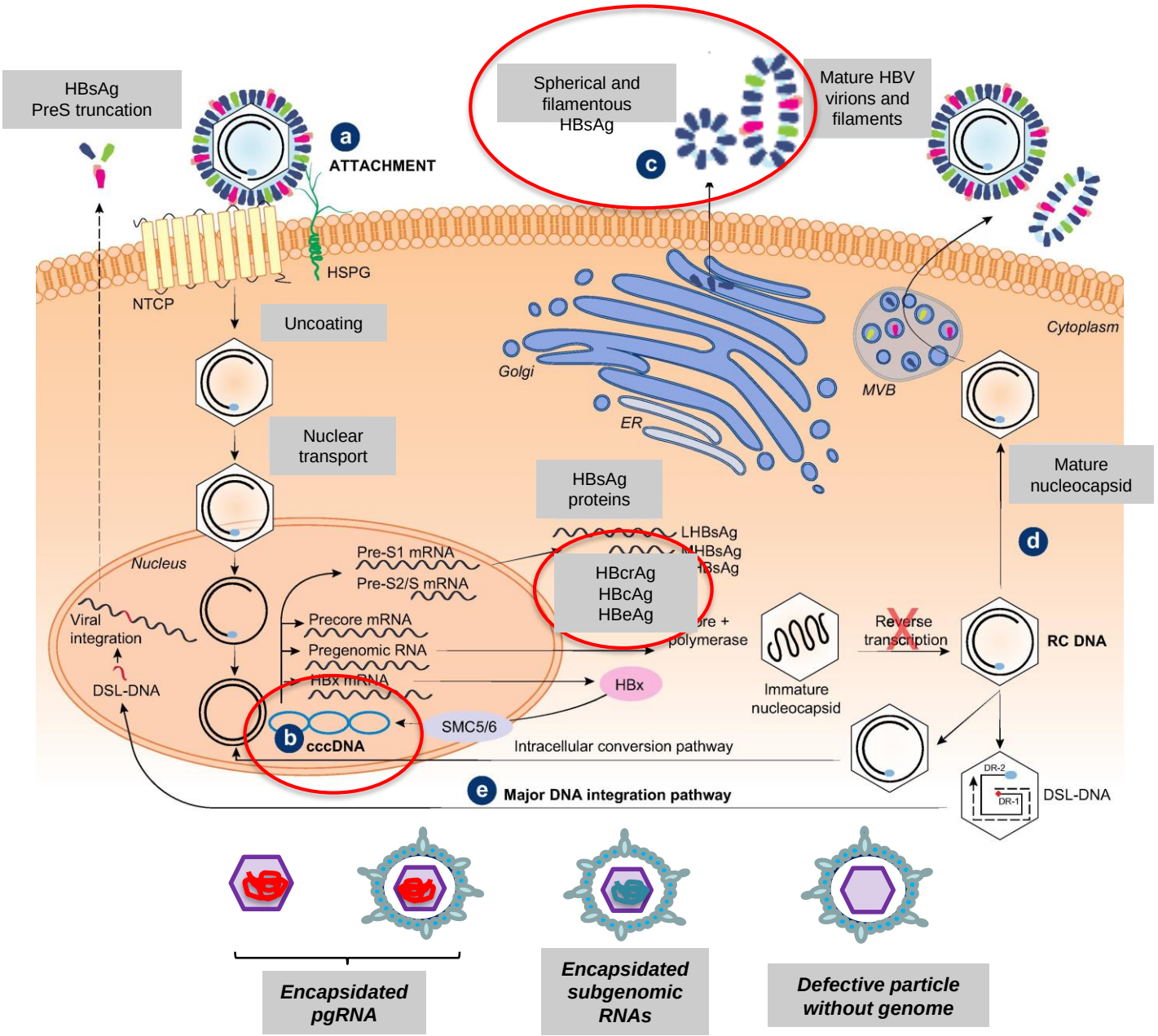

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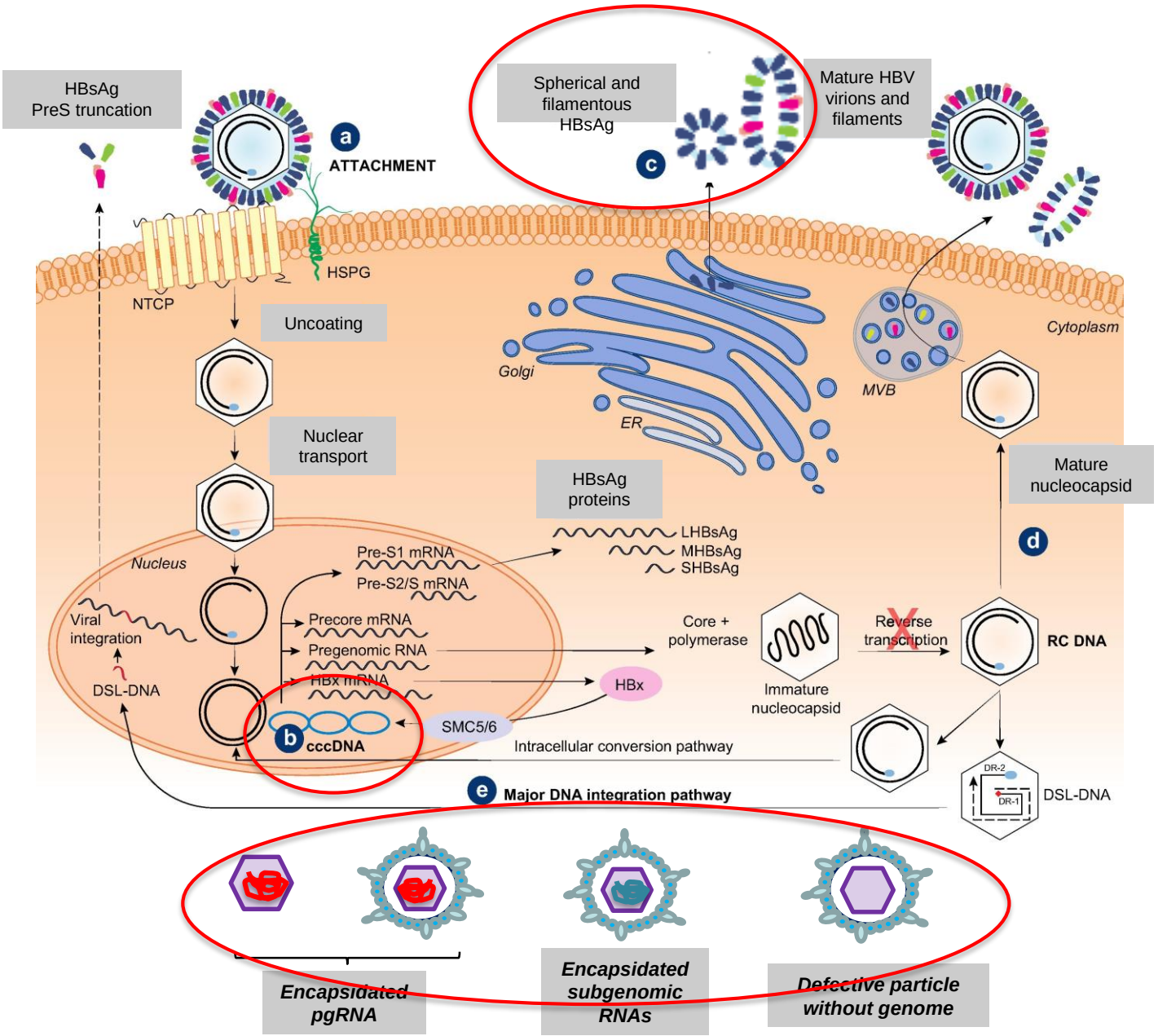
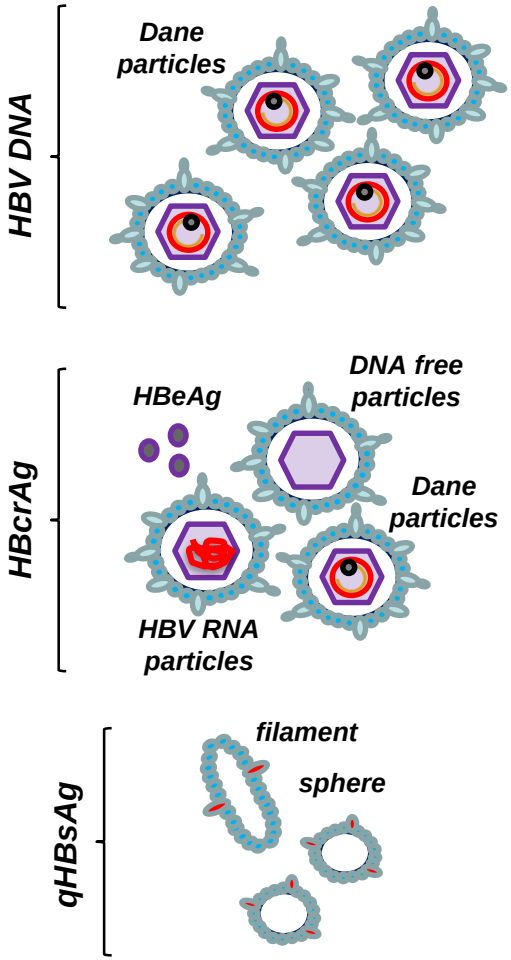
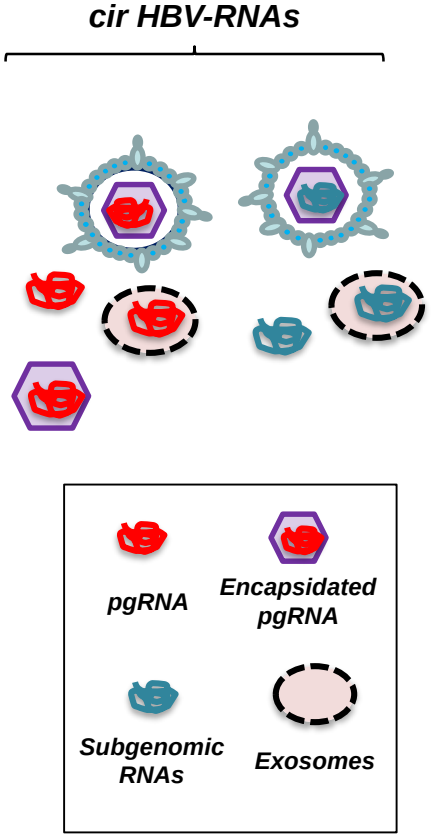
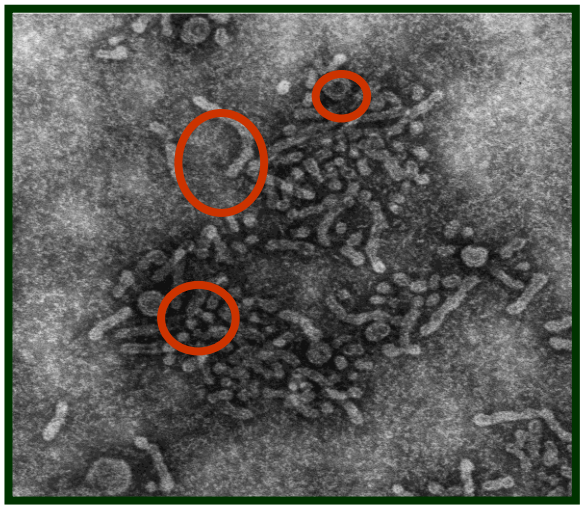


HBV serum/plasma biomarkers

Extracellular – serum / plasma







HBV DNAs

- **rc HBV DNA**
- cccDNA (??)
- integrated HBV DNA (as cfRNA)

HBV RNAs

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- subgenomic RNAs
  - 2.4 - 2.1 Kb envelope RNAs
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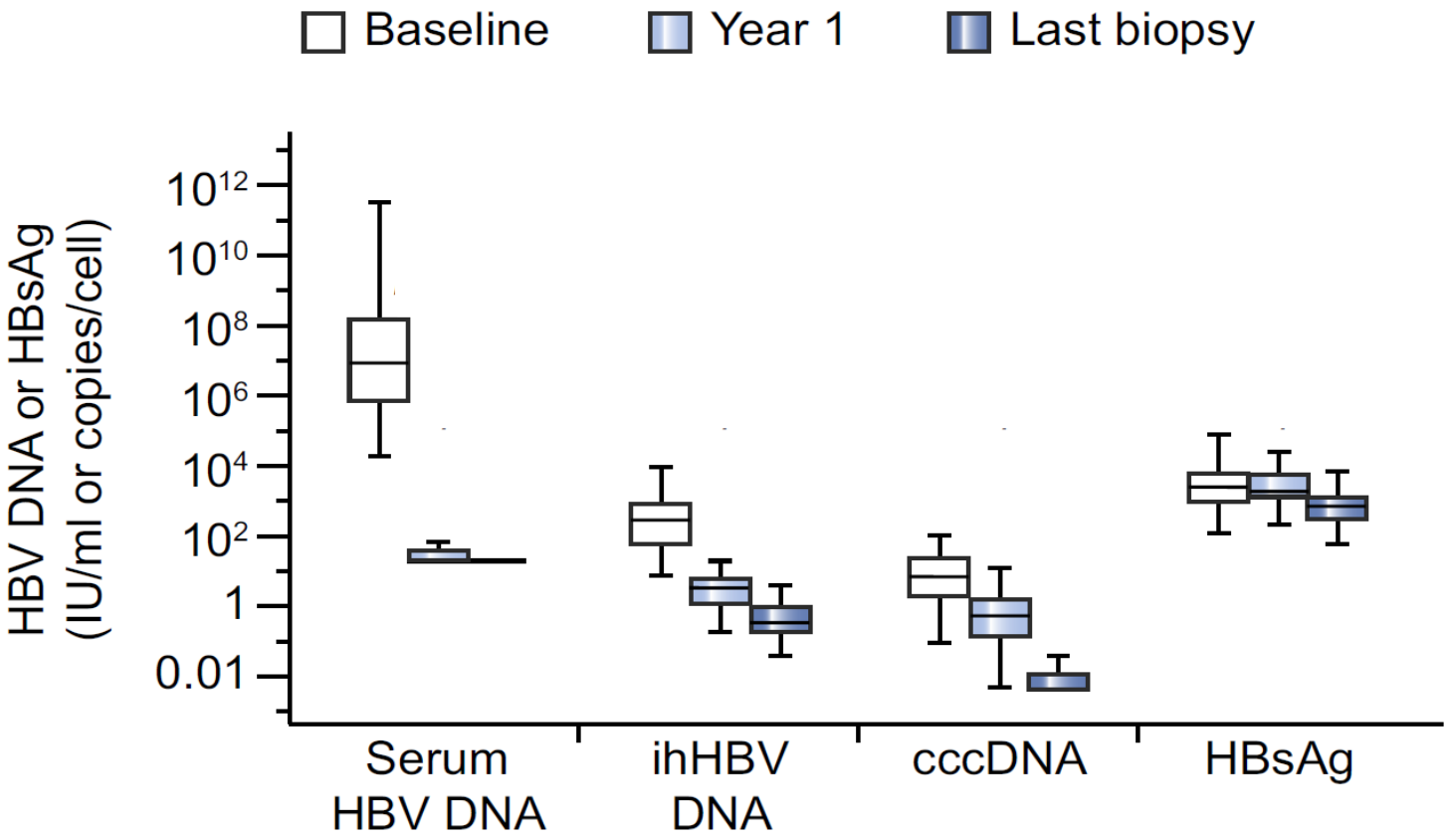
- spliced RNAs

Modified from Testoni et al, Sem Liver Dis, 2017

Effect of NUC treatment on serum and intrahepatic HBV DNA and HBsAg levels



Lai C-L et al. J Hepatol 2017; 66: 275

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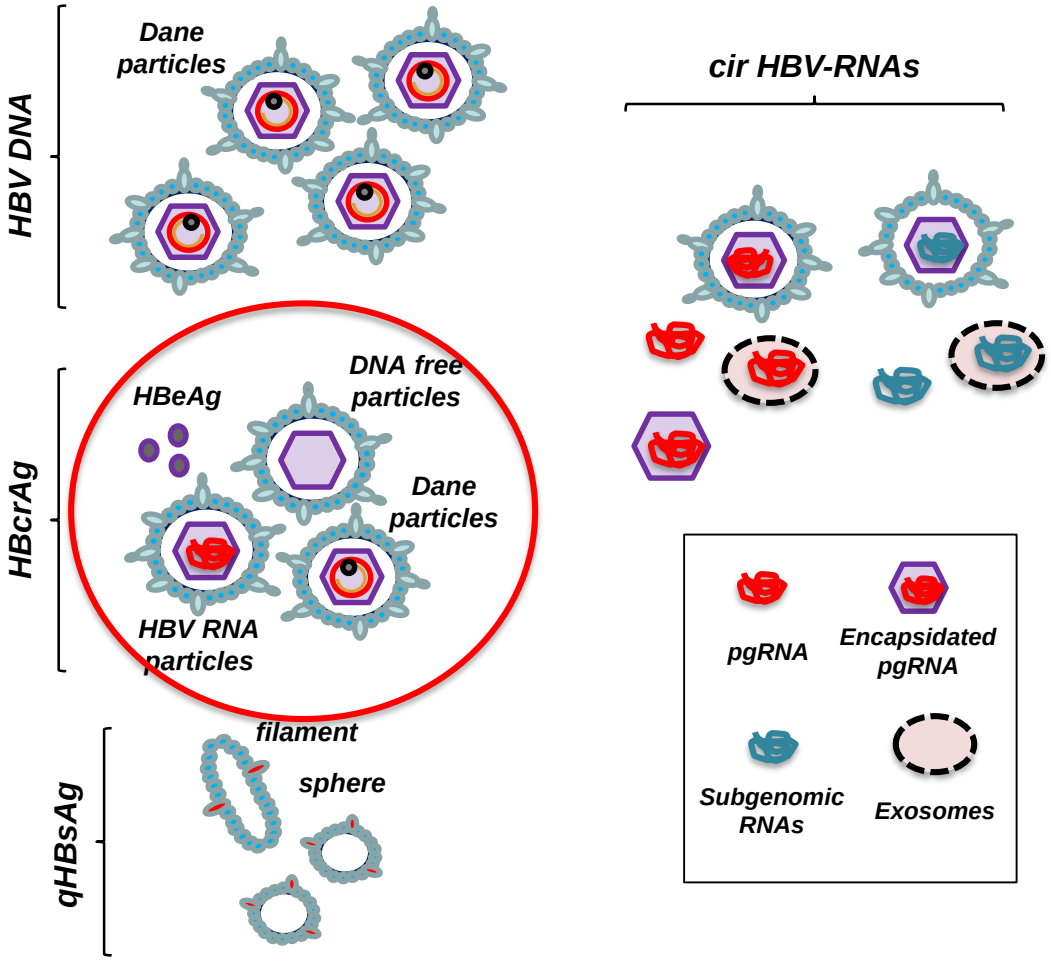

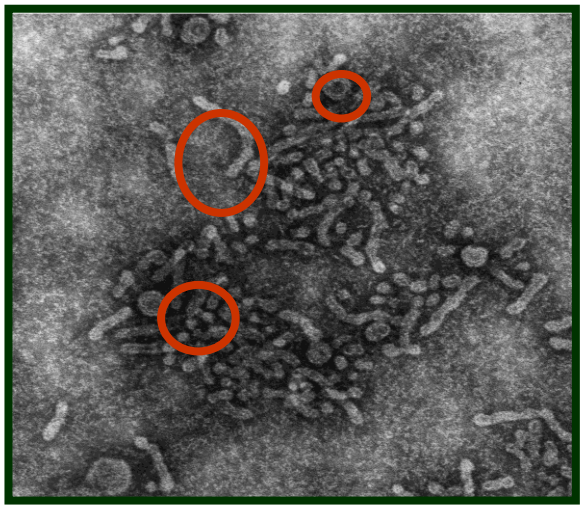

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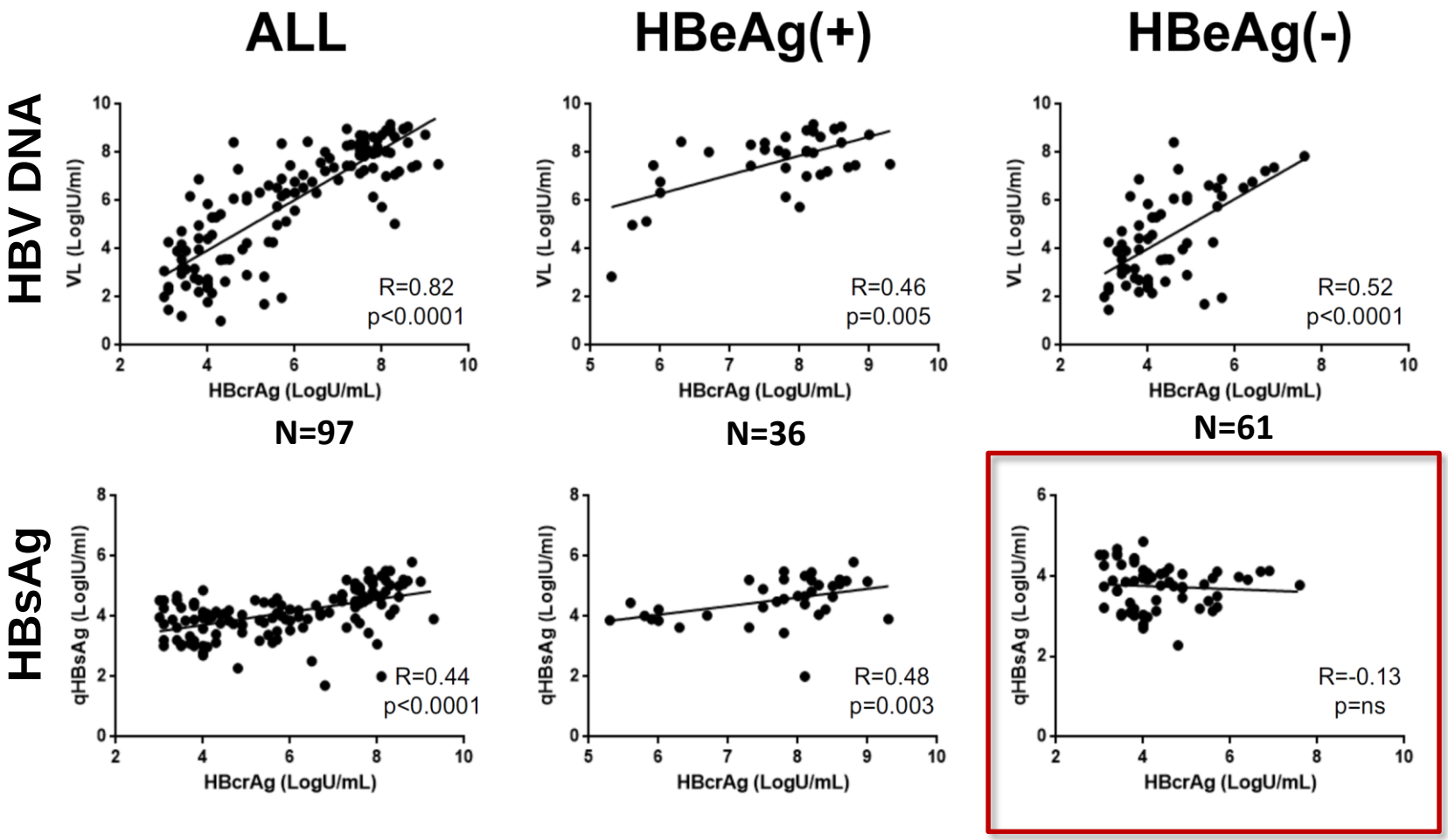
Modified from Testoni et al, Sem Liver Dis, 2017

HBcrAg correlates with cccDNA transcriptional activity

HBcrAg is a surrogate marker of both intrahepatic cccDNA and its transcriptional activity that can be useful in the evaluation of new antiviral therapies aiming at a functional cure of HBV infection either by targeting directly or indirectly the intrahepatic cccDNA pool

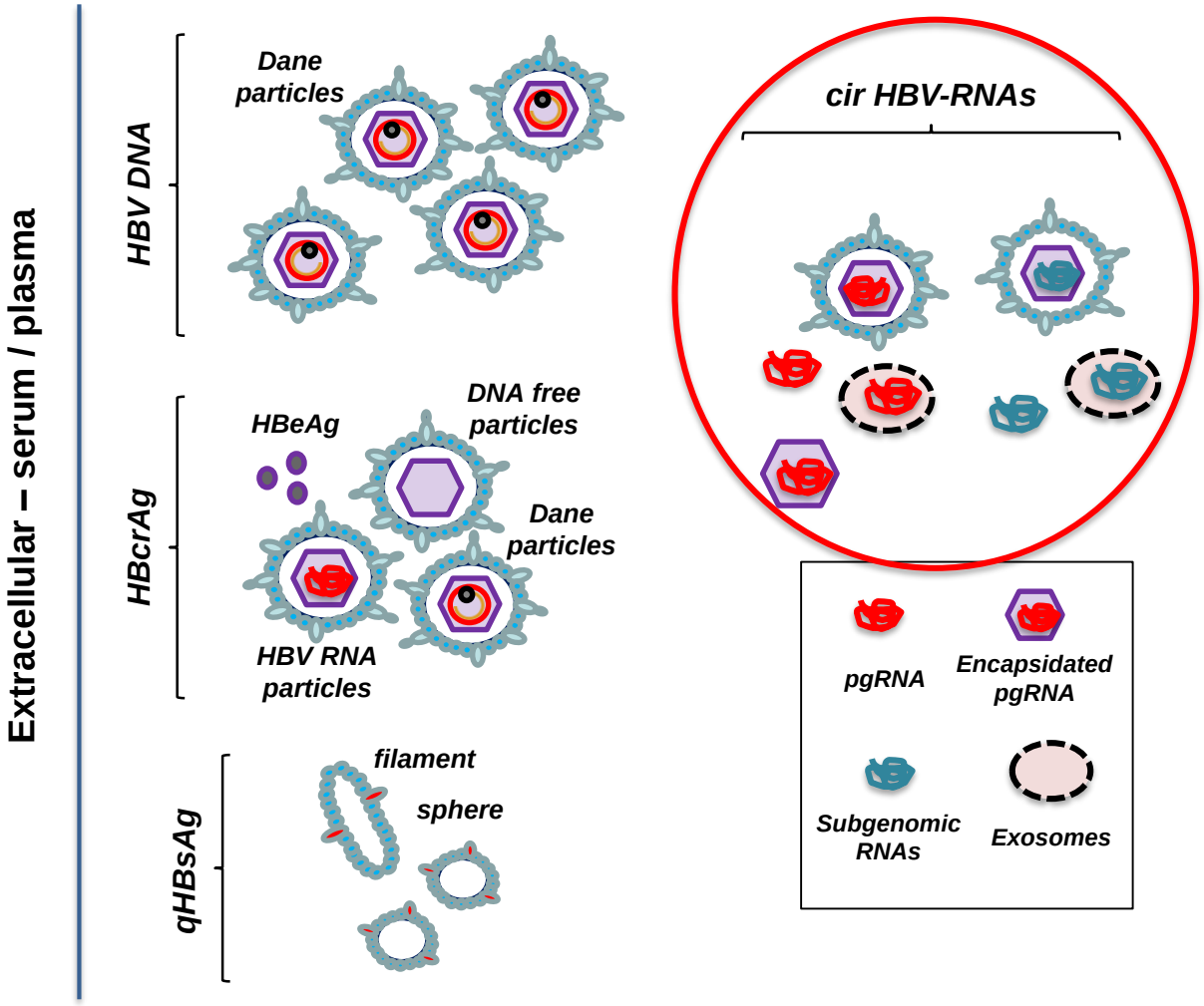
Testoni B et al. submitted; courtesy F. Zoulim

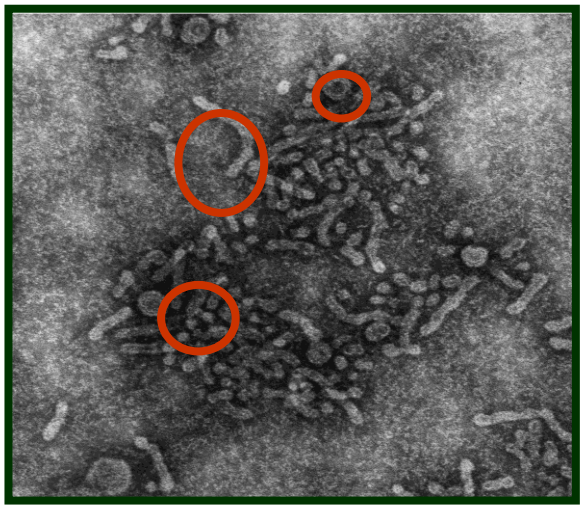
Correlation between HBcrAg, serum HBV DNA and qHBsAg levels



Testoni B et al. submitted; courtesy F. Zoulim

HBV serum/plasma biomarkers





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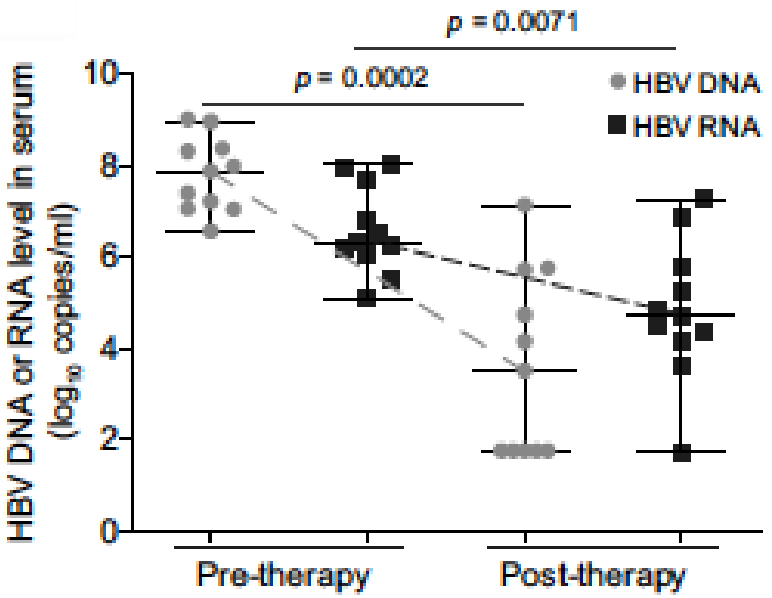
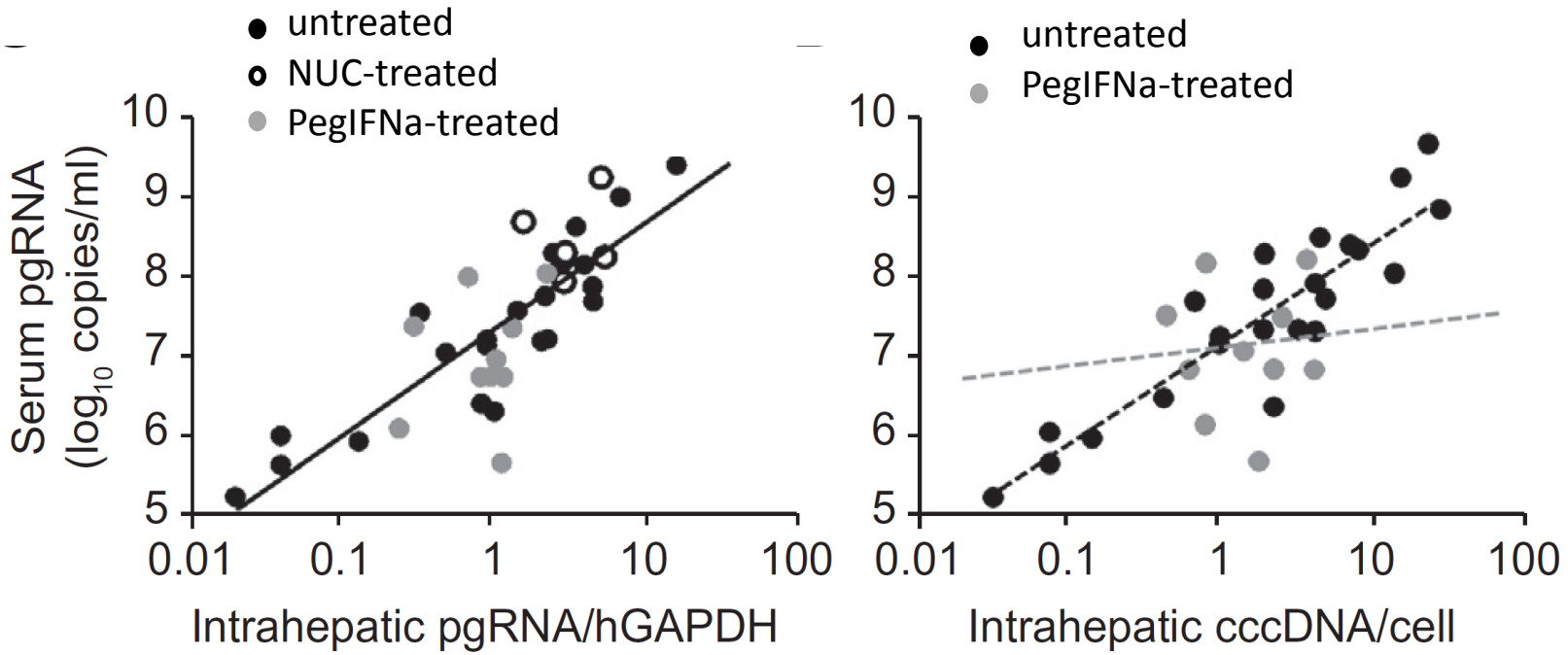
Effect of NUC therapy on serum HBV pgRNA



Wang J. et al. J Hepatol 2016; 65: 700

Serum HBV pgRNA as a clinical marker for cccDNA activity

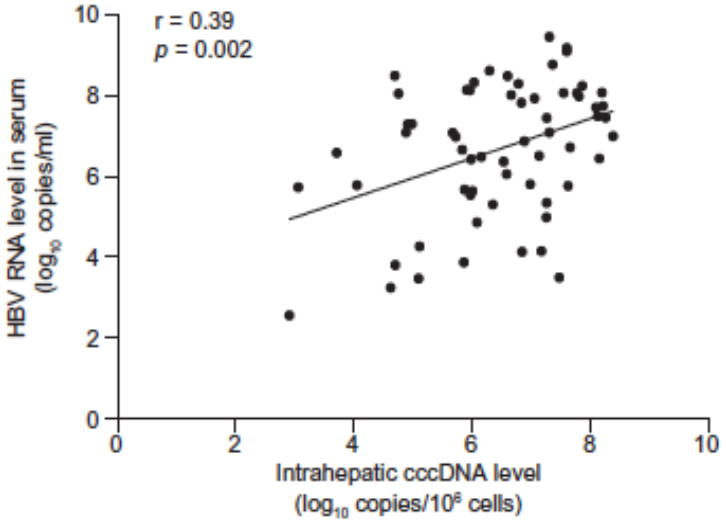


Humanized mouse model infected with HBeAg-positive wild-type HBV

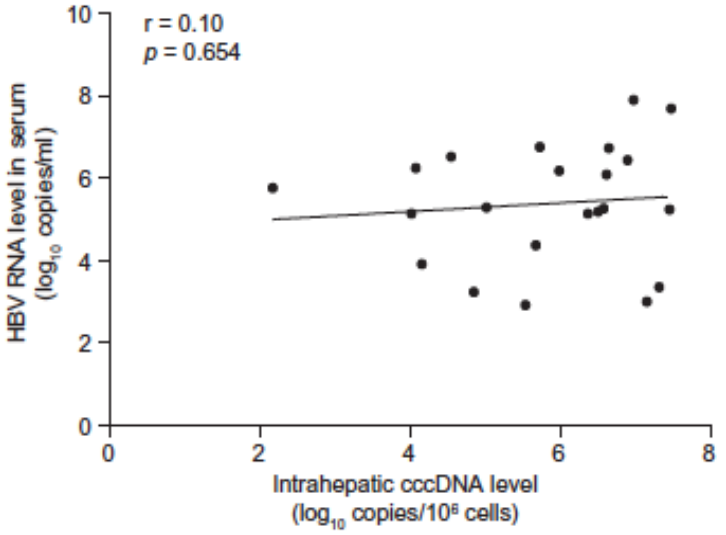
Giersch K et al. J Hepatol 2017; 66: 454

Serum HBV RNA correlations with intrahepatic cccDNA in HBeAg positive and negative patients

HBeAg positive

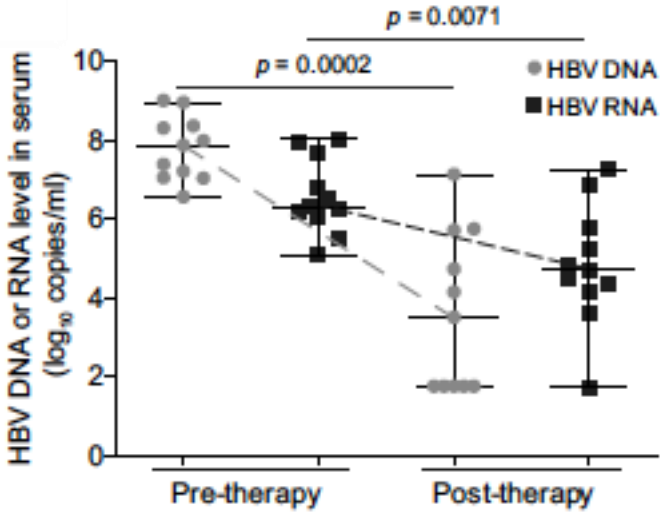


HBeAg negative



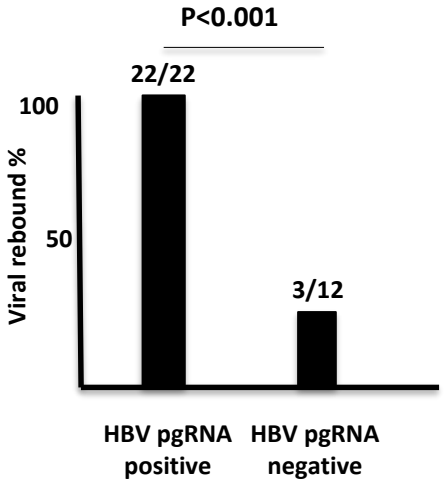
Wang J. et al. J Hepatol 2017; 66: 454

Effect of NUC therapy on serum HBV pgRNA



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.



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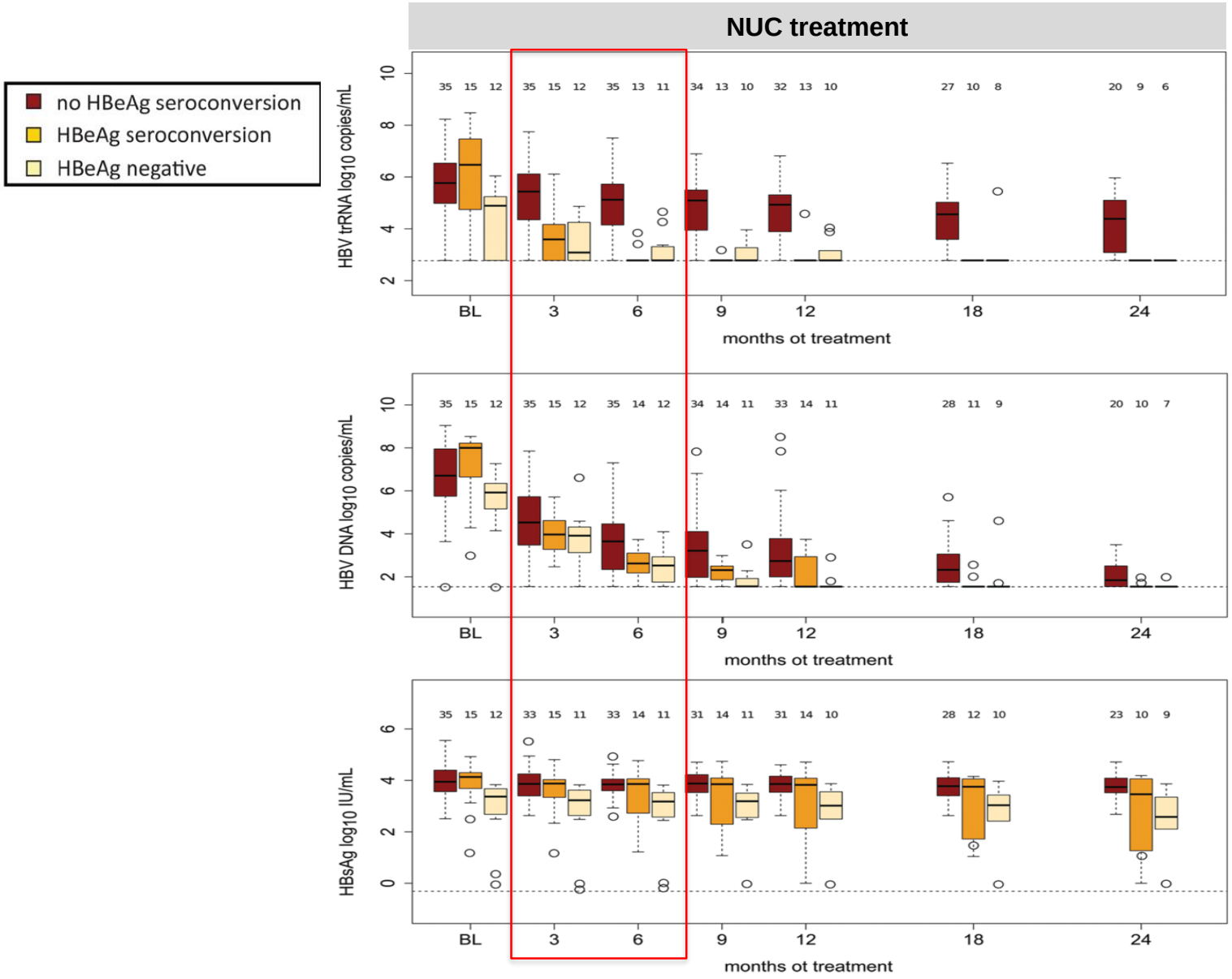
HBV-RNA Quantification – a new biomarker to predict NUC response (HBeAg seroconversion) in HBeAg positive patients



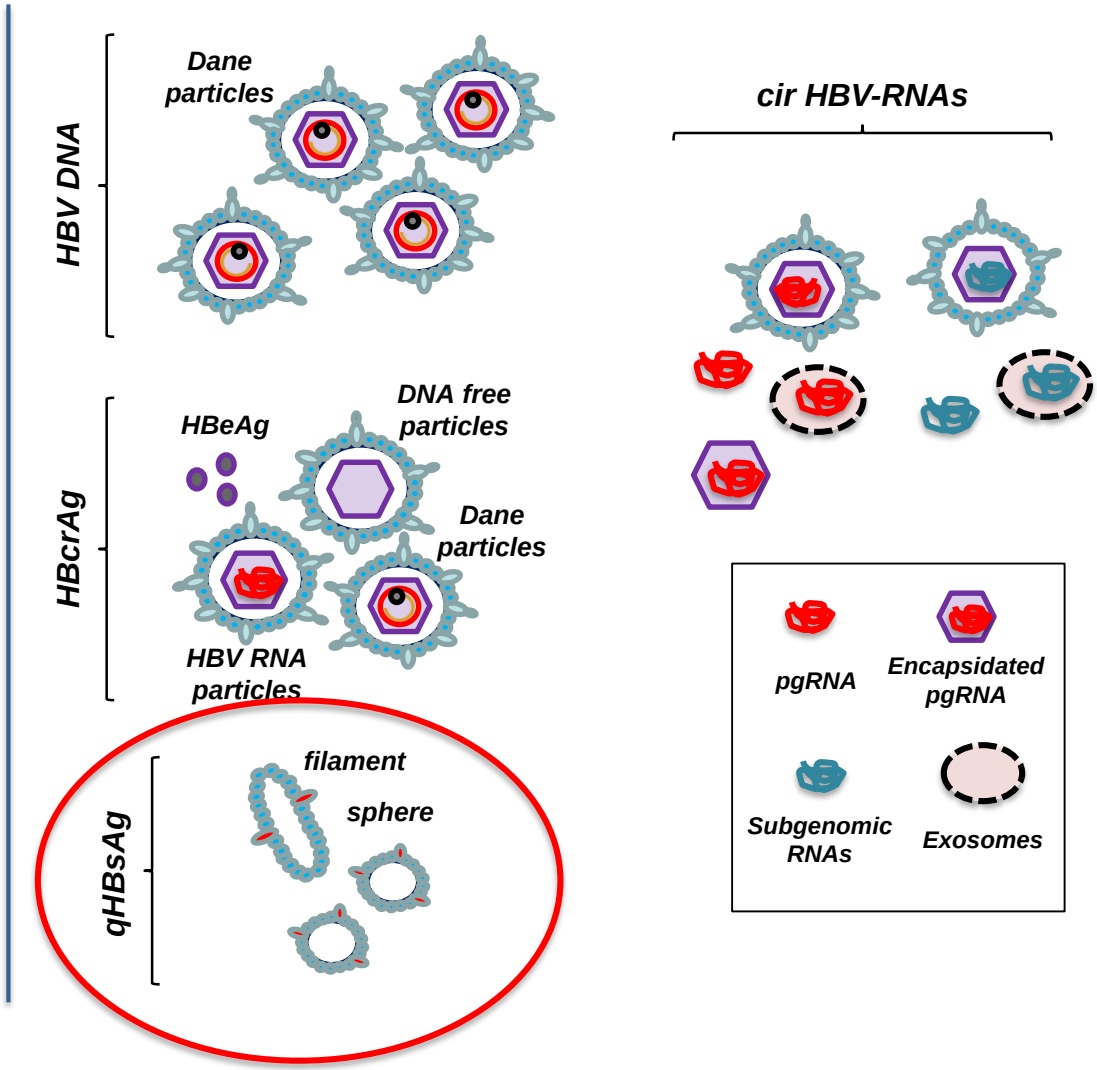
Van Bömmel F et al. Hepatology 2015; 61: 66

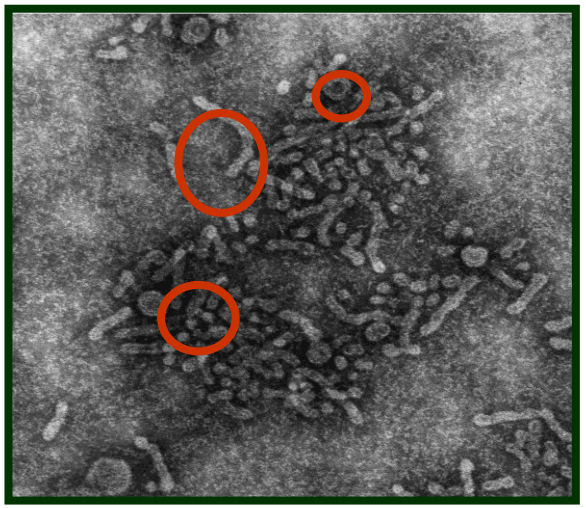
Serum HBV RNA as a clinical marker

- Serum HBV RNA could serve as a useful clinical surrogate marker to estimate the intrahepatic activity of cccDNA
- HBV RNA measurements could help monitoring the effectiveness of drugs aiming to affect cccDNA transcription and/or pgRNA stability
- Could potentially be used as a noninvasive diagnostic biomarker for liver disease activity and progression (in patients receiving NA therapy)
- A marker to define “parafunctional cure”*: persistent loss of serum HBV RNA

*Wang J, … Lu F. J Hepatol 2017; 66: 454

HBV serum/plasma biomarkers





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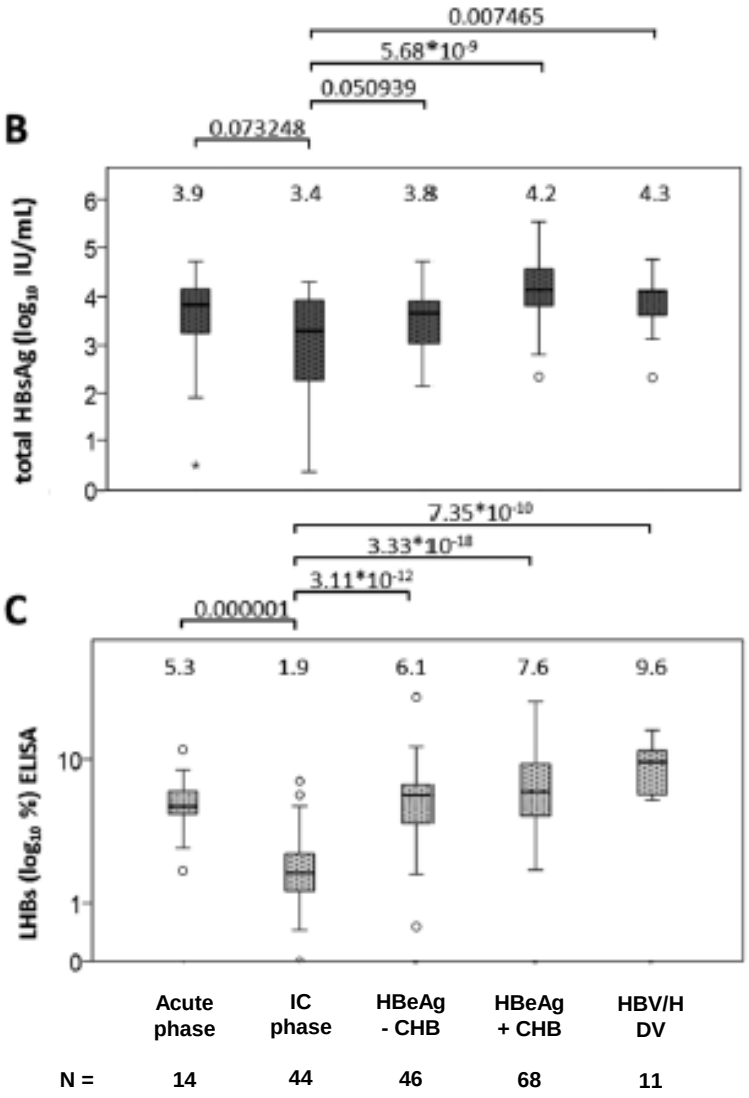
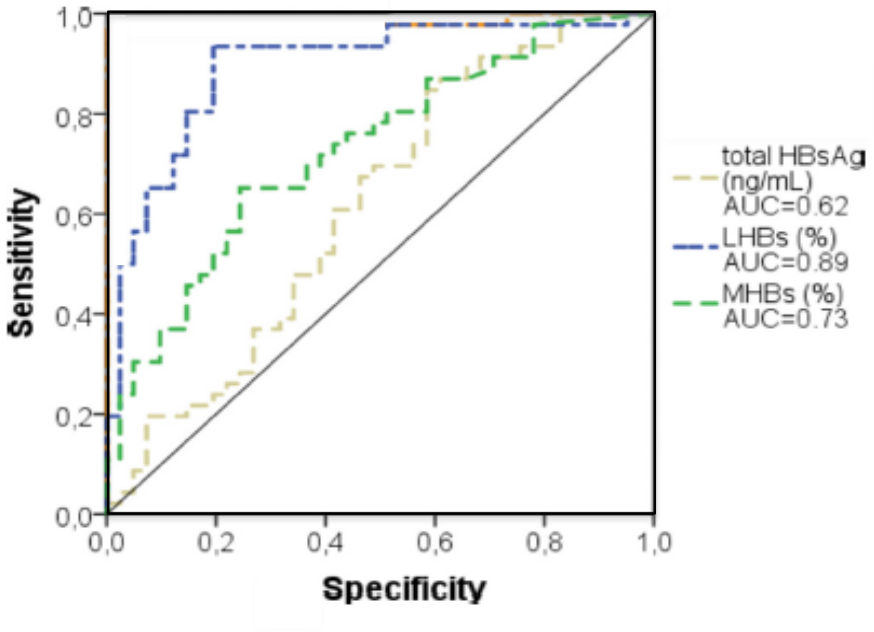
Modified from Testoni et al, Sem Liver Dis, 2017

ORIGINAL ARTICLE

Quantification of large and middle proteins of hepatitis B virus surface antigen (HBsAg) as a novel tool for the identification of inactive HBV carriers





Pfefferkorkorn M. et al, Gut, 2018; 67: 2045

Applications and clinical relevance of new HBV biomarkers

	Functional cure	Parafunctional cure	„true“ inactive carrier
HBsAg	-	+	+
HBsAg components MHBs and LHBs	-	-	-
HBcrAg	-	-	±
HBV RNA	-	-	±

Stable remission without treatment
No disease progression