UNIVERSITÄT LEIPZIG

Medizinische Fakultät

2020 13th Paris Hepatology Conference

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TRANSPLANTATIONSZENTRUM

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25 JAHRE TRANSPLANTATIONS ZENTRUM LEIPZIG

New endpoints and biomarkers for treatment of CHB

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Clinic and Polyclinic for Gastroenterology, Hepatology, Infectiology and Pneumology

University Clinic Leipzig

Guidance for design and endpoints of clinical trials in chronic hepatitis B

Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference

	Sterilizing 'cure'	Idealistic functional 'cure'	Realistic functional 'cure'	Attainable Partial functional 'cure'
Clinical scenario	**Never infected**	**Recovery after acute HBV**	**Chronic HBV with HBsAg loss**	**Inactive carrier off treatment**
HBsAg	Negative	Negative	Negative	Positive
Anti-HBs	Negative/Positive	Positive	Positive/negative	Negative
HBeAg	Negative	Negative	Negative	Negative
Serum HBV DNA	Not detected	Not detected	Not detected	Low level or not detected
Hepatic cccDNA, transcription	Not detected Not active	Detected Not active	Detected Not active	Detected Low level
Integrated HBV DNA	Not detected	Detected?	Detected	Detected
Liver disease	None	None	Inactive, fibrosis regress over time	Inactive
Risk of HCC	Not increased	Not increased	Declines with time	Risk lower vs. active hepatitis

Cornberg M et al. J Hepatol 2019, epub

EASL | JOURNAL OF HEPATOLOGY

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

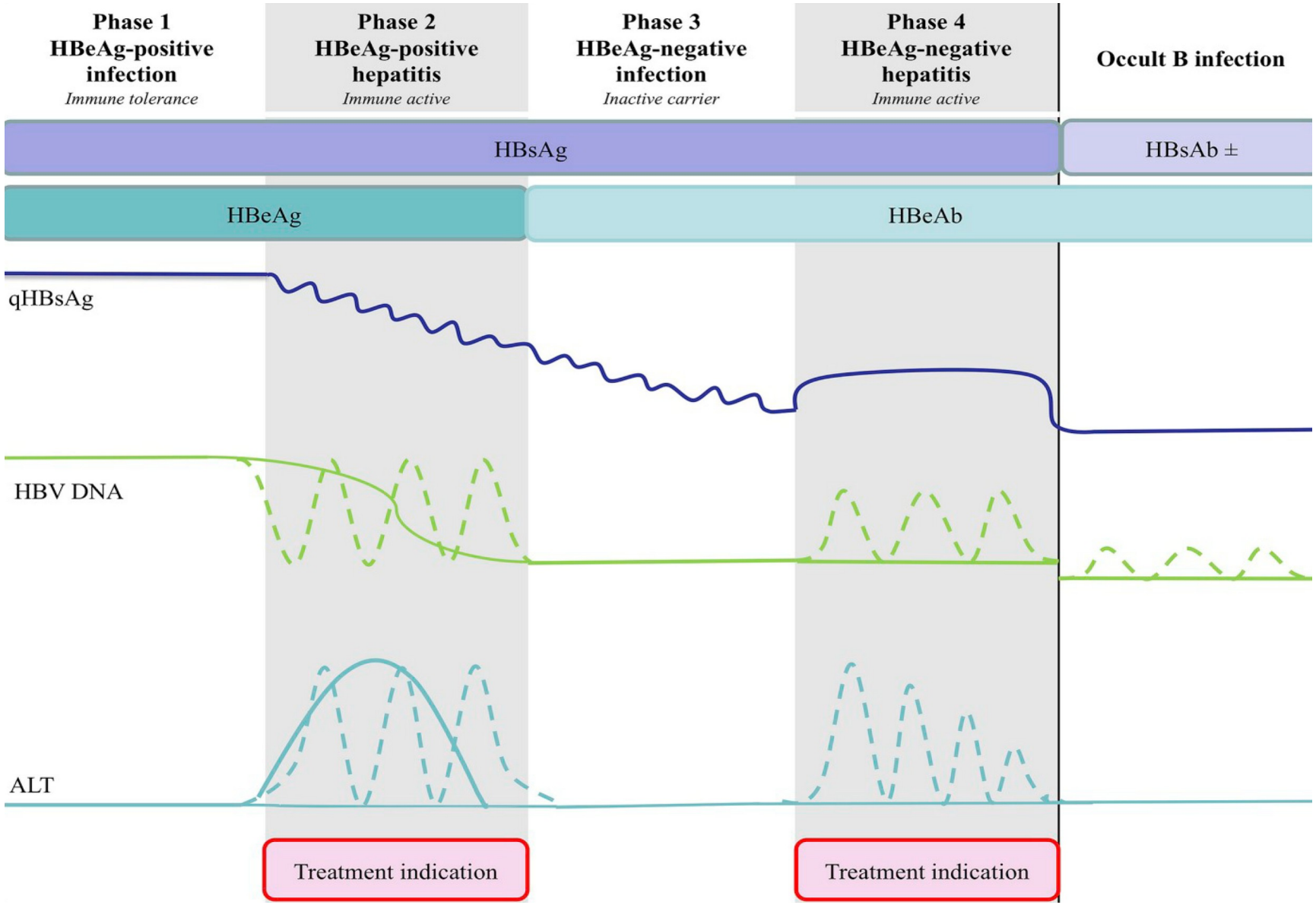
European Association for the Study of the Liver*

HBsAg loss, with or without anti-HBs seroconversion, is an optimal endpoint, as it indicates profound suppression of HBV replication and viral protein expression

(Evidence level II-1, grade of recommendation 1)

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370

Treatment indication in chronic HBV infection – The Phase matters



Charre C et al. Antiviral Res 2019; 169: 104553

Why we are aiming for HBsAg loss if HBsAg per se is not an indicator to start antiviral treatment?

EASL CPG - Why aiming for HBsAg loss?

- As chronic HBV infection cannot be completely eradicated due to the persistence of cccDNA and integrated HBV DNA, it remains unclear whether HBsAg loss adds to the prevention of the long-term complications of chronic HBV infection beyond what can be achieved by the suppression of HBV DNA replication alone

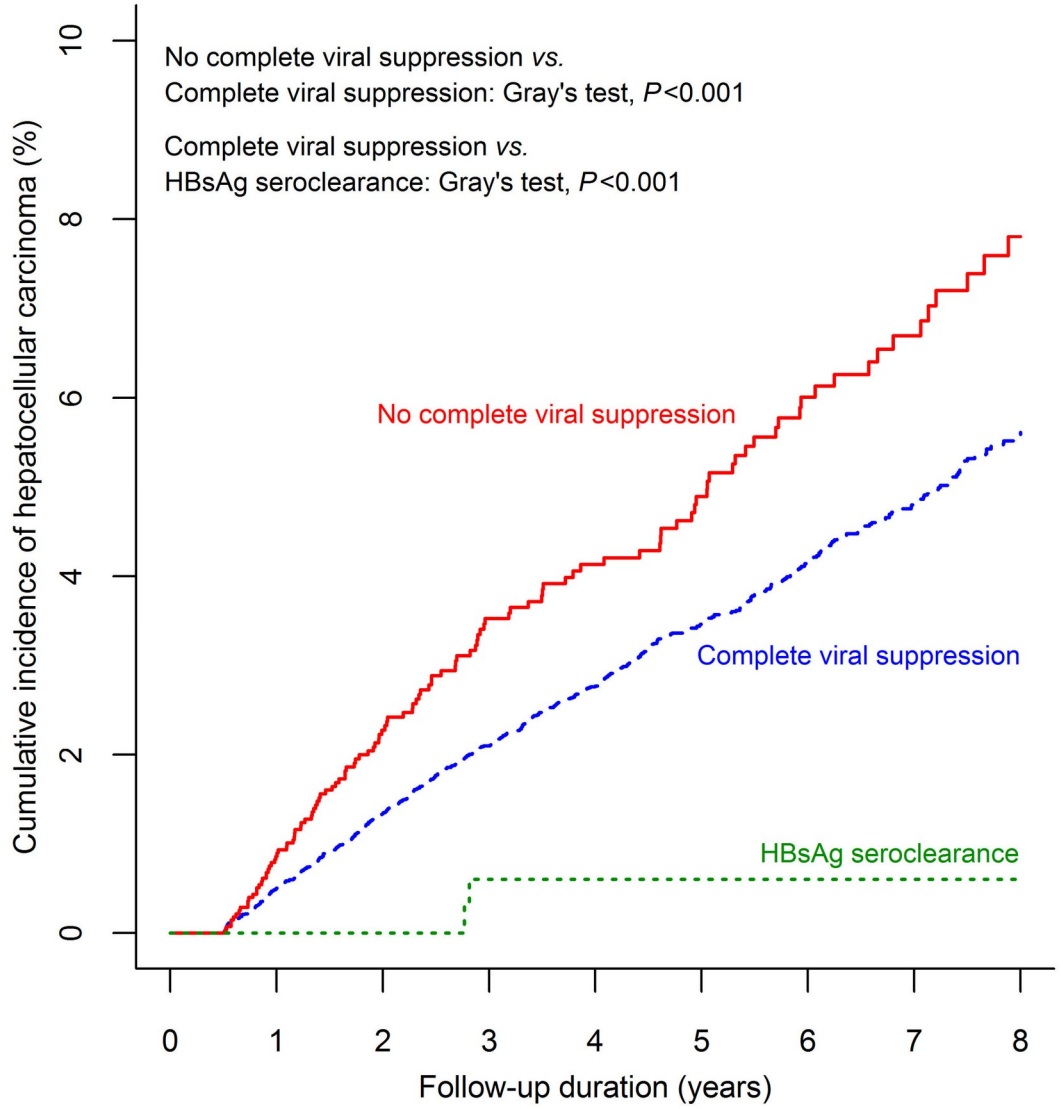
- HCC may still develop even after spontaneous HBsAg loss (annual rate approximately 0.55%)

- The risk, however, is lower if HBsAg loss is achieved at a younger age and/or in the absence of significant fibrosis

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370

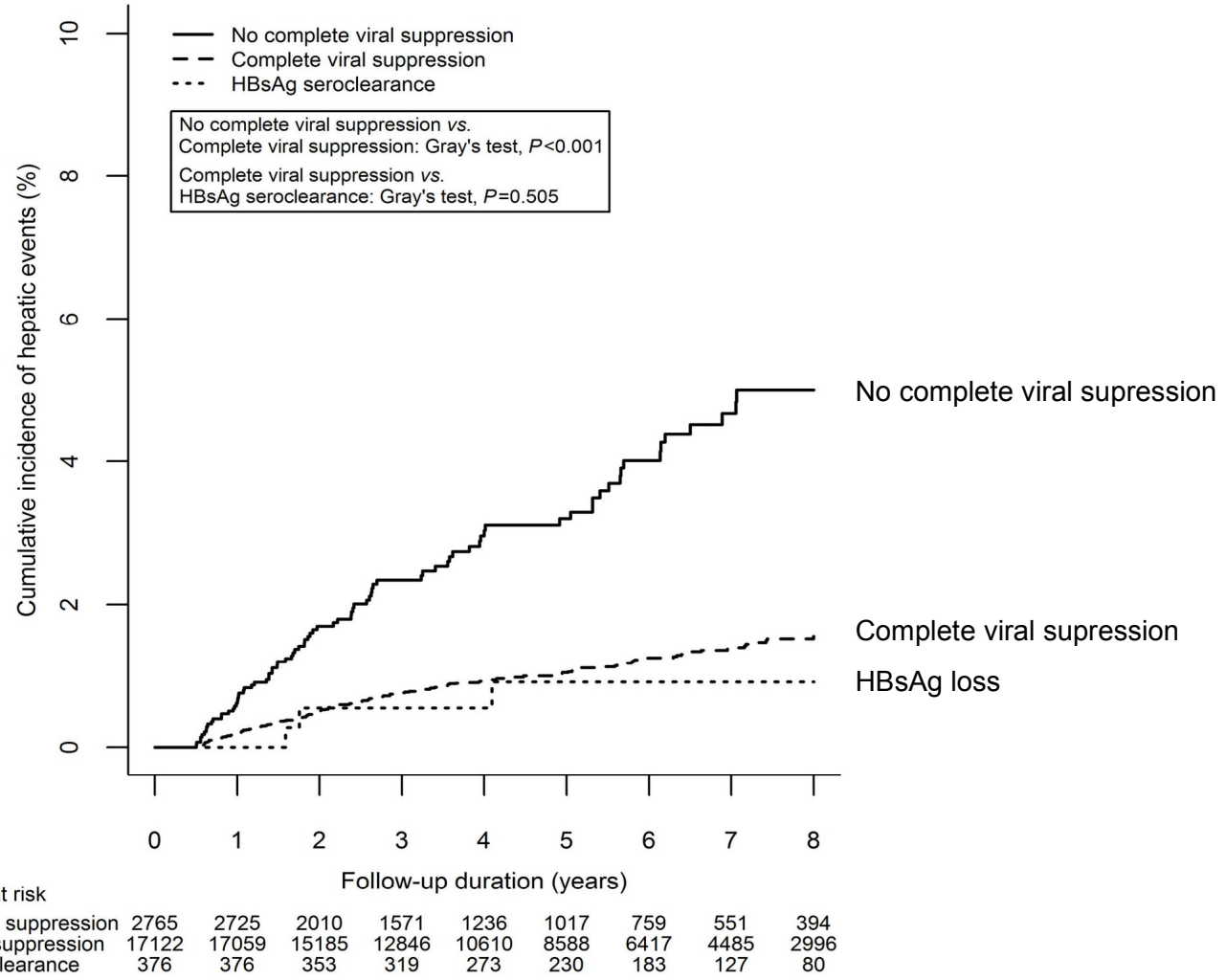
Do we need to achieve HBsAg loss fully prevent any adverse outcome?

HBsAg loss further reduces HCC risk after complete viral suppression with nucleos(t)ide analogues



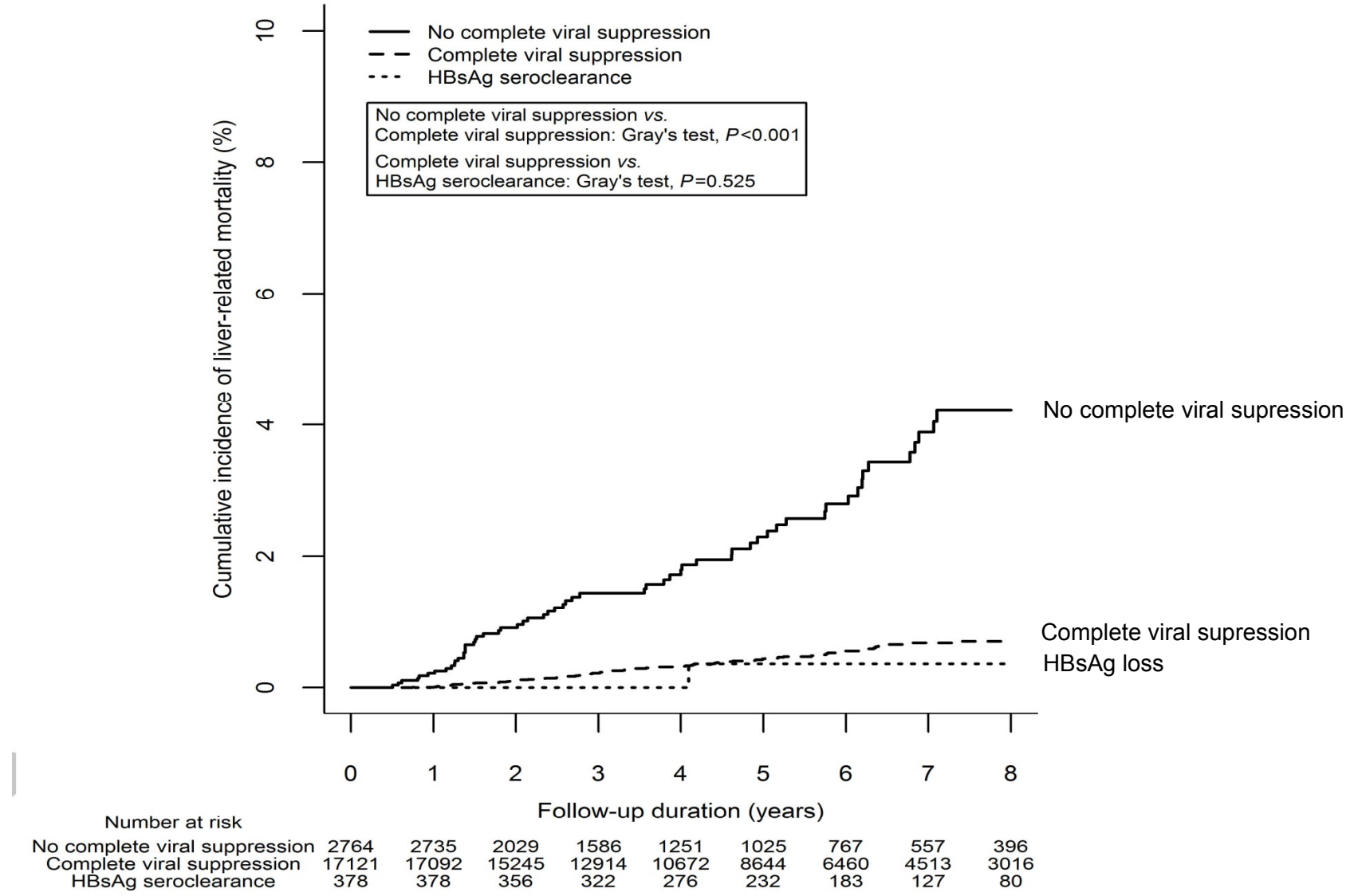
Yip T C-F et al. J Hepatol 2019; 70: 361

Incidence of hepatic events in NA-treated patients according to level of viral suppression and HBsAg loss



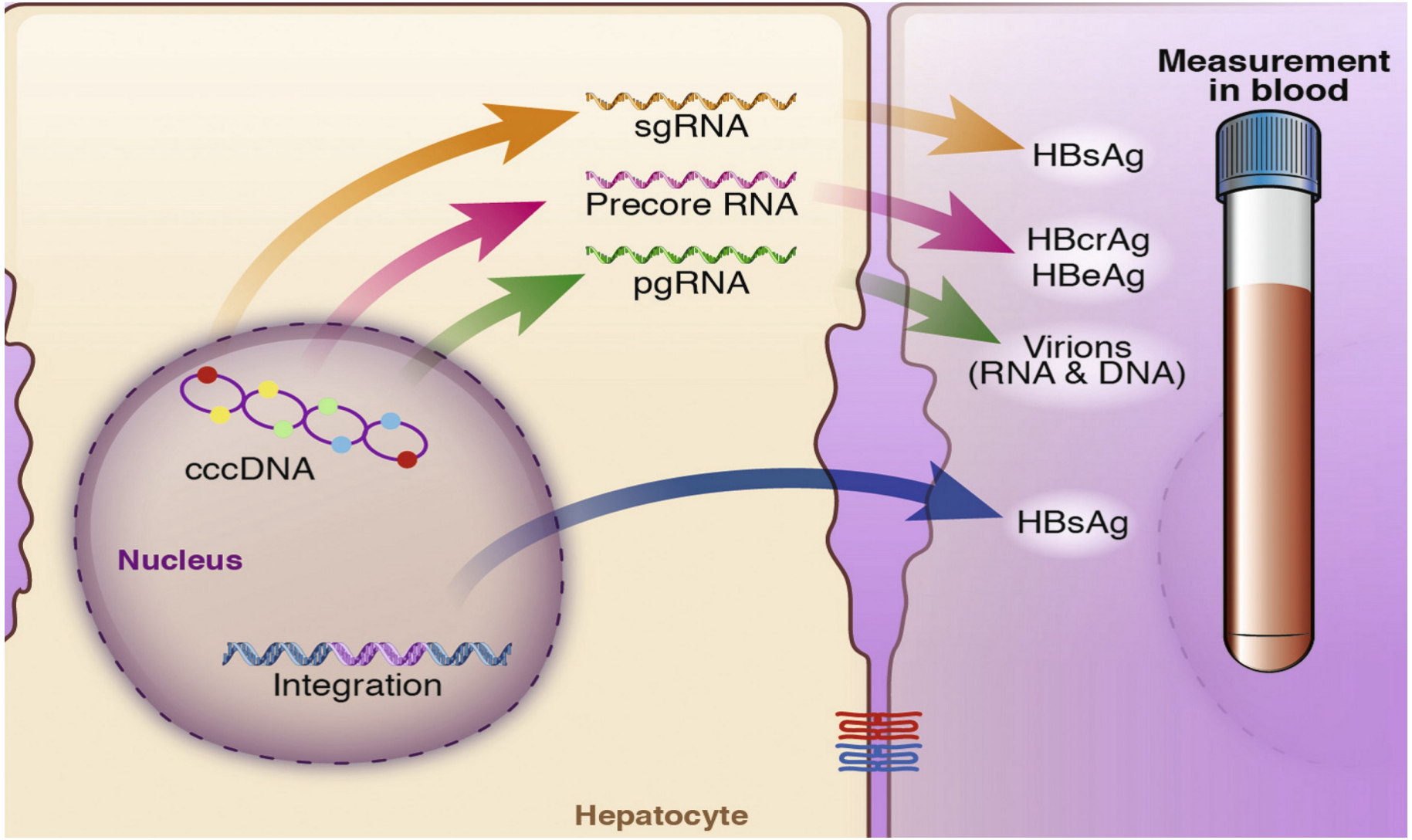
Yip T C-F et al. J Hepatol 2019; 70: 361

Incidence of liver-related mortality in NA-treated patients according to level of viral suppression and HBsAg loss



Yip T C-F et al. J Hepatol 2019; 70: 361

HBsAg a valid endpoint for new antiviral compounds?



Coffin CS et al. Gastroenterology 2019; (Epub)

Guidance for design and endpoints of clinical trials in chronic hepatitis B

Aiming for attainable functional "cure"?

	Sterilizing 'cure'	Idealistic functional 'cure'	Realistic functional 'cure'	Attainable Partial functional 'cure'
Clinical scenario				**Inactive carrier off treatment**
HBsAg				Positive
Anti-HBs				Negative
HBeAg				Negative
Serum HBV DNA				Low level or not de-tected
Hepatic cccDNA, transcription				Detected Low level
Integrated HBV DNA				Detected
Liver disease				Inactive
Risk of HCC				Risk lower vs. active hepatitis

Cornberg M et al. J Hepatol 2019, epub

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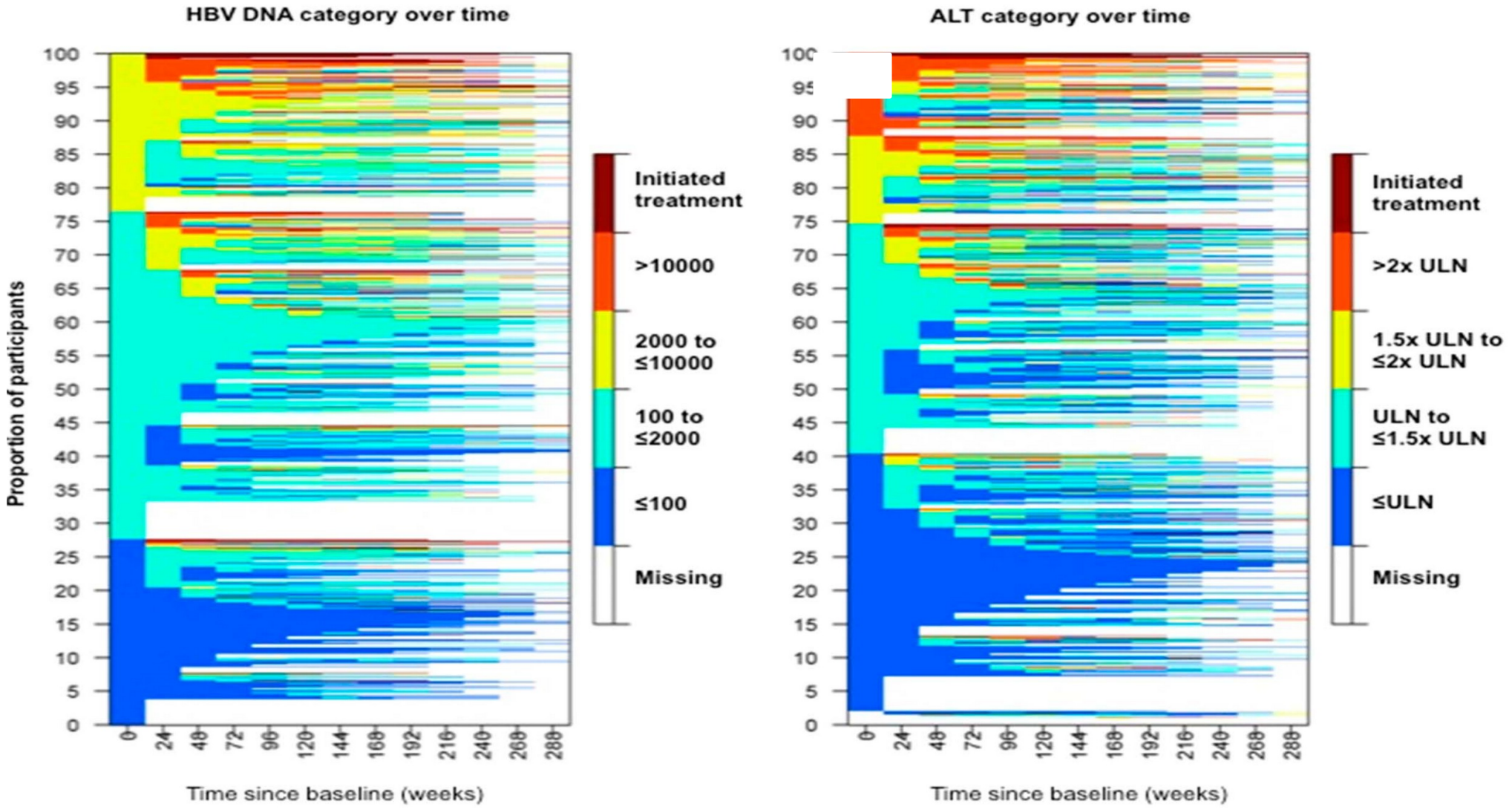
Stability of the response?
Disease reactivation risk?
Long-term HCC risk?
Extrahepatic manifestations?
Long-term monitoring?

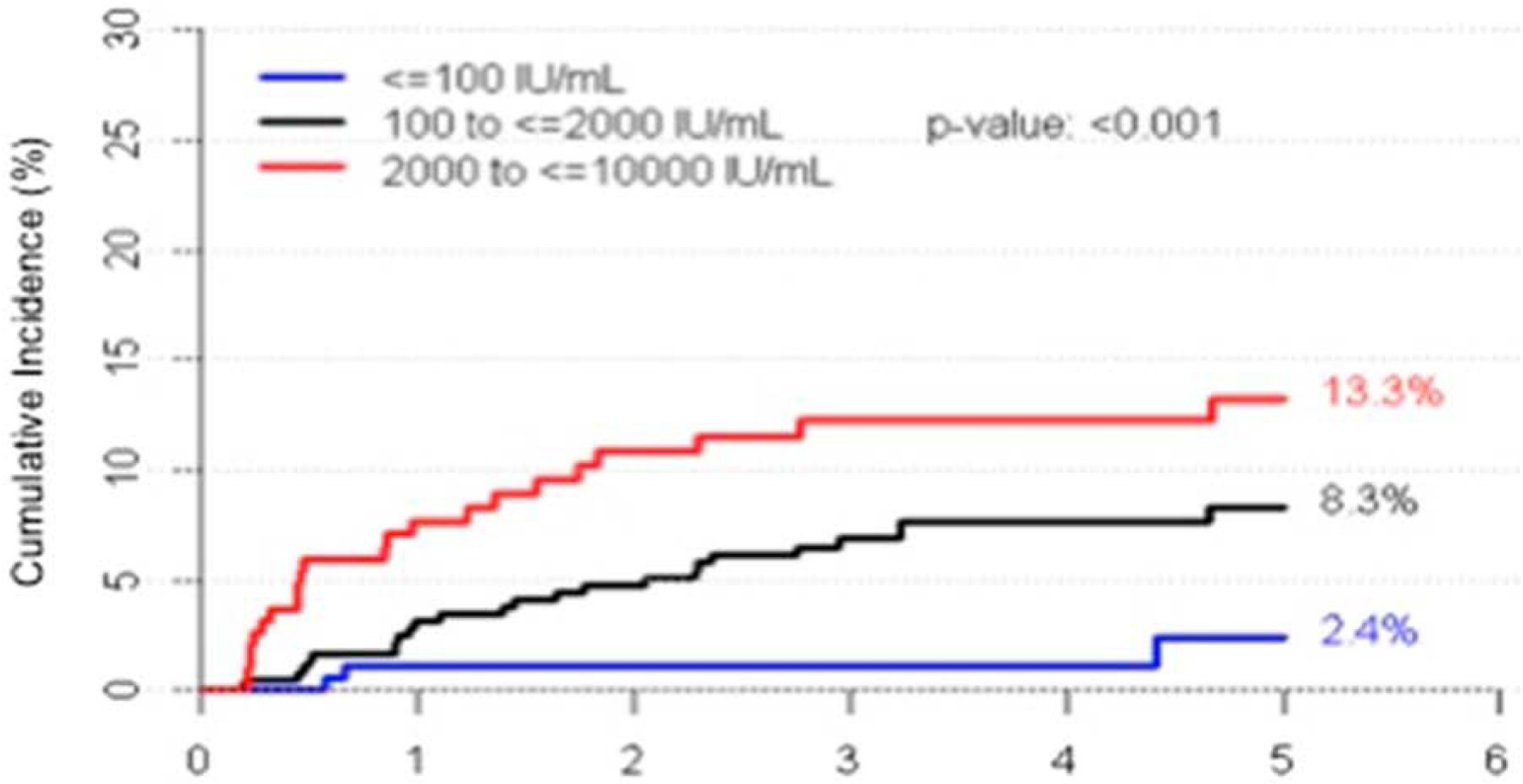
Cornberg M et al. J Hepatol 2019, epub

Phase transition in HBeAg negative infection (carriers) according to baseline HBV DNA and ALT levels



Zhou K et al. Am J Gastroenterol 2019 Oct 24 (Epub

Phase transition in HBeAg negative infection (carriers) according to baseline HBV DNA levels



No. at risk

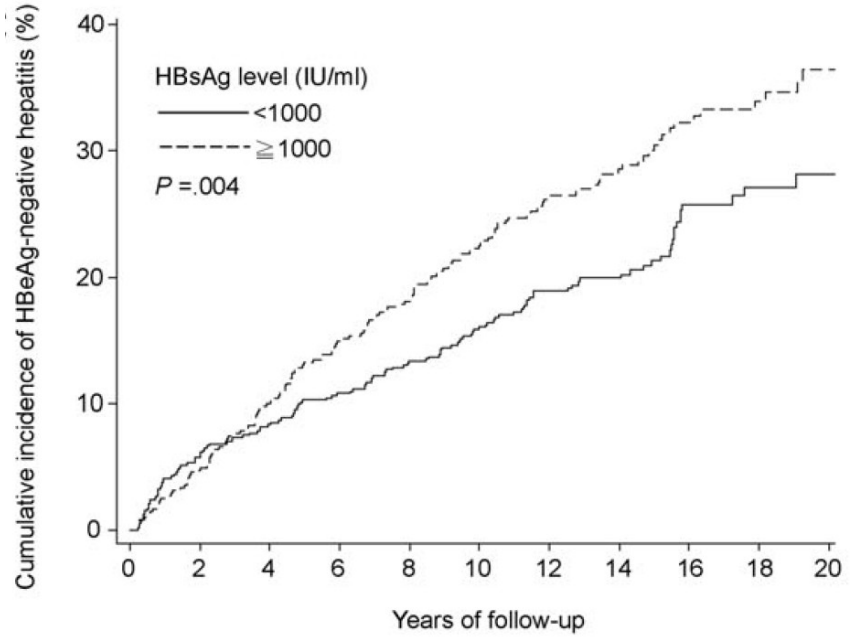
≤100	217	169	148	119	92	51
>100-≤2000	417	320	277	240	193	130
>2000	200	153	134	121	106	74

Zhou K et al. Am J Gastroenterol 2019 Oct 24 (Epub

HBsAg – a disease progression marker? Does the level matters?

HBsAg quantification – a biomarker to predict disease progression in patients with low baseline viral load (< 2000 IU/mL)

Reactivation of HBeAg negative hepatitis

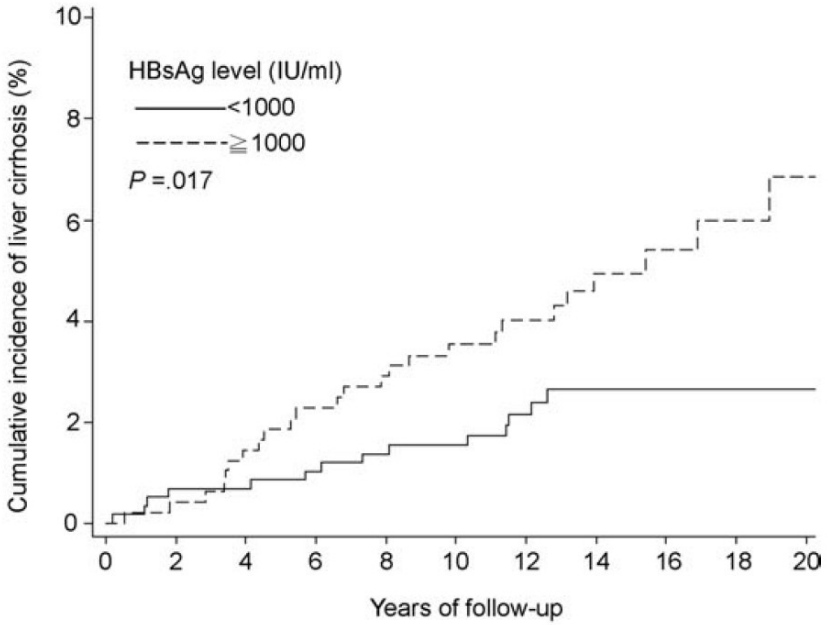


Number at risk

Serum HBsAg levels at baseline (IU/ml)

<1000	585	551	536	521	503	454	357	265	146	90	58
≧1000	483	460	435	410	394	350	288	210	132	100	57

Cirrhosis development



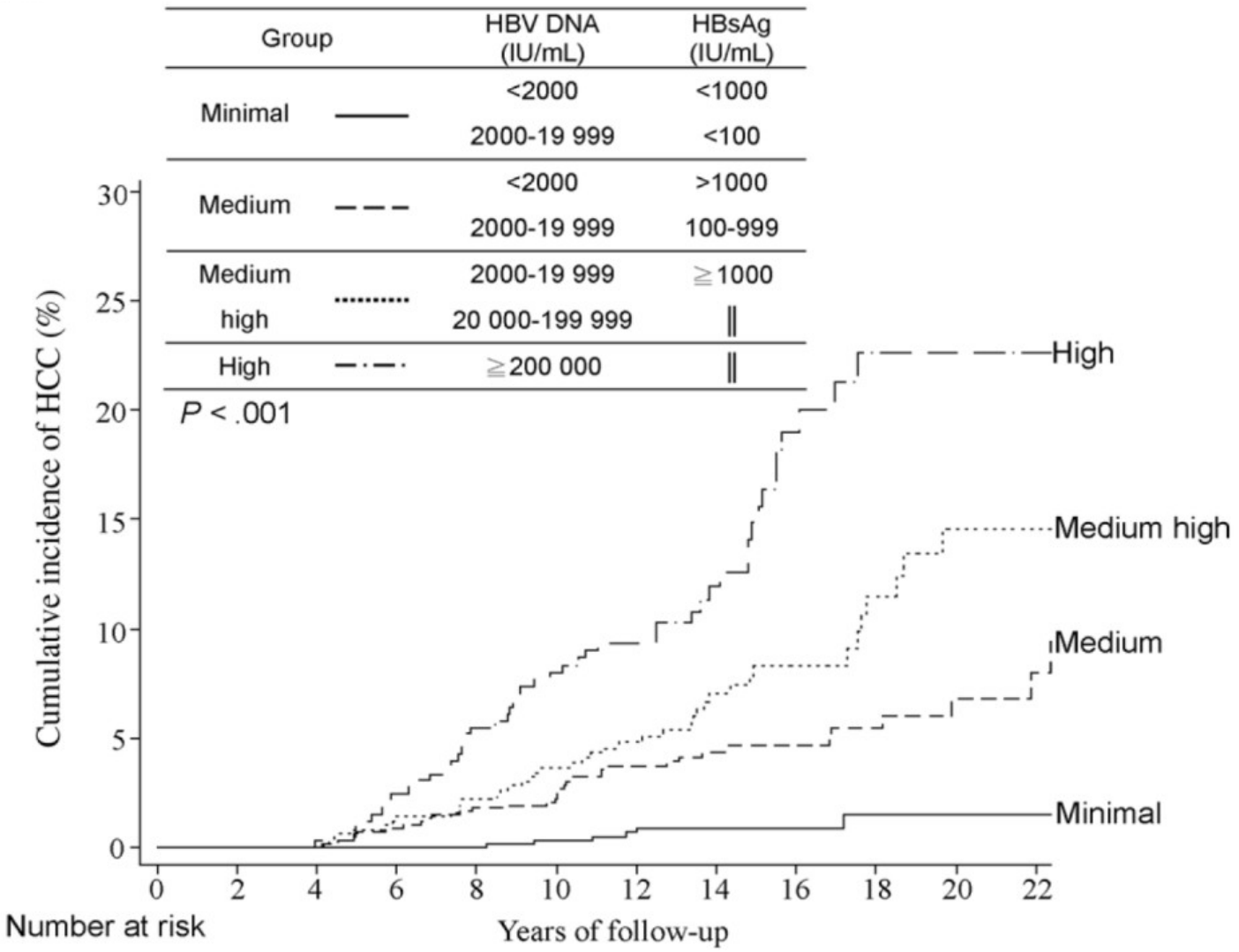
Number at risk

Serum HBsAg levels at baseline (IU/ml)

<1000	585	581	581	578	573	532	432	315	182	111	71
≧1000	483	481	476	471	466	436	373	276	182	131	81

Tseng TC et al. *Hepatology 2013;57:441-450*

HCC risk stratification in HBeAg-negative HBV infection by HBV DNA and HBsAg levels



Tseng TC et al. JID 2013:208; 584-593

Guidance for design and endpoints of clinical trials in chronic hepatitis B

When aiming for attainable functional "cure" – do we need new biomarkers?

	Sterilizing 'cure'	Idealistic functional 'cure'	Realistic functional 'cure'	Attainable Partial functional 'cure'
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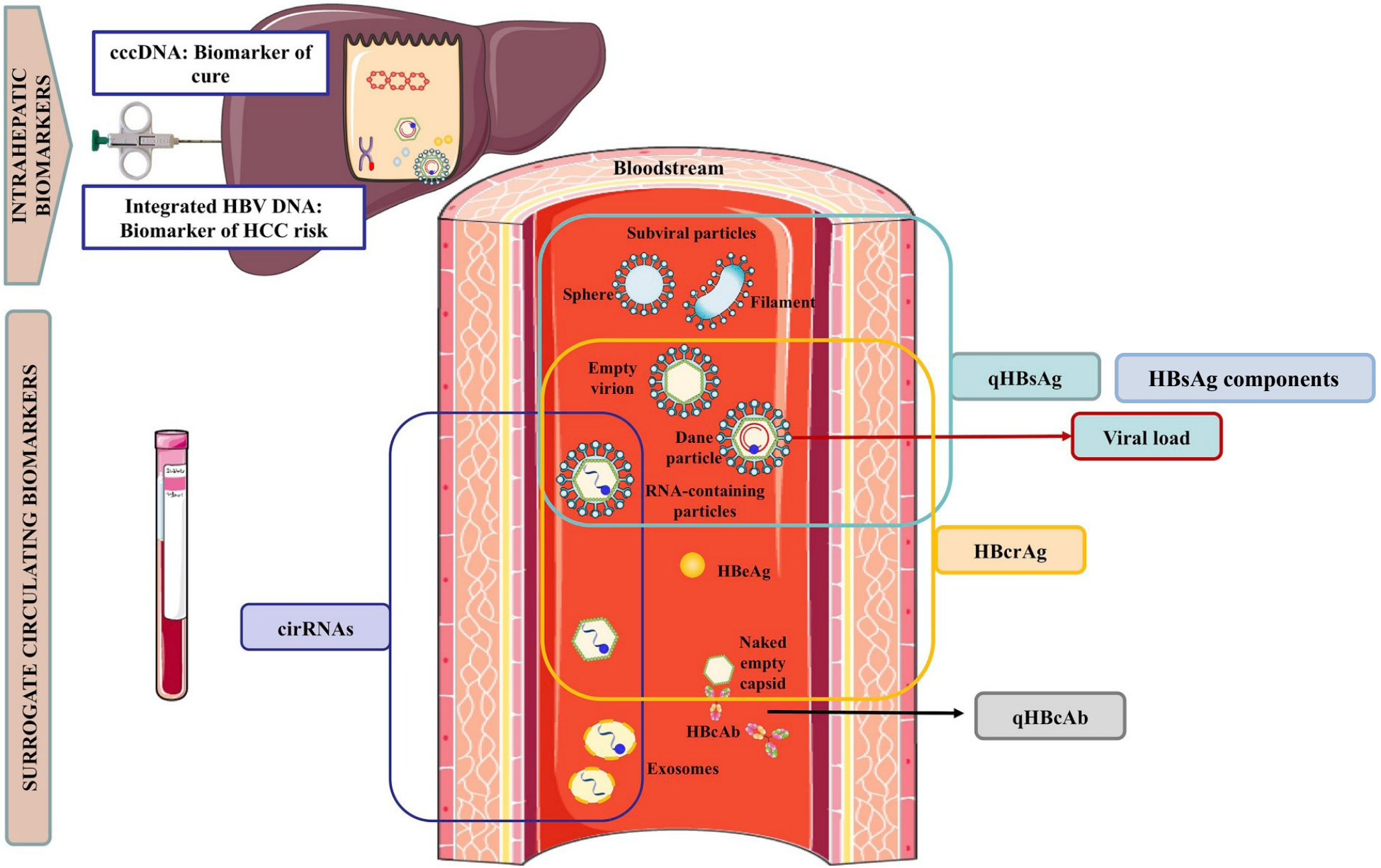
Risk of HCC				Risk lower vs. active hepatitis

New HBV biomarkers

Are they helpful for a more refined characterisation of the activity of the infection and predicting the risk of adverse outcomes?

Cornberg M et al. J Hepatol 2019, epub

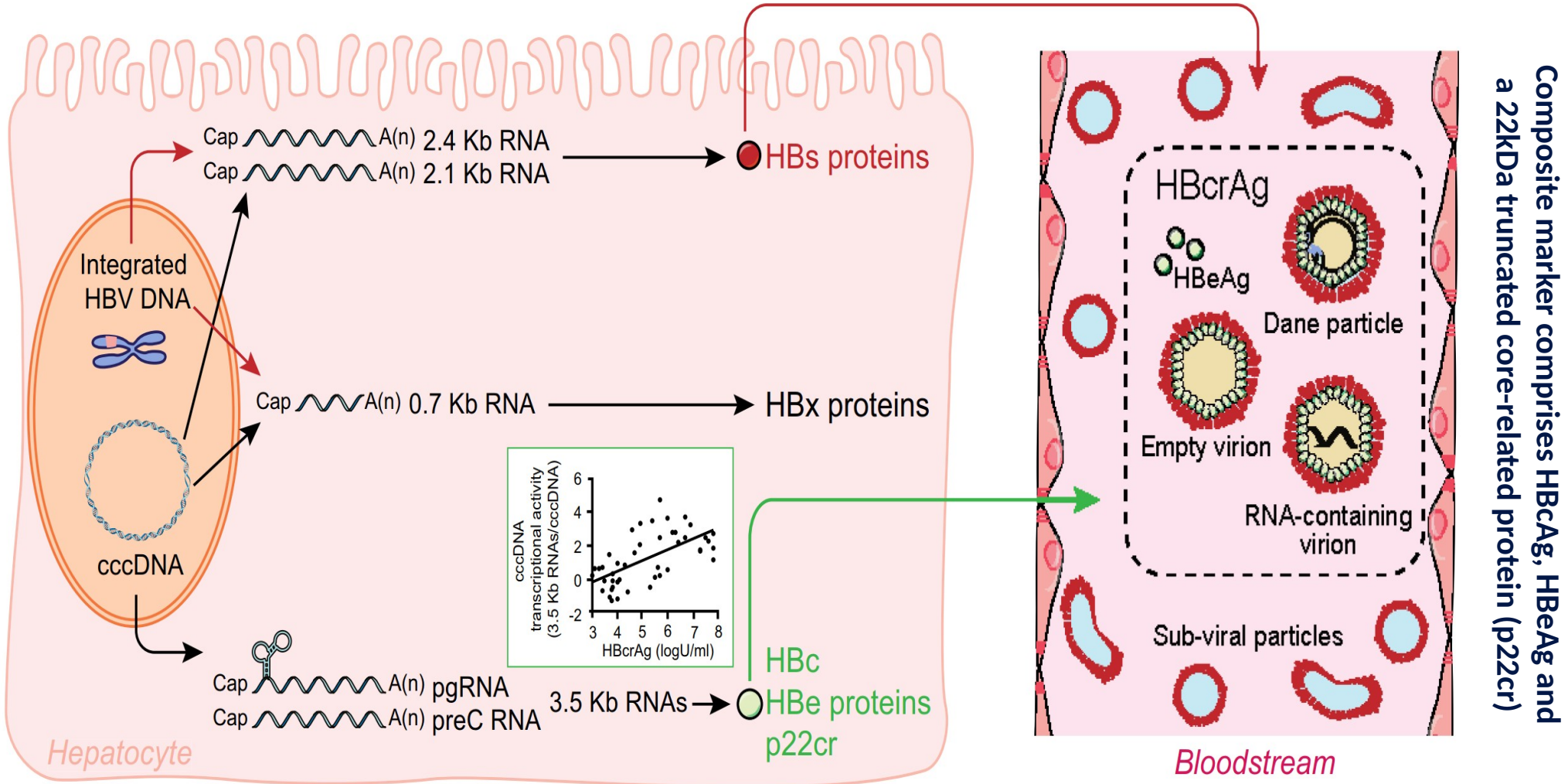
Novel biomarkers for intrahepatic hepatitis B activity



Charre C, et al. Antiviral Res 2019;169:194553

HBcrAg

Hepatitis B core-related antigen (HBcrAg) a biomarker to predict transcriptional acitivity

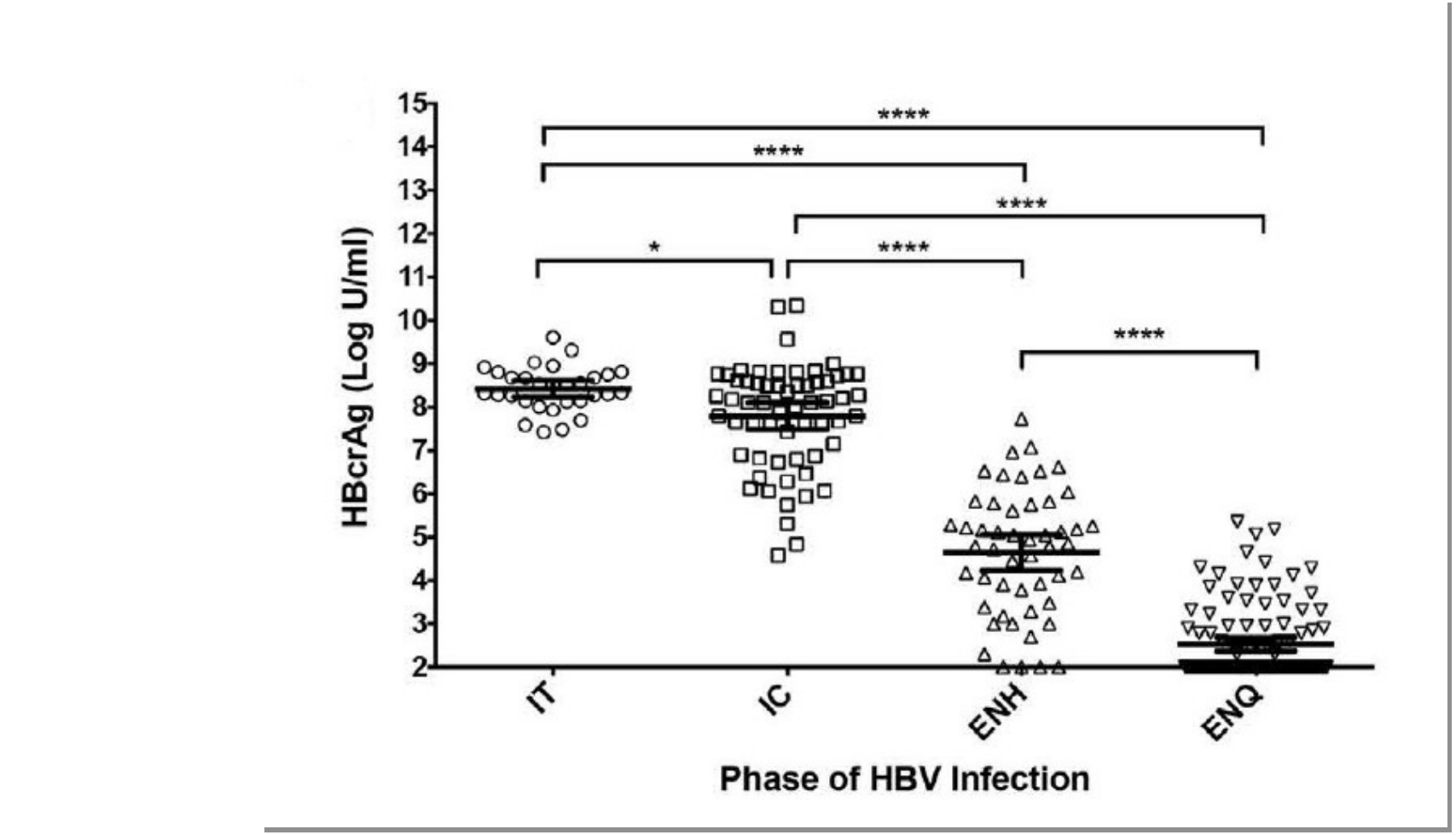


Composite marker comprises HBcAg, HBeAg and a 22kDa truncated core-related protein (p22cr)

Not influenced by translation of integrated sequences

Testoni et al. J Hepatol 2019; 70(4):615-625

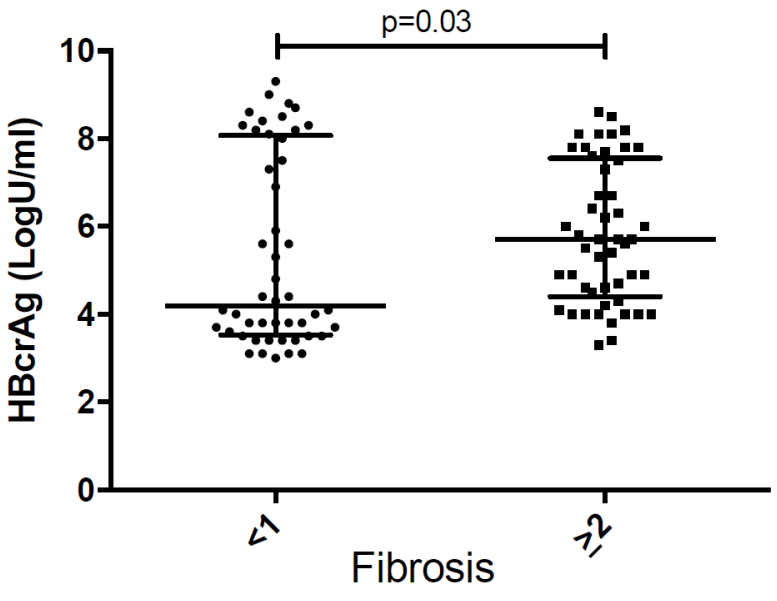
HBcrAg levels across phases of chronic hepatitis B

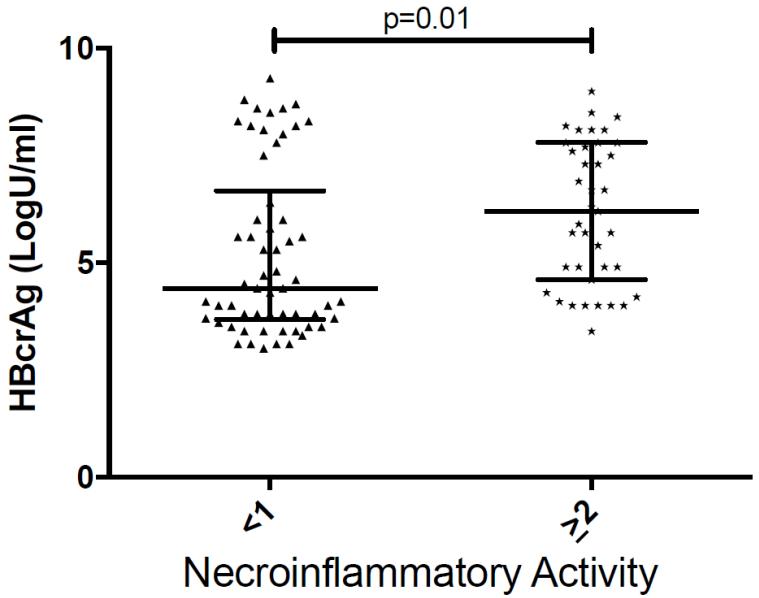


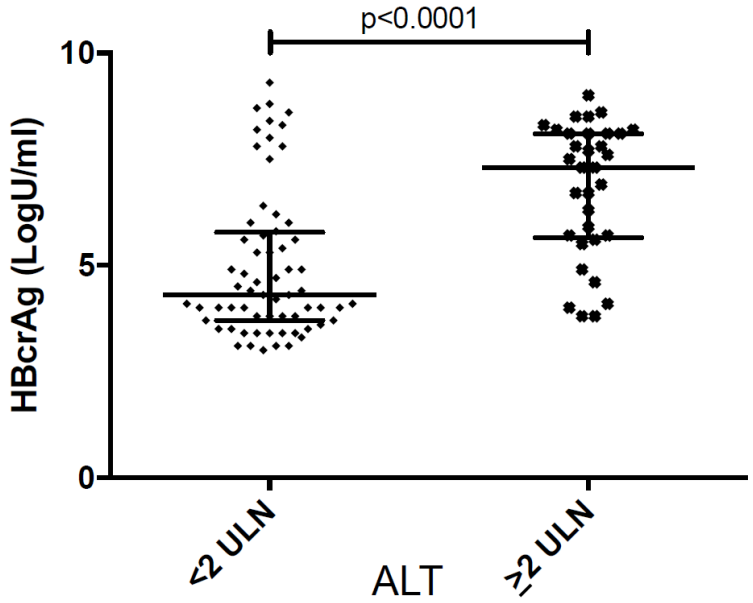
HBeAg-positive immune tolerance (IT) HBeAg-positive immune clearance (IC) HBeAg-negative hepatitis (ENH) inactive carriers (ENQ)

Maasoumy B et al. Clin Microbiol Infect 2015

HBcrAg levels according to liver injury markers

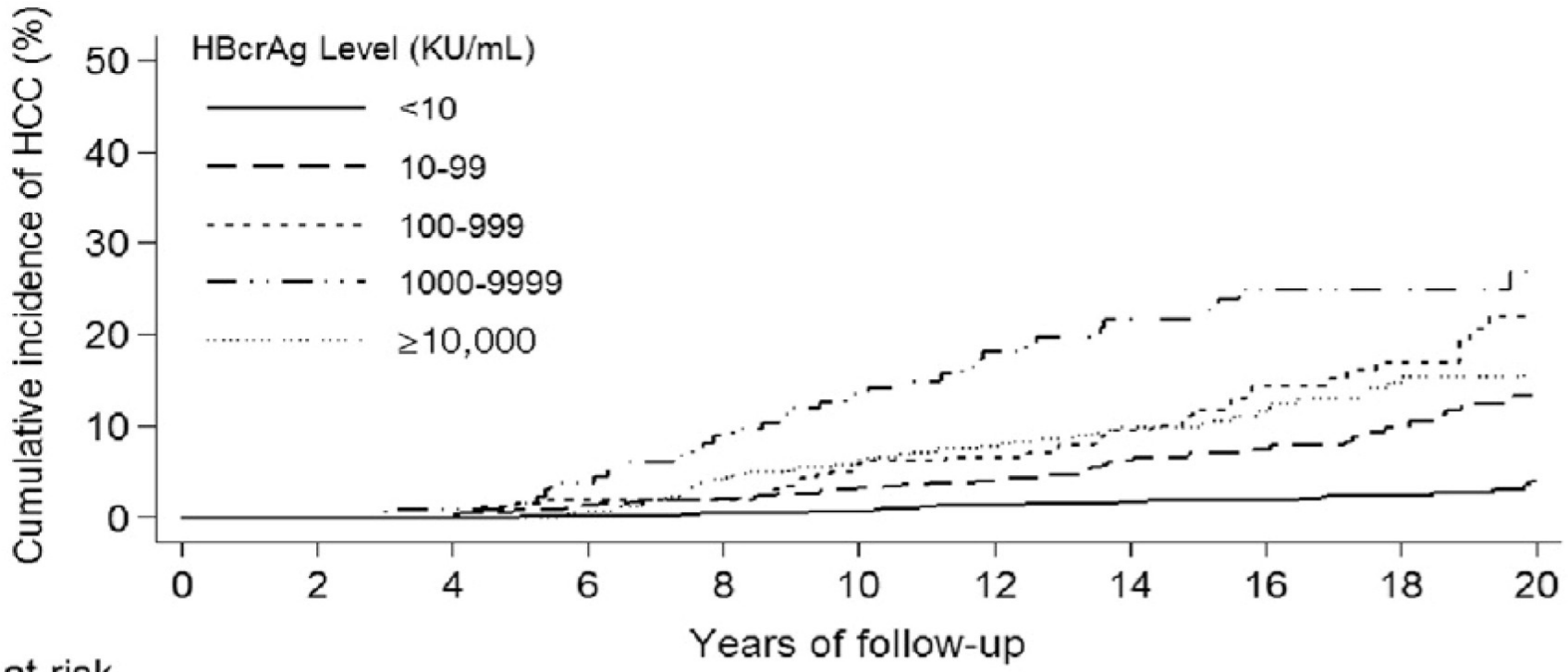






Testoni et al. J Hepatol 2019; 70(4):615-625

Correlation between serum HBcrAg levels and HCC incidence

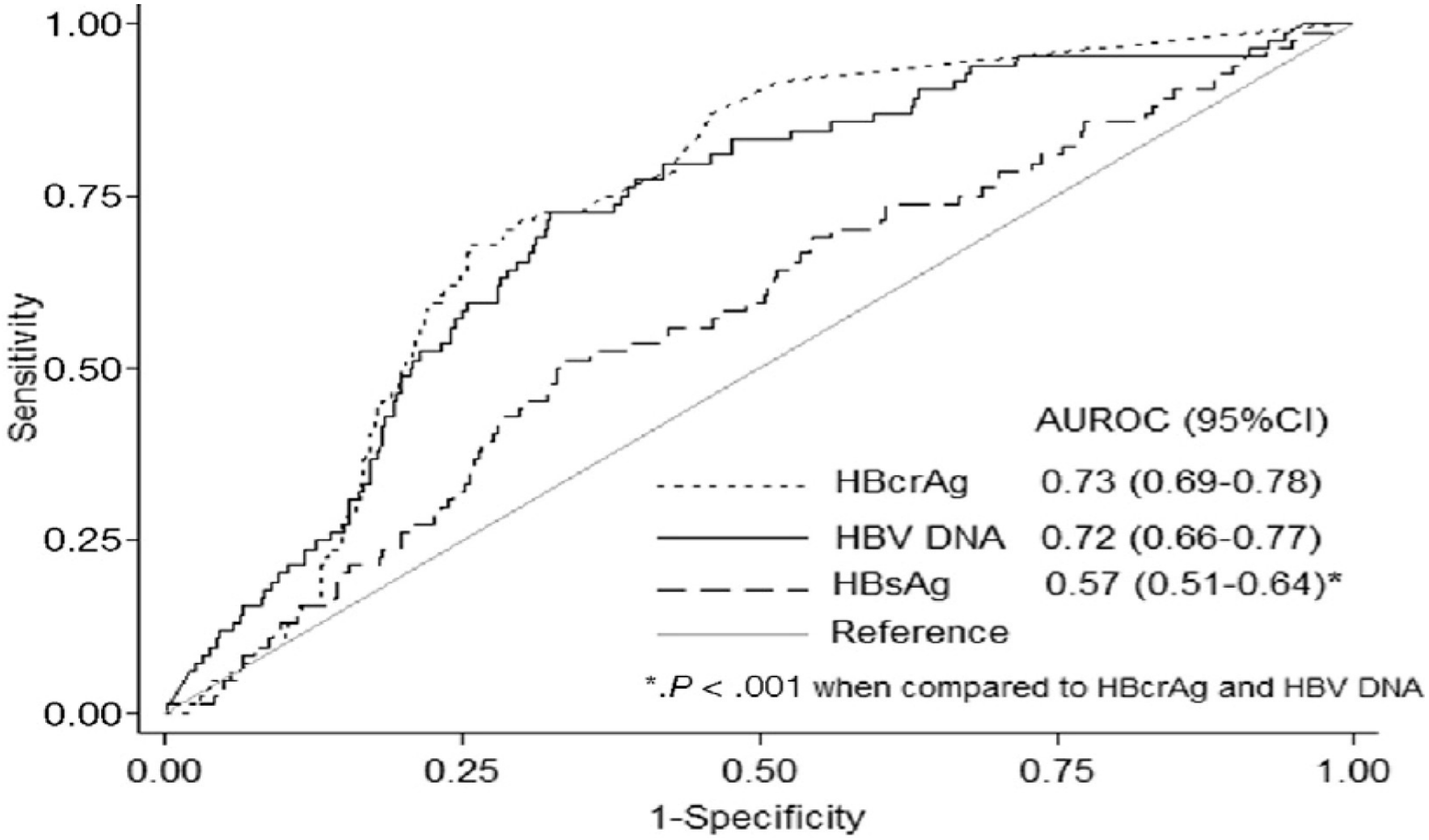


Number at risk

HBcrAg Level (KU/mL)											
<10	1271	1271	1271	1266	1254	1193	1042	817	543	350	230
10-99	540	540	538	532	528	507	441	347	248	155	102
100-999	263	263	263	258	258	241	218	171	122	84	53
1000-9999	137	137	134	130	123	114	104	81	64	53	38
≥10,000	455	455	448	444	426	404	358	282	190	131	89

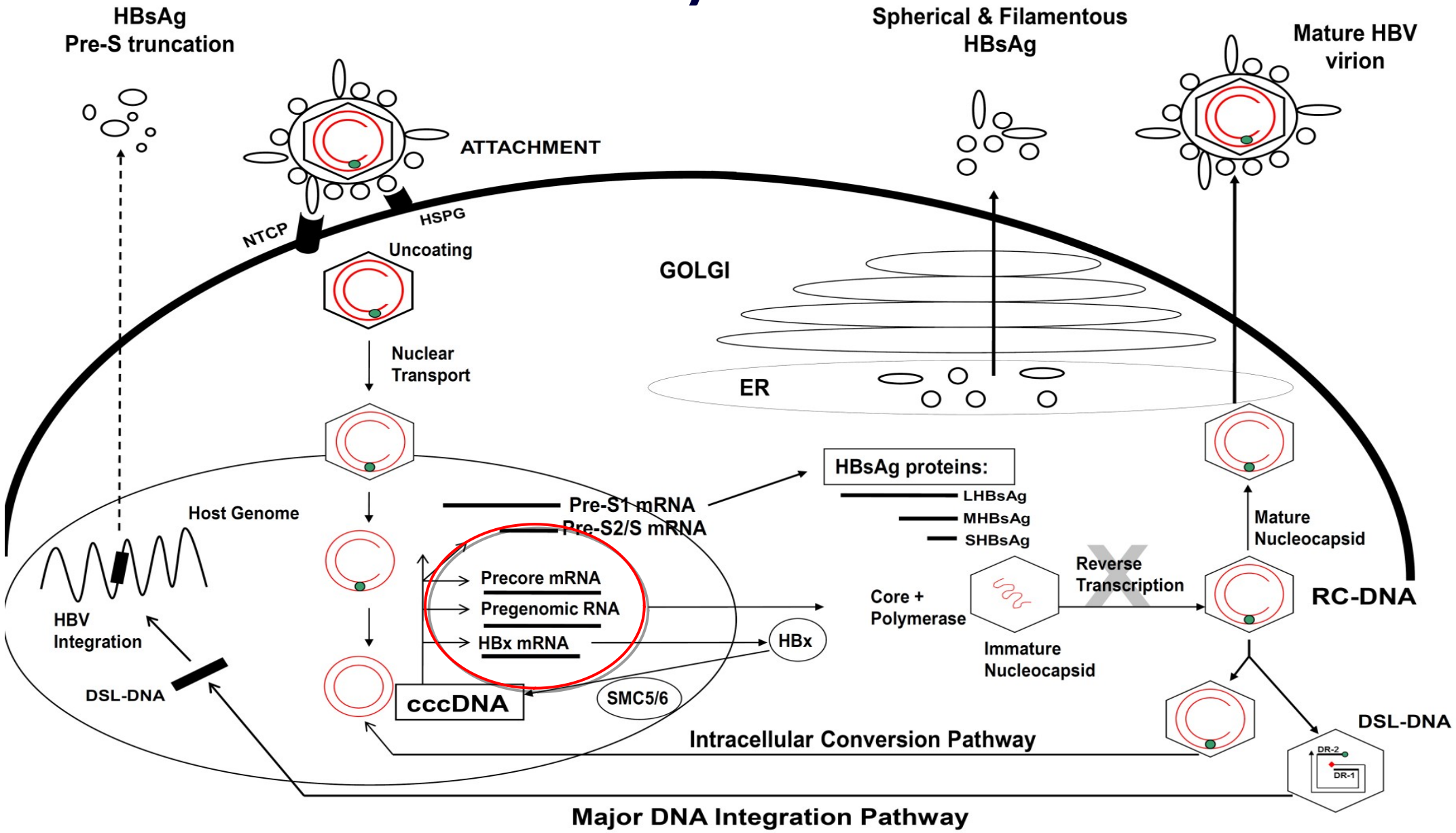
Tseng T-C et al. Gastroenterology 2019; S0016-5085(19)41248-1 (Epub)

Correlation between serum HBcrAg levels and HCC incidence



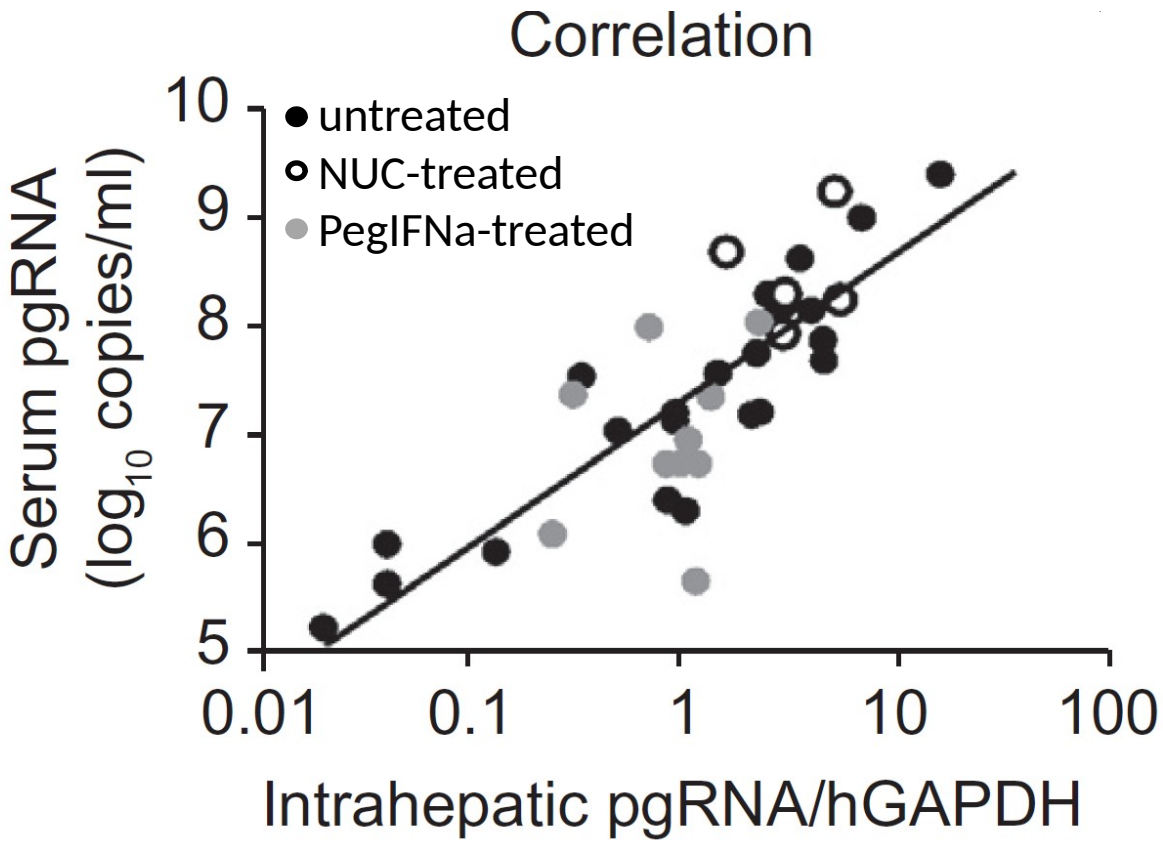
Tseng T-C et al. Gastroenterology 2019; S0016-5085(19)41248-1 (Epub)

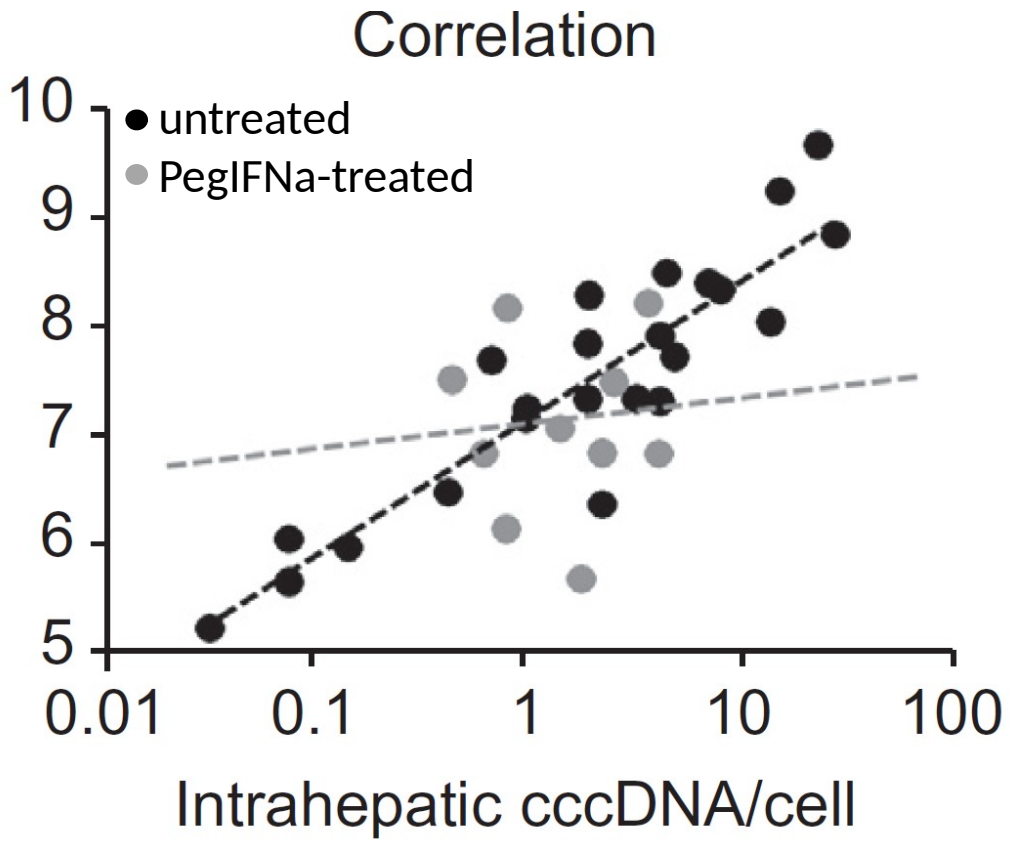
HBV life cycle – HBV RNA



Cornberg M et al. J Hepatol 2016, in press

Serum HBV pgRNA as a clinical marker for cccDNA activity



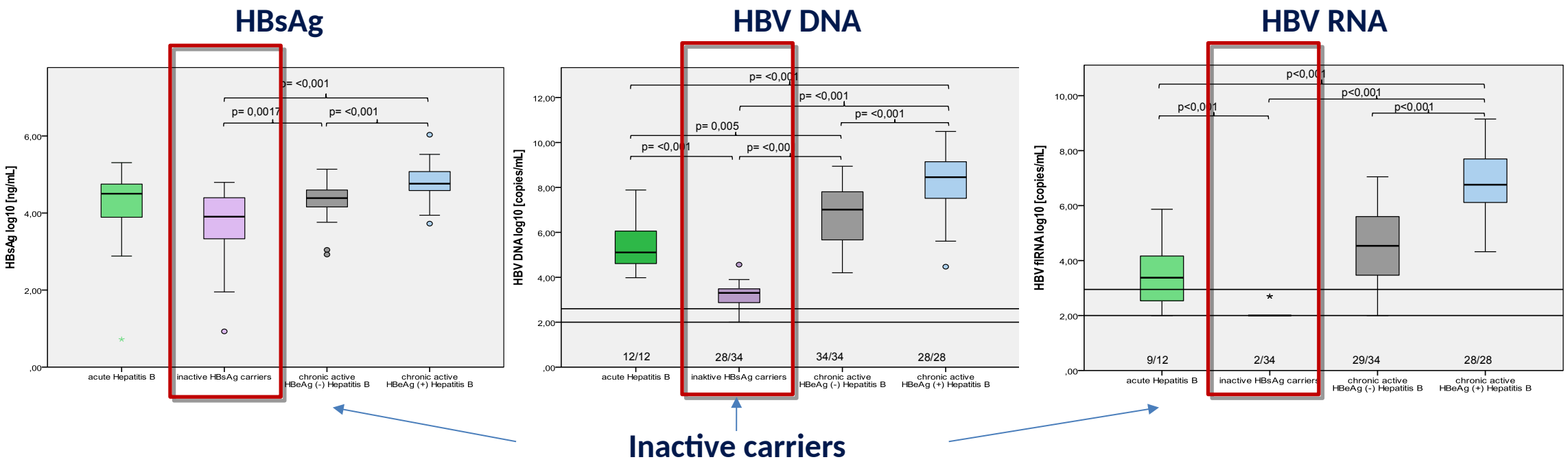


Humanized mouse model infected with HBeAg-positive wild-type HBV

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

Serum HBV RNA - a disease activity marker?

Quantitative serum HBV RNA levels at different phases of the chronic HBV infection

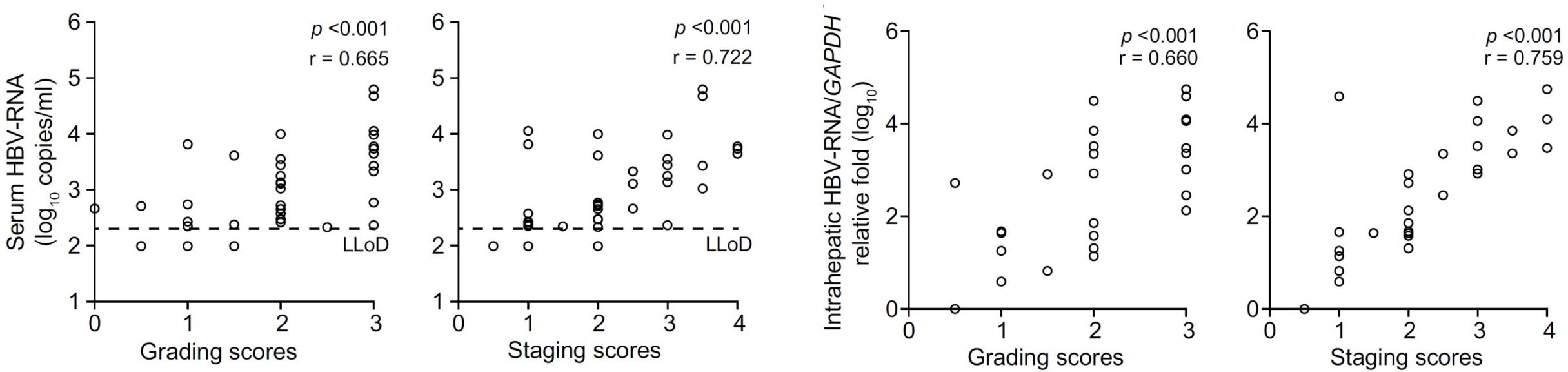


Inactive carriers

The upper and lower end of the bar features the 75- and 25-percentile. The mark inside the bar indicates the median. Significant results are given with significance level in the figure. The proportion of positive samples are indicated among the bars.

Krauel et al. (2016) 32nd annual Meeting of the German Association of the Study of the Liver, GASL

Association between serum and intrahepatic HBV RNA levels and liver histopathology in patients under entecavir treatment

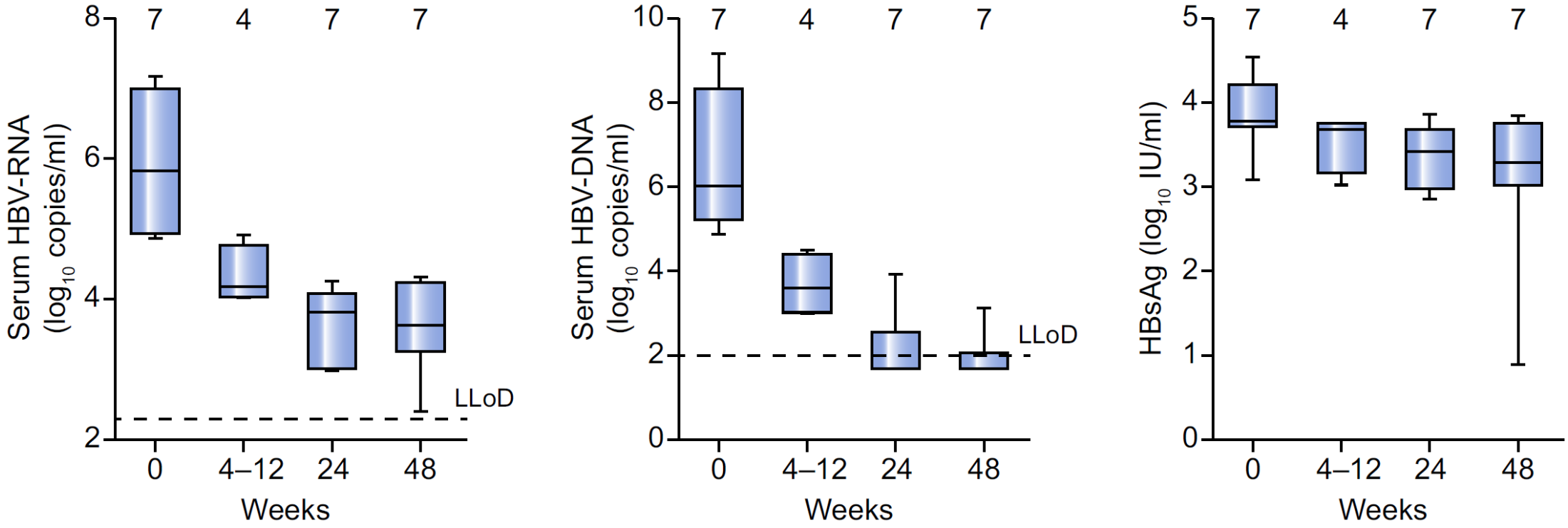


A serum HBV-RNA level cut-off of 2.45 log_{10} copies/mL had the highest accuracy for distinguishing mild (score <2) from severe liver histopathology

Wang J et al. J Hepatol 2018; 68: 16-24

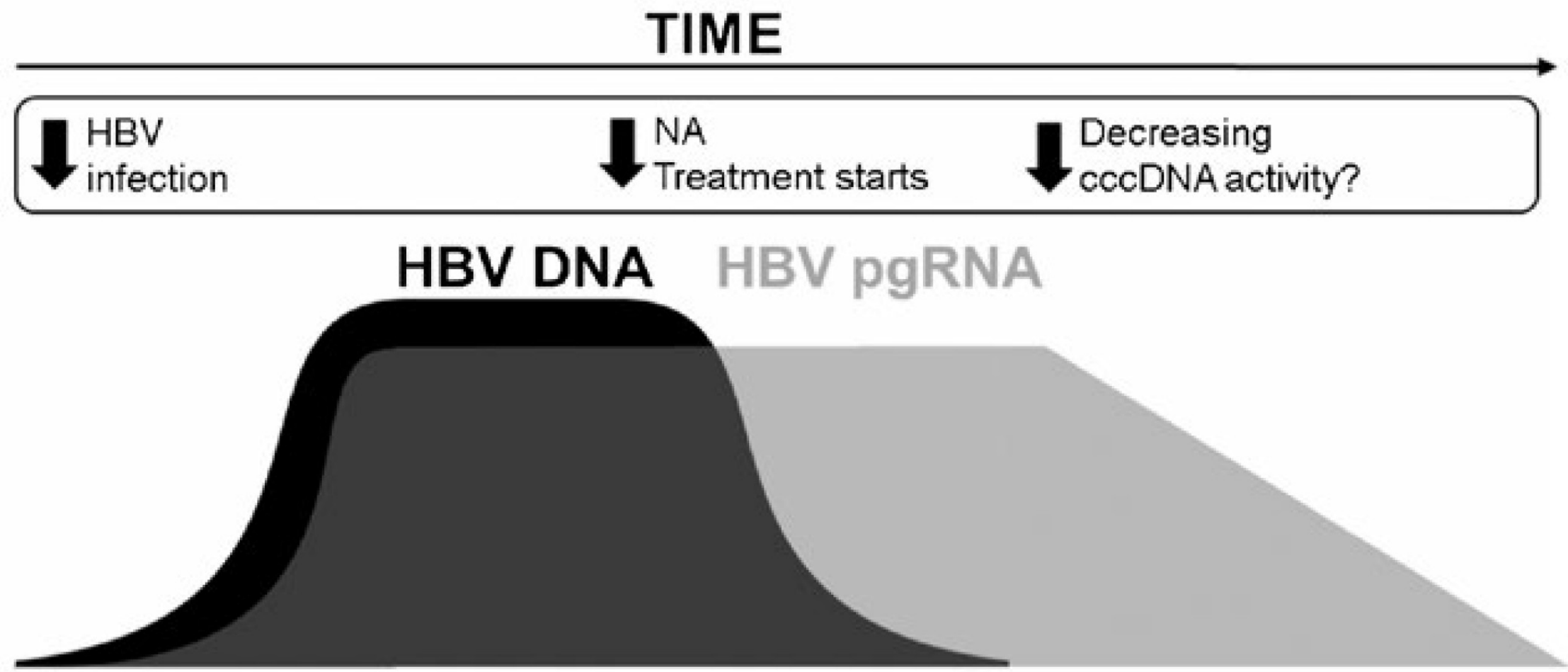
Serum HBV RNA for predicting treatment response?

Kinetics of HBV serum markers during 48 weeks of entecavir therapy



Wang J et al. J Hepatol 2018; 68:16-24

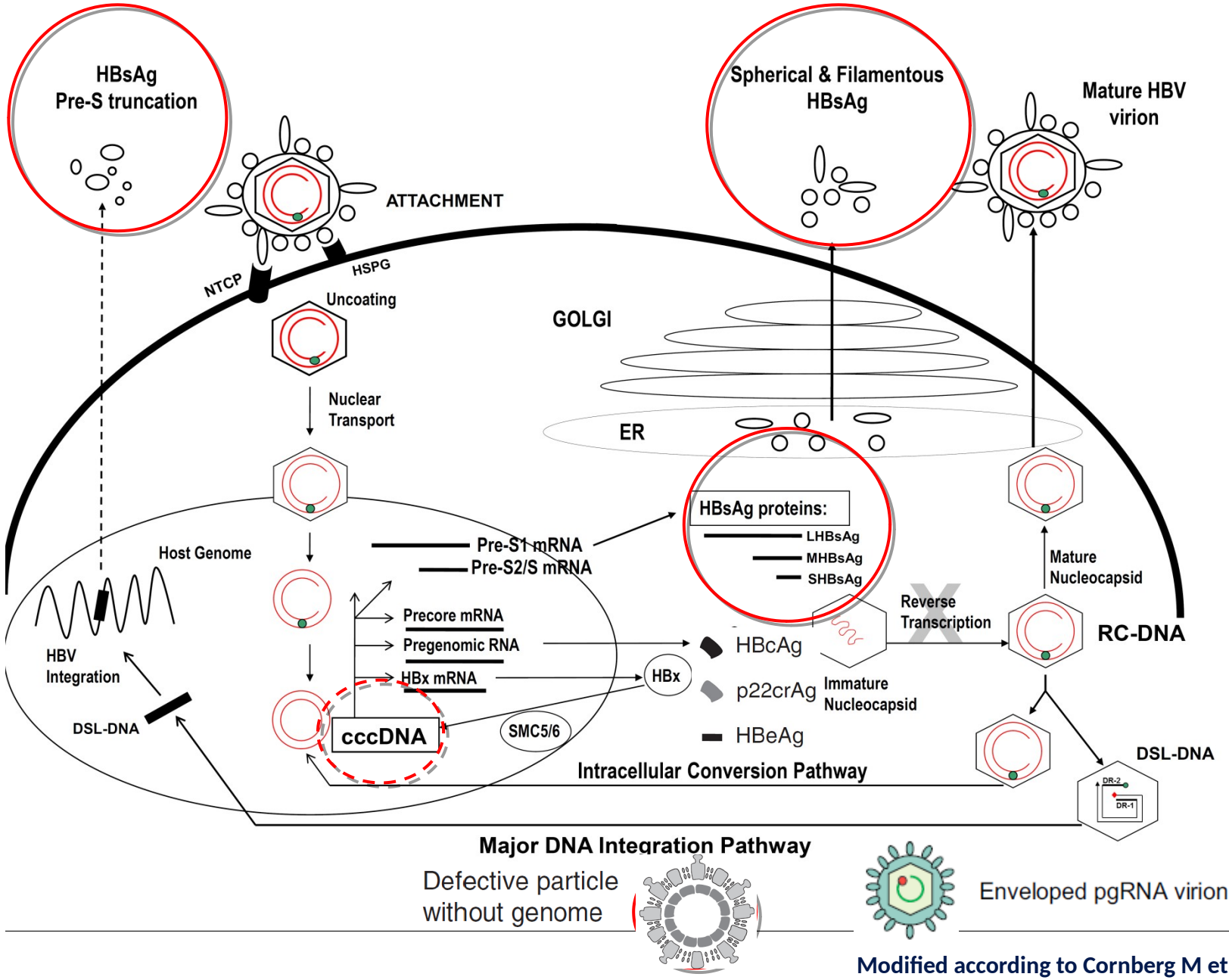
Effect of NA treatment on serum HBV nucleic acids kinetics



Butler EK et al. Hepatology 2018; 68: 2106

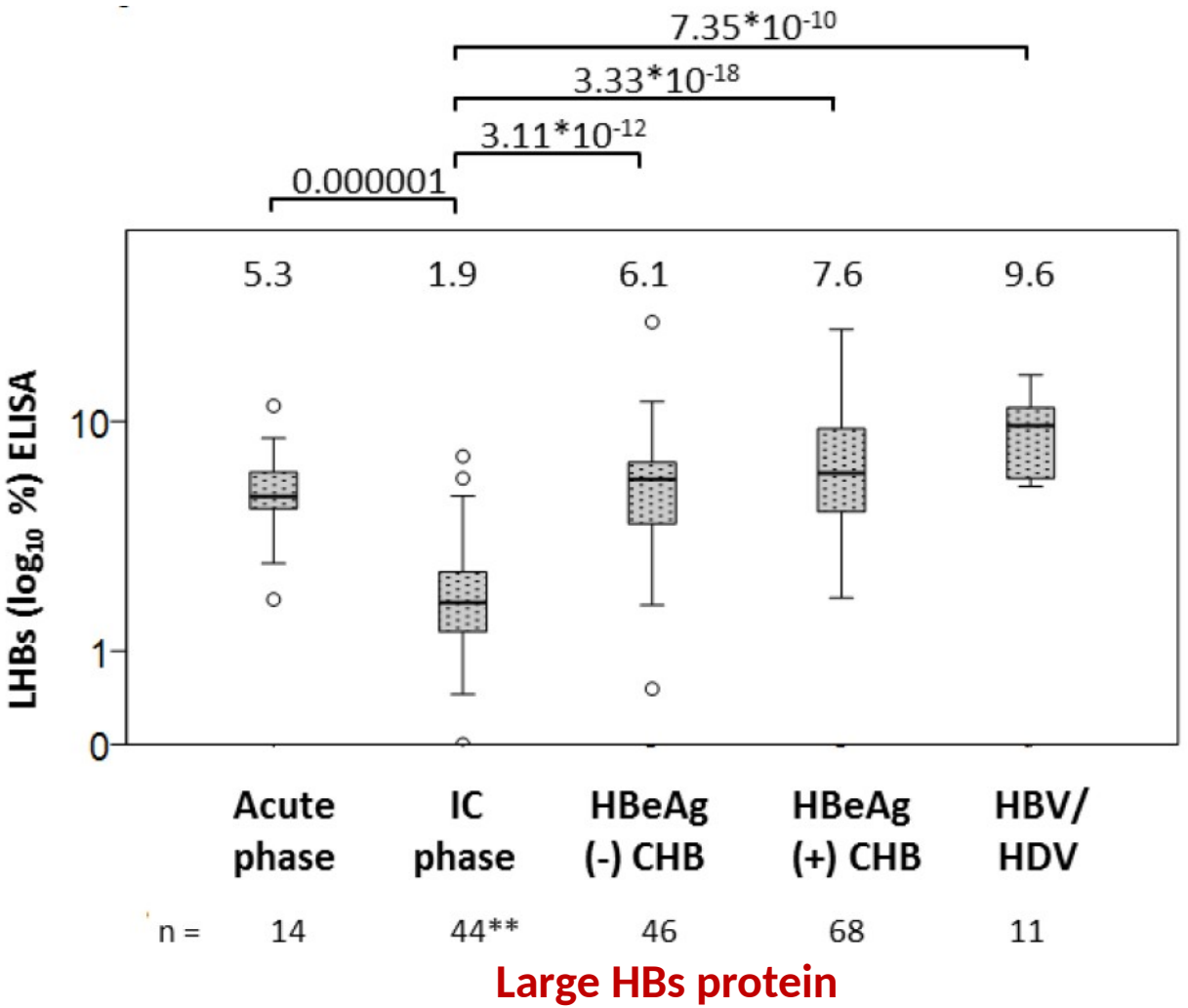
HBsAg components

Potential biomarkers for assessing endpoints – HBsAg components

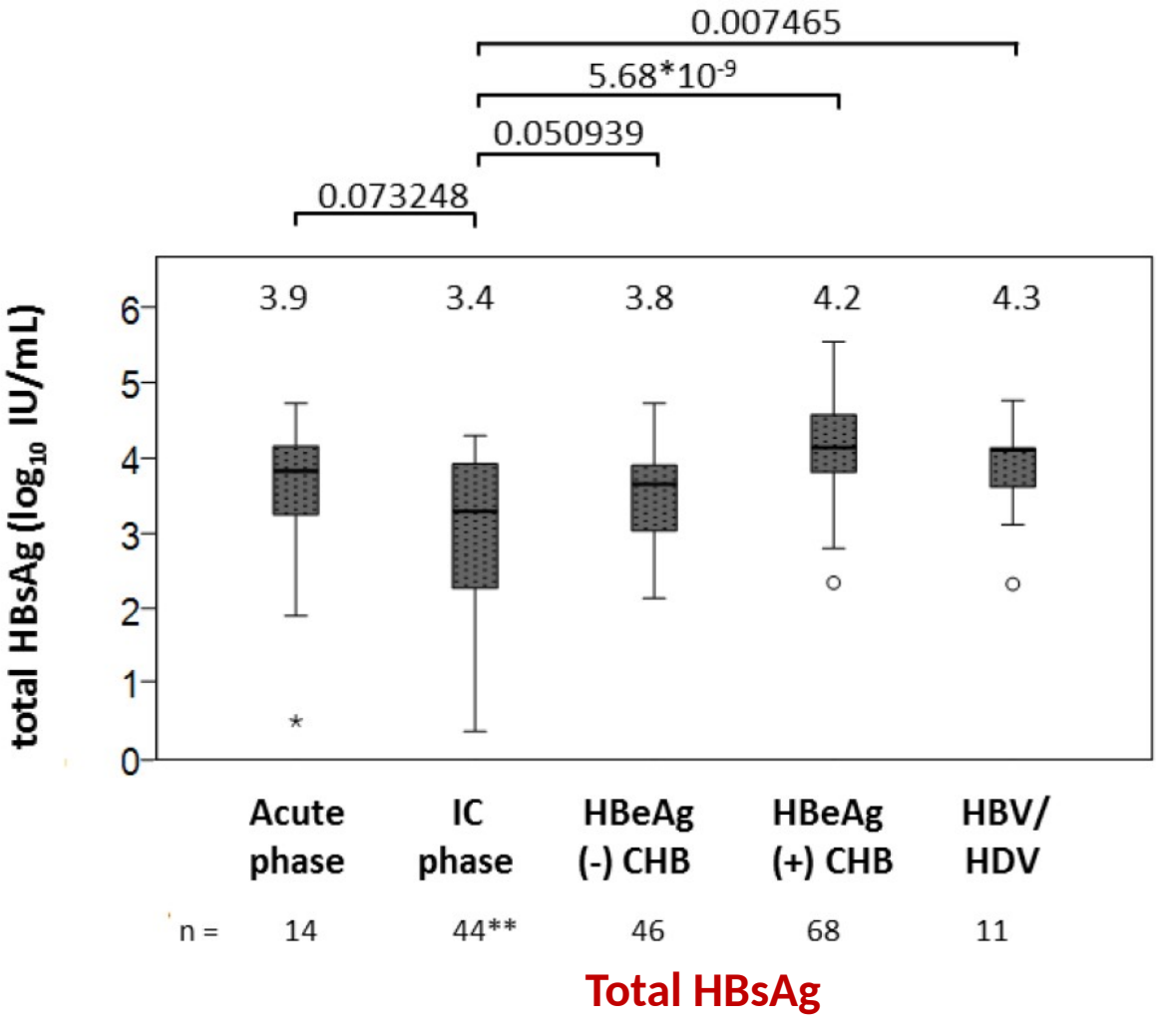


Modified according to Cornberg M et al. J Hepatol 2016, August 17 epub

Low-level of large and middle HBsAg protein better describe inactive infection as compared to total HBsAg



Large HBs protein



Total HBsAg

Pfefferkorn M et al. Gut 2017;0:1–9

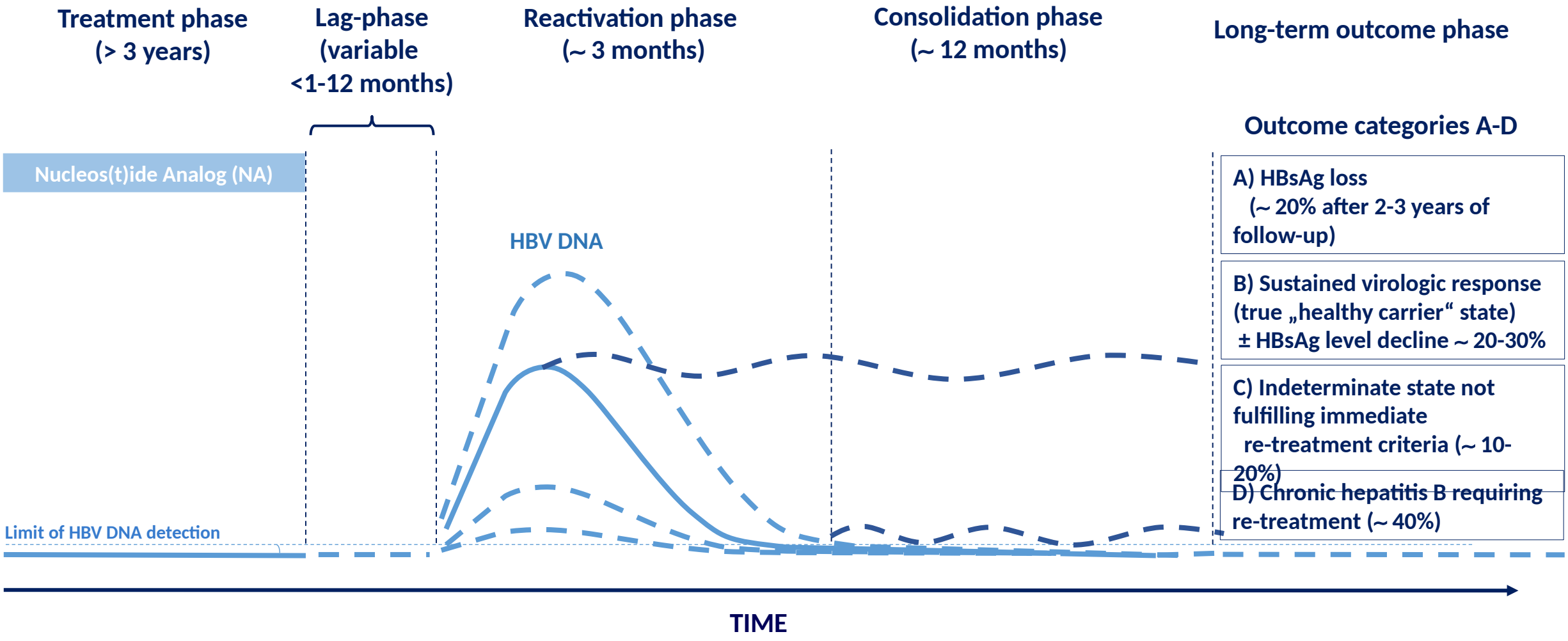
EASL Clinical Practice Guideline - Why aiming for HBsAg loss?

- **The main advantage of HBsAg loss is that it allows a safe discontinuation of antiviral therapy**

EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67:370

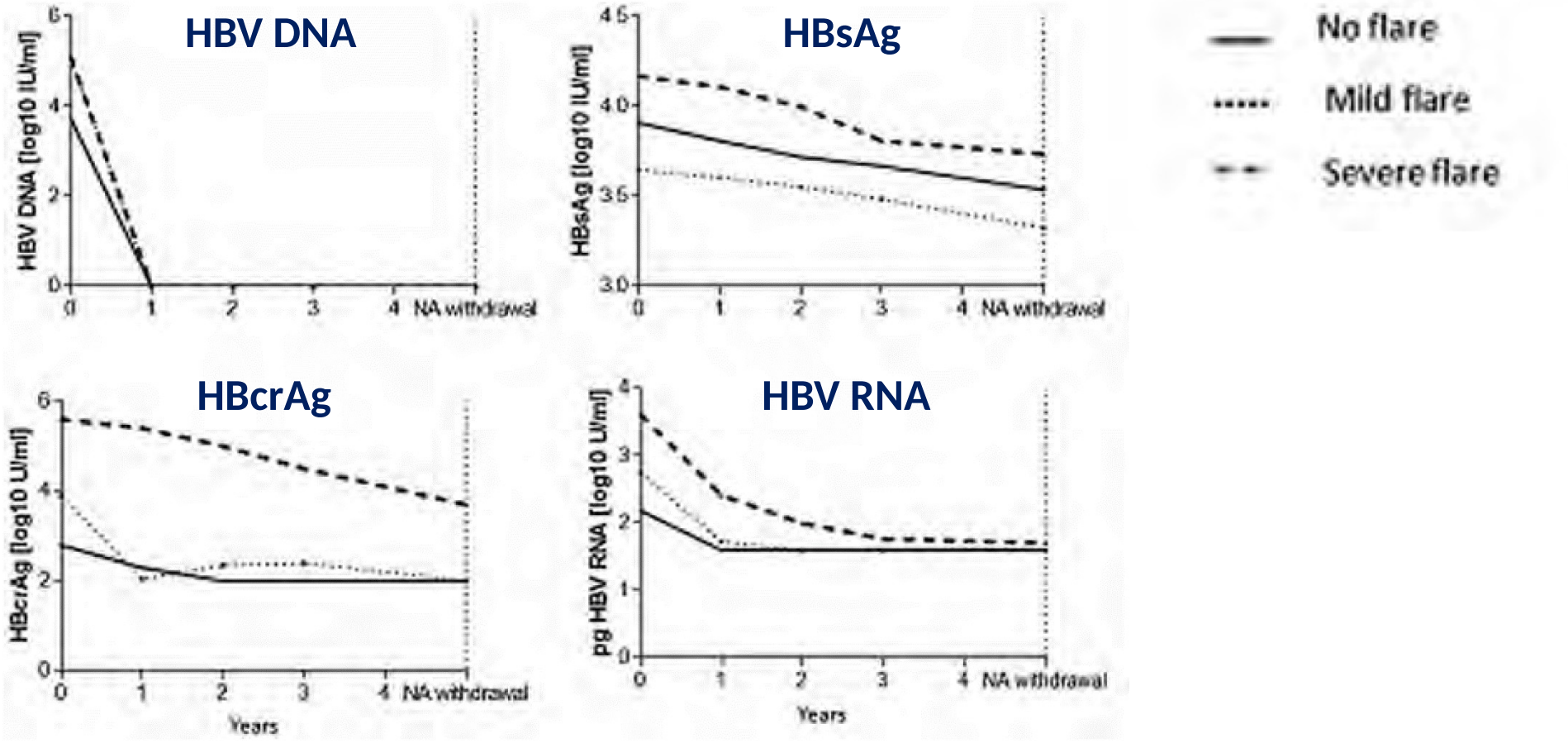
New biomarkers helpful in predicting outcome after stopping a finite course of HBV treatment?

NA discontinuation frequently results in virologic and biochemical flares that runs through different phases



Lampertico P and Berg T. Hepatology 2018; 68: 397

The markers of HBV transcriptional activity-HBcrAg and pgHBV RNA during antiviral therapy with nucleos(t)ide analogue help to predict optimal timing of therapy withdrawal



Carey I et al. J Hepatol 2019;70:e33–e34

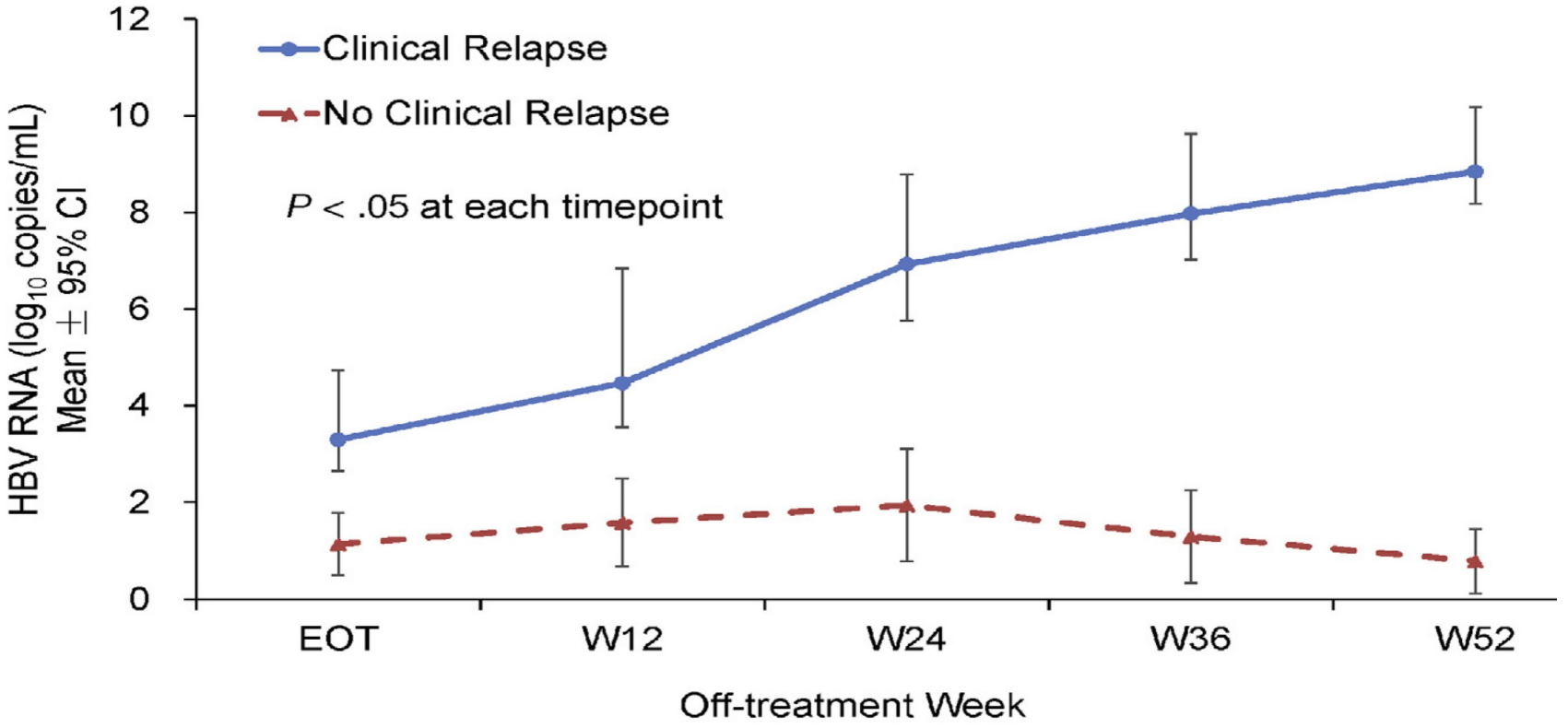
Association of HBV RNA (pgRNA virion levels) and viral rebound after discontinuation of NUCs

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.

Wang J et al. J Hepatol 2016, epub (May 28)

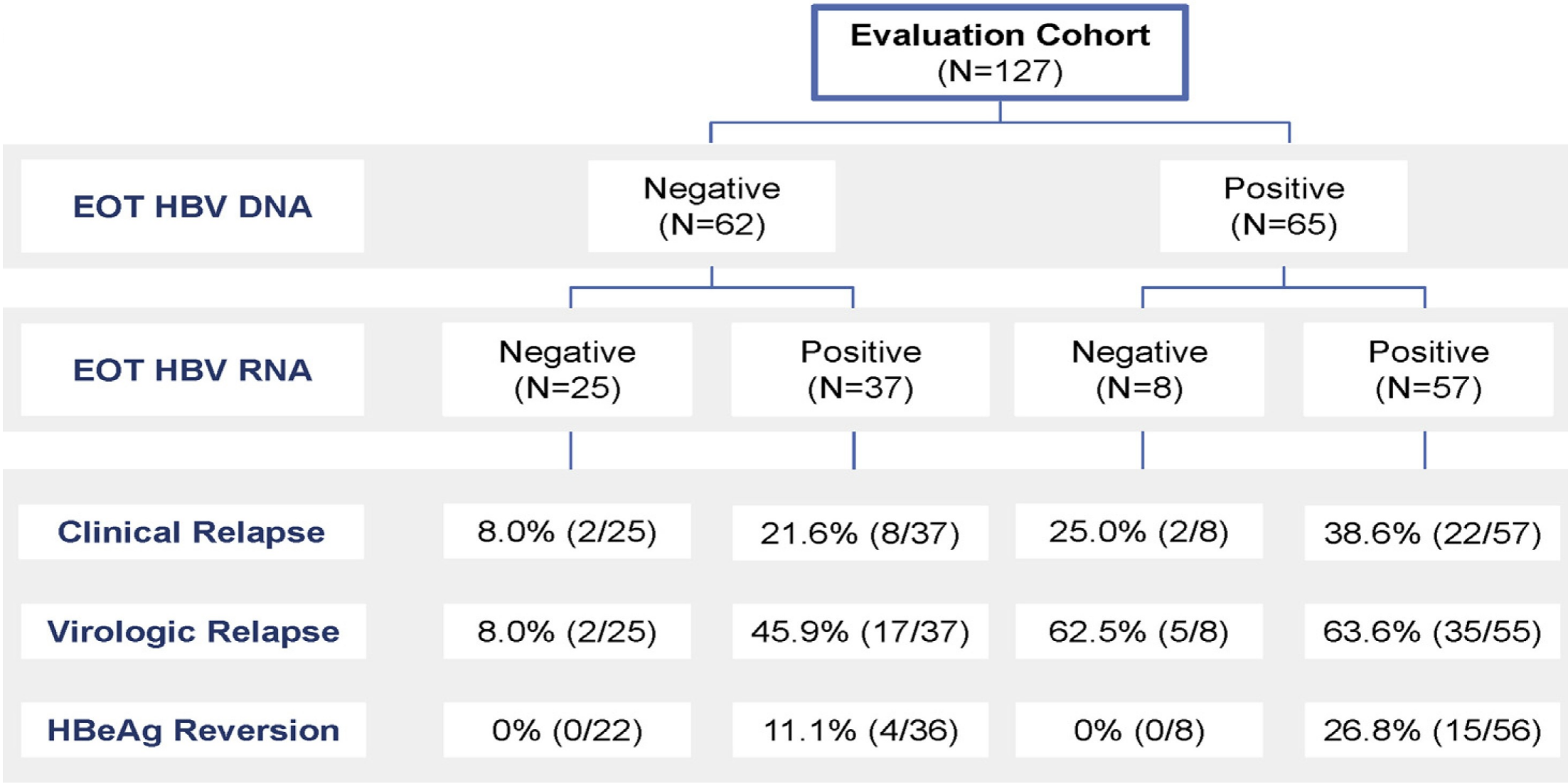
End-of-treatment HBV RNA levels predict the risk of relapse after stopping NA in HBeAg positive patients with seroconversion



Clinical Relapse	N	7	7	6	3	2
	Median	3.7	4.4	7.5	8.1	8.8
	P25-75	3.1 - 4.2	3.2 - 6.1	6.9 - 8.1	7.5 - 8.5	8.7 - 9.0
No Clinical Relapse	N	25	25	24	23	21
	Median	0	0	0	0	0
	P25-75	0 - 3.0	0 - 3.3	0 - 3.2	0 - 3.0	0 - 0.8

Fan R et al. Clin Gastroenterol Hepatol 2019; S1542-3565(19)30790-6 (Epub)

End-of-treatment HBV RNA levels predict the risk of relapse after stopping NA in HBeAg pos. patients with seroconversion



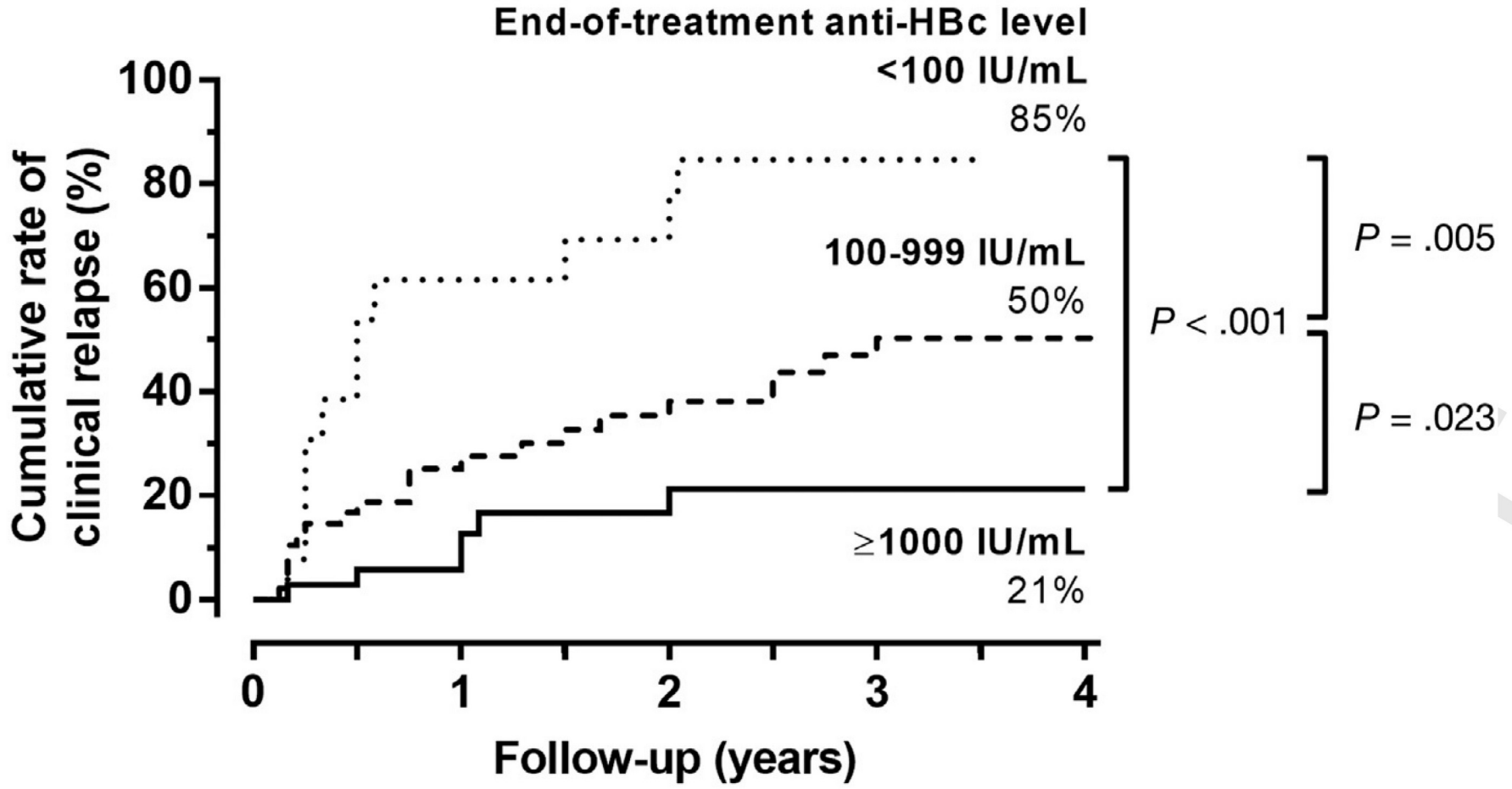
Fan R et al. Clin Gastroenterol Hepatol 2019; S1542-3565(19)30790-6 (Epub)

Clinical utility of quantitative anti-HBc levels

- Anti-HBc levels are higher in HBsAg-positive patients as compared to those being anti-HBs-positive (but anti-HBc affinity was lower in chronic infection than during recovery)[1]
- Low anti-HBc levels are associated with HBsAg seroclearance (cut-off < 3log)[2]
- Serum levels of anti-HBc correlate with cccDNA positivity in OBI[3]
- Anti-HBc levels (cut-off ≥ 6.41 IU/ml) were significantly associated with high risk of HBV reactivation during immunosuppressive therapy[4]

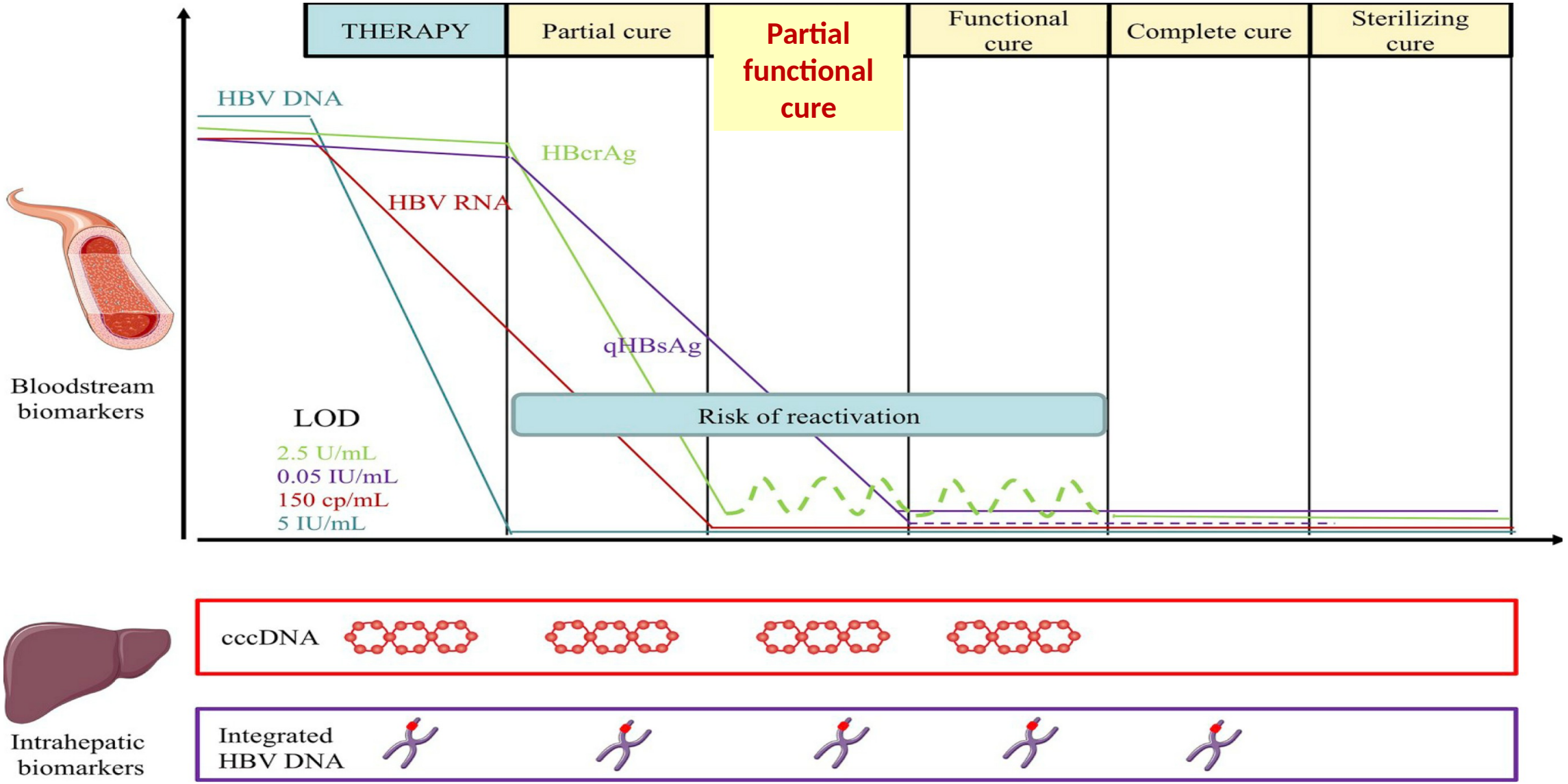
[1]Han et al. J Clin Virol. 2011;52(4):295-9
[2]Hu et al. Clin Gastroenterol Hepatol. 2018 [Epub ahead of print]
[3]Caviglia et al. J Hepatol. 2018;69(2):301-307
[4]Yang et al. J Hepatol. 2018 Aug;69(2):286-292.

Serum level of antibodies against hepatitis B core protein is associated with clinical relapse after discontinuation of nucleos(t)ide analogue therapy



Chi H et al. Clin Gastroenterol Hepatol 2019;17(01):182–191.e1

Classification of HBV-cure with new biomarkers



Charre C et al. Antiviral Res 2019; 169: 104553

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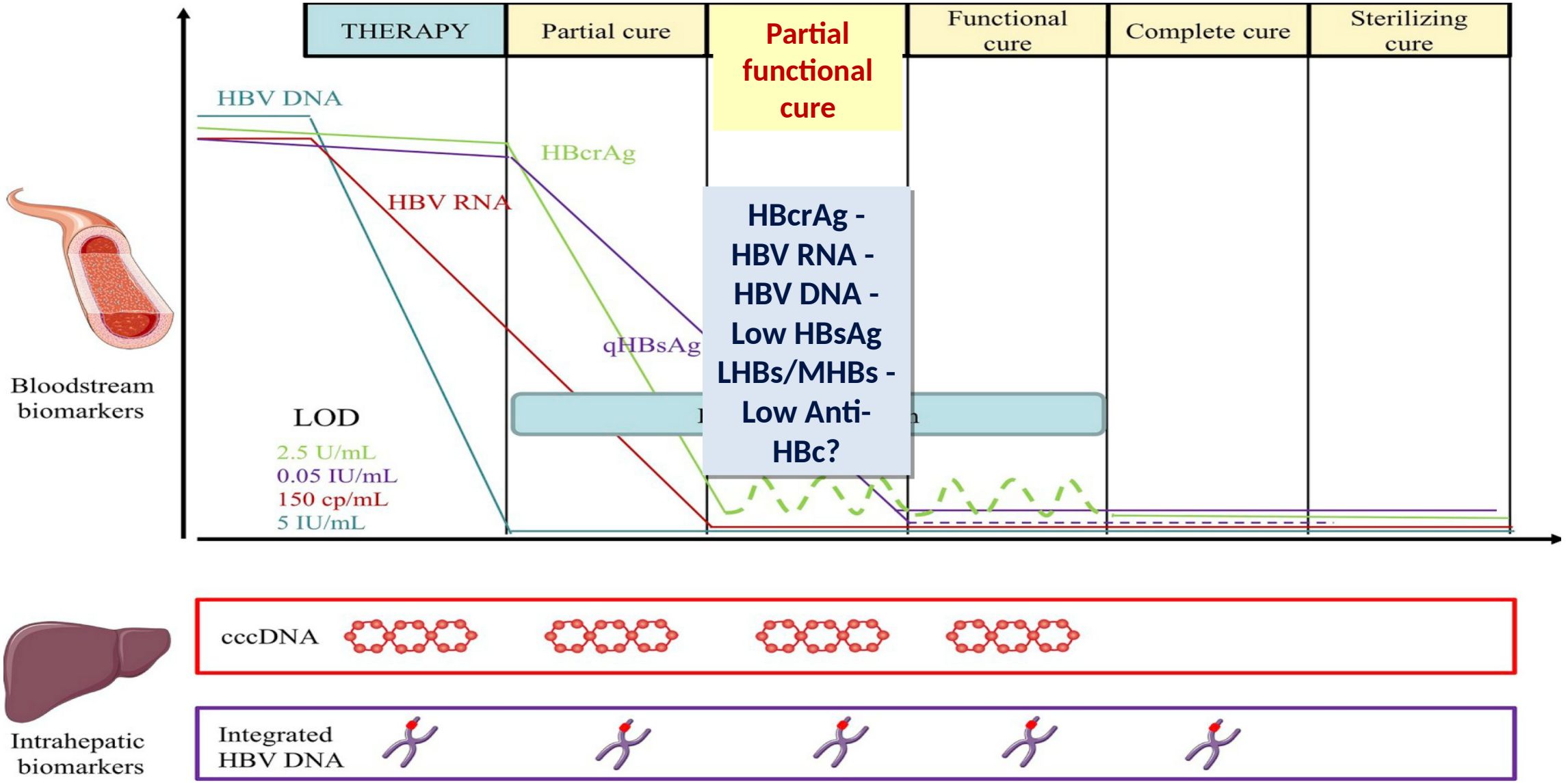
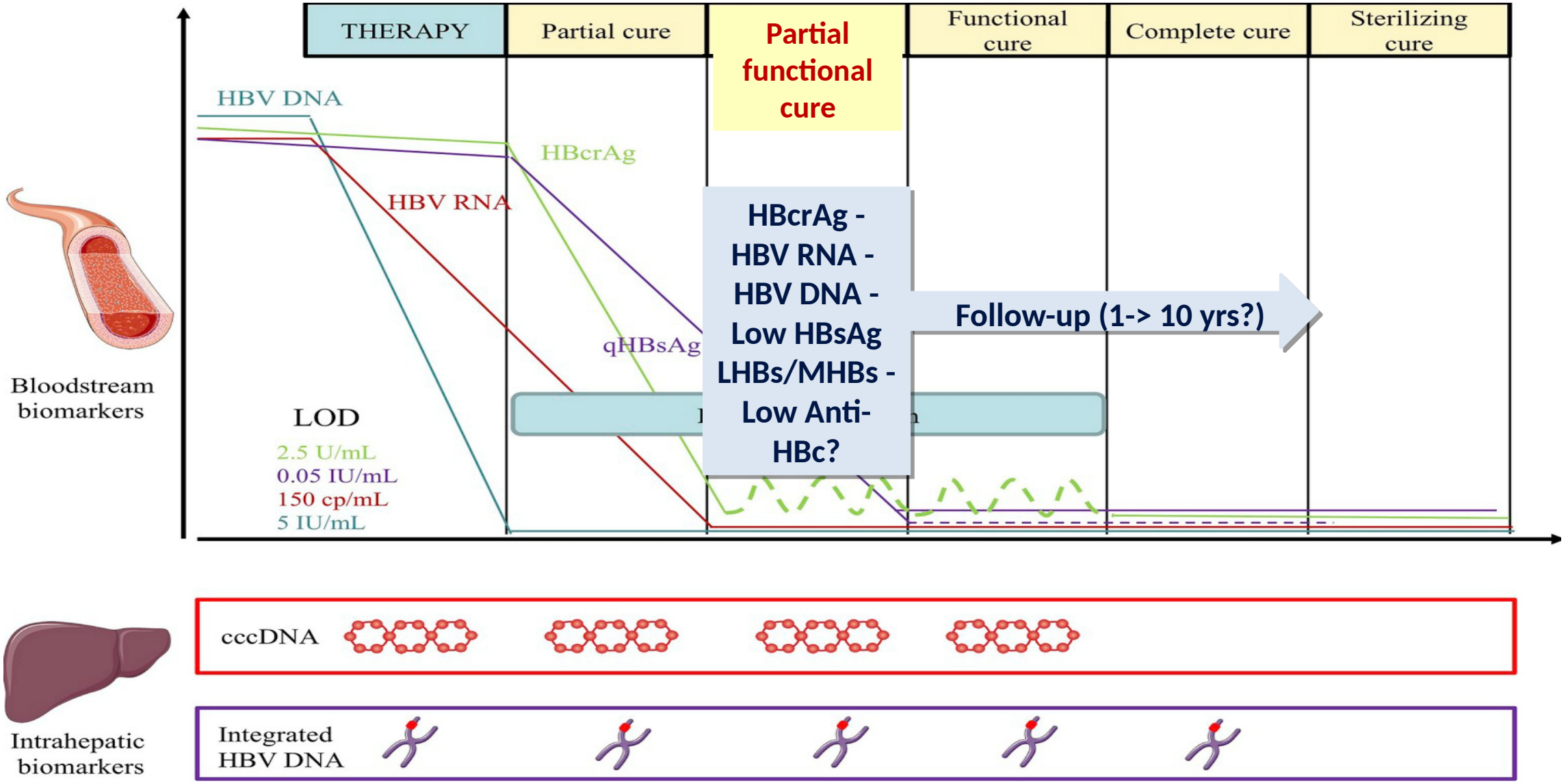


Modified according to Charre C et al. Antiviral Res 2019; 169: 104553

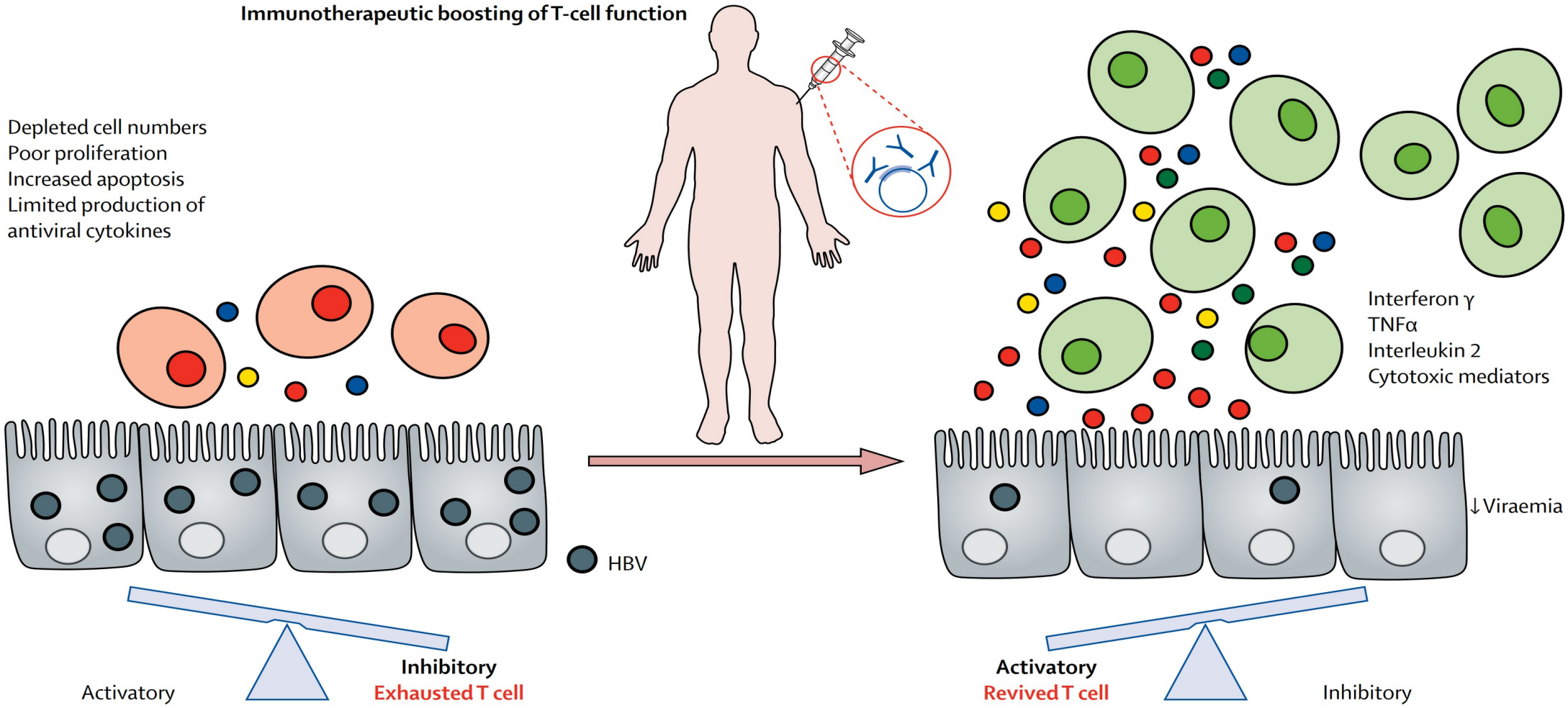
Chance for transition into a true functional or even complete cure stage after having achieved a partial functional cure?



Modified according to Charre C et al. Antiviral Res 2019; 169: 104553

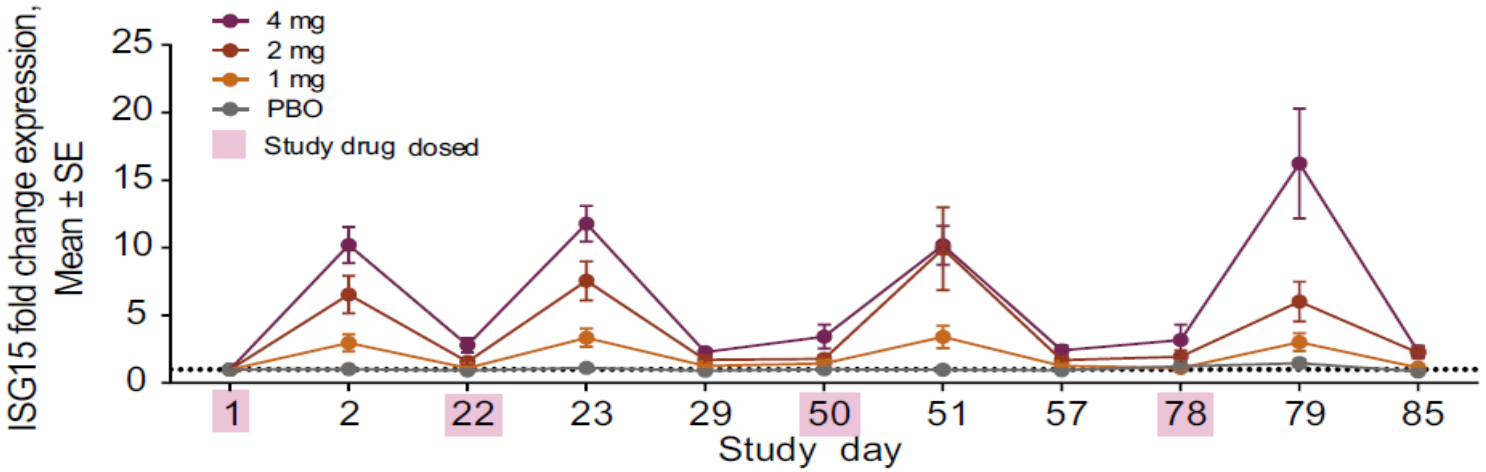
Immunotherapeutic augmentation of therapeutic vaccination

Expand a population of functional T cells, able to clonally expand and produce antiviral cytokines



Maini MK and Pallett LJ. Lancet Gastroenterol Hepatol 2018; 3: 192–202

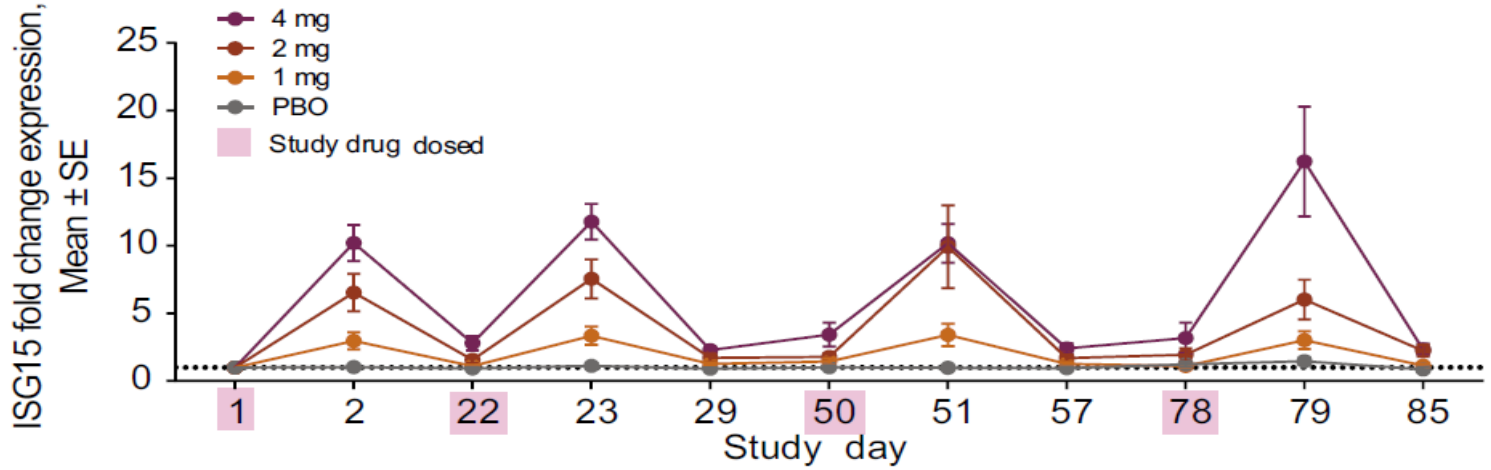
TLR7-Agonist Vesatolimod to Treat Chronic Hepatitis B (Phase-II-Study)



Clear-cut doise-dependent induction of ISG15 expression (ISG15-mRNA, fold changes) under TLR7-stimuation

Janssen, HLA et al., J. Hepatol. 2018; 68: 431-440

TLR7-Agonist Vesatolimod to Treat Chronic Hepatitis B (Phase-II-Study)



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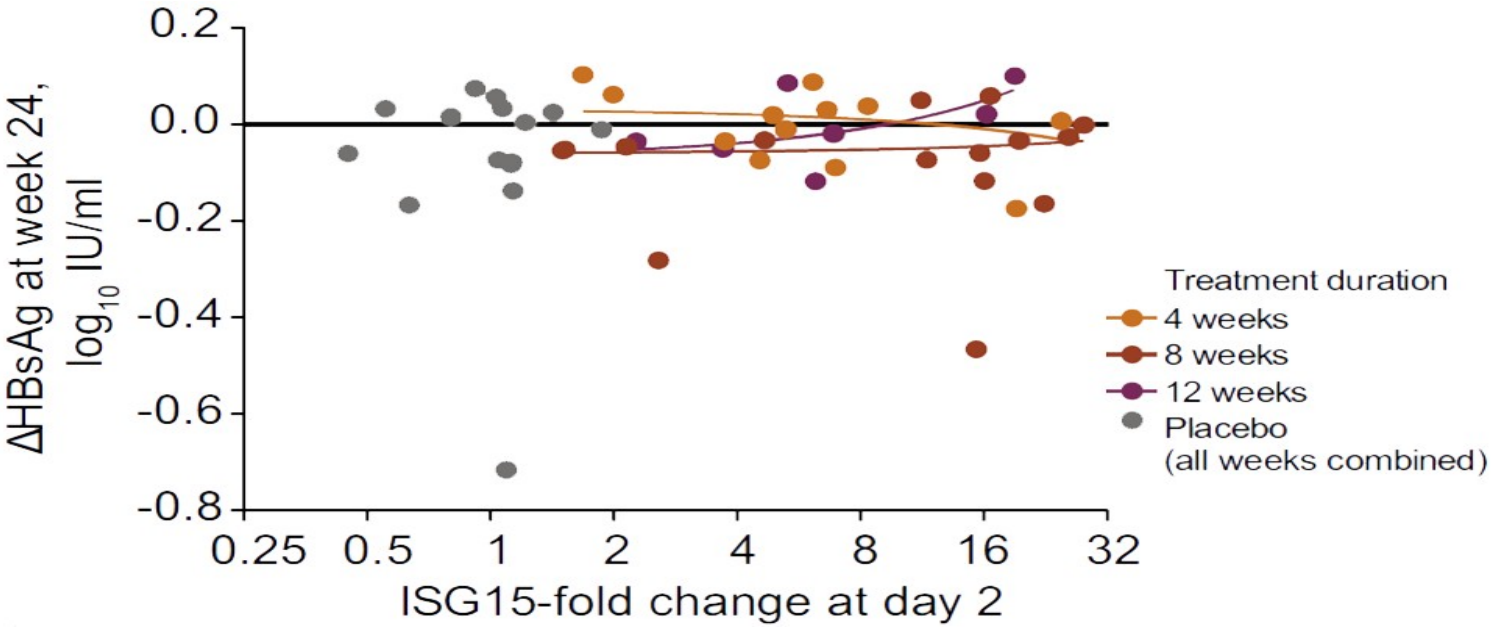
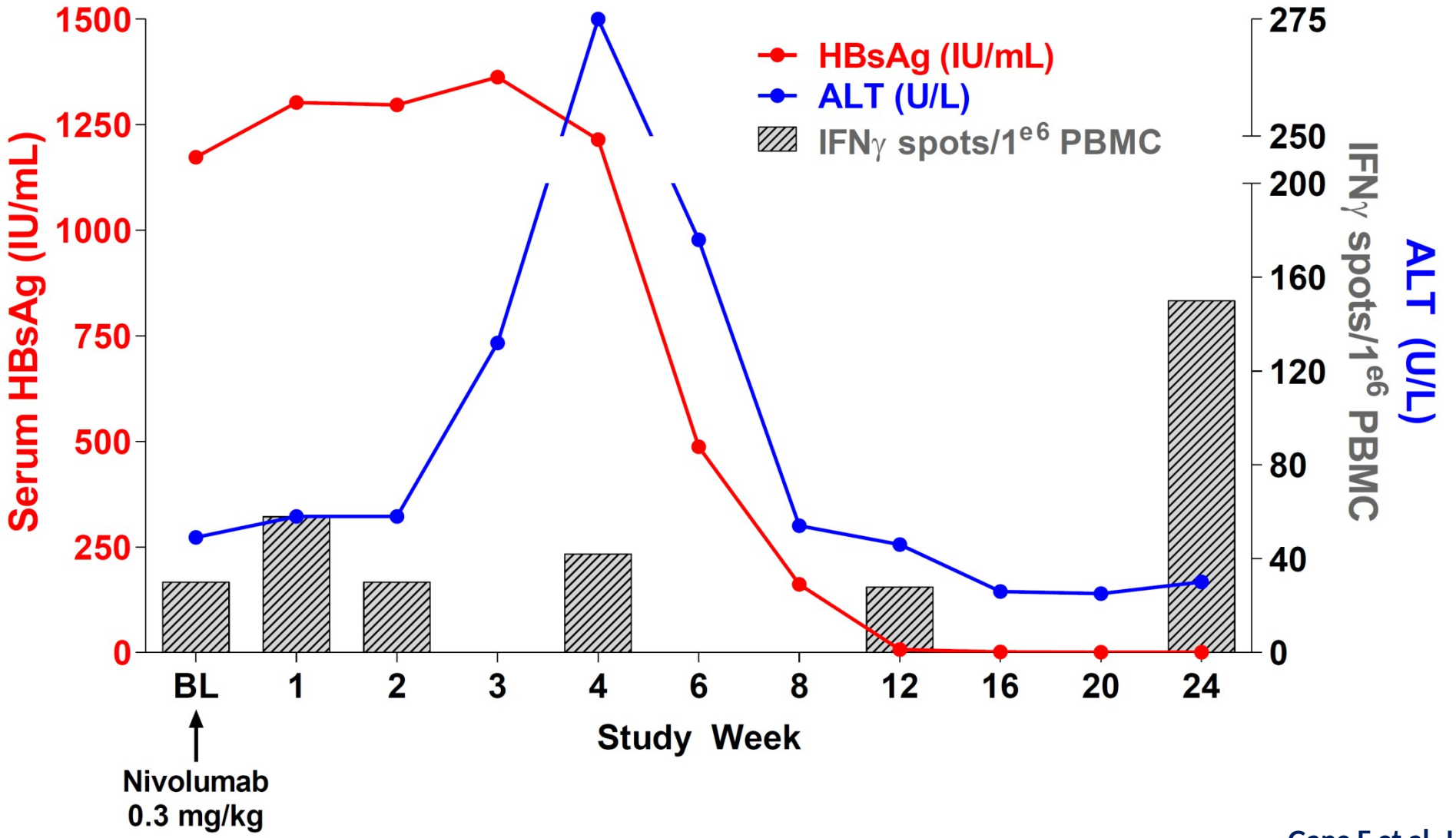


But ….
ISG15 induction not associated with HBsAg decline at week 24

Janssen, HLA et al., J. Hepatol. 2018; 68: 431-440

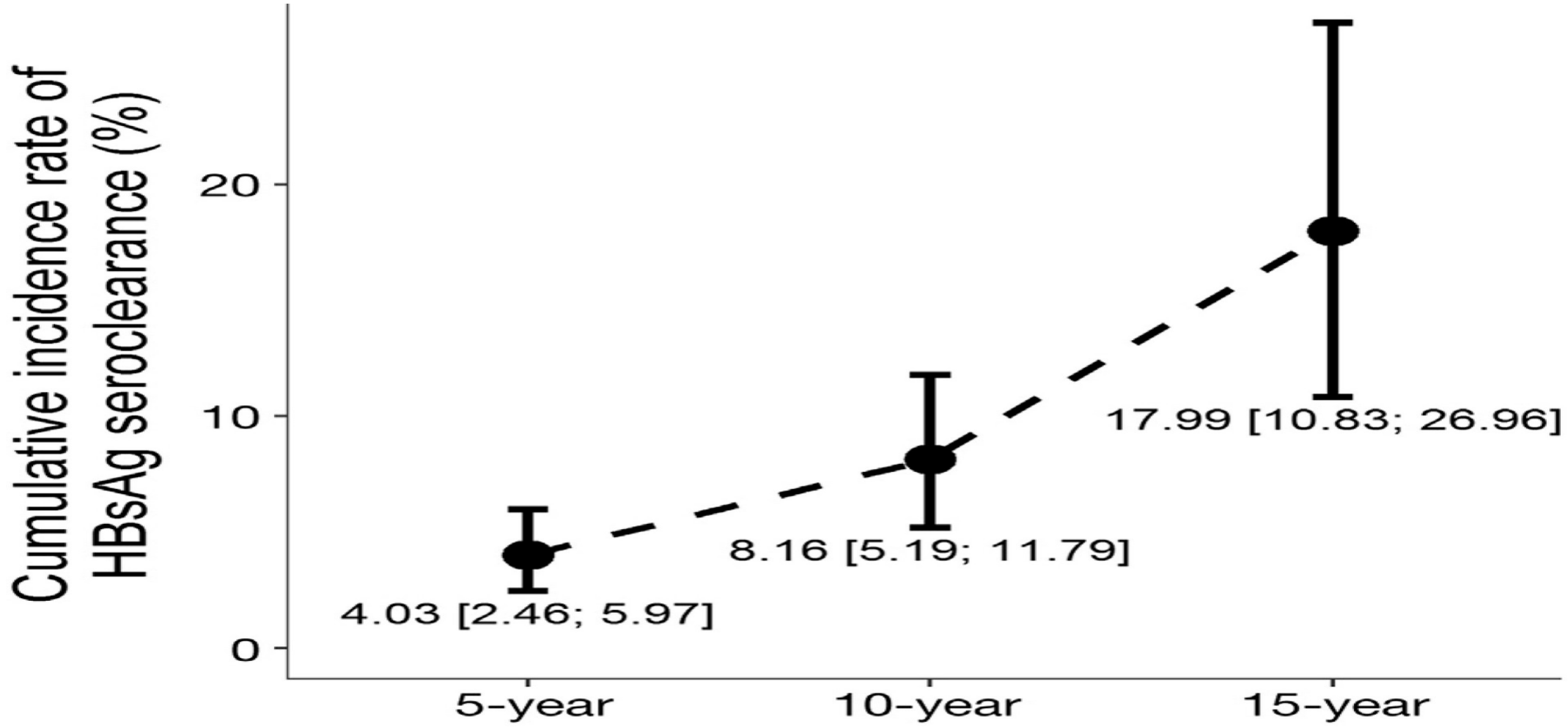
Anti-PD1 (immune checkpoint) blockade with nivolumab w/wo therapeutic vaccine in virally suppressed paitents



Gane E et al. J Hepatol 2019, epub

Inzidenz der HBsAg Serumclearance

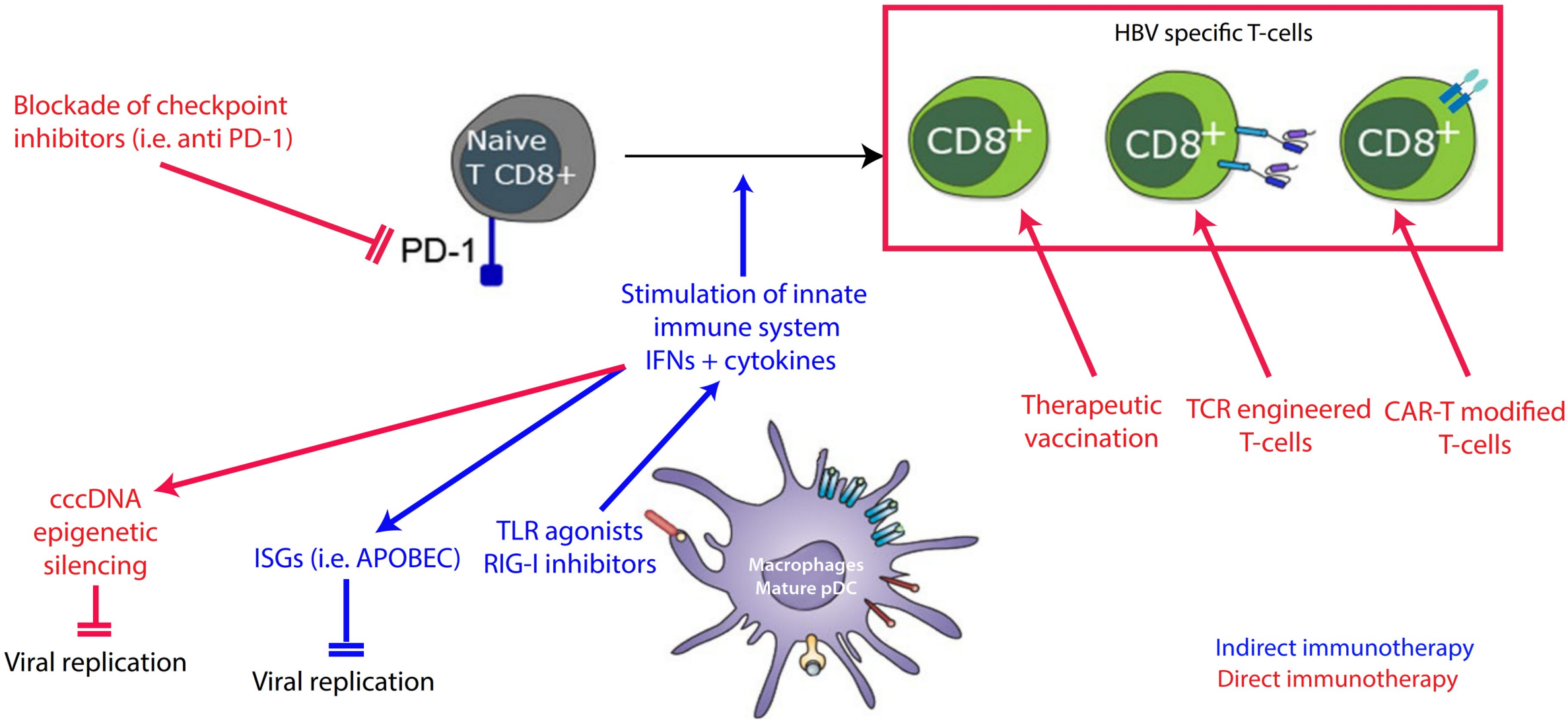
Yeo YH et al. Gastroenterology 2019;156(3):635-646



Hepatitis B core-related antigen

- Composite marker comprises HBcAg, HBeAg and a 22kDa truncated core-related protein (p22cr)
- Available since 2014 fully automated quantitative assay (Lumipulse)
- Not influenced by translation of integrated sequences
- Surrogate marker for cccDNA and its transcriptional activity
- Sensitivity problems (3log)

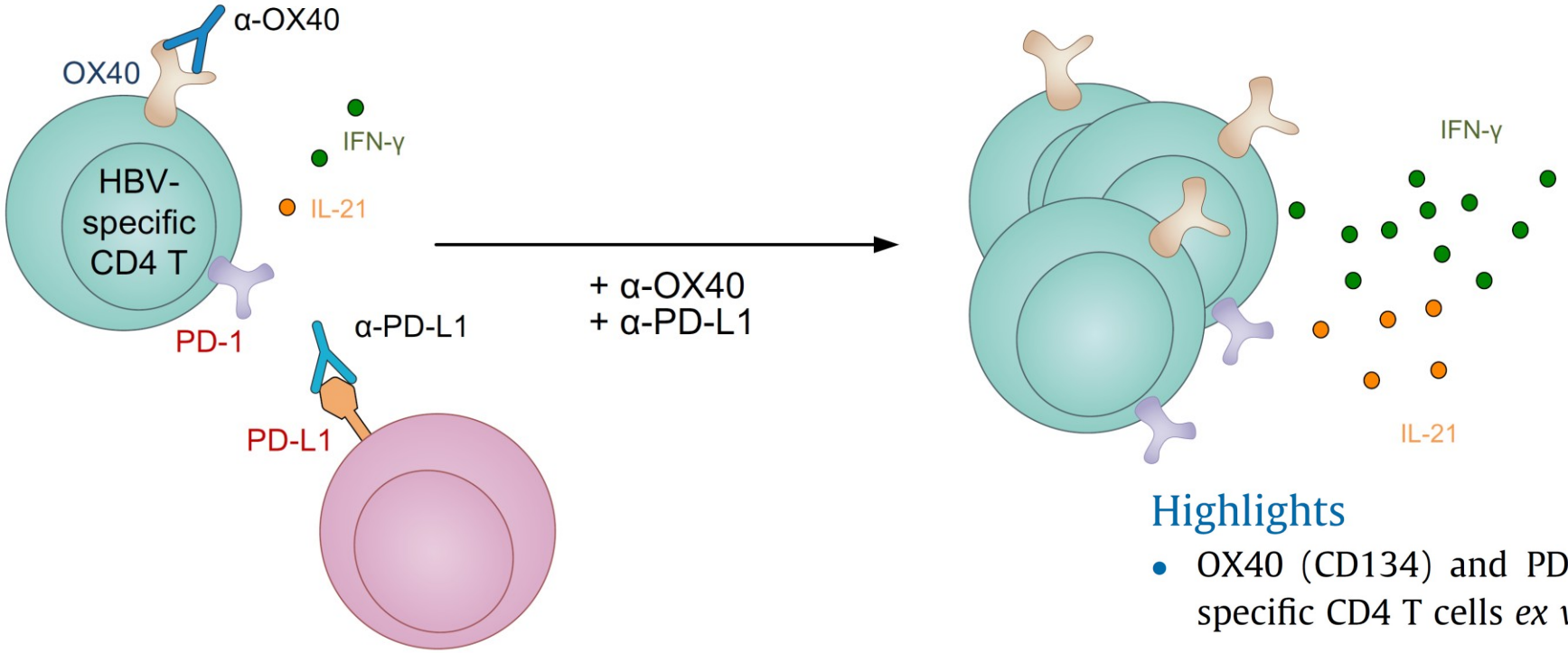
HBV replication cycle and main targets of viral therapies



Martinez M et al. J Viral Hepatol 2019; doi:10.1111/jvh.13090

Augmenting HBV-specific CD4 T cells - it takes two to tango

Functionally augmented HBV-specific CD4 T cells were observed only when combining OX40 stimulation and PD-L1 blockade

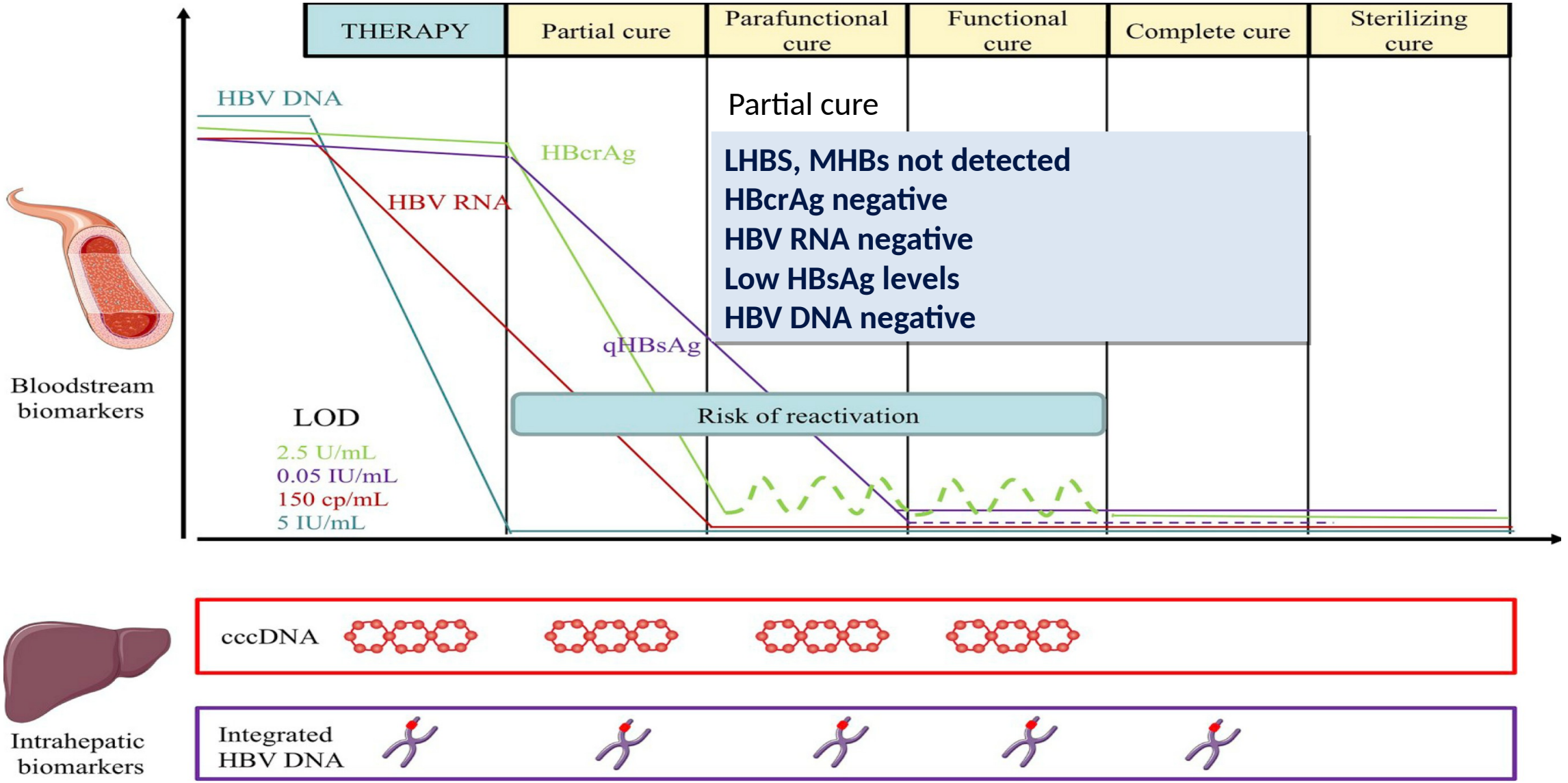


Highlights

- OX40 (CD134) and PD-1 are strongly expressed on HBV-specific CD4 T cells *ex vivo*.
- The HBV-specific CD4 T cells predominantly target the polymerase and core proteins.
- Combined OX40 stimulation and PD-L1 blockade functionally augment HBV-specific CD4 T cells.

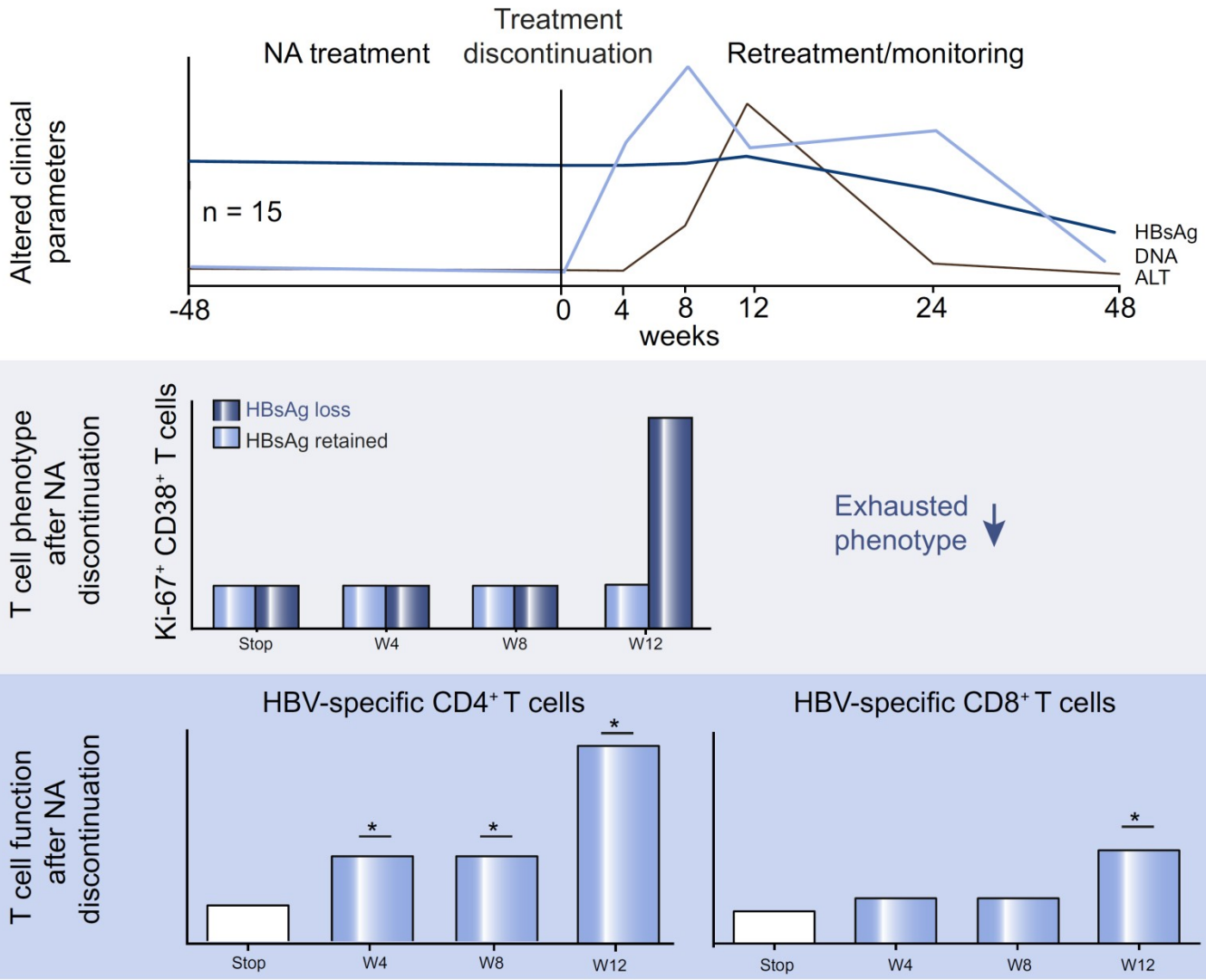
Jacobi FJ et al. J Hepatol 2019; 70: 1103

Does HBsAg positive „cure“ of the disease and disease associatedn outcomes exist? How to best define HBsAg positive cure of active infection



Charre C et al. Antiviral Res 2019; 169: 104553

HBV-specific T cell responses after stopping NA

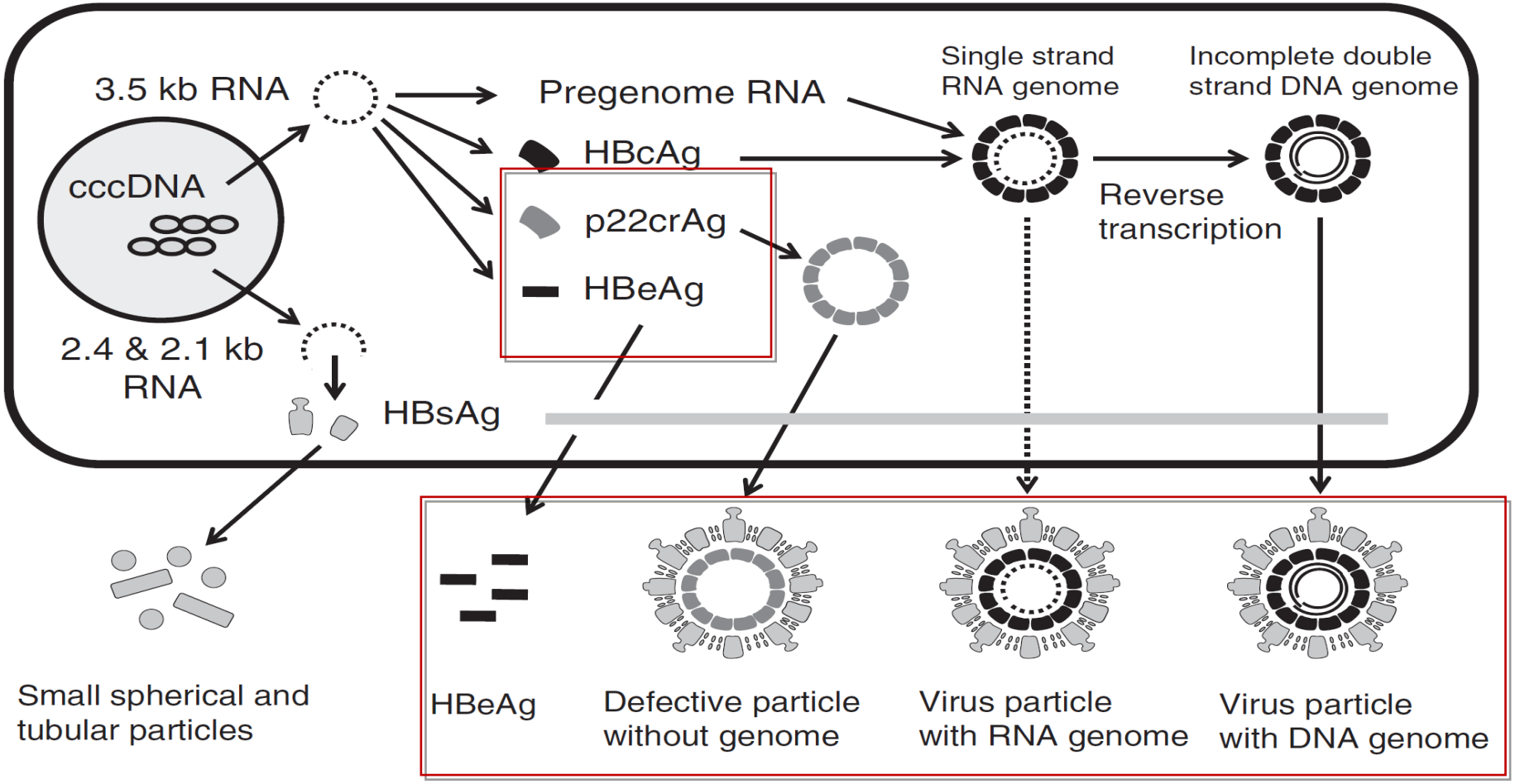


- Discontinuation of NA therapy leads to higher HBsAg loss rates in HBeAg-negative CHB patients.
- T cells from patients with subsequent HBsAg loss show a less exhausted phenotype.
- These T cells also express higher levels of activation and proliferation markers at week 12 after discontinuation of therapy.
- Relapse of active HBV replication may trigger immunological environment that enhances responsiveness of HBV-specific T cells *in vitro*.

Rinker F et al. J Hepatol 2018; 69: 584

Secreted factors of hepatitis B virus

Secreted particles and proteins considered by the measurements of HBcrAg versus HBsAg

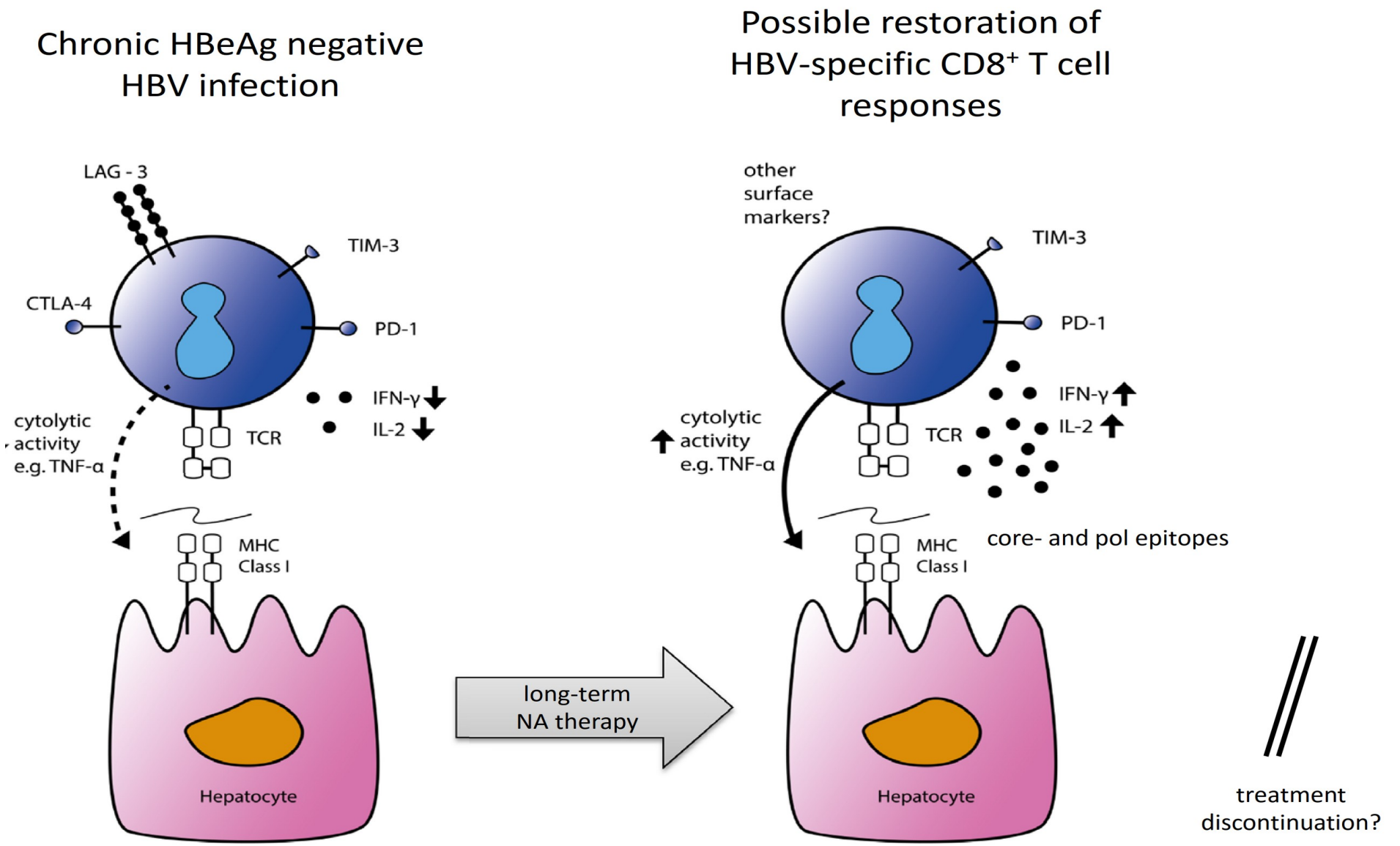


Hepatitis B Virus DNA-negative Dane particles containing a 22-kDa precore protein (exceeding Dane particles by ~ 100 fold)

Kimura T et al. JBC 2005; 280: 21713; Luckenbaugh L et al. J Viral Hepat 2015; 22: 561

Figure modified according to Tanaka E and Matsumoto A. Hepatol Res 2014; 44: 1-8

Possible restoration of HBV specific CD8+ T-cell function

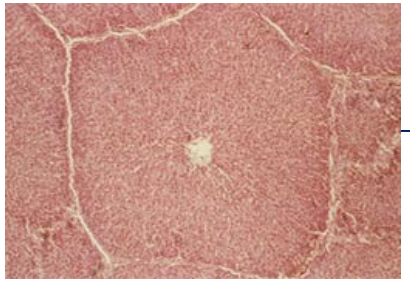


Lang J et al. Hepatology International (2019) 13:113–124

The HBV journey

HBV infection = A fibrotic liver disease

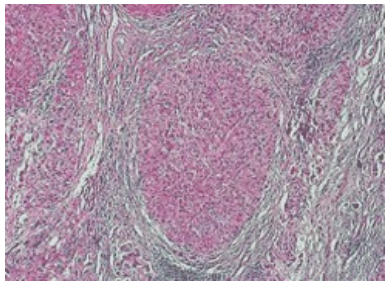
normal liver



Disease progression predictable by fibrosis measurement over time

F1 → F2 → F3 →

Cirrhosis

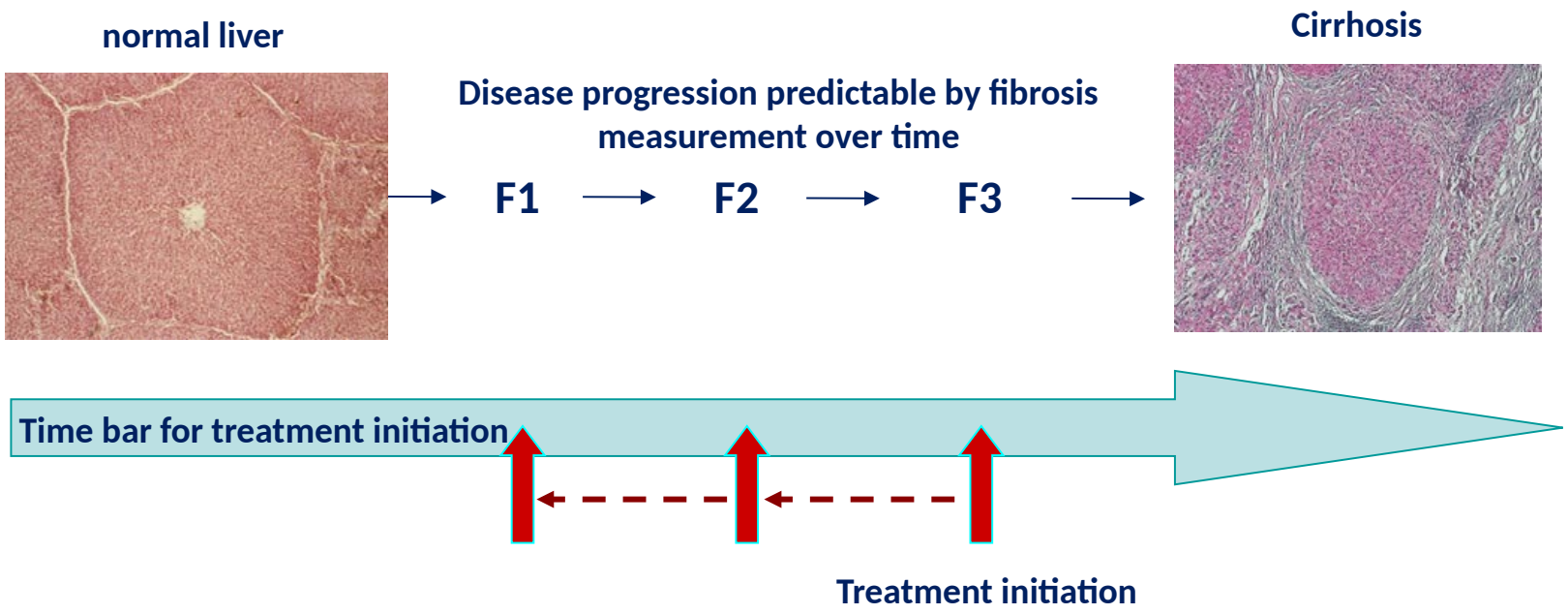


Time bar for treatment initiation

Treatment initiation

The HBV journey

HBV infection = A fibrotic liver disease

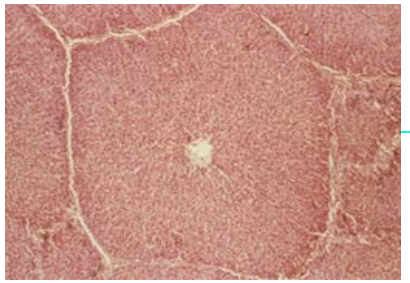


5 years after start of therapy

The HBV journey

HBV infection = A fibrotic liver disease

normal liver



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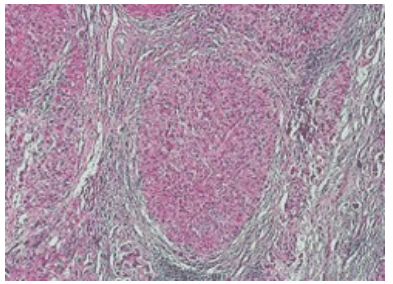

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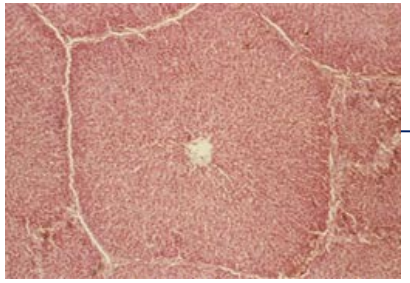
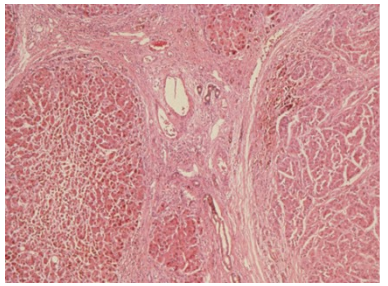


? → ? → ? →

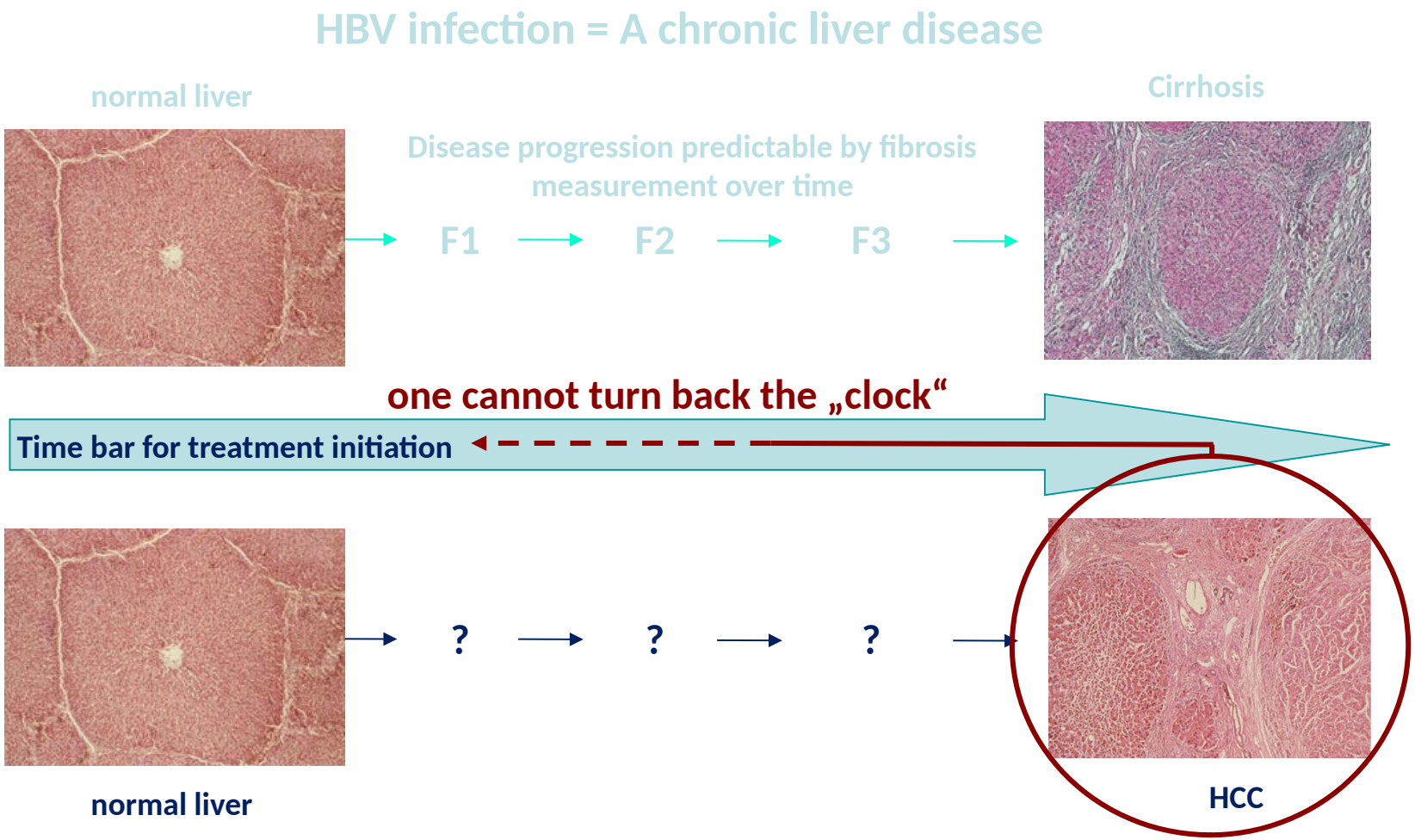


normal liver

HCC

HBV infection = An oncogenic disease

The HBV journey



HBV infection = An oncogenic disease

Risikostratifizierung des HCC bei HBeAg-negativer HBV Infektion durch Kombination viraler Biomarker

Tseng TC et al. *JID 2013:208; 584-593*

Risk group	Minimal (Reference)		Medium		Medium high		High
HBV DNA (IU/mL)	<2000	2000-19 999	<2000	2000-19 999	2000-19 999	20 000-199 999	≧200 000
HBsAg (IU/mL)	<1000	<100	≧1000	100-999	≧1000	‖	‖
Patient number (%)	662 (30.6)		674 (31.1)		501 (23.1)		328 (15.2)

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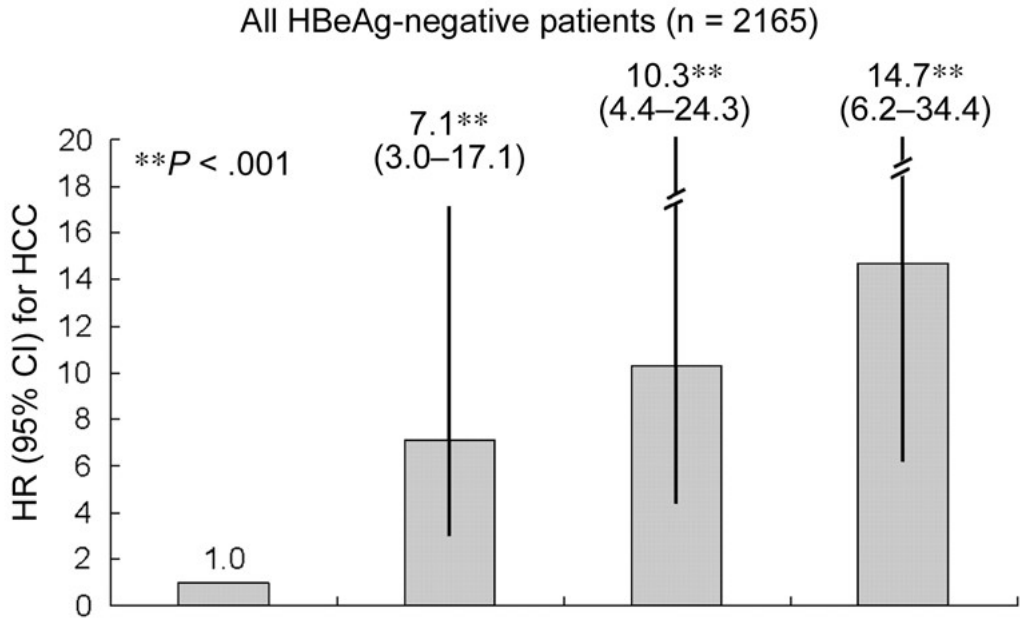

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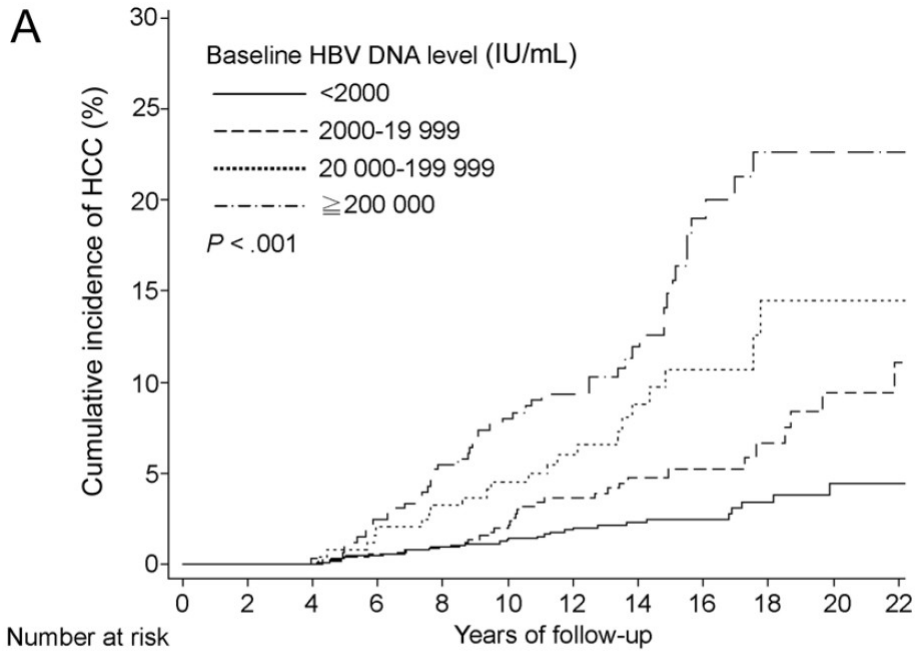

Number at risk

Serum HBV DNA level at baseline (IU/mL)

<2000	1068	1068	1068	1061	1051	981	818	605	375	248	158	90
2000-19 999	521	521	521	518	514	485	409	288	194	120	77	53
20 000-199 999	248	248	248	243	237	218	158	111	67	44	29	25
≧200 000	328	328	327	320	310	282	224	135	80	51	41	27

Risikostratifizierung des HCC bei HBeAg-negativer HBV Infektion durch Kombination viraler Biomarker

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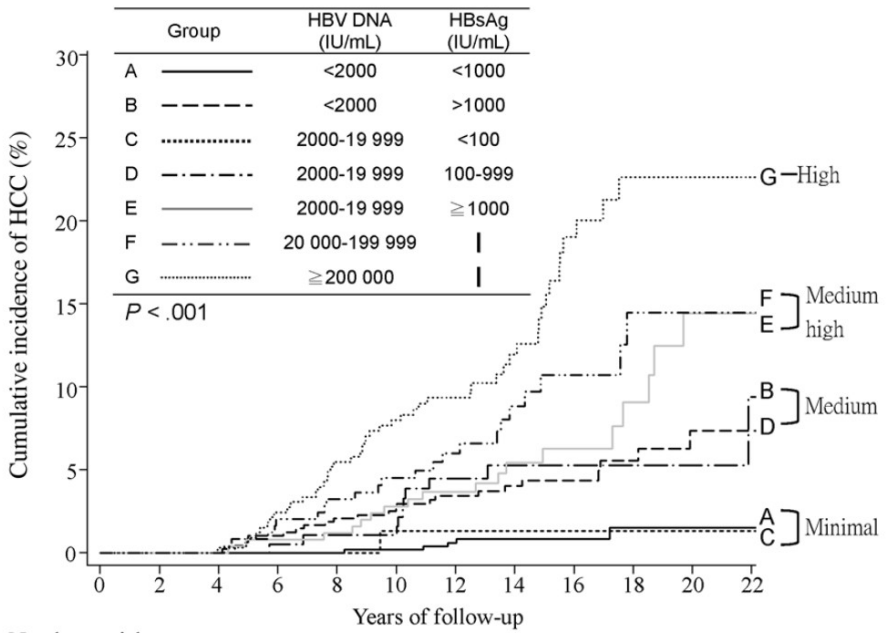
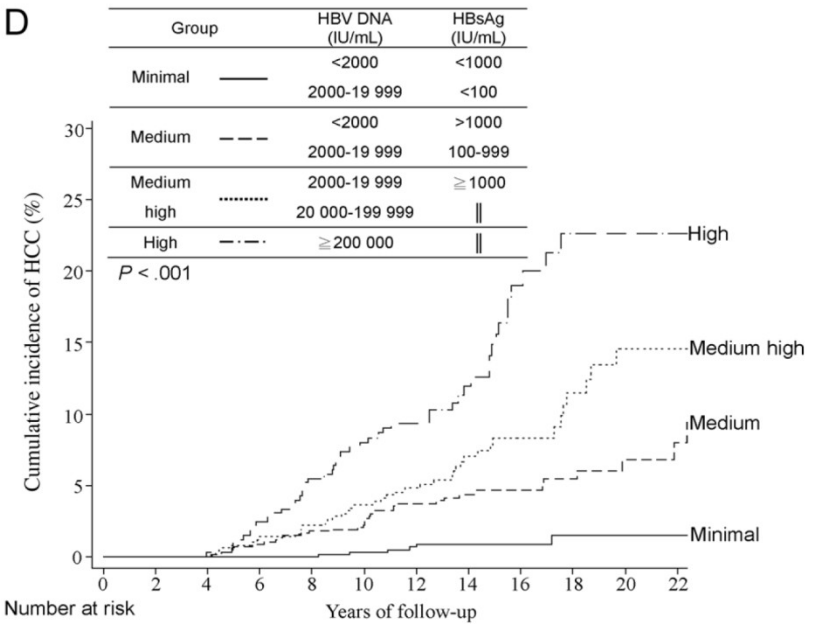
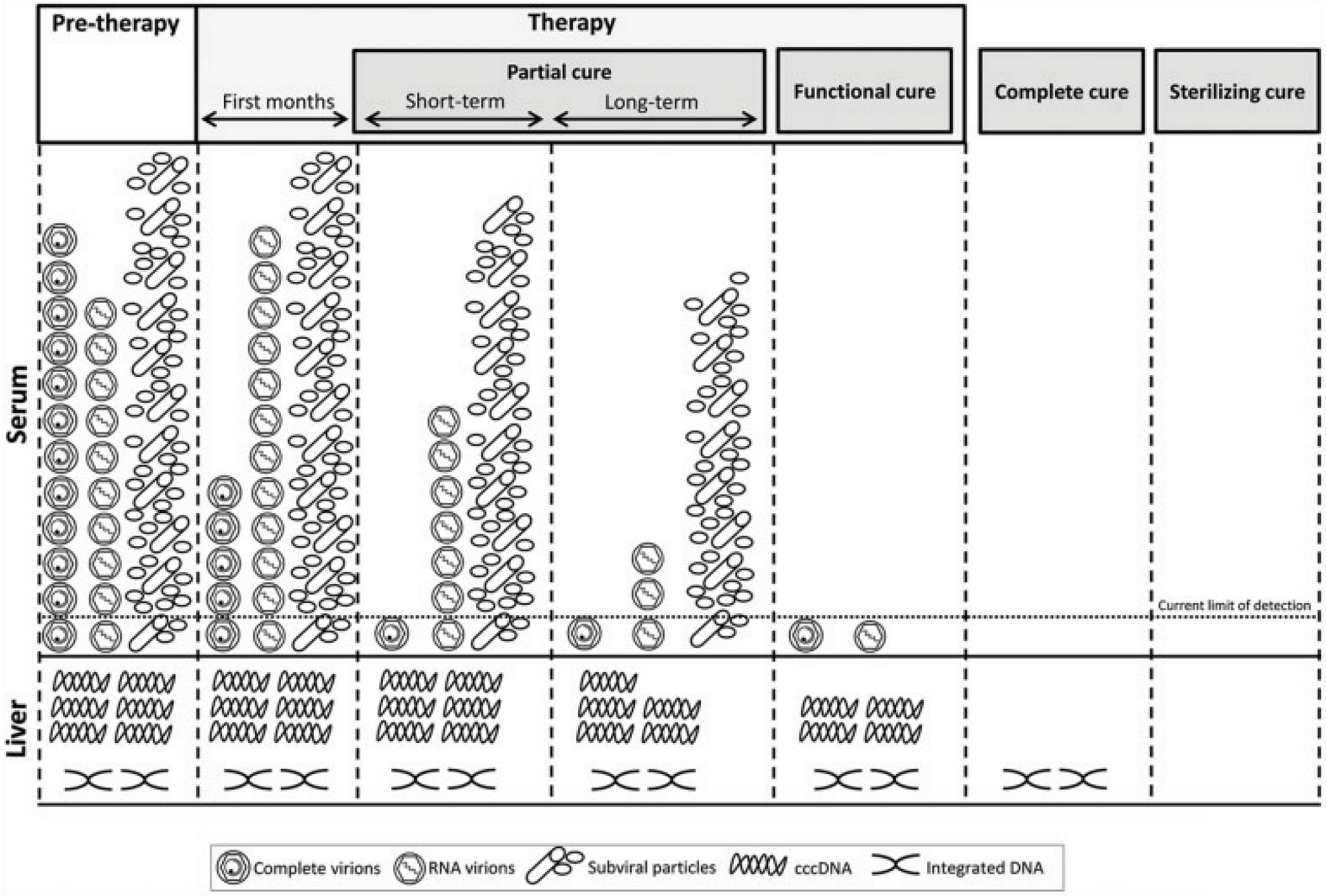




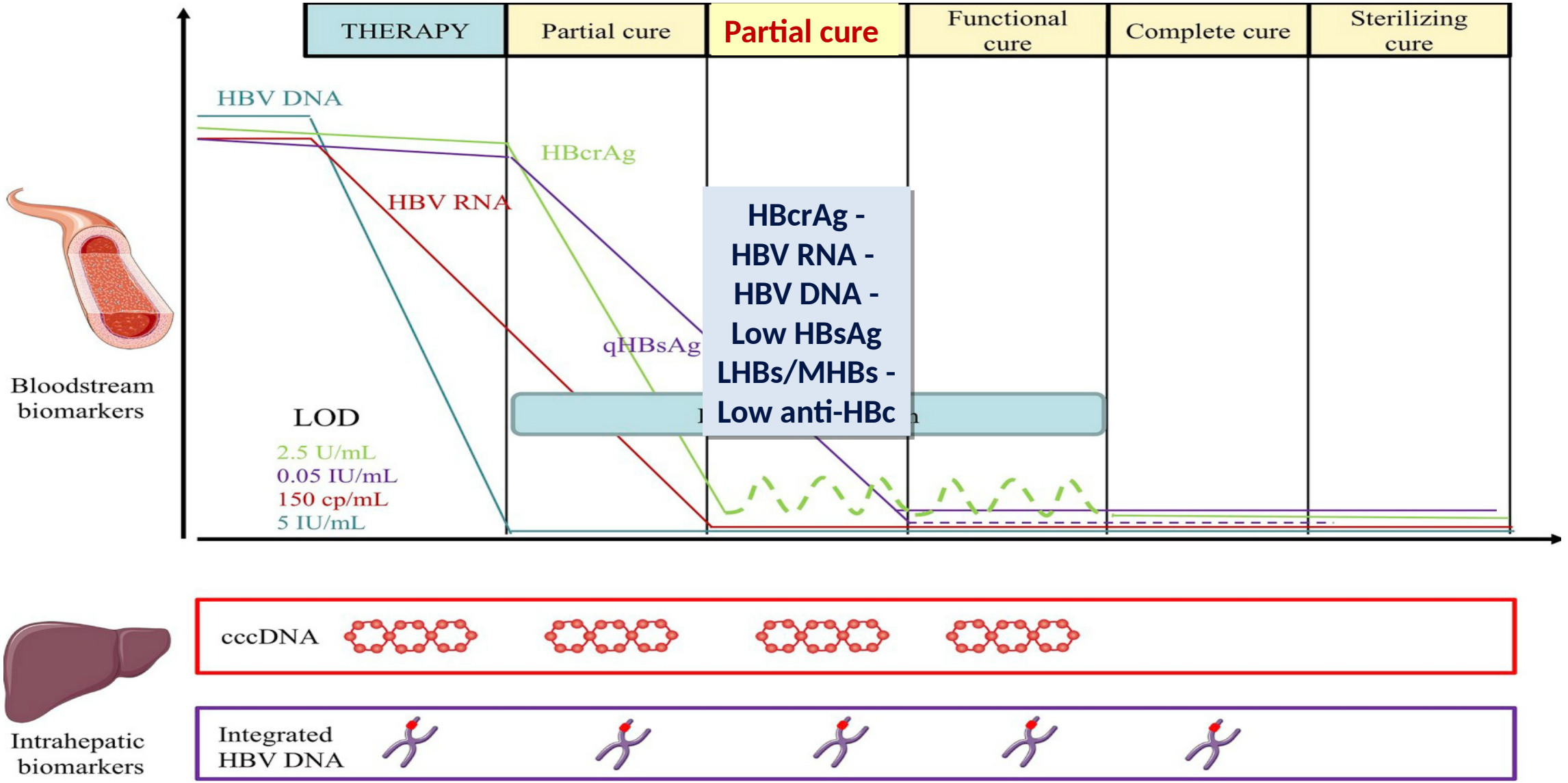
Does HBsAg positive „cure“ of the disease and diseas associaten outcomes exists? How to best define HBsAg positive cure of active infection

HBV particles detected in serum and liver of HBV-infected patients at the various endpoints of HBV cure



Buti M and Riveiro-Barciela M et al. Semin Liver Dis 2019; Dec 5

Chance for transition into a true functional or even complete cure stage after having achieved a partial cure?



Modified according to Charre C et al. Antiviral Res 2019; 169: 104553

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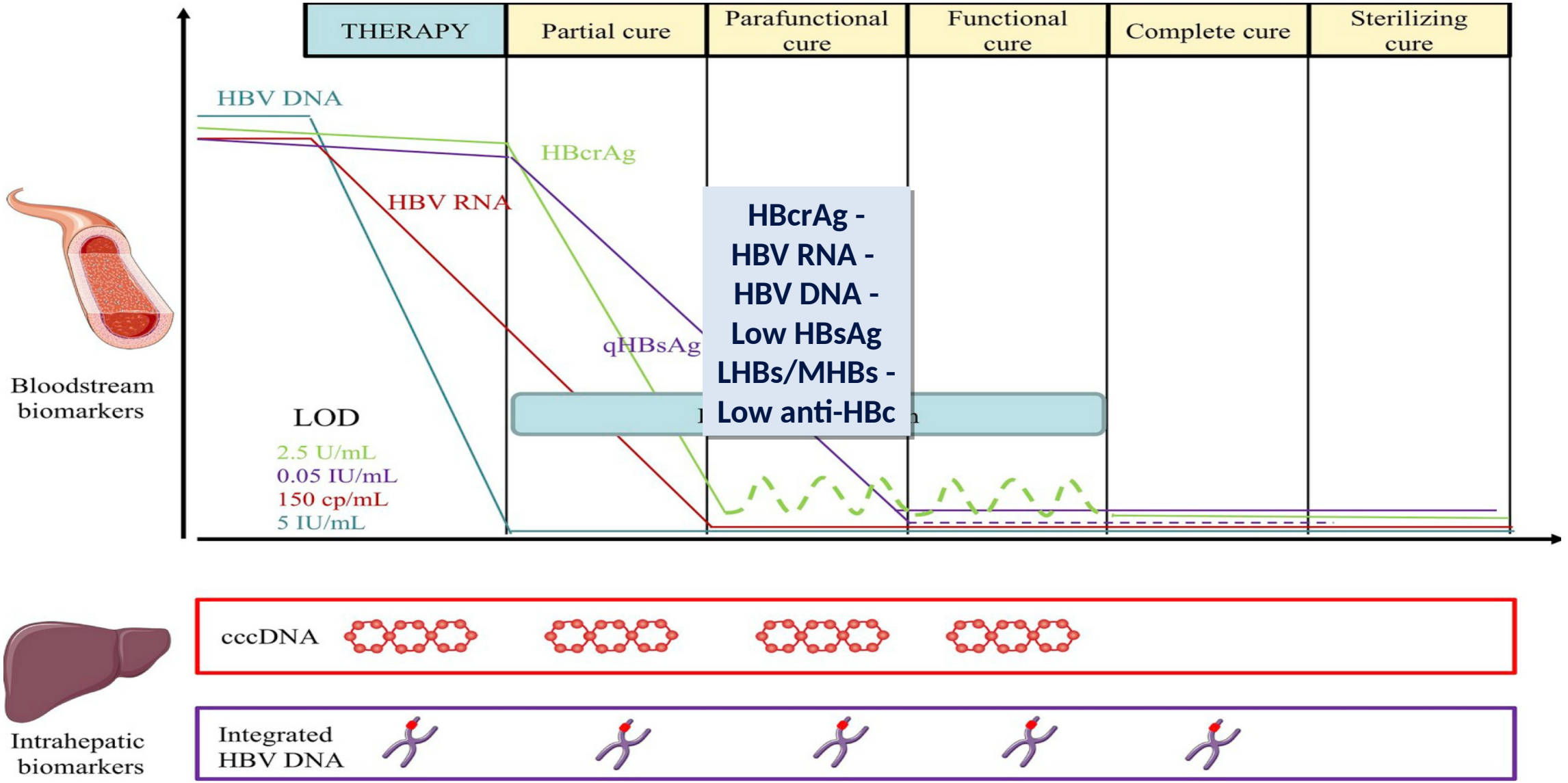

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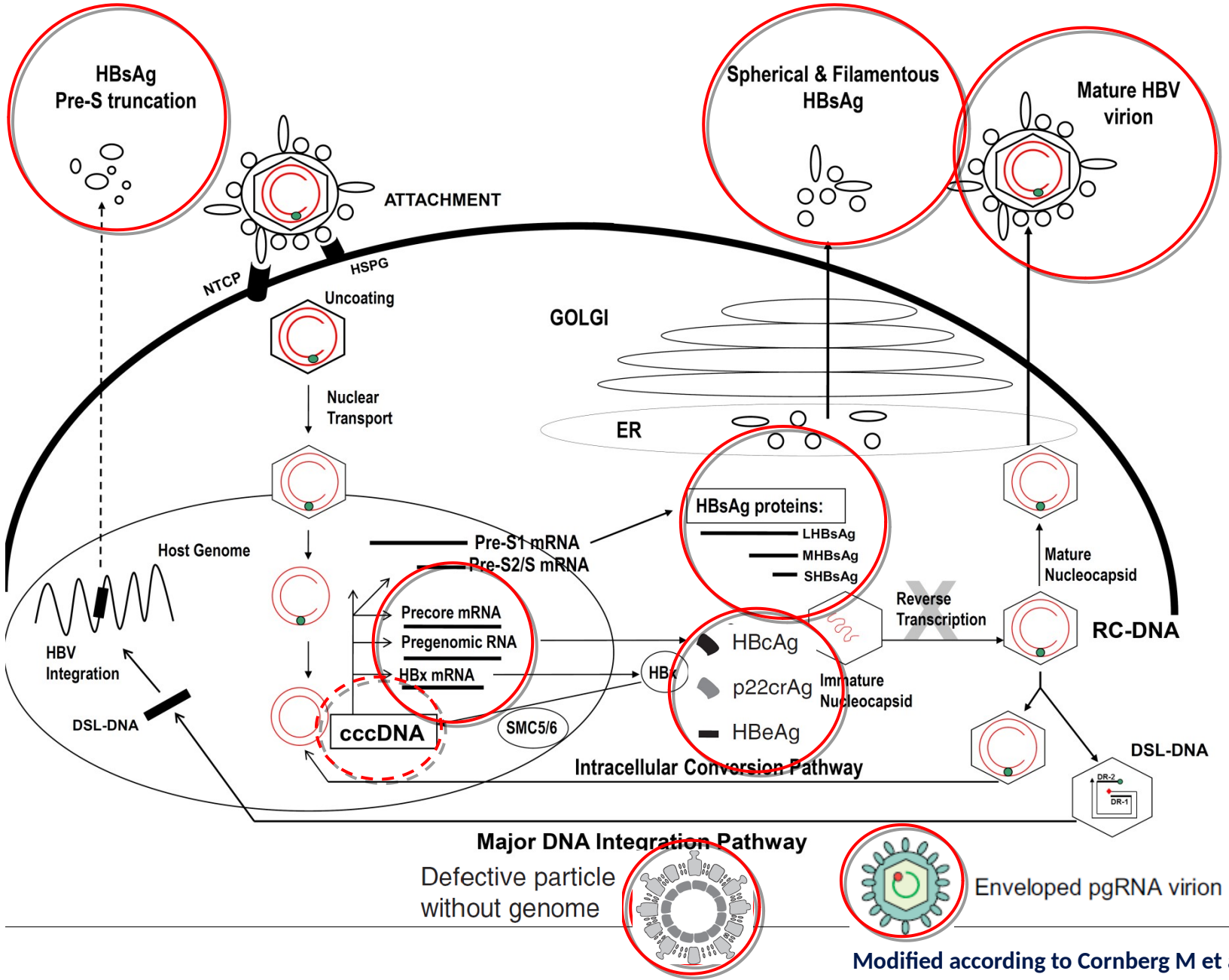
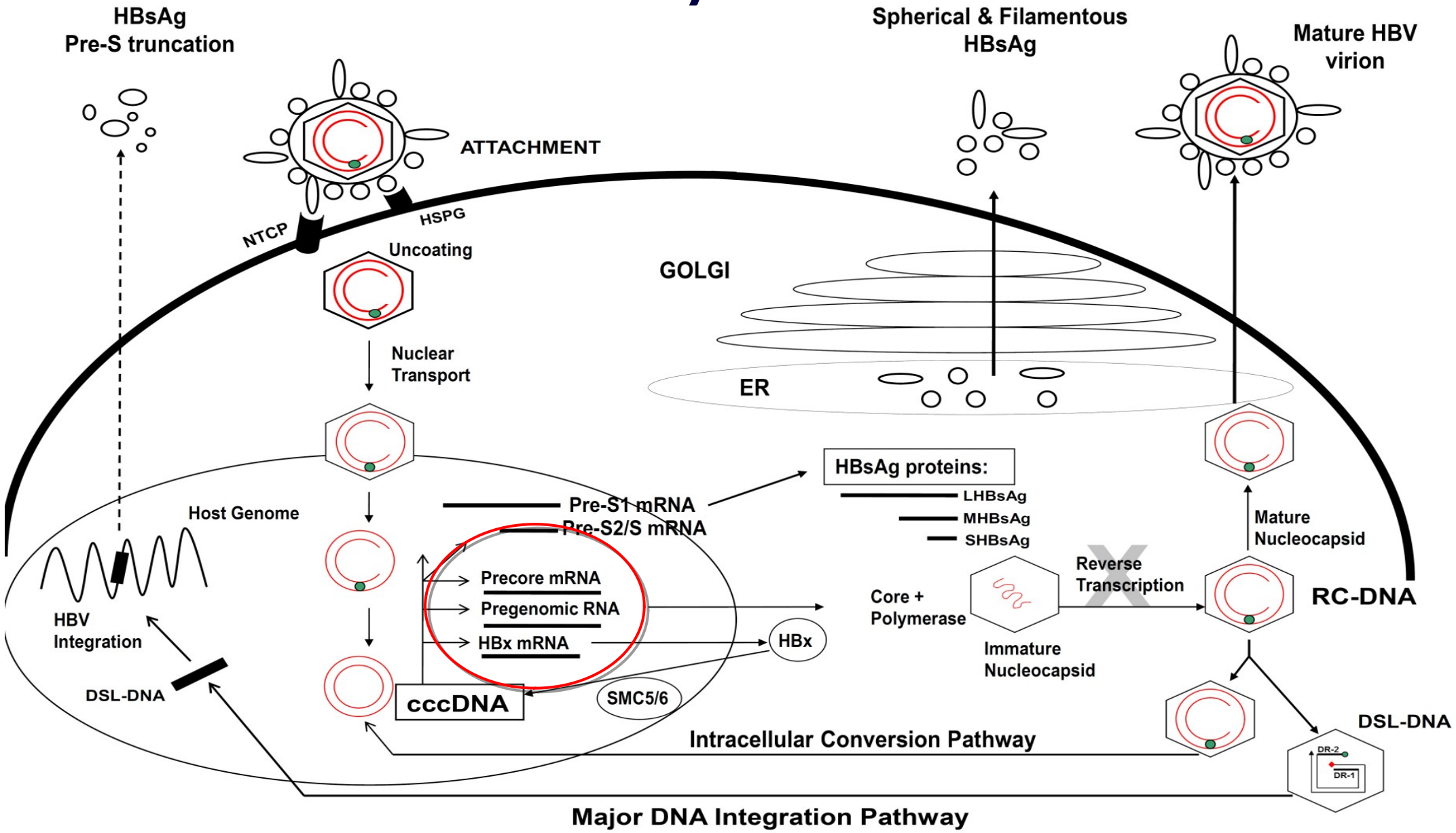
Potential biomarkers for assessing endpoints



Modified according to Cornberg M et al. J Hepatol 2016, August 17 epub

HBV life cycle – HBV RNA



Cornberg M et al. J Hepatol 2016, in press

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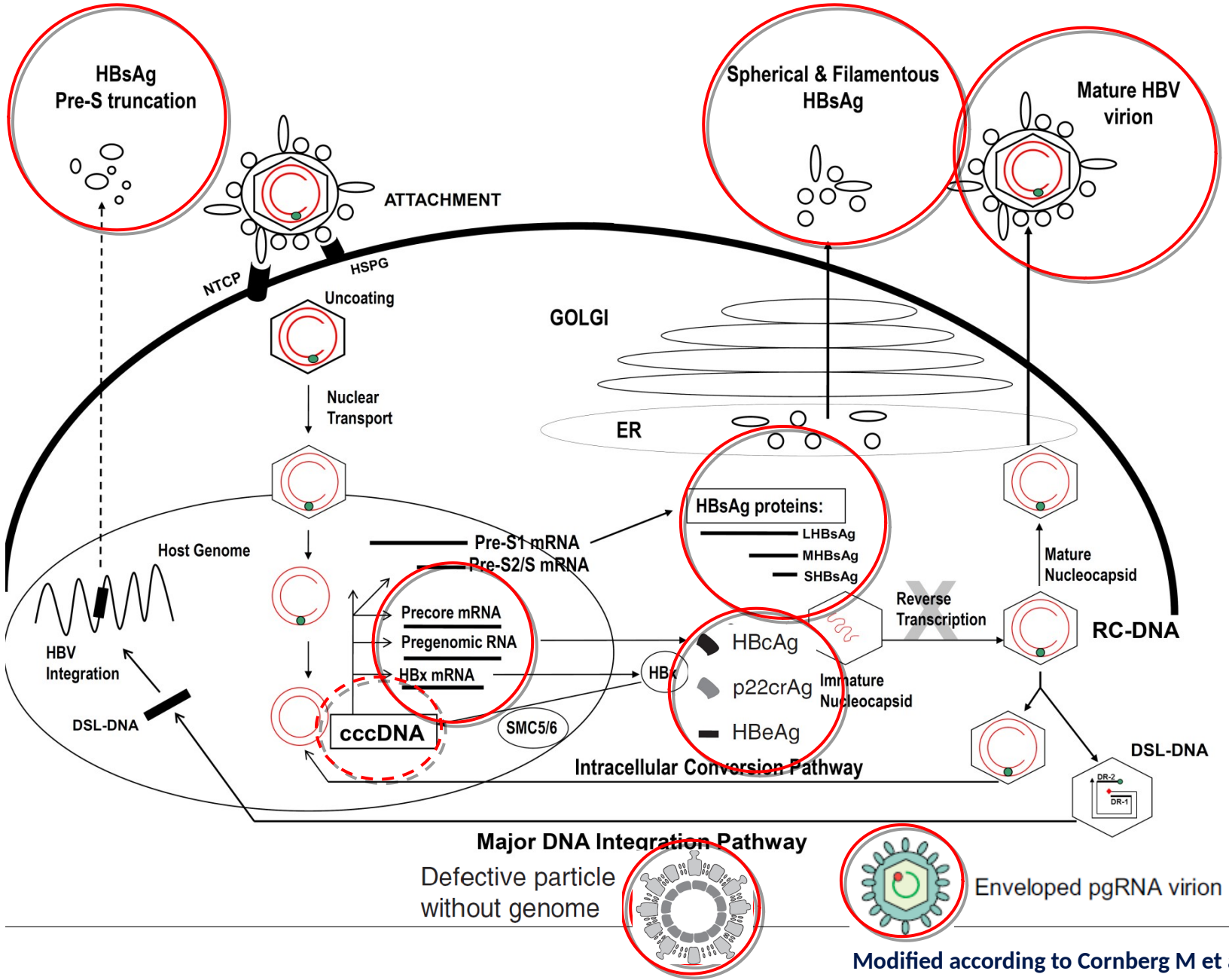

Modified according to Cornberg M et al. J Hepatol 2016, August 17 epub

Clinical utility of quantitative anti-HBc levels

- Anti-HBc levels are higher in HBsAg-positive patients as compared to those being anti-HBs-positive (but anti-HBc affinity was lower in chronic infection than during recovery)[1]
- Low anti-HBc levels are associated with HBsAg seroclearance (cut-off < 3log)[2]
- Serum levels of anti-HBc correlate with cccDNA positivity in OBI[3]
- Anti-HBc levels (cut-off ≥ 6.41 IU/ml) were significantly associated with high risk of HBV reactivation during immunosuppressive therapy[4]

[1]*Han et al. J Clin Virol. 2011;52(4):295-9*
[2]*Hu et al. Clin Gastroenterol Hepatol. 2018 [Epub ahead of print]*
[3]*Caviglia et al. J Hepatol. 2018;69(2):301-307*
[4]*Yang et al. J Hepatol. 2018 Aug;69(2):286-292.*

Why aiming for HBsAg loss

- The loss of HBsAg is regarded as the optimal treatment endpoint, termed ‘functional cure’, but it is only rarely achieved with our current antiviral armamentarium.
- Spontaneous HBsAg seroreversion with reactivation of the inflammatory liver process after HBsAg loss is rare and may occur in patients with a significant impairment of their immune function
- The main advantage of HBsAg loss is that it allows a safe discontinuation of antiviral therapy.

Serum level of antibodies against hepatitis B core protein is associated with clinical relapse after discontinuation of nucleos(t)ide analogue therapy

- Clinical relapse occurred in 39 patients (in 46% of patients at year 4 after discontinuation). High level of anti-HBc at the end of treatment (hazard ratio [HR], 0.31 per log IU/mL; *P* = .002) and low level of HB surface antigen (HBsAg) at the end of treatment (HR, 1.71 per log IU/mL; *P* = .032) were associated with a reduced risk of clinical relapse after adjusting for age, start of nucleos(t)ide analogue therapy, HBeAg-status, and consolidation therapy duration. At year 4, 21% of patients with anti-HBc levels at the end of treatment ≥1000 IU/mL developed a clinical relapse compared to 85% of patients with levels <100 IU/mL (*P* < .001).

Chi H et al. Clin Gastroenterol Hepatol 2019;17(01):182–191.e1