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HBeAg negative HBV infection: an acceptable treatment outcome or rather a treatment indication, today and in the future

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Disclosures

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- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN, SBRING BANK, MYR, EIGER, ANTIOS, ALIGOS, VIR

Outline of the presentation

HBeAg negative chronic infection:

- Diagnosis, management and natural history
- Should these carriers be considered for clinical trials?
- Should this phase be considered as a therapeutic endpoint ?
- Summary and conclusions

EASL 2017 guidelines for HBV: natural history of HBV

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**	None	**Moderate to high**
Treatment	Not indicated***	**Indicated**	Not indicated	**Indicated**

EASL. J Hepatol 2017;67:370–98

*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

Inactive carriers - EASL 2017 HBV guidelines

- "HBeAg-negative chronic HBV infection", previously termed ‘inactive carrier’ phase, is characterised by the presence of:
  - antibodies to HBeAg (anti-HBe)
  - undetectable or low (<2,000 IU/ml) HBV DNA levels
  - normal ALT according to traditional cut-off values (ULN 40 IU/L)*
- Some patients, however, may have HBV DNA levels >2,000 IU/ml (usually <20,000 IU/ml) but persistently normal ALT and only minimal hepatic necroinflammatory activity and low fibrosis.
- Diagnosis can be difficult in patients with another cause of liver disease (abnormal ALT)
- This phase can be the outcome of different clinical/virological situations
- These individuals are not always homogeneous (qHBsAg, DNA, fibrosis….)

EASL CPG HBV. J Hepatol 2017;67:370–98

Natural history of inactive carriers in the long-term follow-up cohort studies

Author (Reference)	Country	Number of patients	Male (%)	Median age (years)	Follow-up (years)	HBsAg loss (%)	HBV reactivation (%)	HCC (%)
De Franchis (9)	Italy	68	81	31	10.8	15	4.4	0
Villeneuve (24)	Canada	200	81	29	16	0.7 per year	0.5	0
Martinot-Peignoux (12)	France	38	54	34	3.2	3.5	2.6	NA
Hsu (25)	Taiwan	189	79	32	8.2	4.8	NA	1.6
Manno (10)	Italy	296	78	36	30	32	2.1	0.7
Fattovich (26)	Italy	40	63	30	23	45	0	5
Habersetzer (27)	France	109	NA	NA	6	10	NA	NA

NA, not available.

EASL 2017 HBV Guidelines:

- These patients have low risk of progression to cirrhosis or HCC if they remain in this phase, but progression to CHB, usually in HBeAg-negative patients, may occur.
- HBsAg loss and/or seroconversion may occur spontaneously in 1–3% of cases per year. Typically, such patients may have low levels of serum HBsAg (<1,000 IU/ml).

Invernizzi F et al, Liver Int 2016; EASL 2017 HBV CPG, J Hepatol 2017

Should these carriers be considered for clinical trials?

EASL 2017 guidelines for HBV: natural history of HBV

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***50-70% of 250 million individuals ?**

EASL. J Hepatol 2017;67:370–98

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EASL 2017 clinical practice guidelines for HBV: indications for treatment

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Baseline diagnostic work-up and monitoring for inactive carriers

- Medical history and physical examination
- Family history of liver disease, HCC
- HBV markers (qHBsAg, HBeAg, HBV DNA. …..)
- Exclude coinfections (HDV, HCV, HIV……)
- Liver tests (Bil, AST, ALT, FA, GGT……..)
- Abdominal ultrasound
- Fibroscan or other non invasive markers of fibrosis
- (Liver biopsy usually not indicated)

To be monitored life-long, every 12 months: visits, liver tests, viral markers, US, Fibroscan…

Invernizzi F, Viganò M, Grossi G, Lampertico P, Liver Int 2016; 36 (Suppl. S1): 100–104

HBeAg negative chronic infection: additional issues

- Stigma of being HBV positive
- Infectivity issues
- Social relationships
- Professional issues
- Migration issues
- ……

These carriers do not always share our «optimistic» view on this clinical situation

HBeAg negative chronic infection: clinical/virological features

- Low HBsAg levels
- Anti-HBe positive
- Low/neg HBV DNA levels
- Low/neg HBV RNA levels
- Low/neg HBcrAg levels
- ALT normal
- ……..

This virological profile indicates: low number of infected cells, low cccDNA activity, low amount of cccDNA……..

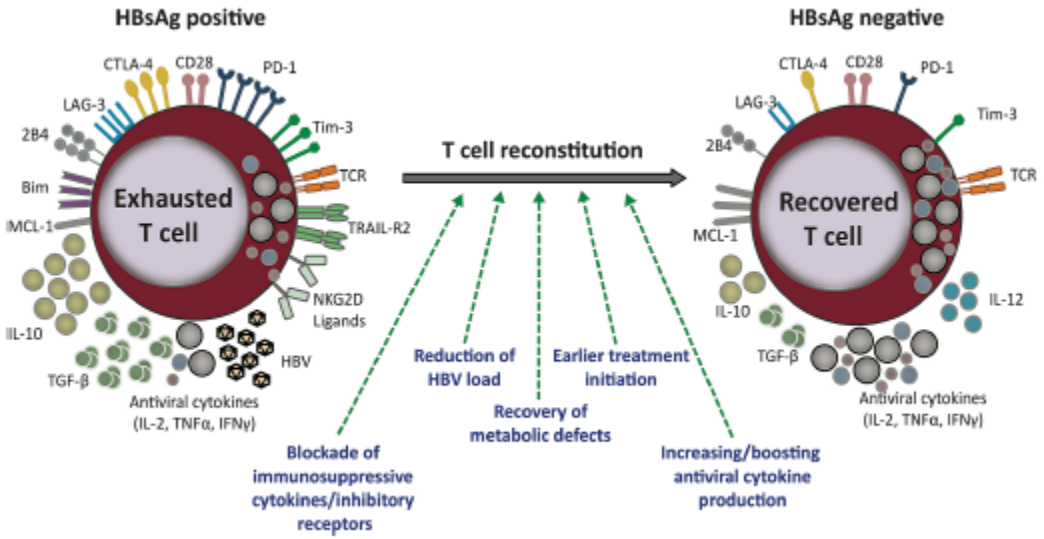
P Lampertico, HBV Forum 9 Nov 2022

HBeAg negative chronic HBV infection - A review article

Guidance on the management of non-cirrhotics with HBeAg-negative chronic infection

	Definition	Recommendation
AASLD (2018)	HBV DNA < 2000 IU/ml Anti-HBe present ALT and or AST levels persistently normal Minimal inflammation variable levels of fibrosis reflecting previous liver injury	Treatment not recommended monitor with ALT and HBV DNA every 3–6 months and HBsAg annually
APASL (2016)	Low or undetectable HBV DNA Anti-HBe present ALT levels persistently normal minimal inflammation variable levels of fibrosis reflecting previous liver injury	Monitor HBV DNA 6–12-monthly monitor ALT 3–6-monthly assess fibrosis non-invasively Treat if biopsy shows moder-ate–severe inflammation or significant fibrosis[a]
EASL (2017)	HBsAg low HBV DNA < 2000 IU/ml[b] Anti-HBe present ALT levels normal No liver disease	Monitor every 6–12 months Could consider treatment in case of extra-hepatic manifestations of HBV or a family history of HCC and/or cirrhosis

Mechanisms of immune cell constitution

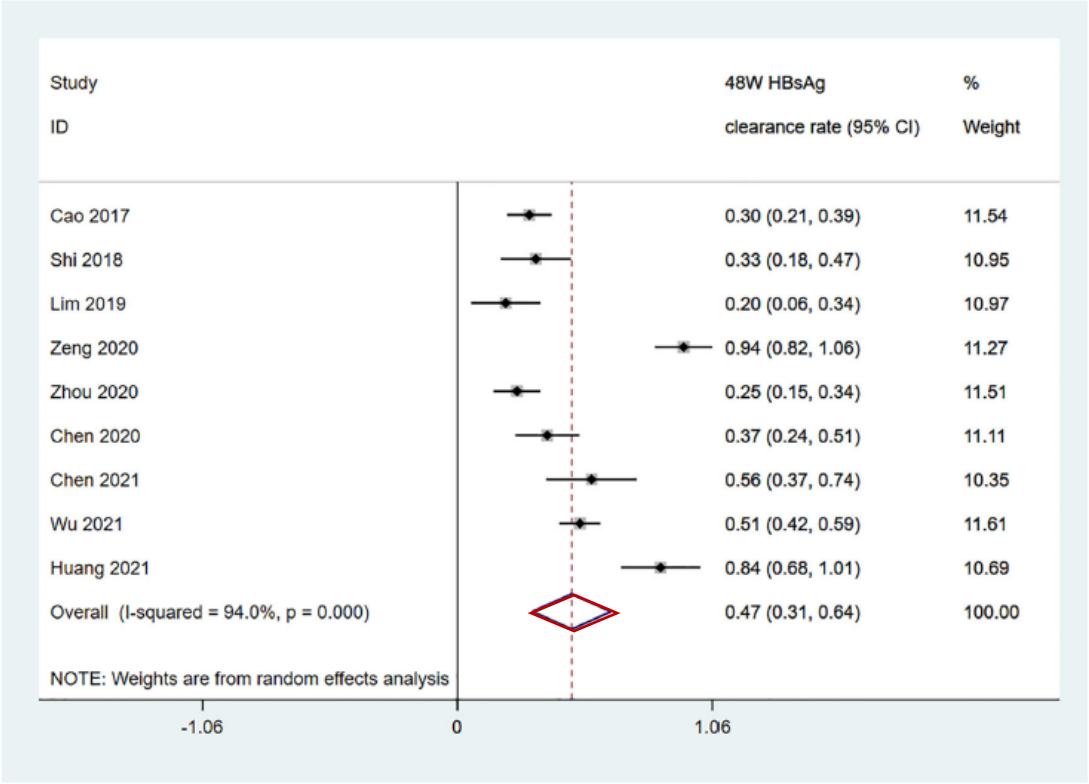


These are «inactive carriers» because of a «strong» immune control…....

Apostolos Koffas et al, Hepatology International (2021) 15:290–300

Peg-IFN treatment for inactive carriers of HBV: HBsAg response
A Meta-Analysis

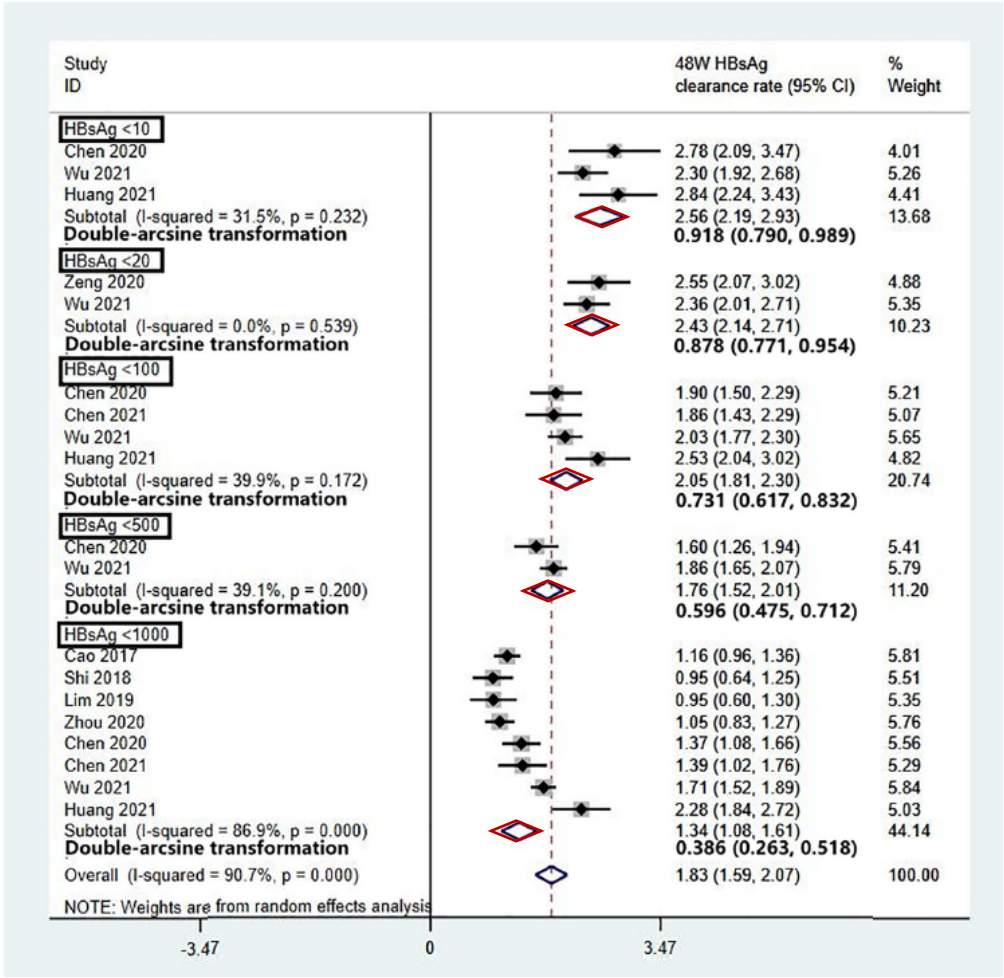
HBsAg clearance rates



HBsAg seroconversion rates after peg-IFN: 26%

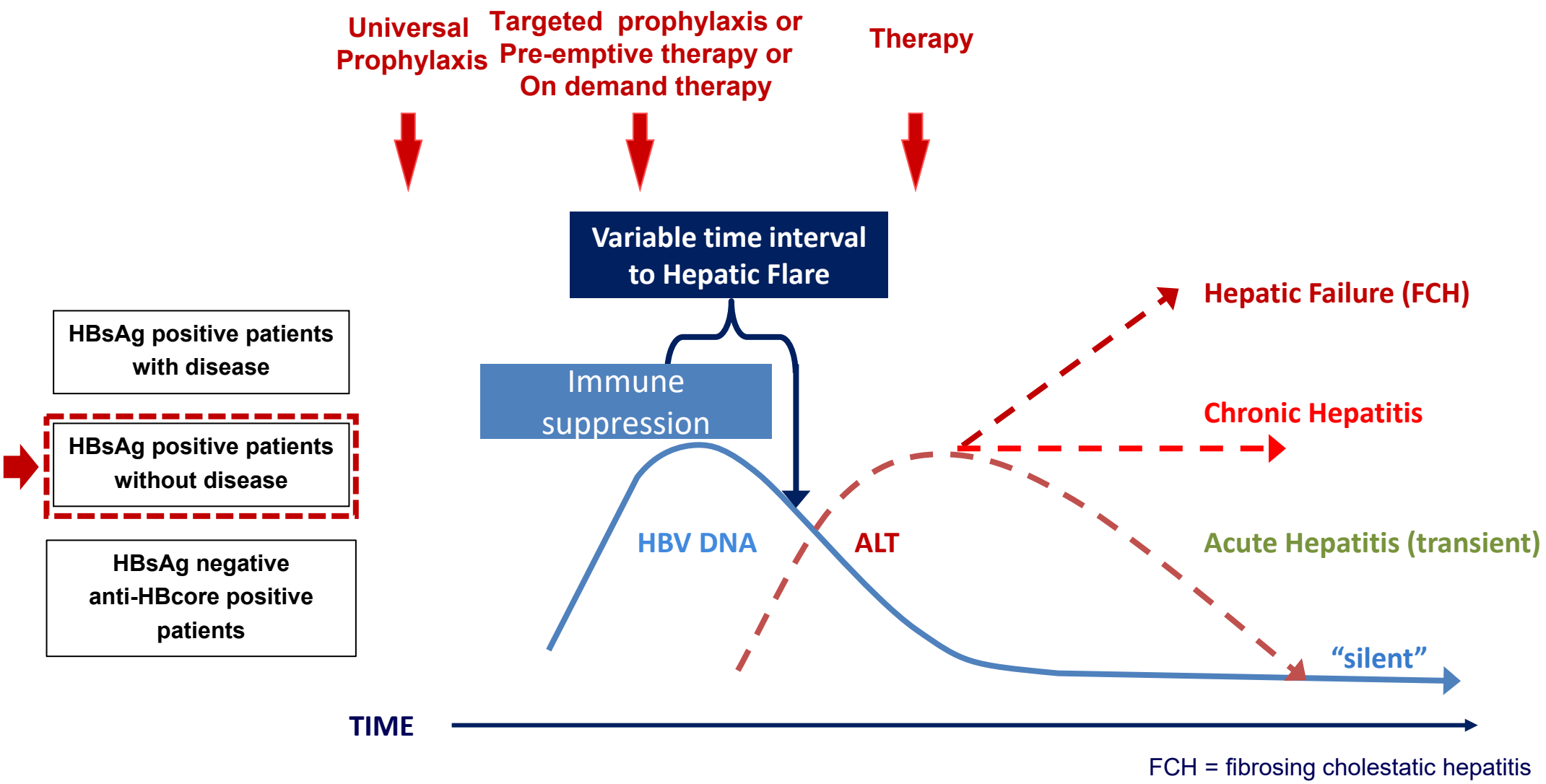
HBsAg clearance rates in the untreated group: 1.5%

HBsAg clearance rates according to BSL HBsAg levels



Aixin Song et al, Frontiers in Immunology 2021

Management of HBV reactivation during immunosuppresion

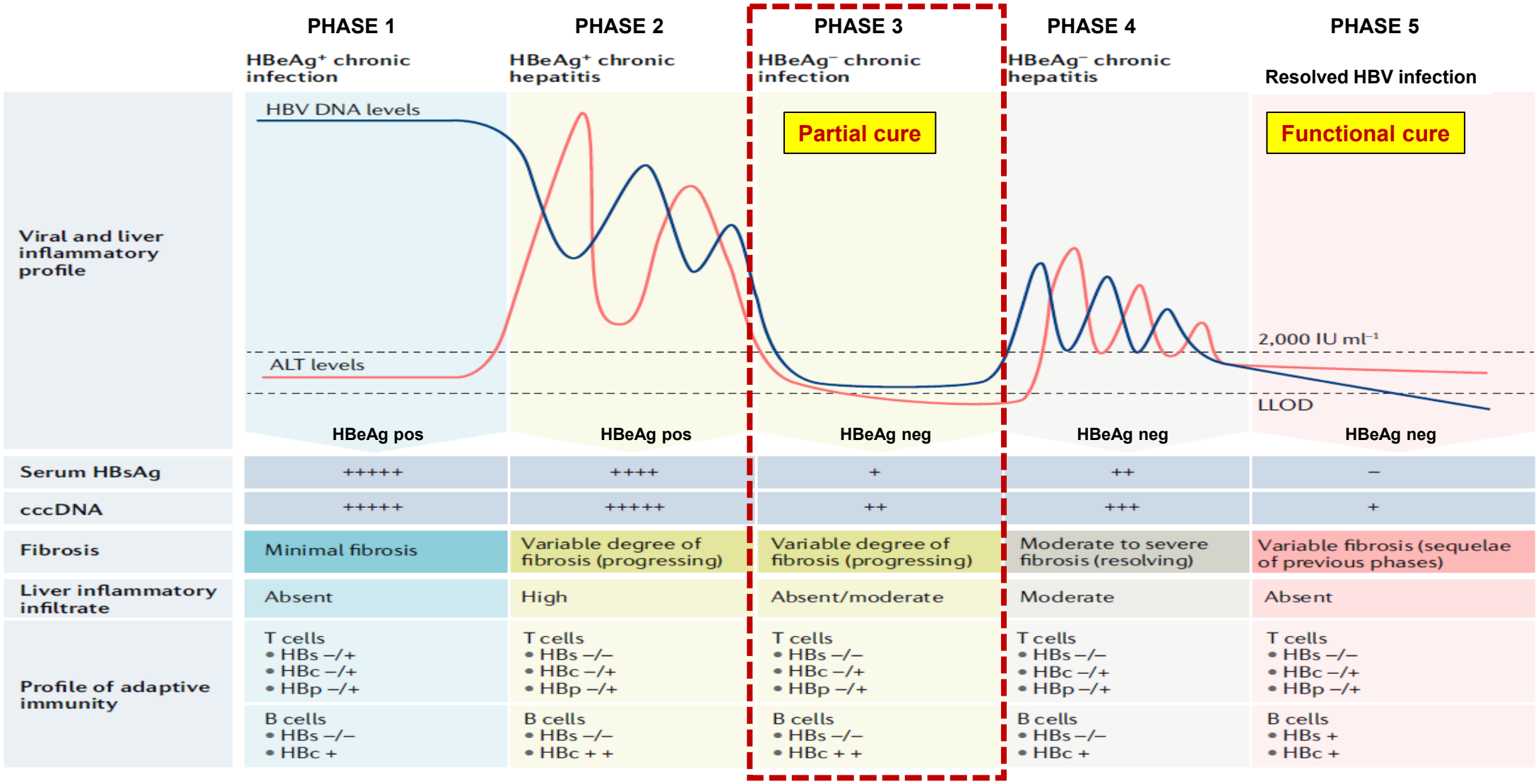


FCH = fibrosing cholestatic hepatitis

Adapted from Lau GKK, et al. Crit Rev Oncol Hematol 1999;31:71-76

Should this phase be considered a therapeutic endpoint

Natural history of HBV infection: partial and functional cure



Modified from Fanning, G.C., Zoulim, F., Hou, J. *et al. Nat Rev Drug Discov* 18, 827–844 (2019)

EASL CPG HBV. J Hepatol 2017;67:370–98

Endpoints for HBV therapeutics

VARIABLES	HBeAg neg CI (natural history)	NUC THERAPY (on-therapy)	PARTIAL CURE (off-therapy)	FUNCIONAL CURE (off-therapy)
HBsAg	Pos	Pos	Pos	Neg
Anti-HBe	Pos	Pos	Pos	Pos
HBV DNA	<2000	<10	<10	<10
ALT levels	Normal	Normal	Normal	Normal
Clinical outcomes	Improved	Improved	Improved	Improved
Residual HCC risk	Low	Low	Low	Very low
Stability over time	YES*	YES*	??	YES
Stigma for HBV	YES	YES	YES	NO

Functional Cure is the best outcome
Partial Cure can be an excellent outcome (if stable over time)

P. Lampertico, HBV Forum 9, Nov 2022

Durability of Partial Cure over time: strategies

- Change the timing of the definition (from week 24 to week 48 off-therapy)

AND / OR

- Change the definition itself (additional biomarkers ?)

Durability of Partial Cure over time: new definition ?

VARIABLES	PARTIAL CURE (24 weeks off-therapy)	FUNCIONAL PARTIAL CURE (24 weeks off-therapy)
HBsAg	pos	pos
HBsAg levels, IU/ml	any	<100
Anti-HBe	pos	pos
HBV DNA levels	<10	<10
HBV DNA levels	<10	TND
HBV RNA levels	any	neg
HBcrAg levels	any	neg
ALT levels	normal	normal
Durability over time	YES/NO*	YES
Residual HCC risk	Low	very low
Evolution to FC (HBsAg loss)	low	high

Durability of PC can be guaranteed by a new more stringent definition

P. Lampertico, HBV Forum 9, Nov 2022

HBeAg negative chronic infection - an opportunity

- Should these carriers be considered for clinical trials?
  - ✓ YES (many reasons)

- Should HBeAg negative chronic infection be considered as a therapeutic endpoint ?
  - ✓ YES (but definition of Partial Cure revisited to guarantee durability)

Thank you