Management of chronic hepatitis B: Challenging therapeutic paradigms?

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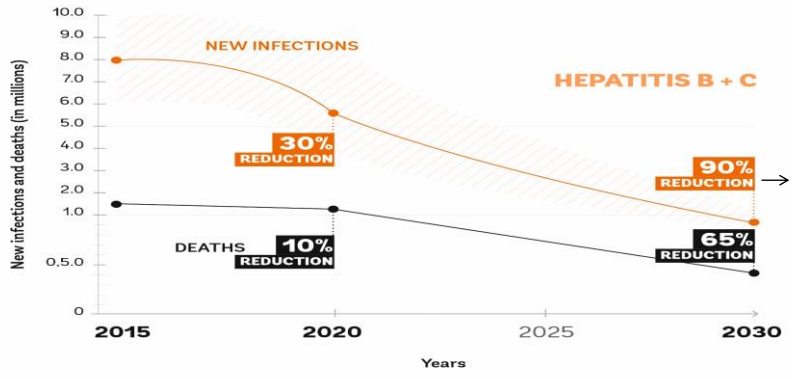
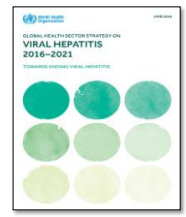
WHO global hepatitis elimination goals by 2030

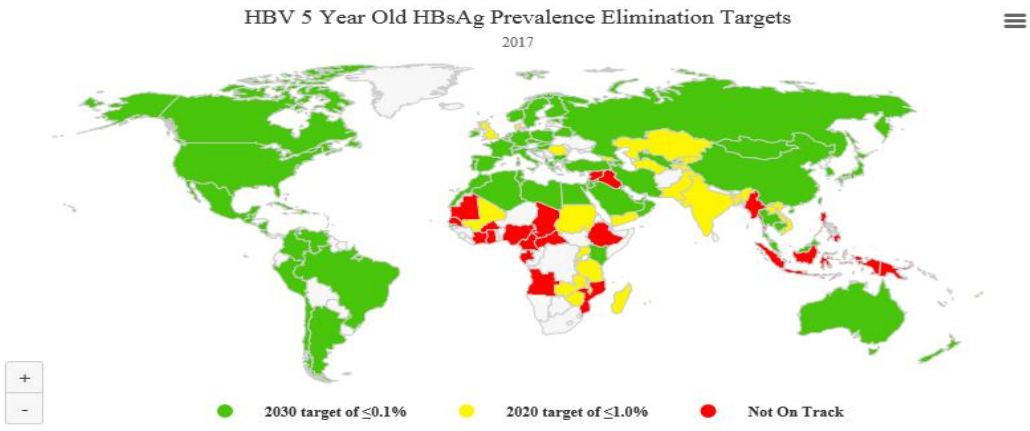




80% ↓HCV incidence
95% ↓HBV incidence

Testing **to reach** 90% and Treatment **to reach** 80% from 2015-2030

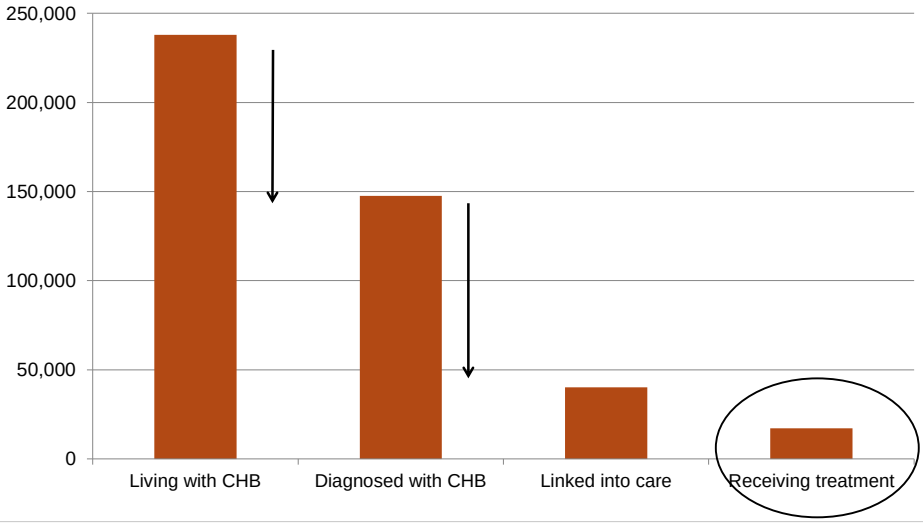
Vaccination coverage is improving but varies



….and will take decades to move through

CDA 2017: Polaris Observatory (http://centerforda.com/polaris/)

HBV care cascade in Australia :2016



Fourth National Hepatits B mapping report

What are the endpoints of therapy for HBV?

- Clinical goals
  - Stop liver related death
  - Stop liver failure
  - Stop HCC
  - Prevent transmission

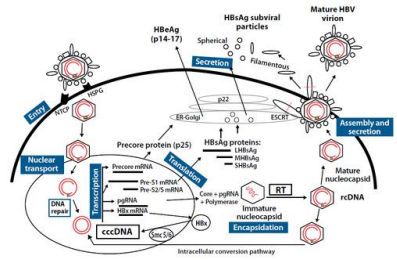
- Surrogate markers of treatment success

  Current

  HBV DNA suppression

  ALT normalisation

  HBeAg seroconversion



Future?

HBV RNA suppression

HBcrAg levels

quantitative HBsAg decline

HBsAg loss = functional cure

cccDNA loss = absolute cure

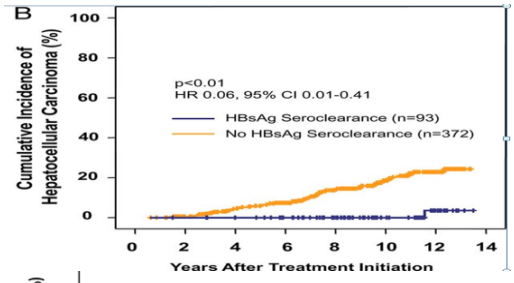
Current states of control/cure

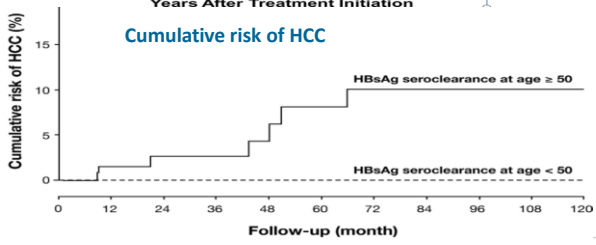
Inactive State
Sustained, off drug: • No inflammation: normal ALT and liver biopsy • HBV DNA low or undetectable • HBsAg-positive
Functional Cure (Clinical Resolution)
Sustained, off drug: • No inflammation: normal ALT and liver biopsy • HBsAg loss • Anti-HBs gain
Complete Cure (Virologic Cure)
• All of the above plus • Loss of cccDNA in the liver

Peters, MG & Locarnini, S. 2016. Gasroenterol and Hepatol;13(6):348-356.

Why does HBsAg loss matter?

HBsAg clearance improves survival rates and reduces risk of HCC





5,409 CHB patients treated with LAM or ETV

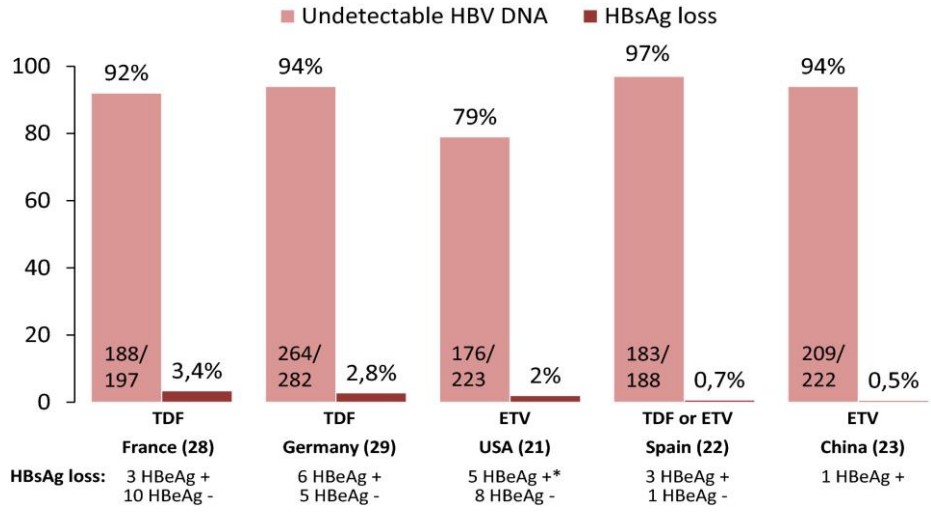
HBsAg clearance associated with reduced risk HCC

Klm et al. GUT 2014

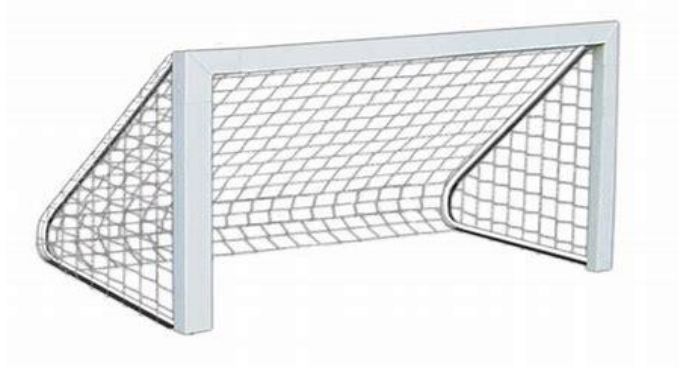
Clearance < age 50 reduces HCC risk significantly

Yuen M-F, et al. Gastroenterology 2008; 135:1192

Rates of HBsAg loss are low with current therapies



Buti et al, Liver International 2018



The goal posts in Hepatitis B therapy are clearly shifting

Current guidelines

Who should be treated?

Which treatment is optimal?

When should treatment be stopped?

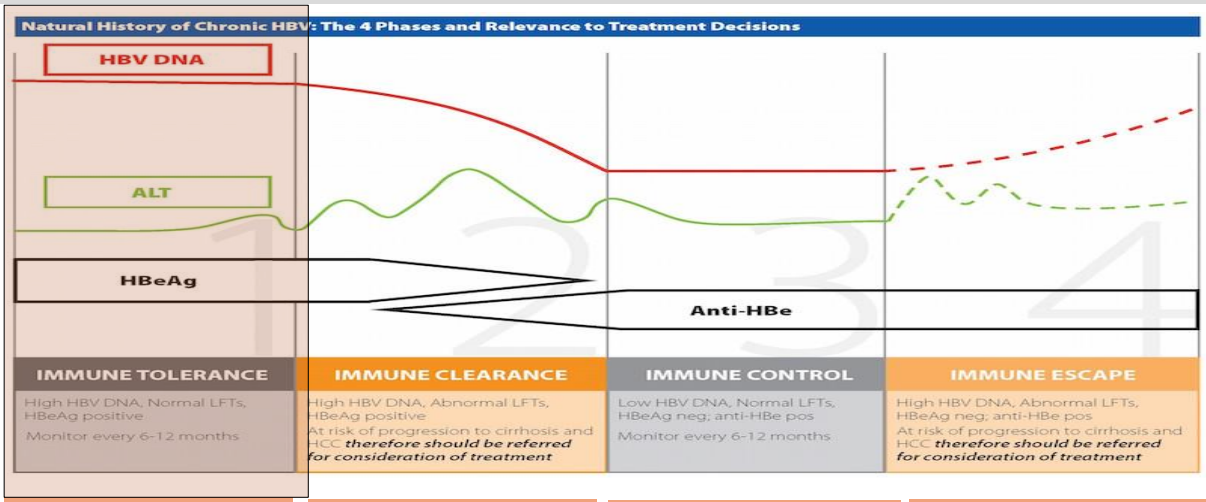
Current guidelines

Who should be treated?

Which treatment is optimal?

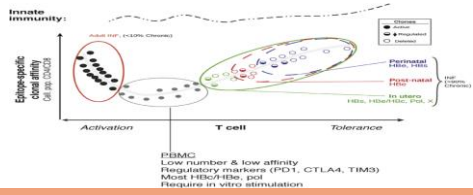
When should treatment be stopped?

Natural history of chronic hepatitis B infection



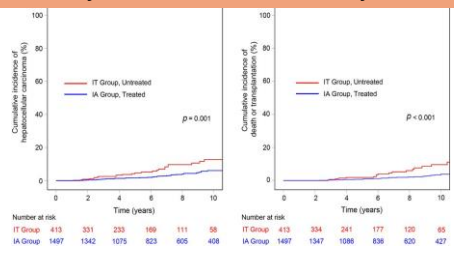
HBeAg + chronic infection | HBeAg + chronic hepatitis | HBeAg -ve chronic infection | HBeAg -ve chronic hepatitis

Immune tolerance: is it benign?



Clonal hepatocyte expansion and DNA integration can be shown to occur frequently in IT patients
Associated with detectable (impaired) HBV specific T cells in the periphery
Immune tolerance is not necessarily a state of inactivity

Beware reliance of normal ALT especially in older patients
Ensure international ALT levels used as standard (19 IU/ml female: 30 IU/ml for male)
Moderately elevated DNA levels may be a warning of greater activity – new biomarkers may provide better insight



Korean cohort study 4965 non-cirrhotic CHB comparing IT vs IA (NA treated)

Estimated cumulative incidence of any clinical events (HCC, death or LT) in the IT vs IA groups was 5.3% vs 2.2% at 5 years and 16.9% vs 7.7% at 10 years (p<0.001).

Risk much higher in those with ALT 1-2 X ULN, lower HBV DNA (but still > 20,000, older age, male)

Kim et al , GUT 2015

Should IT patients be treated?

AASLD 2018

The AASLD suggests antiviral therapy in the select group of adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis

APASL 2016

- Assess fibrosis noninvasively
- Monitor 3 monthly
- Individualize liver biopsy@
- Treat if moderate to severe inflammation

No evidence to treat outside these recommendations currently
(but this could change into future)
Close observation recommended in patients over 40 years with delayed HBeAg seroconversion

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).

Current guidelines

Who should be treated?

Which treatment is optimal?

When should treatment be stopped?

Are any current therapies better than others?

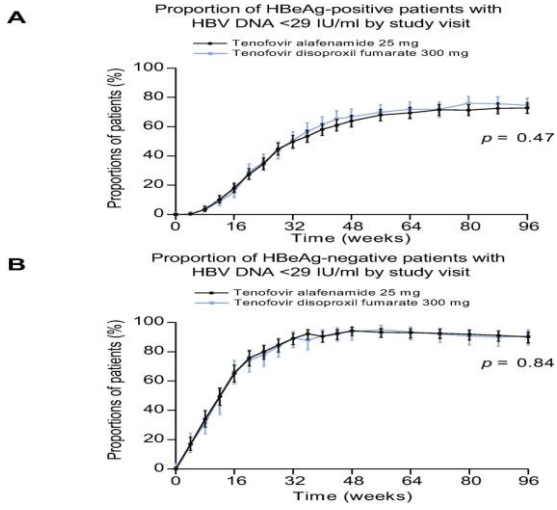
- Single nucleoside?
- Combination nucleoside?
- Combination immunomodulator/nuceloside

Current Preferred therapies for HBV

	AASLD 2018	EASL 2017	APASL 2015
Lamivudine	Not preferred	Not preferred	Not preferred
Adefovir	Not preferred	Not preferred	Not preferred
Entecavir	**First line**	**First line**	**First line**
Telbivudine	Not preferred	Not preferred	Not preferred
Tenofovir	**First line**	**First line**	**First line**
PEG-IFN	**First line**	**First line**	**First line**
TAF	**First line**	**First line**	**N/A**

In many regions the cost of anti-CHB therapy poses significant financial burden to patients and to the resource-constrained national healthcare systems
Financial burden of treatment remains unaffordable for most patients because of lack of full or adequate reimbursement for treatment

TDF (300mg) vs TAF (25mg) : 96 weeks

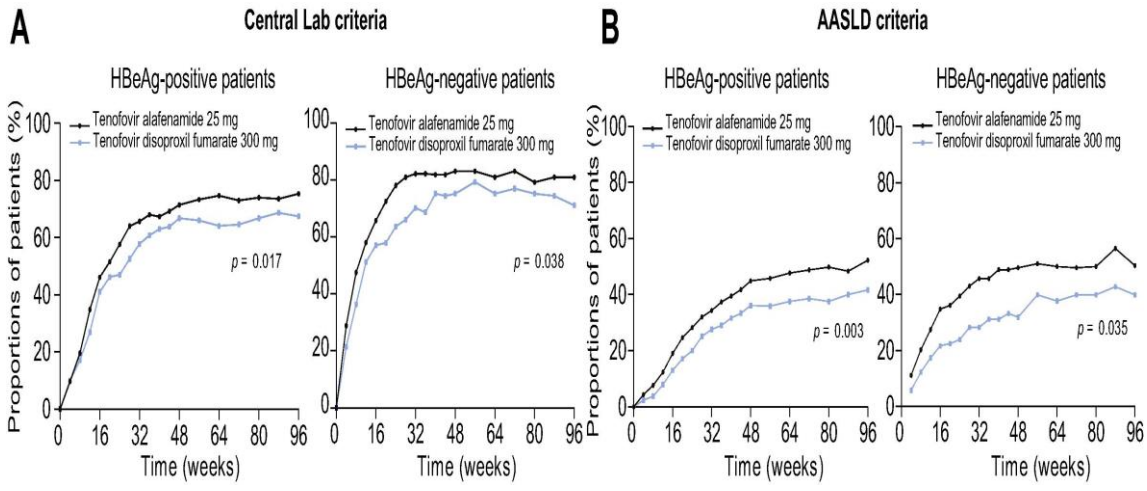


n=1300 patients from 2 phase III RCT
2/3 HBeAg positive
Mostly Asian male GT C infection

	HBeAg SC	HBsAg loss	qSag decline
TDF	18%	1%	0.51 log
TAF	22%	1%	0.64 log

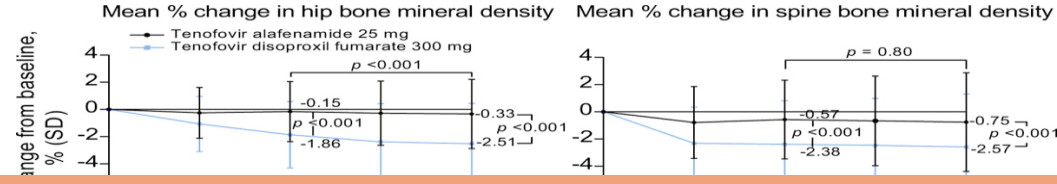
Aggarwal et al J Hepatology 2018

ALT normalisation

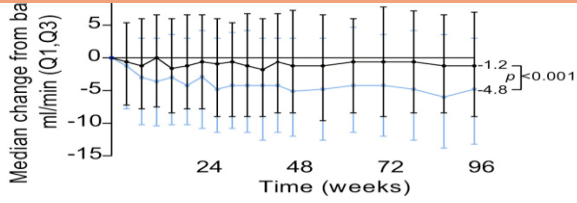


Aggarwal et al J Hepatology 2018

Renal and bone toxicity



On standard efficacy endpoints TAF is comparable to TDF (HBsAg loss is rare with both)
Significance of ALT effect is unknown
Safety markers are improved with TAF but clinical significance is unclear
All else being equal TAF is probably a better choice, esp within high risk populations
NOTE: TAF not yet recommended in pregnancy



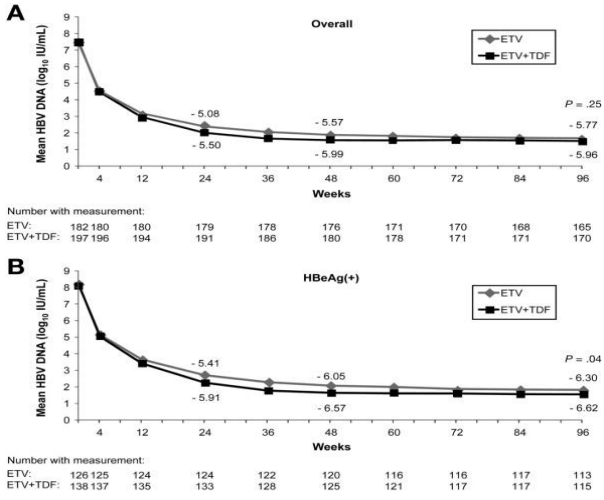
osteoporosis or had a relevant #

No patient had a renal SAE

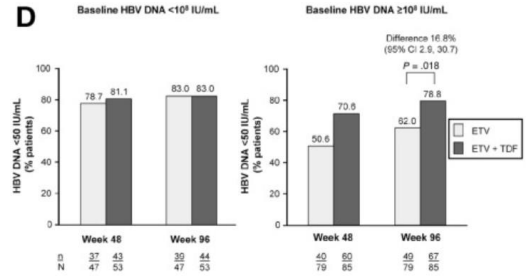
Aggarwal et al J Hepatology 2018

Is there any way to improve efficacy – particularly related to HBsAg loss?

ETV plus TDF?



n=379 CHB
Followed for 96 weeks

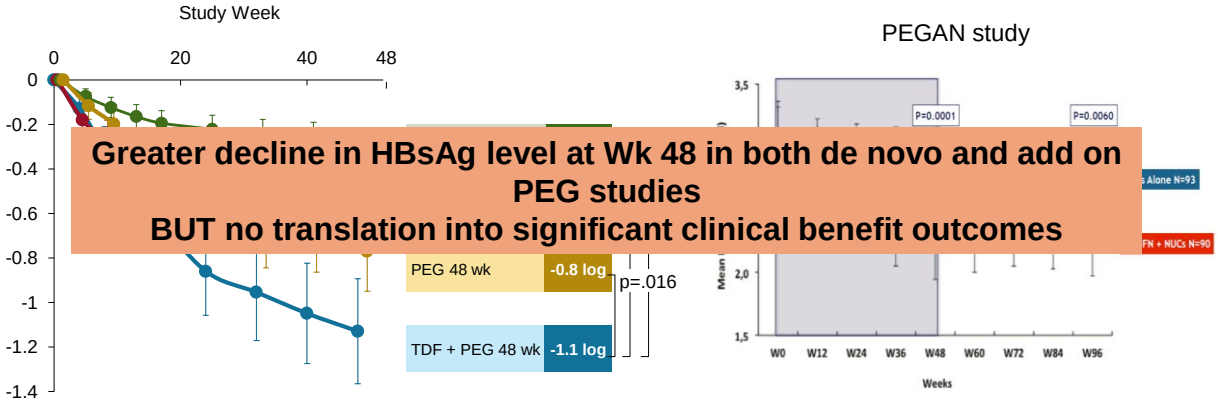


HBsAg loss 2.7% vs 3.6%

Some benefit in DNA suppression
– but not enough to matter

Lok Gastro 2011

NA plus immune modulator?



Greater decline in HBsAg level at Wk 48 in both de novo and add on PEG studies
BUT no translation into significant clinical benefit outcomes

740 CHB patients randomised to 4 groups
sAg loss 9.13% (combo) vs 0% (TDF) vs 2,8% (PEG)

185 HBeAg -ve patients on ETV randomised to add PEG for 48 weeks
sAg loss 7.8 (add-on) vs 3,2 % (NS)

Marcellin et al Gastroenterology 2016, Bouliere et al Lancet Gastro Hep 2017

- Single agents remain cornerstone of current therapy
- Combination NA may be recommended for patients with persistent viraemia especially with cirrhosis
- No recommendation for dual NA/IM although evidence for small but significant benefit exists

Current guidelines

Who should be treated?

Which treatment is optimal?

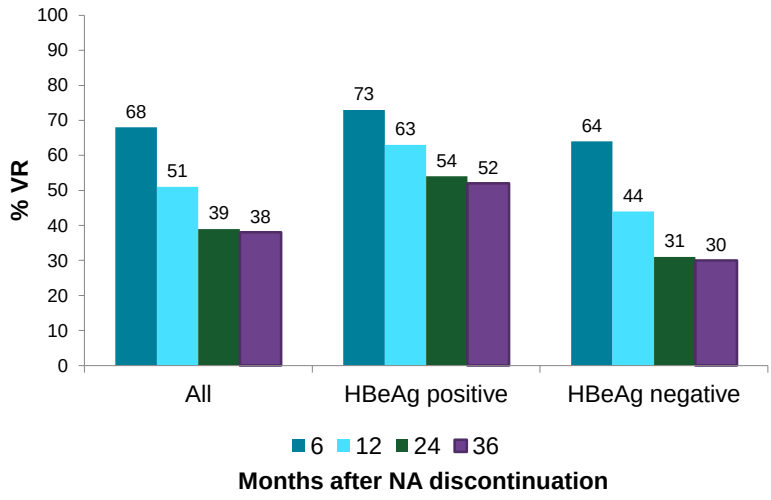
When should treatment be stopped?

Why should treatment be stopped at all?

- Cost?
- Toxicity?
- Complexity?

- Reluctance for life-long therapy
- Pregnancy/breast feeding
- Stigma/reinforcement

Discontinuation of oral antivirals in CHB



A systematic review

25 studies involving 1,716 patients
733 HBeAg positive
967 HBeAg negative
18% cirrhosis

Definition of virological remission (VR) varied from HBV DNA < 200 - 20,000

Papatheodoridis Hepatology 2016 ; 63, 1481

Is stopping an effective and safe strategy?

- Overall durable response observed in approximately 46%
- Most of the relapses occurred within the first or second year after NA discontinuation accompanied by biochemical and virological elevation
- No consistent pre-treatment predictors of VR identified - except in HBeAg neg:

	VR at 1 year	
On therapy suppression <24m	36%	OR 5.45, 95% CI 1.68-17.70; P = 0.005
On therapy suppression >24m	75%	

- Strategy was GENERALLY safe
  - Two (0.8%) of 243 patients with baseline cirrhosis decompensated
  - Six (2,5%) developed jaundice
  - One died of liver failure (others all successfully retreated)

Current guidelines: HBeAg positive

	EASL (2017)	AASLD (2018)	APASL (2015)
HBeAg-positive	HBeAg seroconversion + ≥ 6 or preferably 12m of consolidation	HBeAg seroconversion + ≥ 12m of consolidation* * AASLD suggests indefinite therapy for HBeAg-positive adults with cirrhosis … who seroconvert to anti-HBe on NA therapy	HBeAg seroconversion + ≥ 12m of consolidation (preferably 3yrs)

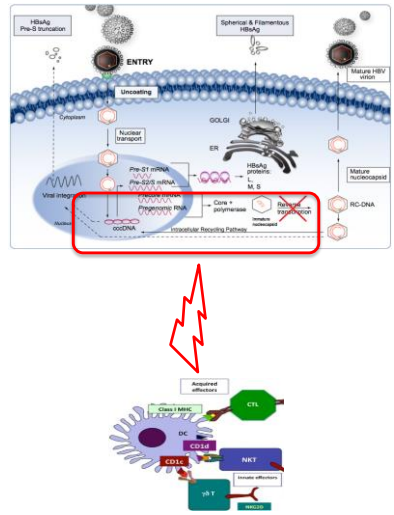
Or until HBsAg loss…..

Current guidelines: HBeAg negative

	EASL (2017)	AASLD (2018)	APASL (2015)
HBeAg-negative	Confirmed HBsAg loss +/- *anti-HBs seroconversion* Or *Selected non-cirrhotic patients with long-term (>3 years) suppression if close monitoring guaranteed*	Indefinite treatment is recommended (unless compelling rationale) Stopping "MBC" in persons with HBsAg loss * * Not if cirrhotic	<u>No cirrhosis:</u> i) HBsAg loss PLUS anti-HBs seroconversion OR ≥ 12 months of consolidation ii) after at least 2 years with undetectable HBV DNA on three separate occasions, 6 m apart (B1). <u>Cirrhosis:</u> Stopping "MBC" in cirrhotic patients with a careful off-therapy monitoring plan

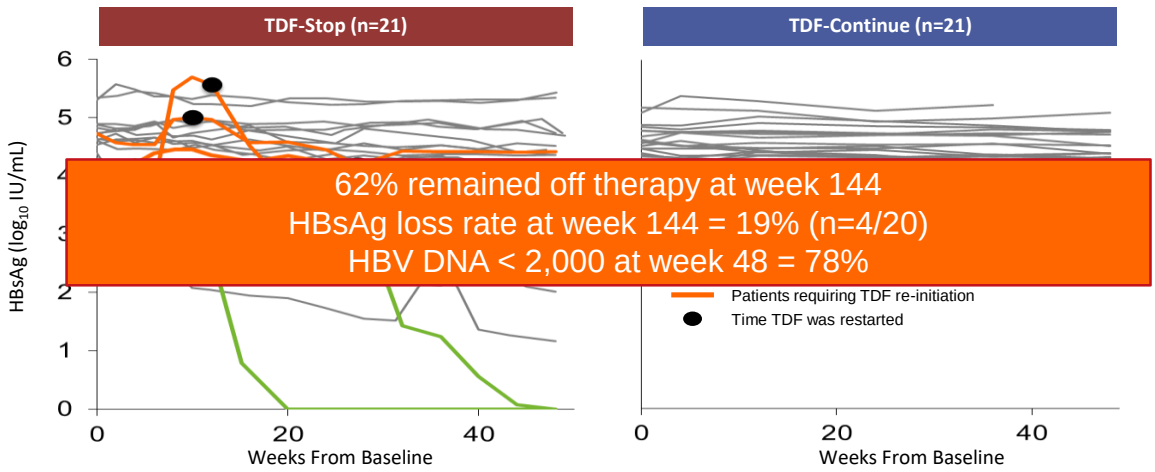
Is post STOP flare a good thing?

- long-term NA
  - deplete cccDNA
  - restore anti-HBV immunity
- STOP
- virological relapse
- Therapeutic hepatitis flare:
  - sustained immune control (SVR)
    - phase 3
  - ± HBsAg loss



Modified from Chan, J Hepatology, 2012

"Natural" immunotherapy?



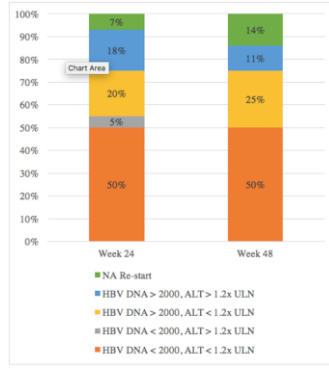
Berg et al The FINITE study J Hepatol 2017

HBV STOP study : Australia

Ongoing study of NA cessation in HBeAg negative patients with 2 years HBV DNA suppression
All non-cirrhotic, mostly Asian male
Data on first 46

All experienced virological rebound after cessation

Peak HBV DNA (0-48 wks)	
HBV DNA < 2000	13 (29.5%)
> 2000-20,000IU/mL	9 (21%)
> 20,000-200.000IU/mL	8 (18%)
> 200,000IU/mL	14 (32%)
Peak ALT (0-48 wks)	
- ALT ≥ 1.2-5 x ULN	12 (27%)
- ALT > 5-10 x ULN	4 (9%)
- ALT > 10 x ULN	10 (23%)



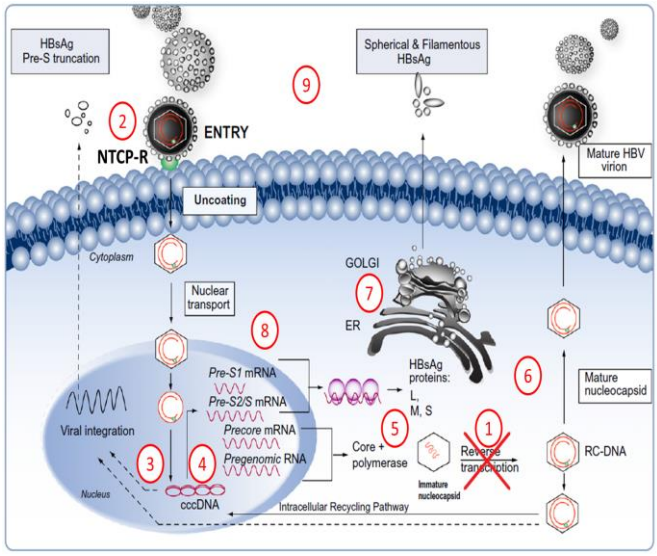
At week 48 55% in immune control and only 14% have restarted NA

Hall et al AGW 2017

A combination and innovative approach to functional cure is needed

Potent NA	→	agent to prevent viral spread and cccDNA re-amplification
cccDNA Inhibitor	→	safe and selective agent to reduce or silence cccDNA
HBV Antigen Inhibitor	→	agent(s) to block/inhibit the HBV life-cycle [entry, cell-spread, capsid assembly, HBx, HBeAg, HBsAg]
Immune Activator	? →	agent(s) to activate specific antiviral immune responses or relieve repression/exhaustion of the system

HBV life-cycle targets



Strategy		Candidate	Clinical development phase
Direct antiviral agents			
1	HBV polymerase inhibitor	Tenofovir alafenamide	Phase 4
2	Entry inhibitors	Myrcludex-B	Phase 2
3 / 4	cccDNA inhibitors - Silencing - Elimination	LT-βR agonist Zinc finger nucleases TALENs CRISPR-Cas9-based strategies	Preclinical *
5	Capsid inhibitors	NVR 3-778	Phase 1/2
6	Assembly inhibitors	HAPs Phenylpropenamide	Phase 1
7	HBsAg release inhibitor	REP-9AC' PEP-2139-Ca	Phase 2
Host targeting agents			
8	RNA interference *	ARC-520 TKM-HBV ALN-HBV	Phase 2 Phase 1 Preclinical
9	TLR agonists	GS-9620 (TLR7)	Phase 2
	Anti-PD-1	Nivolumab Pembrolizumab	Preclinical ** Preclinical **
	cIAP inhibitor	Birinapant	Phase 1
	Therapeutic vaccine	GS-4774 INO-1800 TS1050 ABX302	Phase 2 Phase 1 Phase 1 Phase 2b/3

Adapted from Chan, Thompson et al. J Hepatol, 2011

Huge challenges exist

Vaccine coverage

Timing of first birth dose

Diagnosis and linkage to care

Access to affordable antivirals

Understanding 'cure'

Innovative biomarkers

Combining novel drugs

A public health approach…..

An individualised approach…..

Acknowledgements

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