Nucleos(t)ide analogues for chronic hepatitis B: Cessation of treatment.

Alex Thompson

Gold Coast, 31st September 2016

Acknowledgement to Country

- We recognise the traditional custodians of the land and sea on which we live and work

Disclosures

- Advisory board member - Gilead, Abbvie, Bristol-Myers Squibb (BMS), Merck, and Roche Diagnostics
- Speaker - Gilead, Janssen, Merck, BMS, Abbvie
- PI - Gilead, Merck, Roche, BMS, Janssen, Spring Bank
- Research / grant support – Gilead, Merck, BMS, Abbvie
- My presentation includes discussion of drugs which are not approved for clinical use

Stopping NAs: Guideline recommendations

	EASL (2012)	AASLD (2015)	APASL (2015)
HBeAg-positive	HBeAg seroconversion + ≥ 12m of consolidation	HBeAg seroconversion + ≥ 12m of consolidation	HBeAg seroconversion + ≥ 12m of consolidation (preferably 3yrs)
HBeAg-negative	Confirmed HBsAg loss PLUS anti-HBs seroconversion + ≥ 12m of consolidation	Indefinite treatment is recommended Stopping "MBC" in persons with HBsAg loss Treatment discontinuation in persons with cirrhosis is not recommended	**No cirrhosis:** i) HBsAg loss PLUS anti-HBs seroconversion OR ≥ 12 months of consolidation ii) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (B1). **Cirrhosis:** Stopping "MBC" in cirrhotic patients with a careful off-therapy monitoring plan

EASL guidelines J Hepatol, 2012; 57:167-85
Terrault N, Hepatology, 2016; 63(1):261-83
Sarin, SK. Hepatol Int, 2016; 10:1–98

HBEAG-POSITIVE CHB

Stopping NAs: Guideline recommendations

	EASL (2012)	AASLD (2015)	APASL (2015)
HBeAg-positive	HBeAg seroconversion + ≥ **12m** of consolidation	HBeAg seroconversion + ≥ **12m** of consolidation	HBeAg seroconversion + ≥ 12m of consolidation (preferably **3yrs**)

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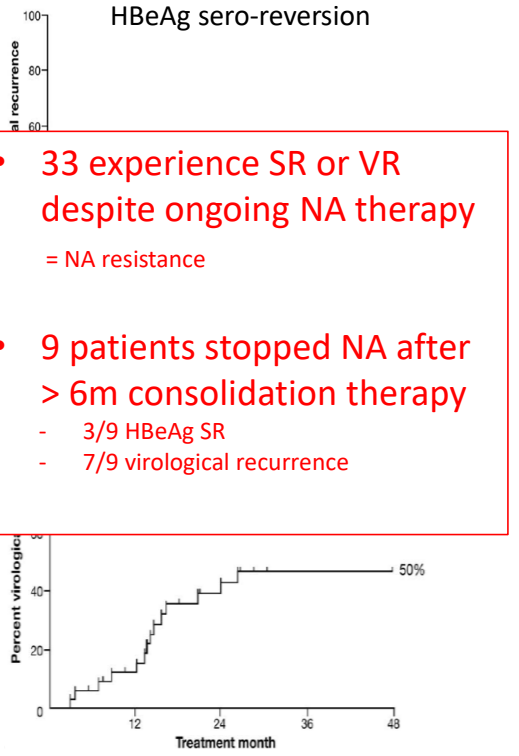
HBeAg S/C is not always durable

- Single centre observational study, n=132

Age, y	38 ± 15
Sex (male, %)	100 (76%)
Race	
Caucasian	77 (58%)
Asian	41 (31%)
Other	14 (11%)
Body mass index	24 ± 4.1
ALT, ×upper limit of normal[a]	2.3 (1.4-4.8)
HBV-DNA level, log_{10} copies/mL	8.2 ± 1.6
Genotype (N = 127)[b]	
A	45 (35%)
B	25 (20%)
C	19 (15%)
D	33 (26%)
Other	5 (4%)
Cirrhosis	23 (17%)
Treatment course	
Lamivudine	67 (51%)
Adefovir	33 (25%)
Entecavir	22 (17%)
Other	10 (7%)
Nucleos(t)ide analogue treatment-naive	117 (89%)

- 42 patients achieved HBeAg S/C*



- 33 experience SR or VR despite ongoing NA therapy
  = NA resistance
- 9 patients stopped NA after > 6m consolidation therapy
  - 3/9 HBeAg SR
  - 7/9 virological recurrence

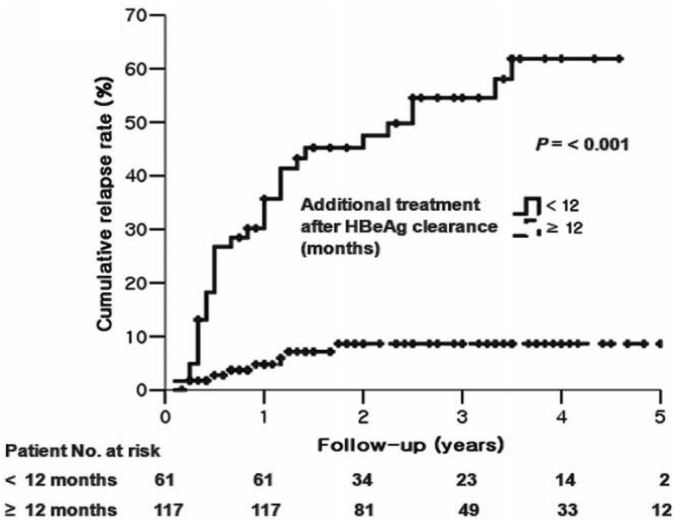
Reijnders Gastro 2010

Consolidation therapy ≥ 12 months is important for reducing the risk of relapse

Retrospective multi-centre study of Korean patients treated with lamivudine monotherapy

Characteristic	HBeAg (+) CHB n = 178 (%)
Male:female	129:49
Mean age (years)	39.0 ± 10.3
≤40	101 (56.7)
>40	77 (43.3)
Mean serum ALT (IU/L)	265.1 ± 225.3 (48-678)
>1 and ≤2 times ULN*	14 (7.9)
>2 and ≤5 times ULN*	73 (41.0)
>5 and ≤10 times ULN*	61 (34.3)
>10 and <20 times ULN*	30 (16.9)
Mean serum HBV DNA (log_{10} copies/mL)	7.8 ± 1.0 (5.2-9.4)
≤8.0	94 (52.8)
>8.0	84 (47.2)
Family history of CHB	56 (31.5)
Previous IFN-α therapy	17 (9.6)
Mean treatment duration, months (range)	26 (12-77)
Mean total follow-up duration, months (range)	53 (24-90)

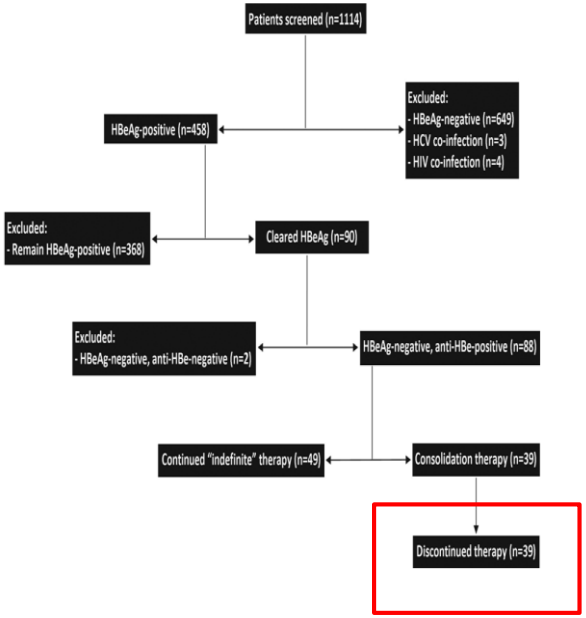
Relapse = HBV DNA > 2800 IU/mL

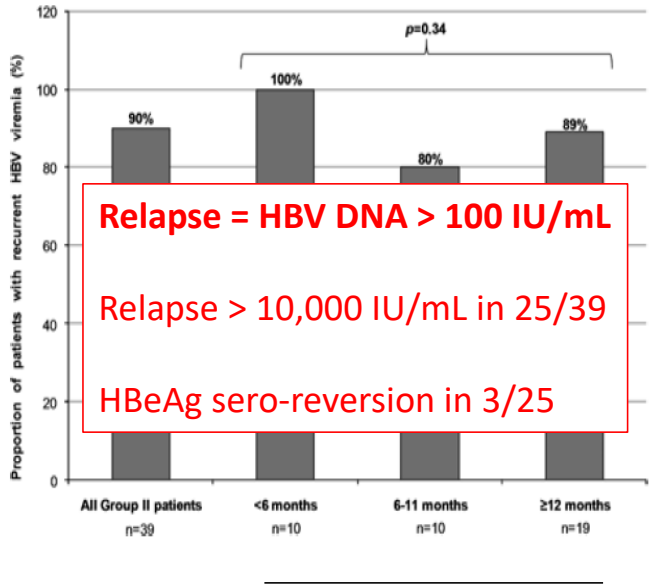


Lee, Hepatology, 2010

Is 12 months consolidation enough?

Relapse is more common using a more sensitive HBV DNA assay





Relapse = HBV DNA > 100 IU/mL

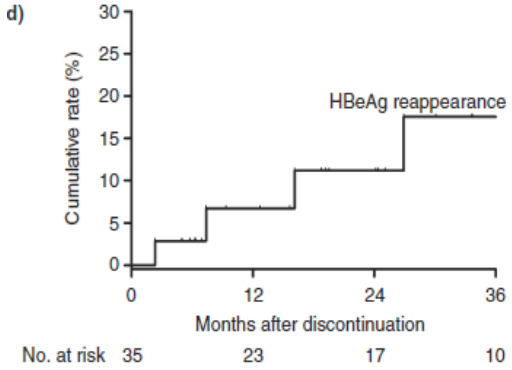
Relapse > 10,000 IU/mL in 25/39

HBeAg sero-reversion in 3/25

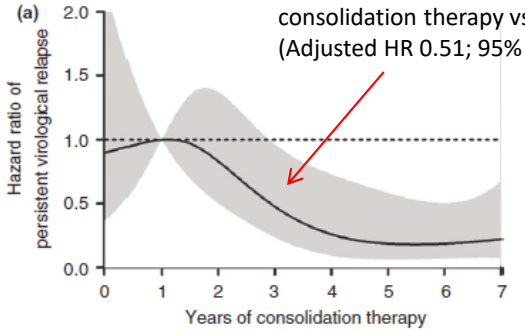
Duration of consolidation therapy

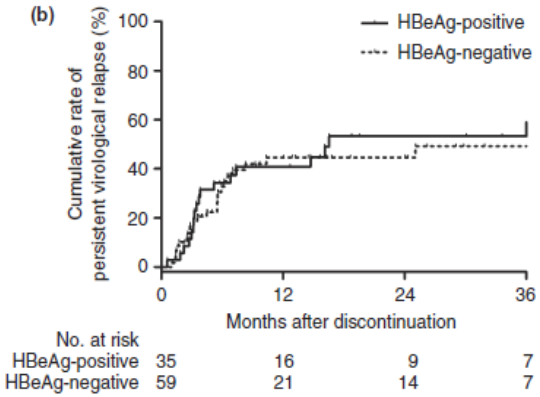
Chaung, J Clin Gastro, 2012

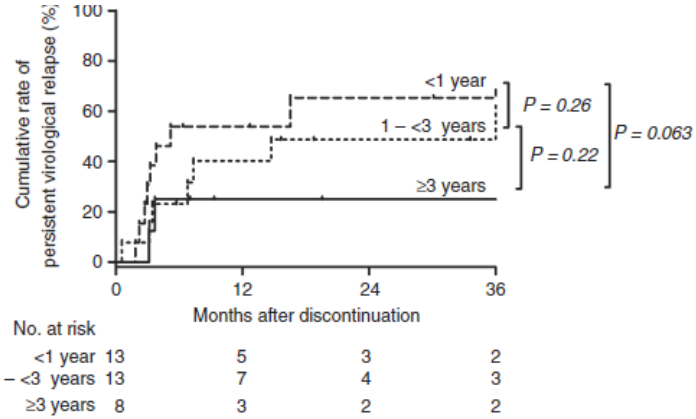
Consolidation > 3 years may reduce relapse rate



Risk of persistent virological relapse significantly reduced at > 2.9 yrs of consolidation therapy vs. 1 yr (Adjusted HR 0.51; 95% CI 0.25–0.99).







Conclusion

- **No cirrhosis**
  - Stopping NA after HBeAg S/C is reasonable
    - HBeAg loss, anti-HBe seroconversion
    - Consolidation ≥ 12m post S/C is important
    - The role of longer consolidation therapy needs to be evaluated
  - People who stop antiviral therapy should be monitored for recurrent viremia, ALT flares, and seroreversion
    - every 3 months for at least 1 year, then 6 monthly

- **Cirrhosis**
  - Stopping NA after HBeAg S/C is controversial
  - AASLD - recommends indefinite antiviral therapy
  - EASL - …stopping might be considered, but …NA therapy should usually be continued indefinitely in cirrhotic patients
  - APASL - NA therapy may also be considered in cirrhotic patients with acareful off-therapy monitoring plan
    - Every 1 month for 3 months, every 3 months to 1 year, then 6 monthly

HBEAG-NEGATIVE CHB

Management of HBeAg-negative CHB

- Nucleoside analogues (NA) are the mainstay of current therapy
  - Potent antiviral activity
  - High genetic barrier to resistance

- But…optimal treatment duration for patients with HBeAg-negative chronic hepatitis B (CHB) remains uncertain

Stopping NAs: Guideline recommendations

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HBeAg-negative	Confirmed HBsAg loss PLUS anti-HBs seroconversion + ≥ 12m of consolidation	Indefinite treatment is recommended Stopping "MBC" in persons with HBsAg loss Treatment discontinuation in persons with cirrhosis is not recommended	**No cirrhosis:** i) HBsAg loss PLUS anti-HBs seroconversion OR ≥ 12 months of consolidation ii) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (B1). **Cirrhosis:** Stopping "MBC" in cirrhotic patients with a careful off-therapy monitoring plan

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Terrault N, Hepatology, 2016; 63(1):261-83
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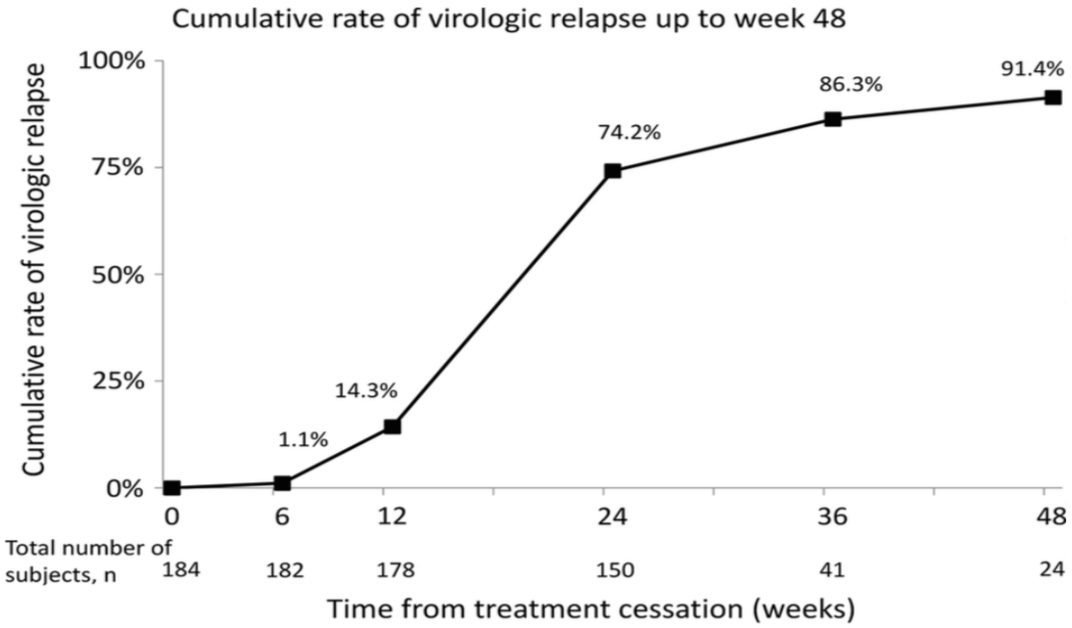
HBeAg-negative CHB: Virologic relapse occurs when NA stopped

Virological relapse defined as HBV DNA >2000 IU/mL.



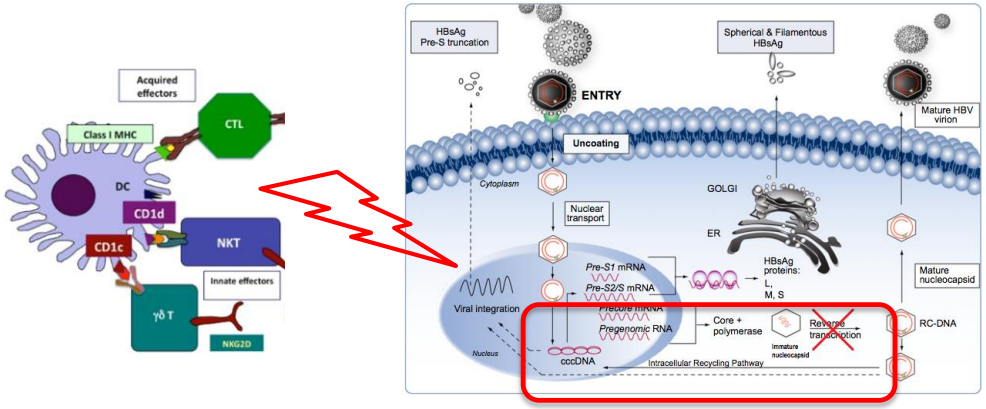
Seto 2015

Why STOP?

- Long-term therapy presents challenges
  - adherence can be challenging
  - risk of resistance
  - risk of adverse events (e.g. renal, bone AEs)
  - $$$

Why STOP?

- STOPping long-term NA may have benefit
  - NA deplete cccDNA
  - NA promote restoration of anti-HBV immunity
  - STOPping → virological relapse → therapeutic hepatitis flare:
    - sustained immunological control (phase 3)
    - ± HBsAg loss

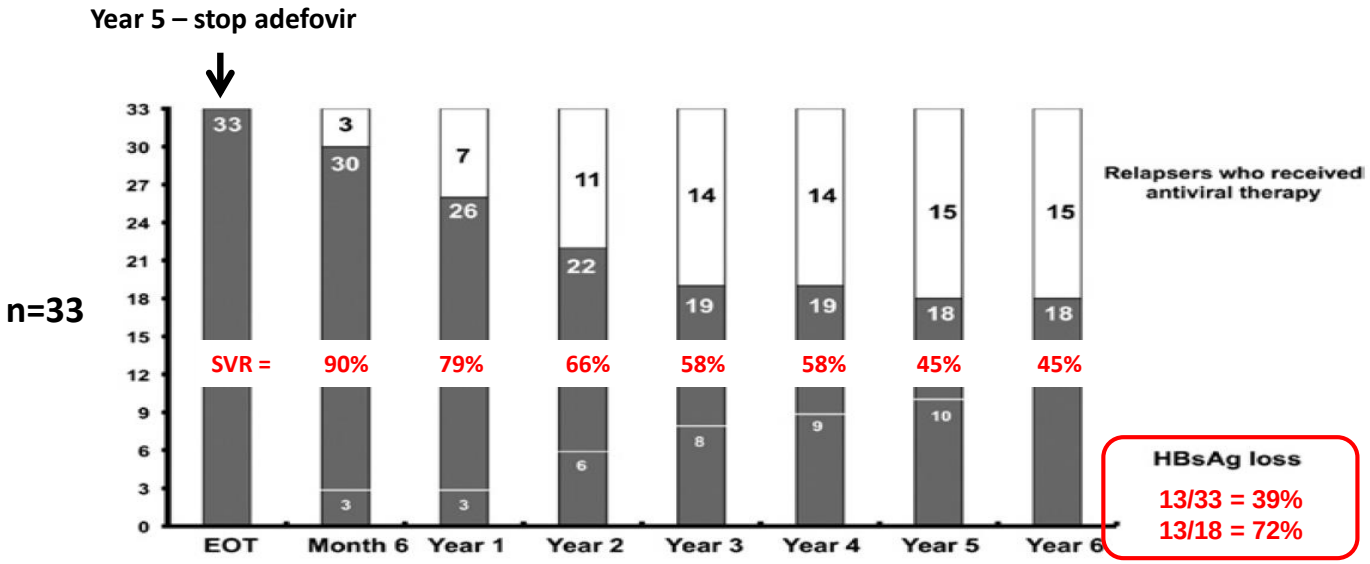


Modified from Chan, J Hepatology, 2012

Data from small studies suggest:

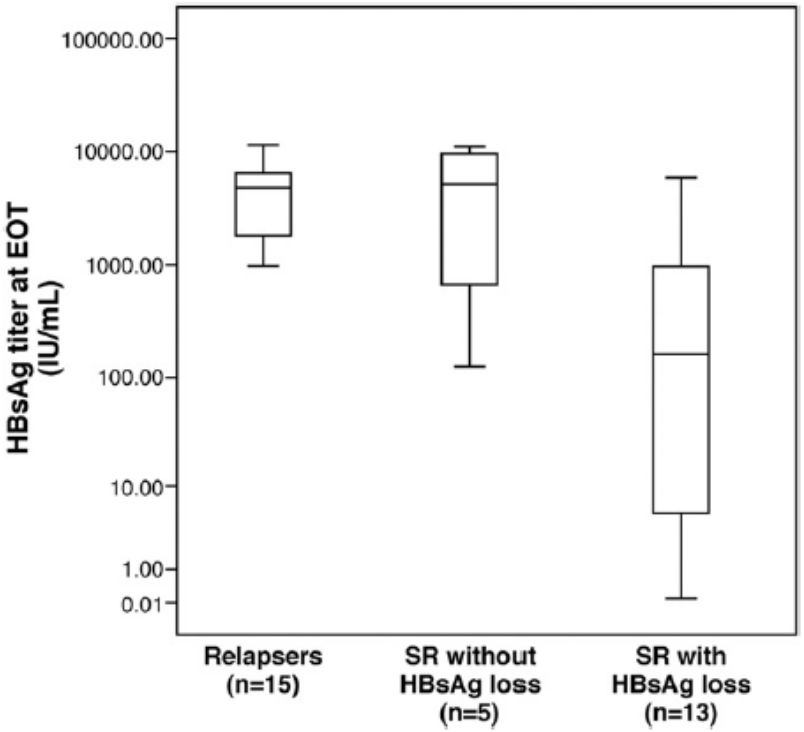
- long-term SVR is possible
- HBsAg loss may occur

- Prospective observational study of patients who stopped long-term adefovir
- n = 33, HBeAg-negative CHB, European genotype D disease
- Primary end-point = **sustained response**
  = HBV DNA persistently ≤ 2000 IU/mL combined with persistently normal ALT values (≤ 40 U/L) following post-treatment month 6 sustained to the end of follow-up.



Hadziyannis, Gastro, 2012

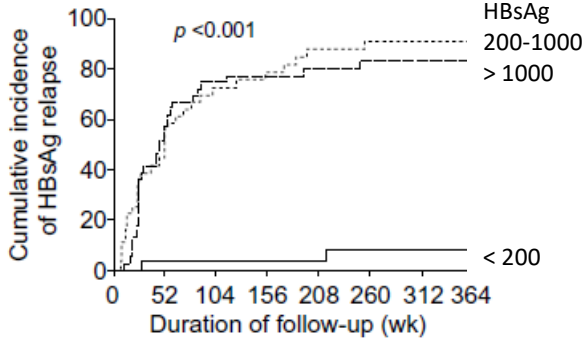
HBsAg levels at EOT may predict for risk of relapse



Hadziyannis, Gastro, 2012

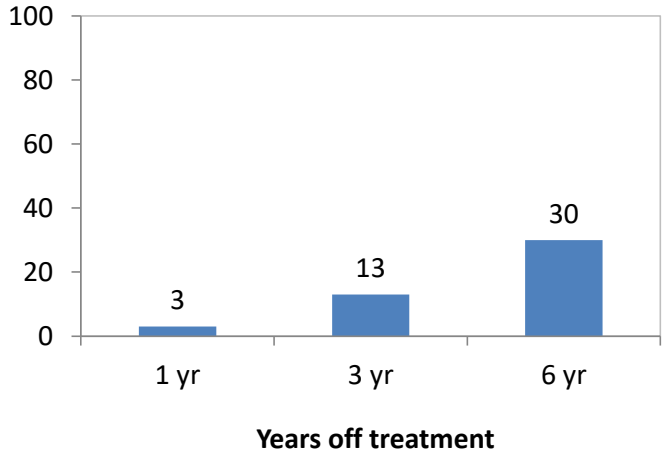
HBsAg levels may also identify patients who achieve HBsAg loss after stopping NA therapy

Virological relapse (DNA > 2000 IU/mL x 2)



No. at risk HBsAg								
<200 IU/ml	30	29	28	25	20	16	10	9
200-1000 IU/ml	36	19	9	7	4	3	3	1
>1000 IU/ml	39	19	10	8	7	5	2	1

HBsAg loss

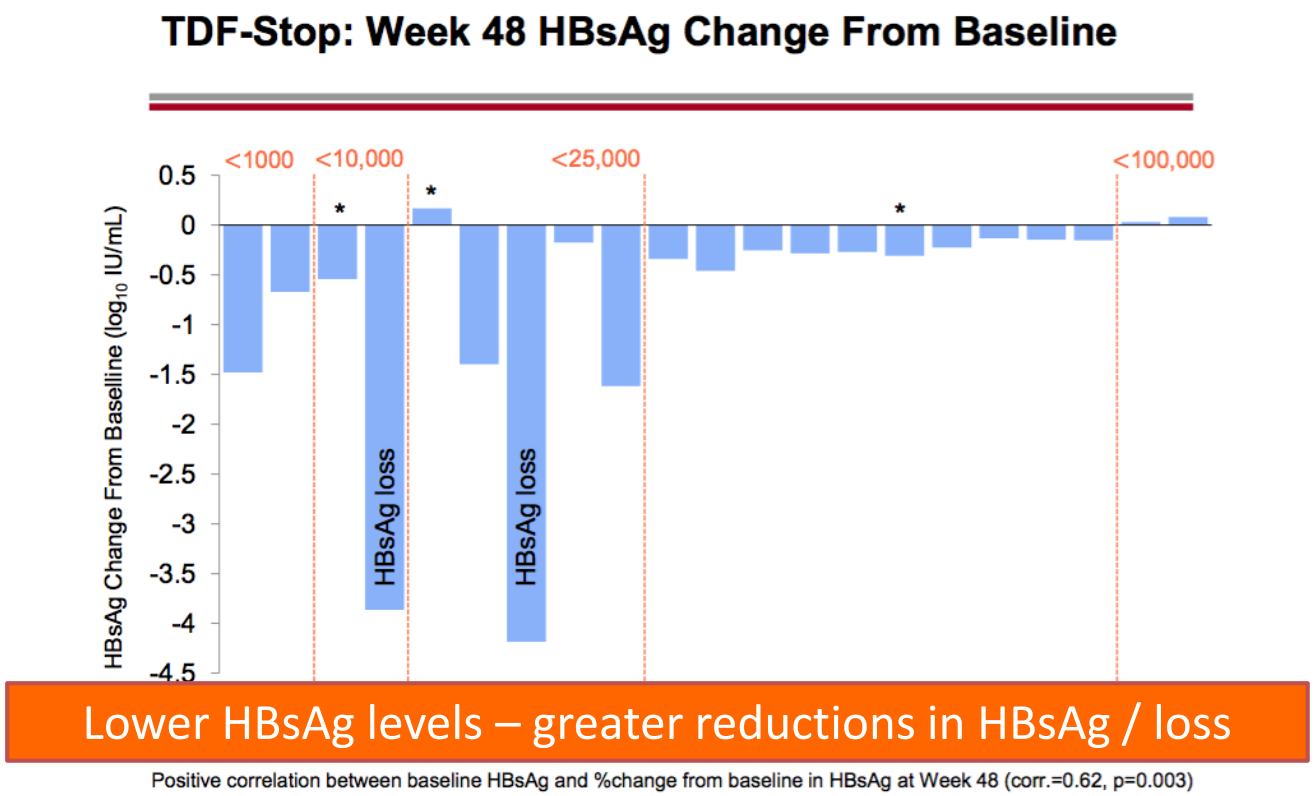


MVA – sustained response – low HBsAg levels (EOT), younger age and F gender
MVA – HBsAg loss – low HBsAg, low HBV DNA (PT), longer treatment duration

Chen J Hepatol 2014

HBsAg levels predict for HBsAg decline

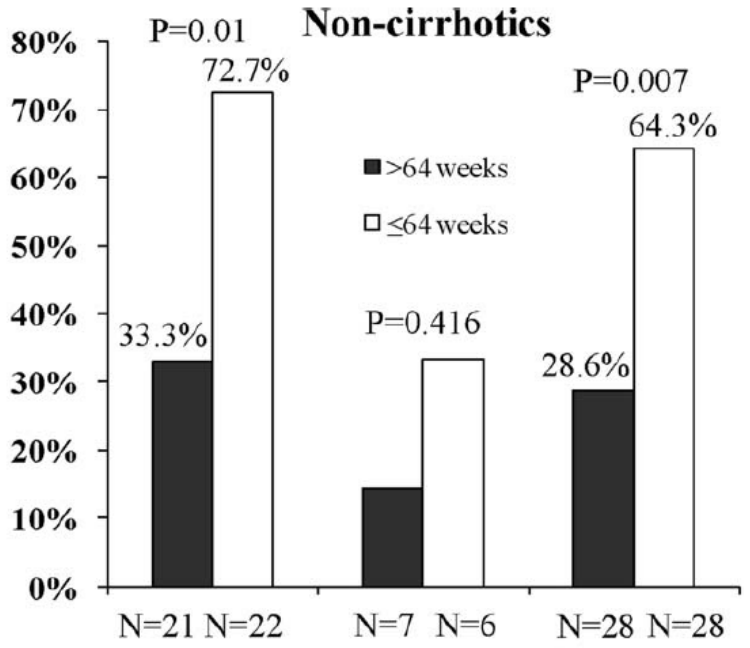
(FINITE-CHB study)



T Berg et al., O0119 EASL 2015

Long-term consolidation therapy may reduce the risk of relapse in patients with HBeAg-negative CHB

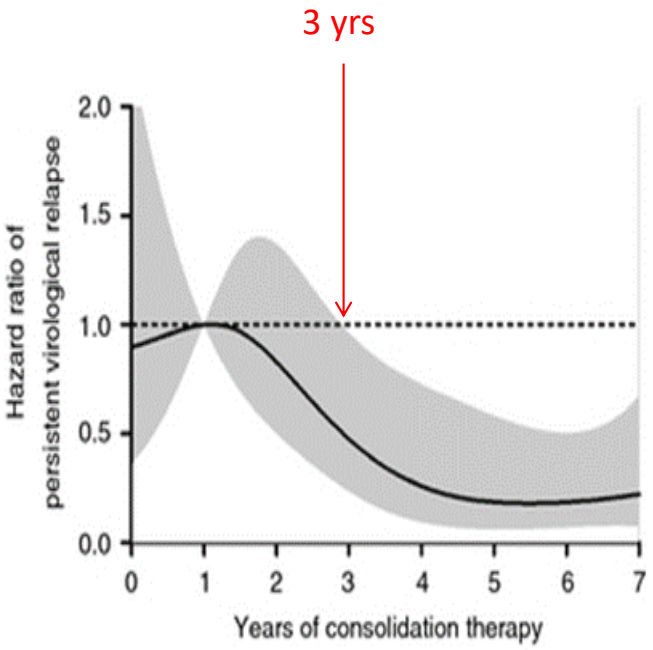
Risk of relapse
HBV DNA > 2,000
+
ALT > 2xULN

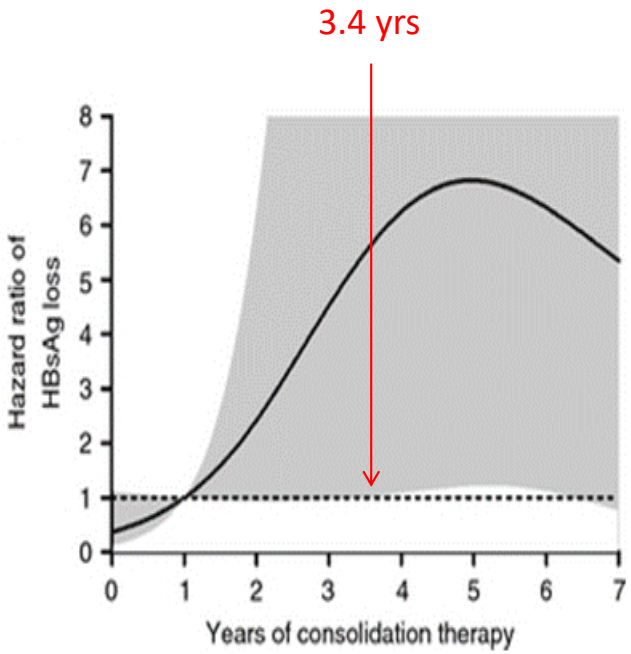


Consolidation > 64 weeks assoc with lower relapse in pts without cirrhosis and high DNA

Jeng Hepatology 2013

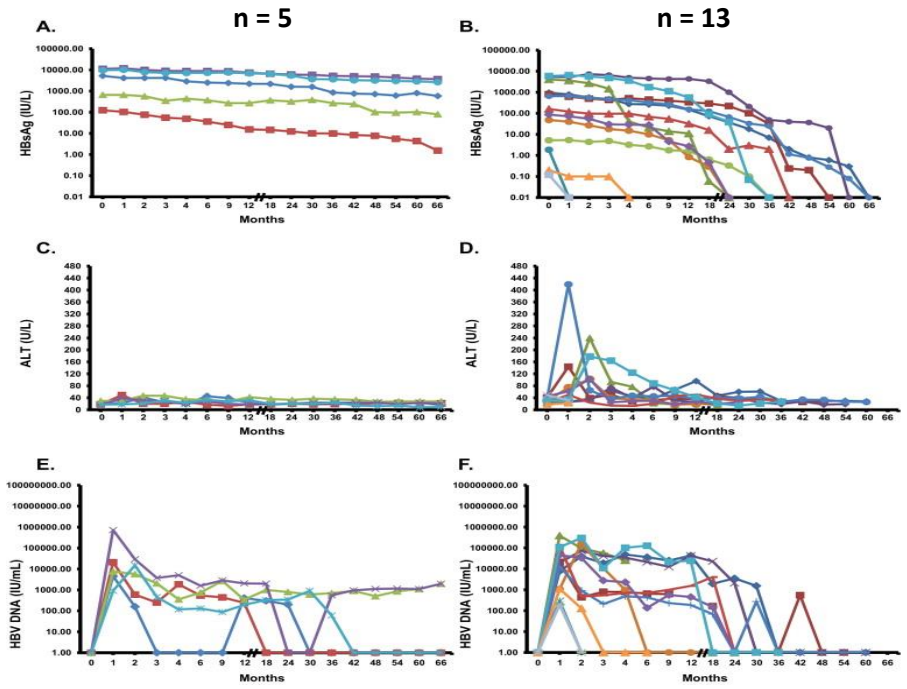
Long-term consolidation therapy may reduce relapse and increase HBsAg loss





Chi, APT, 2015

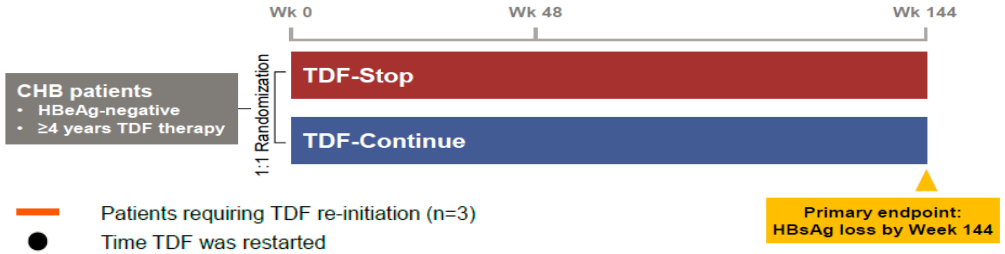
Early biochemical flare may predict for HBsAg loss in sustained responders

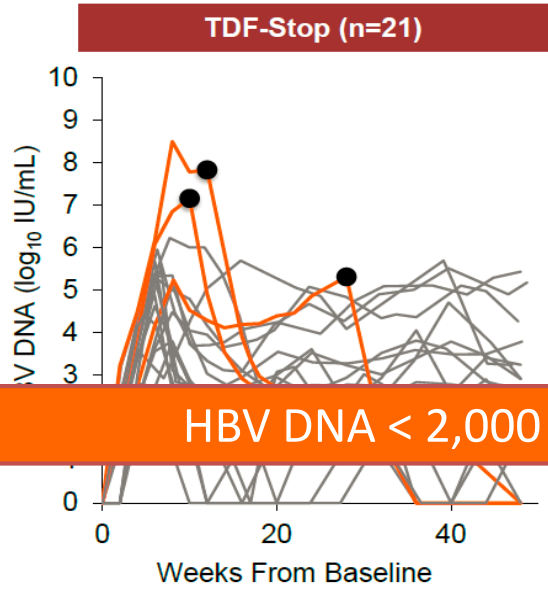


No HBsAg loss was observed in patients who had NA restarted

Hadziyannis, Gastro, 2012

FINITE-CHB study





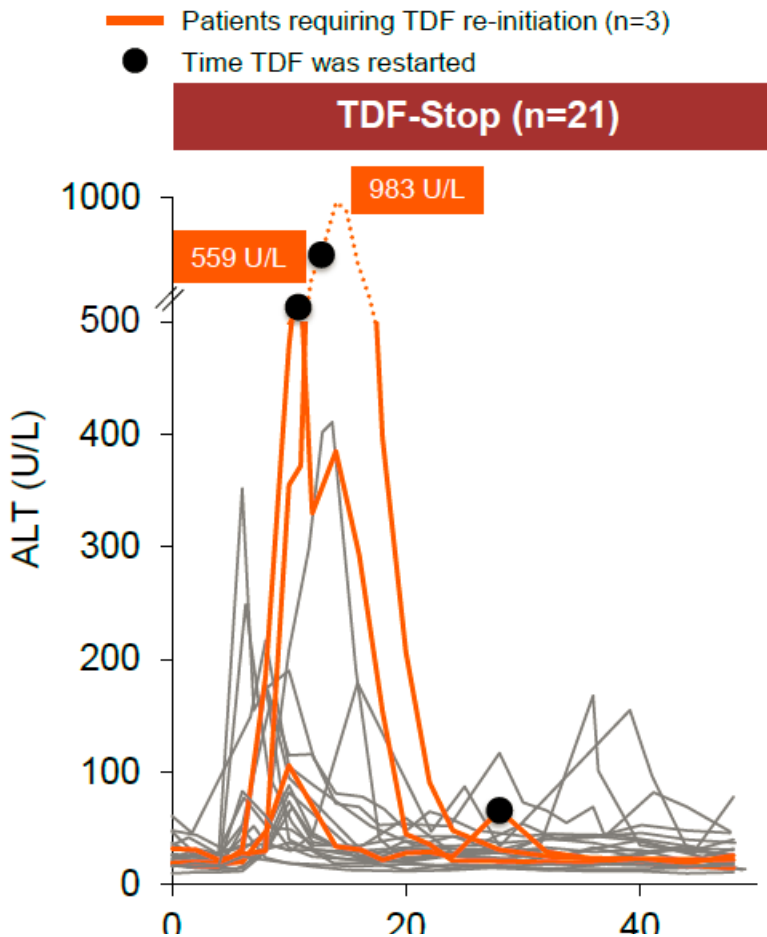
- HBV DNA became detectable in 21/21 (100%) of TDF-Stop subjects
- HBV DNA up to W48:
  - Median: 5.32 $\log_{10}$ IU/mL
  - Min: 4.41 $\log_{10}$ IU/mL
  - Max: 8.50 $\log_{10}$ IU/mL
- At W48*

HBV DNA < 2,000 at week 48 = 78%

* TDF-Restart excluded

T Berg et al., O0119 EASL 2015

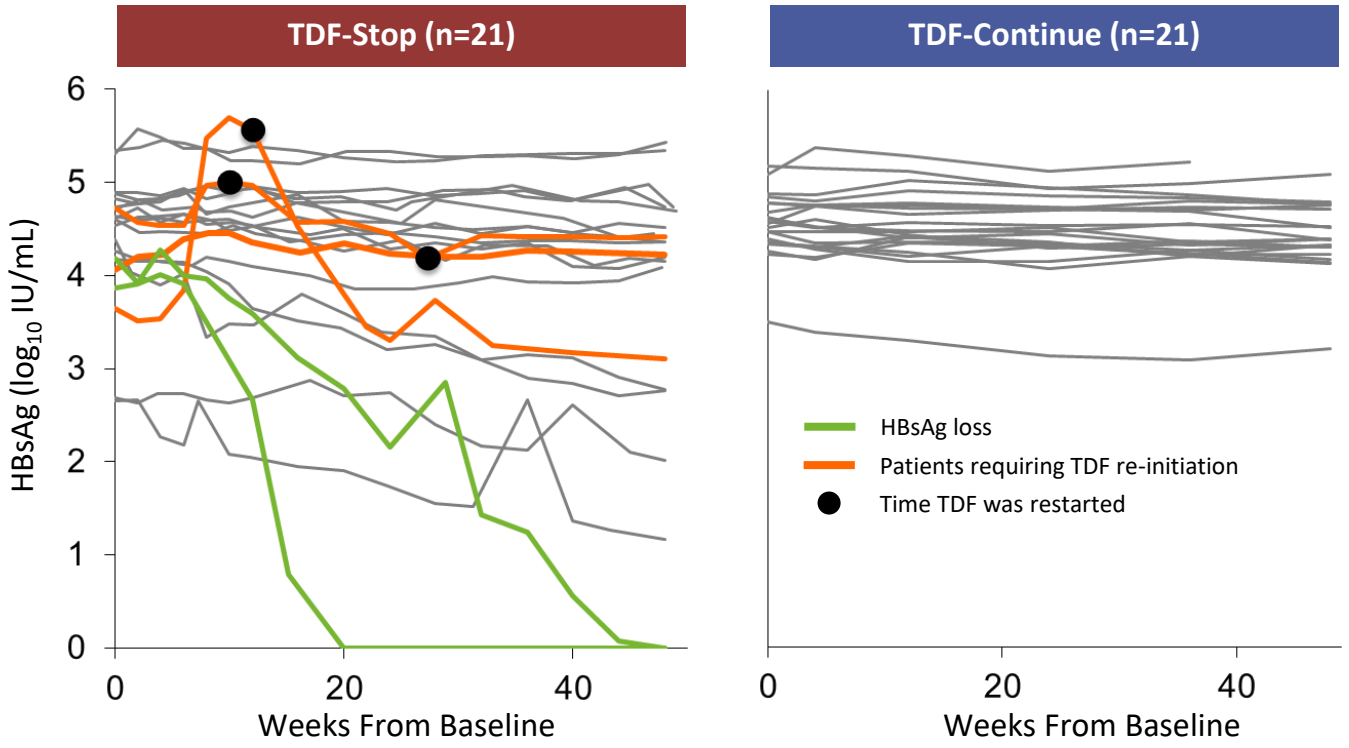
ALT Profiles



- ALT peaked at >2xULN in 12/21 TDF-Stop subjects (57%)
- ALT up to W48
  - Median: 162 U/L
  - Min: 25 U/L
  - Max: 983 U/L
- At W48*
  - 100% (18/18) ALT < 2xULN
  - 83% (15/18) ALT < ULN

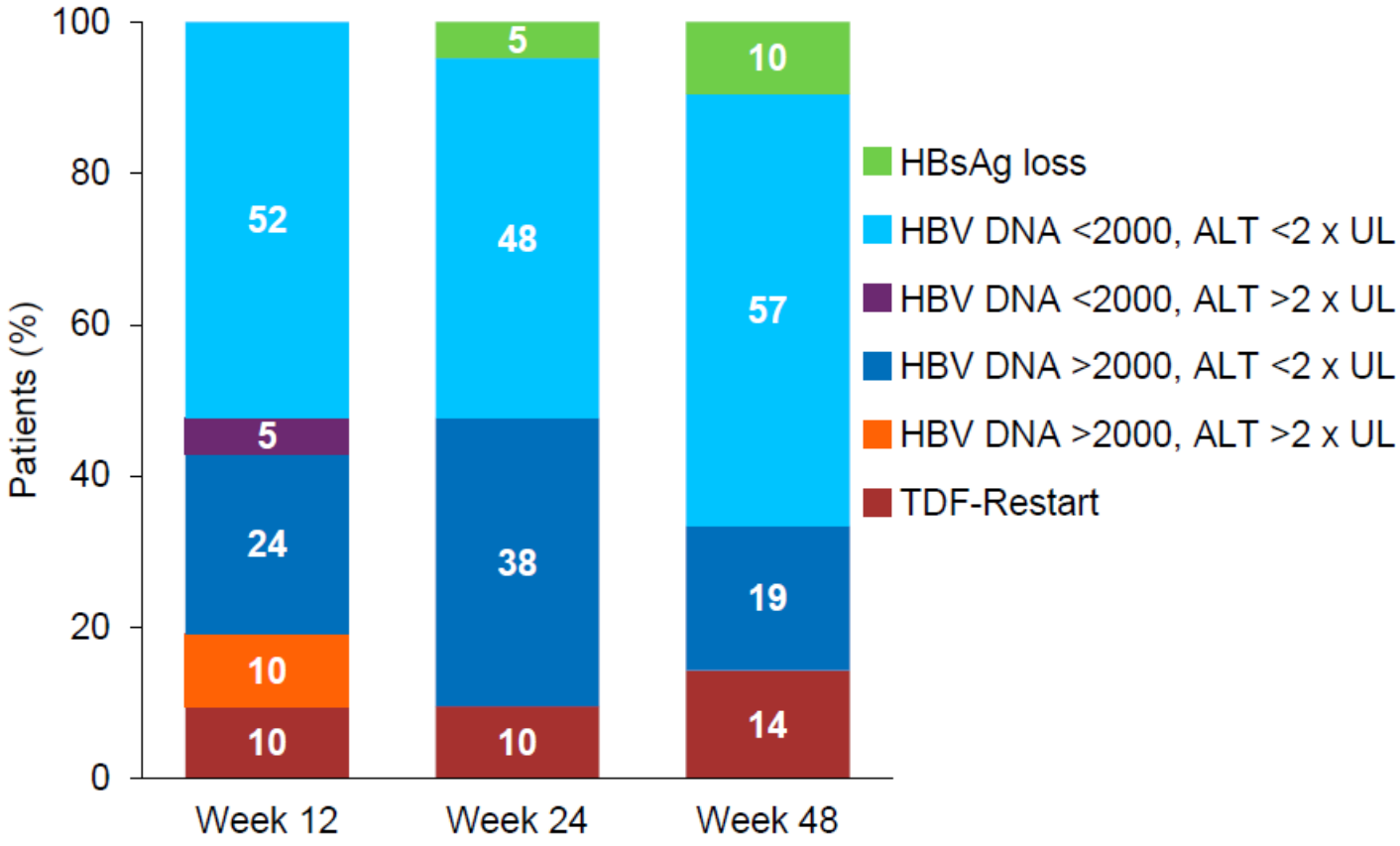
* TDF-Restart excluded

FINITE-CHB study

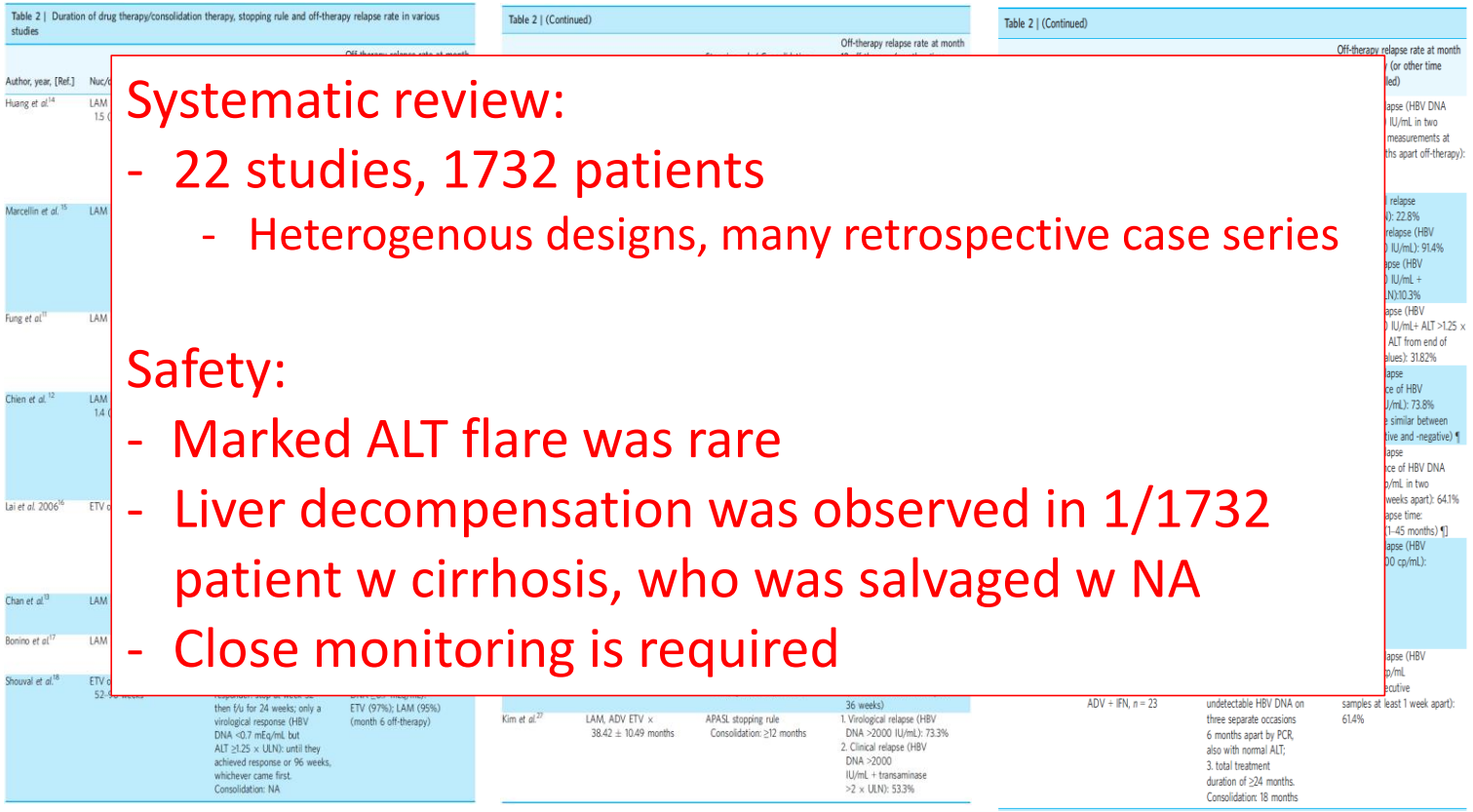


T Berg et al., O0119 EASL 2015

TDF-Stop: HBsAg loss, HBV DNA, ALT, TDF-Restart



Stopping NA therapy is safe*



Systematic review:

- 22 studies, 1732 patients
  - Heterogenous designs, many retrospective case series

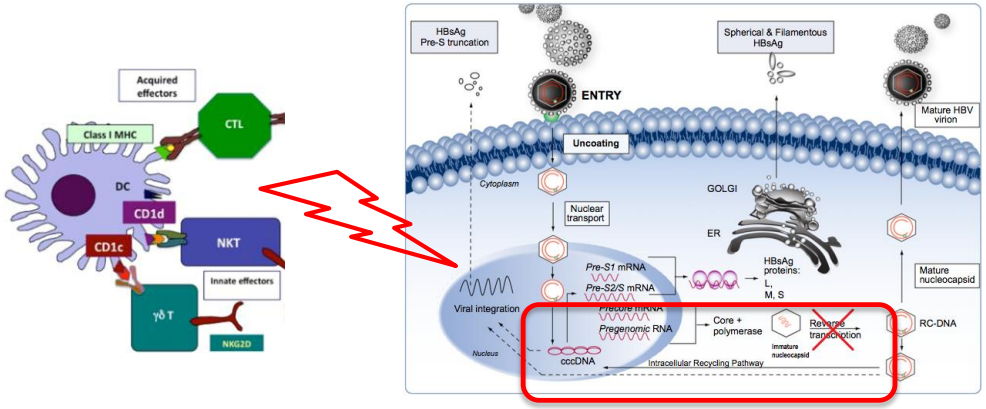
Safety:

- Marked ALT flare was rare
- Liver decompensation was observed in 1/1732 patient w cirrhosis, who was salvaged w NA
- Close monitoring is required

Chang, APT, 2015

Why STOP?

- STOPping long-term NA may have benefit
  - NA deplete cccDNA
  - NA promote restoration of anti-HBV immunity
  - STOPping → virological relapse → therapeutic hepatitis flare:
    - sustained immunological control (phase 3) = SVR
    - ± HBsAg loss

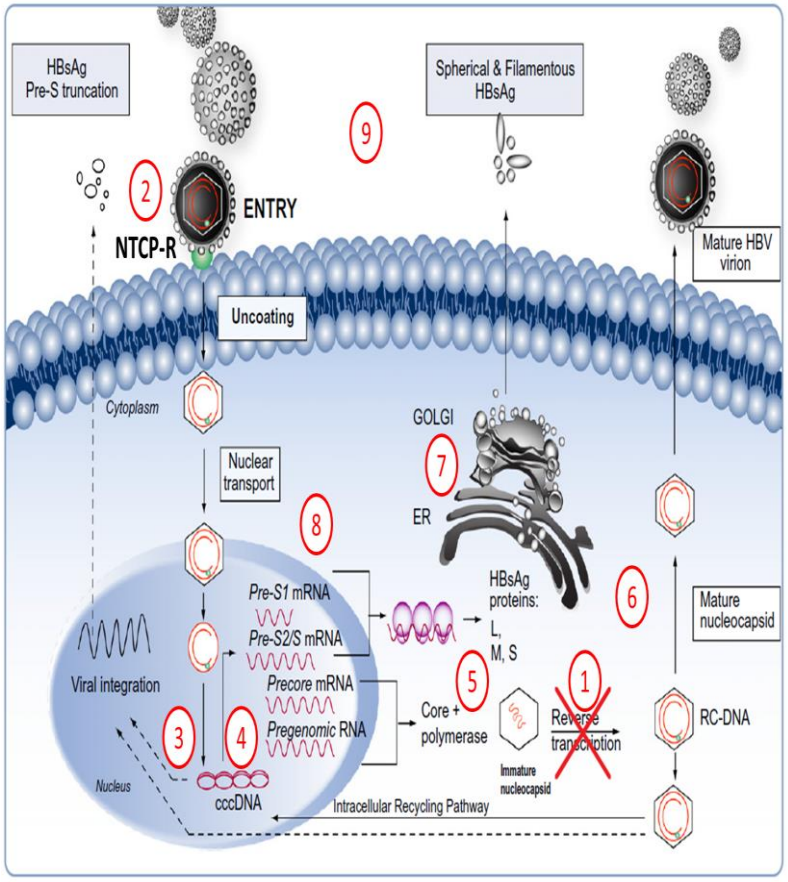


Modified from Chan, J Hepatology, 2012

The STOP strategy

- Paradigm shift:
  - Early virological relapse is expected
  - ALT flare is important for achieving SVR and HBsAg loss
    - “therapeutic” flare = immune control
    - close monitoring is necessary
- Prospective studies are needed
  - NHMRC project 1066536

STOPping vs novel immunotherapies?

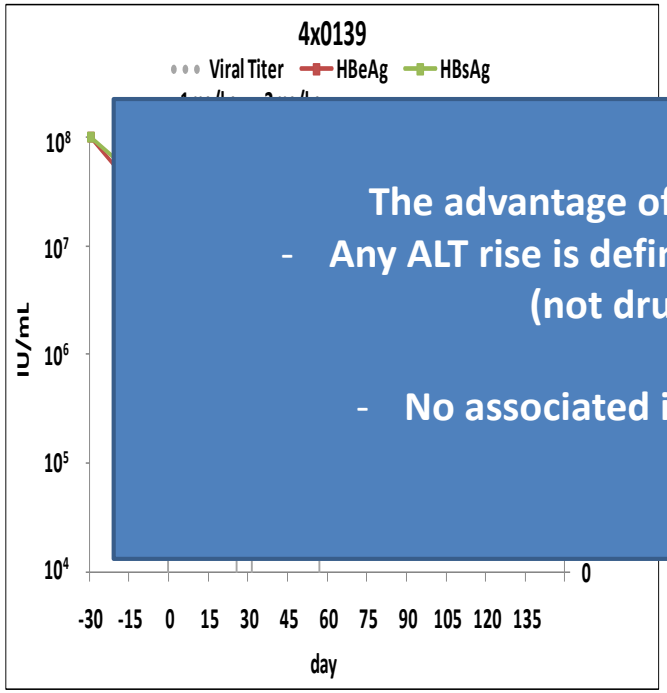


Adapted from Chan, Thompson et al. J Hepatol, 2011

Strategy		Candidate	Clinical development phase
Direct antiviral agents			
1	HBV polymerase inhibitor	Tenofovir alafenamide	Phase 3
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

Novel immunomodulators: "therapeutic flare vs. drug toxicity"

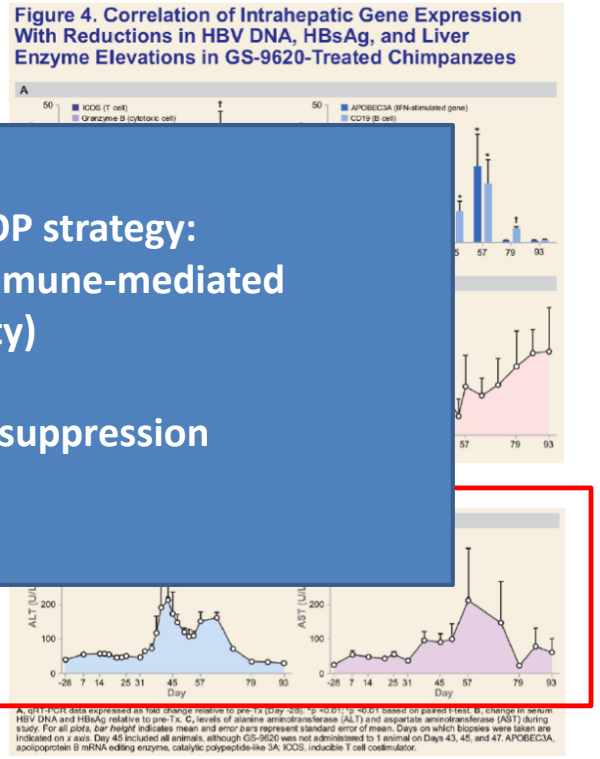
GS-9620 (TLR7 agonist): Chimpanzee studies



The advantage of the STOP strategy:

- Any ALT rise is definitely immune-mediated (not drug toxicity)

- No associated immunosuppression



Lanford, Gastroenterology, 2013

Conclusion

	EASL (2012)	AASLD (2015)	APASL (2015)
HBeAg-positive	HBeAg seroconversion + ≥ 12m of consolidation	HBeAg seroconversion + ≥ 12m of consolidation	HBeAg seroconversion + ≥ 12m of consolidation (preferably 3yrs)
HBeAg-negative	Confirmed HBsAg loss PLUS anti-HBs seroconversion + ≥ 12m of consolidation	Indefinite treatment is recommended Stopping "MBC" in persons with HBsAg loss Treatment discontinuation in persons with cirrhosis is not recommended	**<u>No cirrhosis:</u>** i) HBsAg loss PLUS anti-HBs seroconversion OR ≥ 12 months of consolidation ii) after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart (B1). **<u>Cirrhosis:</u>** Stopping "MBC" in cirrhotic patients with a careful off-therapy monitoring plan

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Conclusion

- HBeAg-negative CHB?
  - Prospective studies of NA cessation in HBeAg-negative CHB are ongoing
  - Goal = HBsAg loss
  - Suitable for **non-cirrhotics**
  - Close monitoring post-cessation is required