
2021 SCSG
LIVER
SYMPOSIUM
"State of HBV Cure"
Norah Terrault, MD, MPH
Professor of Medicine
University of Southern California

Disclosures

- Institutional grant support from Roche-Genentech, GlaxoSmithKline, Gilead Sciences, Helio Health
- EXIGO and Saol Therapeutics (Consultant)
- Moderna (DSMB)
- Advisory board for GSK (unpaid), Gilead (unpaid), Vir Biotech (unpaid)

Current Treatment of Chronic HBV

- **Goals are to prevent HBV complications**
- **Target those at risk for disease progression = active CHB and cirrhosis**

Treat now

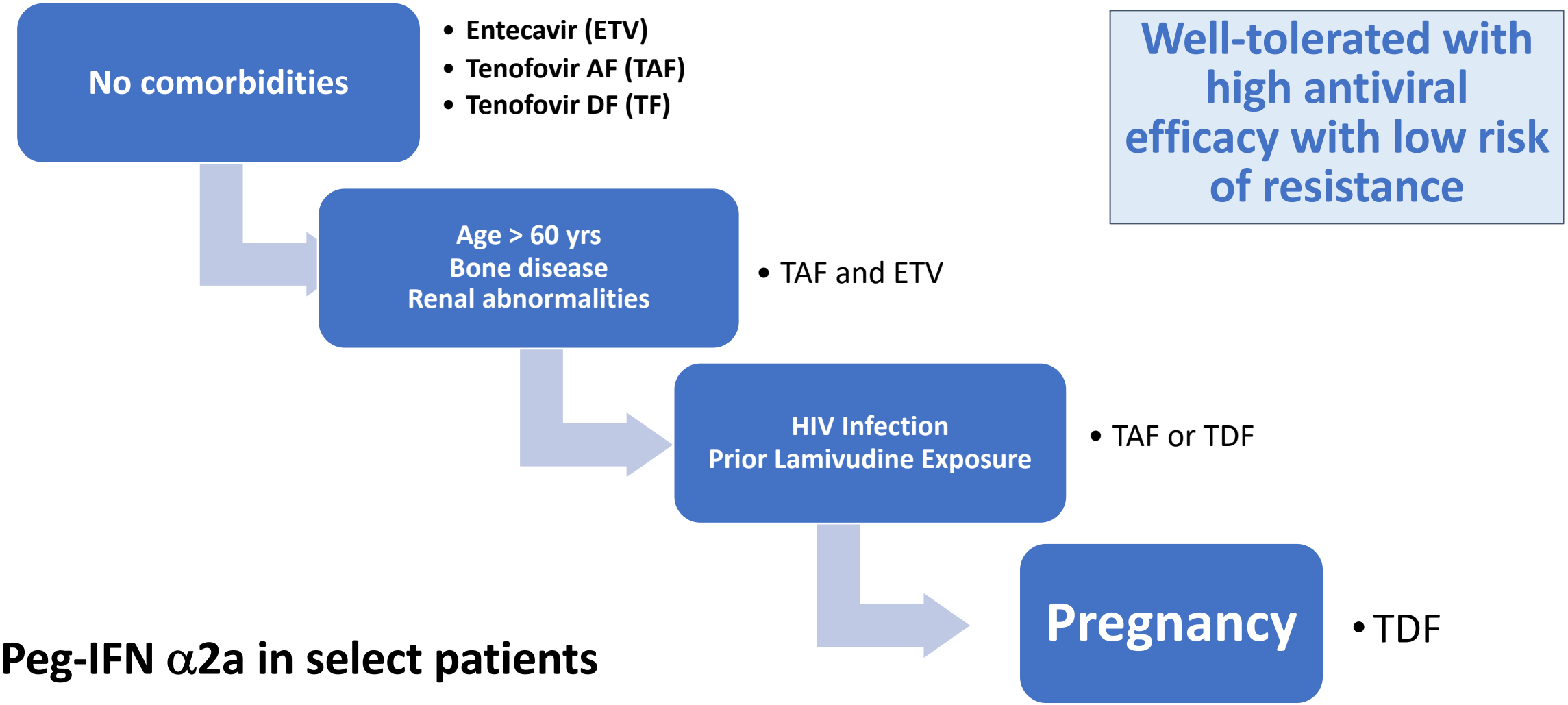
- Active CHB (HBeAg+/-)
- Advanced fibrosis/cirrhosis
- Coinfection with HIV
- Special populations:
  - Immuno-modulatory therapy
  - Pregnancy

Defer treatment

- Inactive CHB (HBV DNA <2000 IU/mL, normal ALT)
- Immune-tolerant (young)

AASLD HBV Treatment Guidelines 2018

Preferred Therapies for CHB



Well-tolerated with high antiviral efficacy with low risk of resistance

Peg-IFN α2a in select patients

Lamivudine, adefovir, telbivudine should not be used

Terrault NA, Hepatology 2018; 67:1560-15

Achievable Outcomes with HBV Antivirals

Sustained HBV DNA suppression associated with:

- **Lower rates of cirrhosis**
- **Reversal of fibrosis/cirrhosis**
- **Reverse liver decompensation**
- **Reduce risk of HCC**
- **Reduce liver-related mortality**
- **Improved survival**

AASLD HBV Treatment Guideline 2018
Marcellin P, et al. Lancet 2013

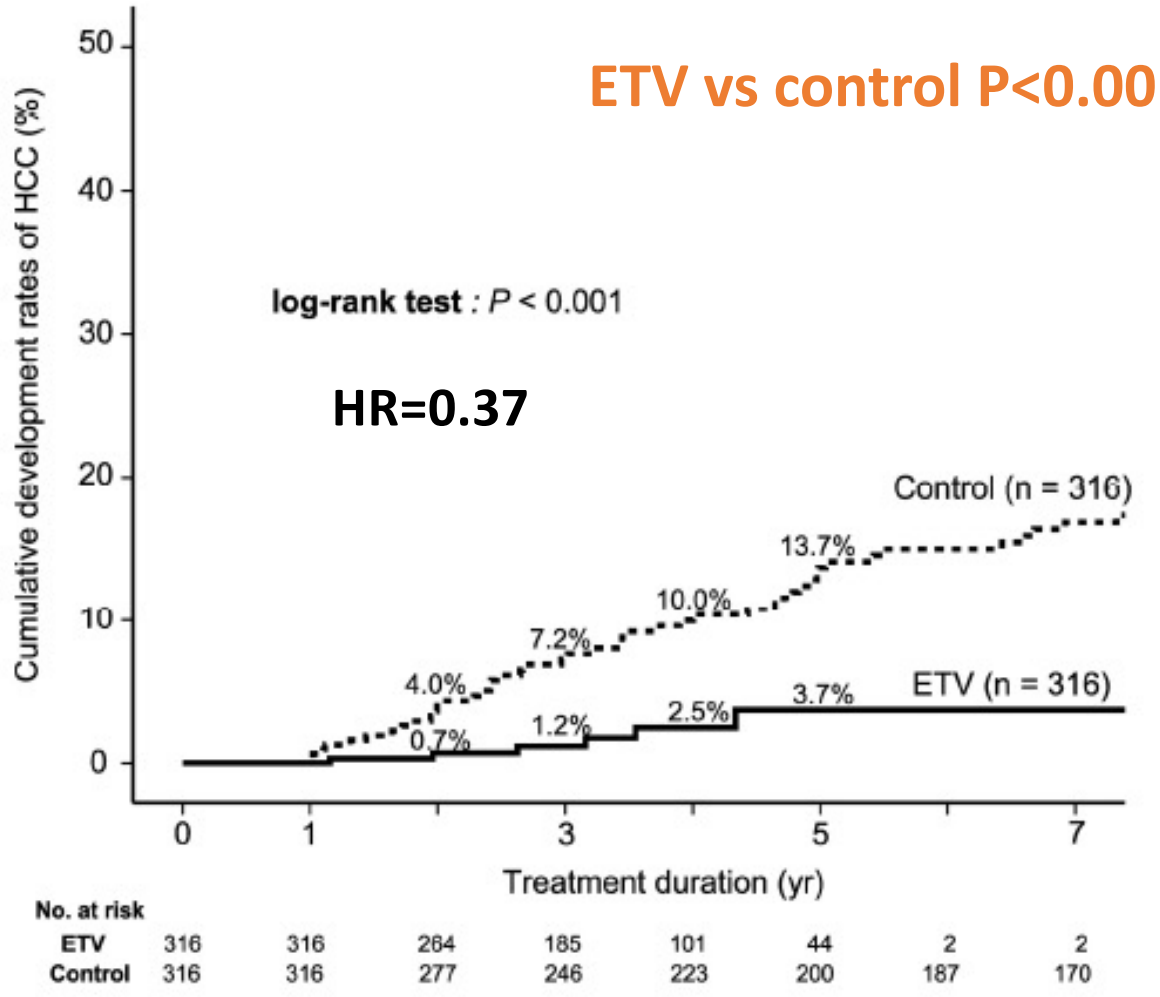
HBV Antiviral Therapy Reduces Risk of Liver Related Complications

Propensity score matched ETV treated vs Controls

- 316 treatment-naïve, immune-active CHB, 25% cirrhosis, treated with ETV for 5 yrs
- 316 propensity-matched controls

With up to 7 years of entecavir therapy, 63% reduction in risk of HCC

(greatest risk reduction in those with cirrhosis at baseline)



Hosaka T, et al, Hepatology 2013;58:98-107.

Current Therapies Infrequently Achieve HBsAg Loss

HBsAg loss	Peg-IFN (%)	Entecavir (%)	Tenofovir DF (%)	Tenofovir AF (%)
HBeAg+ CHB	11 (3 yrs)	4-5 (2 yrs)	8 (3 yrs)	1 (2 yrs)
HBeAg-Neg CHB	6 (3-yrs)	0-1 (1-5 yrs)	0 (1-5 yrs)	0 (1 yr)

Off-treatment **On-treatment** **On-treatment** **On-treatment**

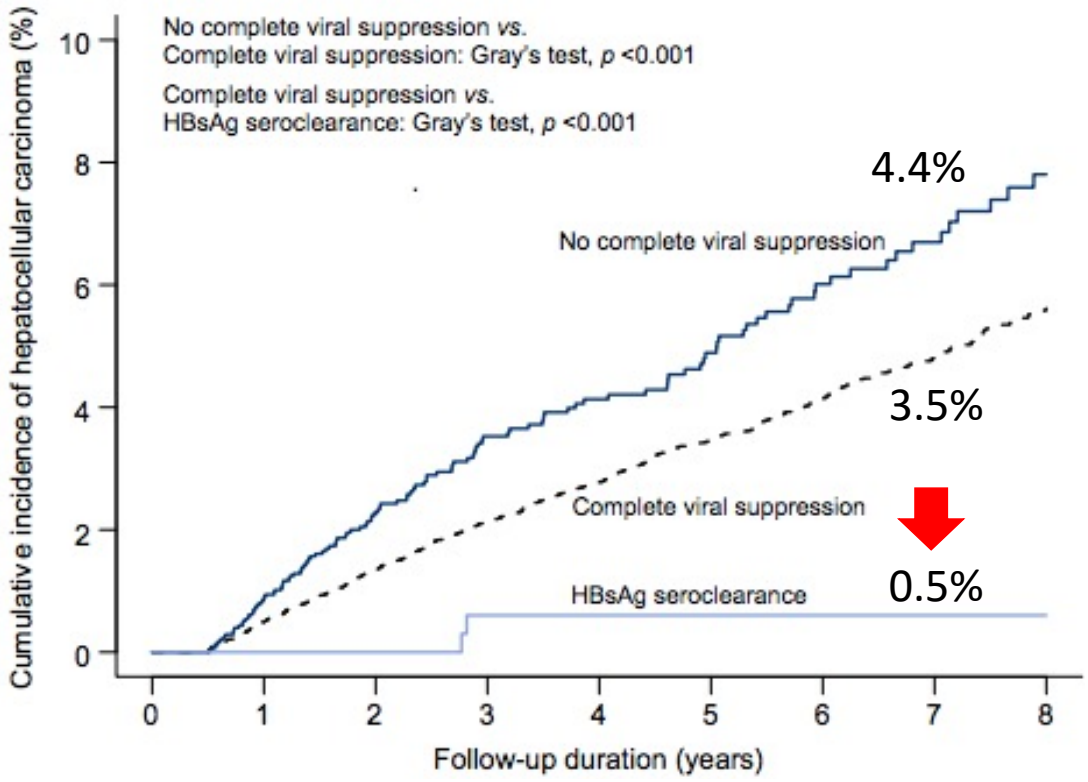
- **Higher with Peg-IFN than NA**
- **Higher in HBeAg-positive than HBeAg-negative**
- **Pooled estimated HBsAg loss 1-1.5% per year**

The impetus to develop new drug targets/approaches

AASLD HBV Treatment Guideline 2018
Yeo YM, Gastroenterology 2019

Suppression Good, HBsAg Clearance Better

Hong-Kong Cohort:
20,263 NA-treated patients with chronic hepatitis B



- **Median follow-up 4.8 (IQR: 2.8–7.0) yrs**
- **86.4% had complete viral suppression**
- **2.1% achieved HBsAg seroclearance**

Incidence of HCC lowest in those who achieve HBsAg loss

Yip TCK, J Hepatology 2019;70:361-370

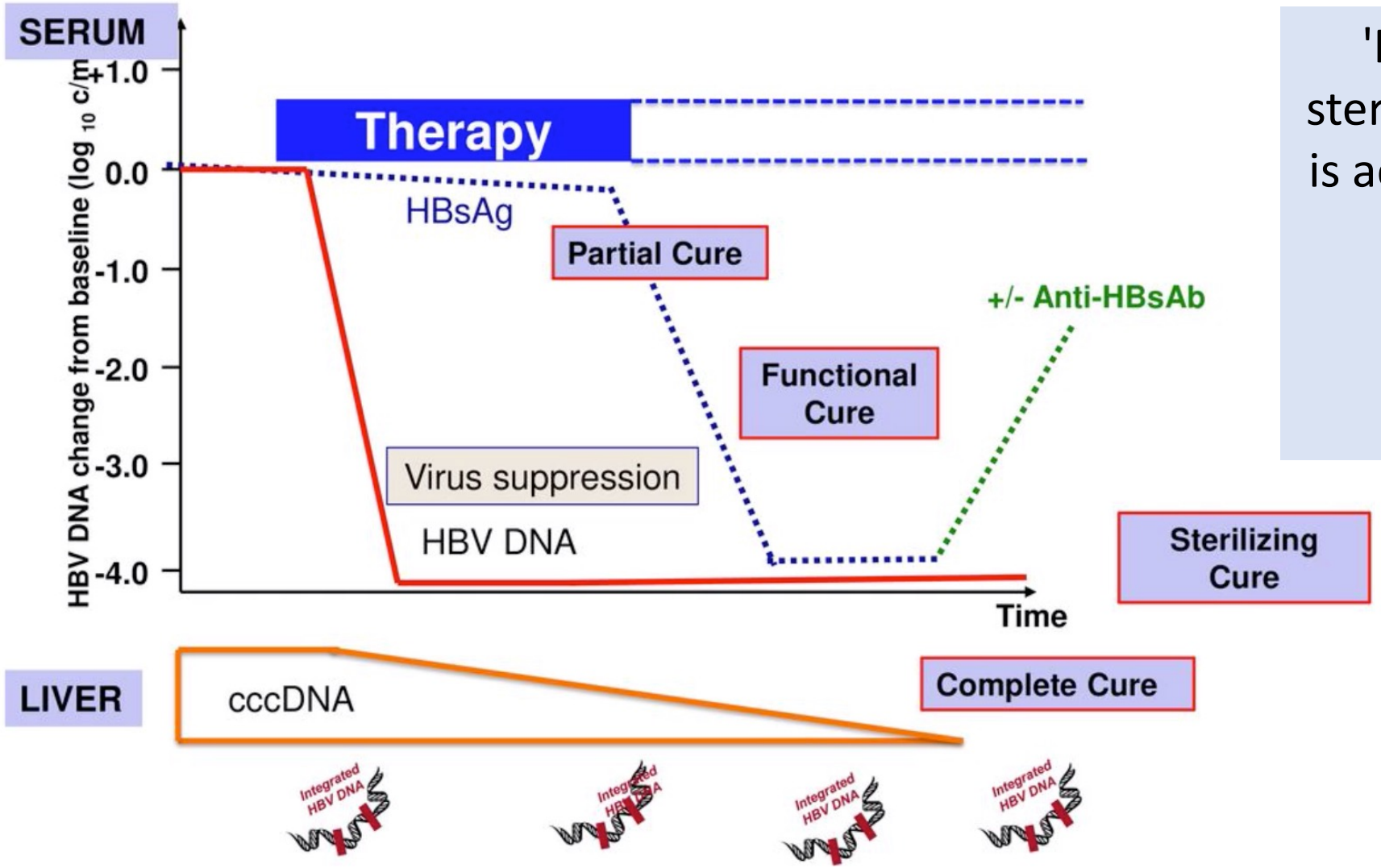
Why the Push for New Therapies?

Limitations of Current Therapies

- **NA therapy requires long-term, often life-long treatment**
- **Persistently HBsAg-positive → Stigmatization**
- **Not curative!**

Also fueled by the successes achieved with antivirals for HCV!

Pushing for HBV Cure: Definitions



'Functional' but not sterilizing/complete cure is achievable at this time

Functional cure=
HBsAg negative
off treatment

Cornberg, Lok, Terrault, Zoulim 2020

Shifts in the HBV Treatment Paradigm

Current=Suppressive	**Functional Cure = HBsAg loss**
On-treatment HBV DNA suppression	**Off-treatment sustained HBV DNA suppression = inactive CHB**
Long-term or indefinite NA treatment	**Finite courses of therapy**

Are we close to cure? **No**

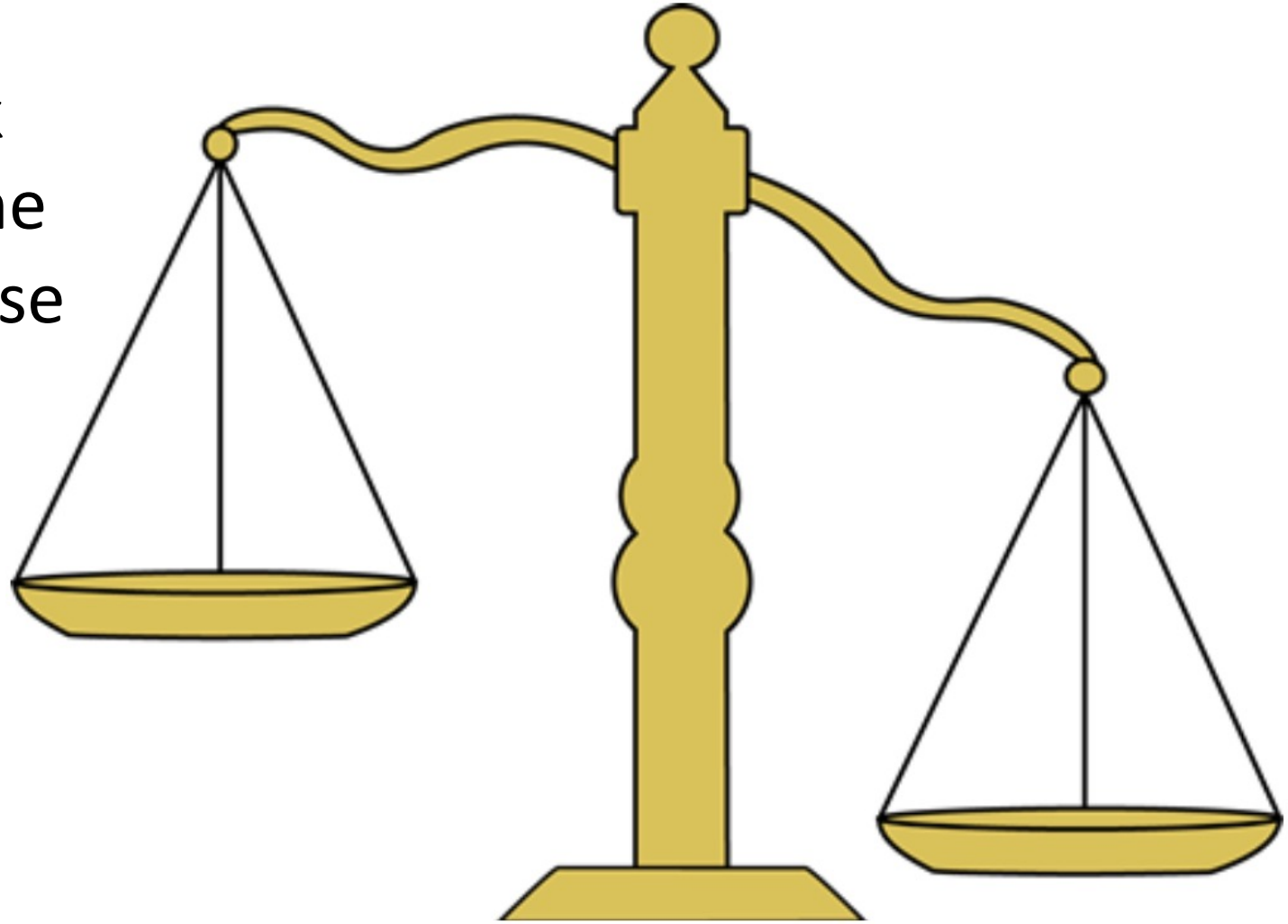
Are we closer? **Absolutely Yes**

Recent advances:

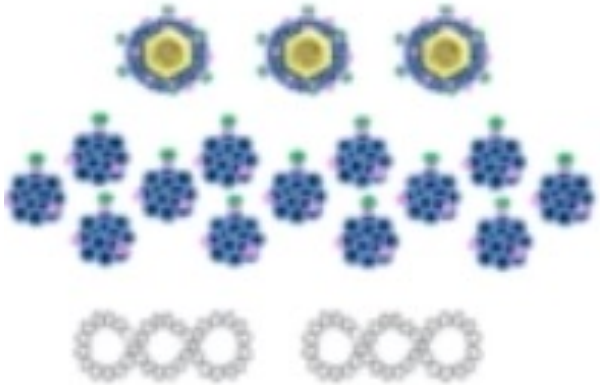
- Novel therapies being used in combinations earlier
- Refining NA withdrawal protocols to enhance HBsAg loss
- Re-emergence of Peg-IFN as important immune-modulatory therapy

Barriers to HBV Functional Cure

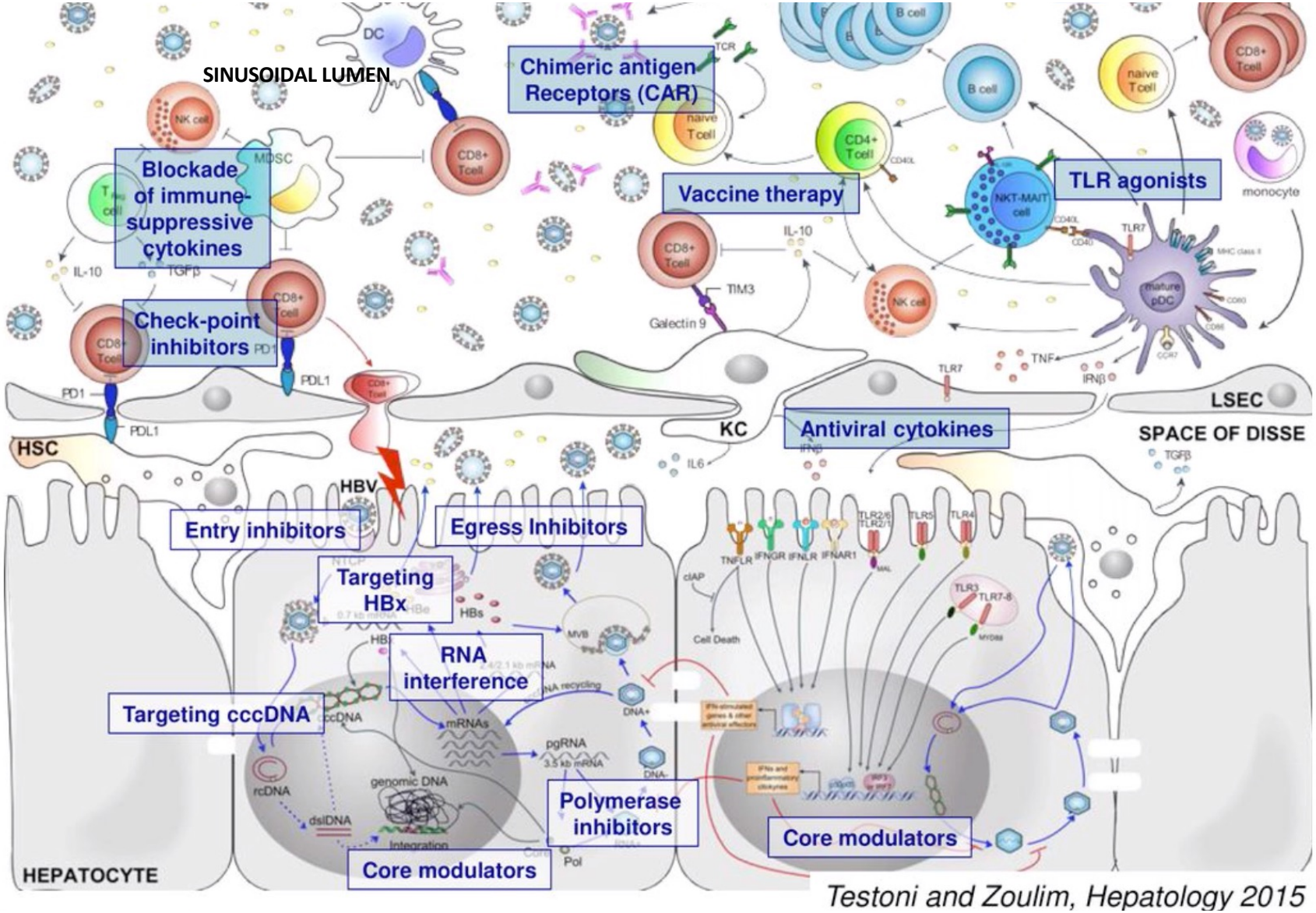
Weak Immune Response



High viral burden



Many Antivirals and Immune Modulatory Targets



Testoni and Zoulim, Hepatology 2015

More than 50 drugs in various phases of drug development

>25 drugs in beyond phase 1

https://www.hepb.org/treatment-and-management/drug-watch/

Therapeutic Strategies to Achieve Functional Cure

Inhibit Viral Replication

- **NA**: ETV, TDF, TAF
- **Entry inhibitor**: bulevirtide
- **Capsid assembly modulators (CAM)**: ABI-H0731, JNJ-6379, RO7049389

Reduce Viral Antigen Burden

- **siRNA**: JNJ-3989, VIR-2218, AB-729, RF-6346
- **ASO**: GSK3228836
- **LNA:** RO7062931
- **Nucleic acid polymers:**REP2139/2165, ALG10133

Boost Immune Responses

- **PEG-IFN**
- **TLR7 agonist:** GS9620, R07020531, JNJ-9464
- **TLR-8 agonist**: GS9688
- **Anti-PD1/L1**: nivolumab, REGN2810, GS,4224, ASC22
- **Therapeutic vaccines**

More than one class of drug likely needed to achieve high rates of functional cure

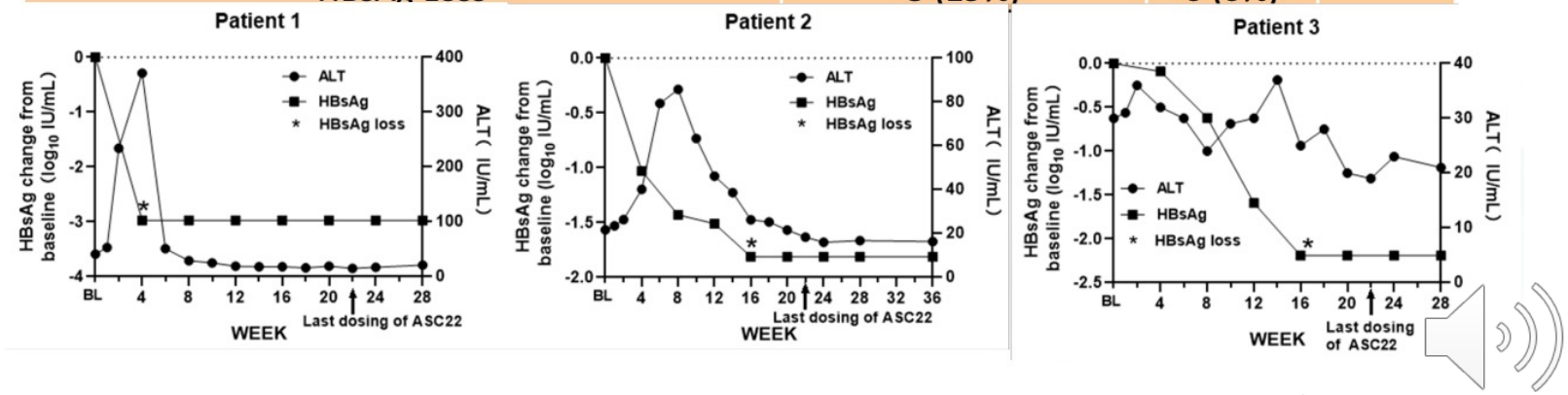
Combination NA + anti-PDL1 (ASC22: Envafolimab)

- Phase 2B trial, n=149
- ASC22 SC Q2wks at 2 different doses for 24 weeks, in NA-suppressed patients
- At baseline: HBeAg-neg, HBsAg ≤ 10,000 IU/mL and HBV DNA < 20 IU/ml

- HBsAg loss in 3 participants

Interim Analysis, N=44 at 1mg/kg dose

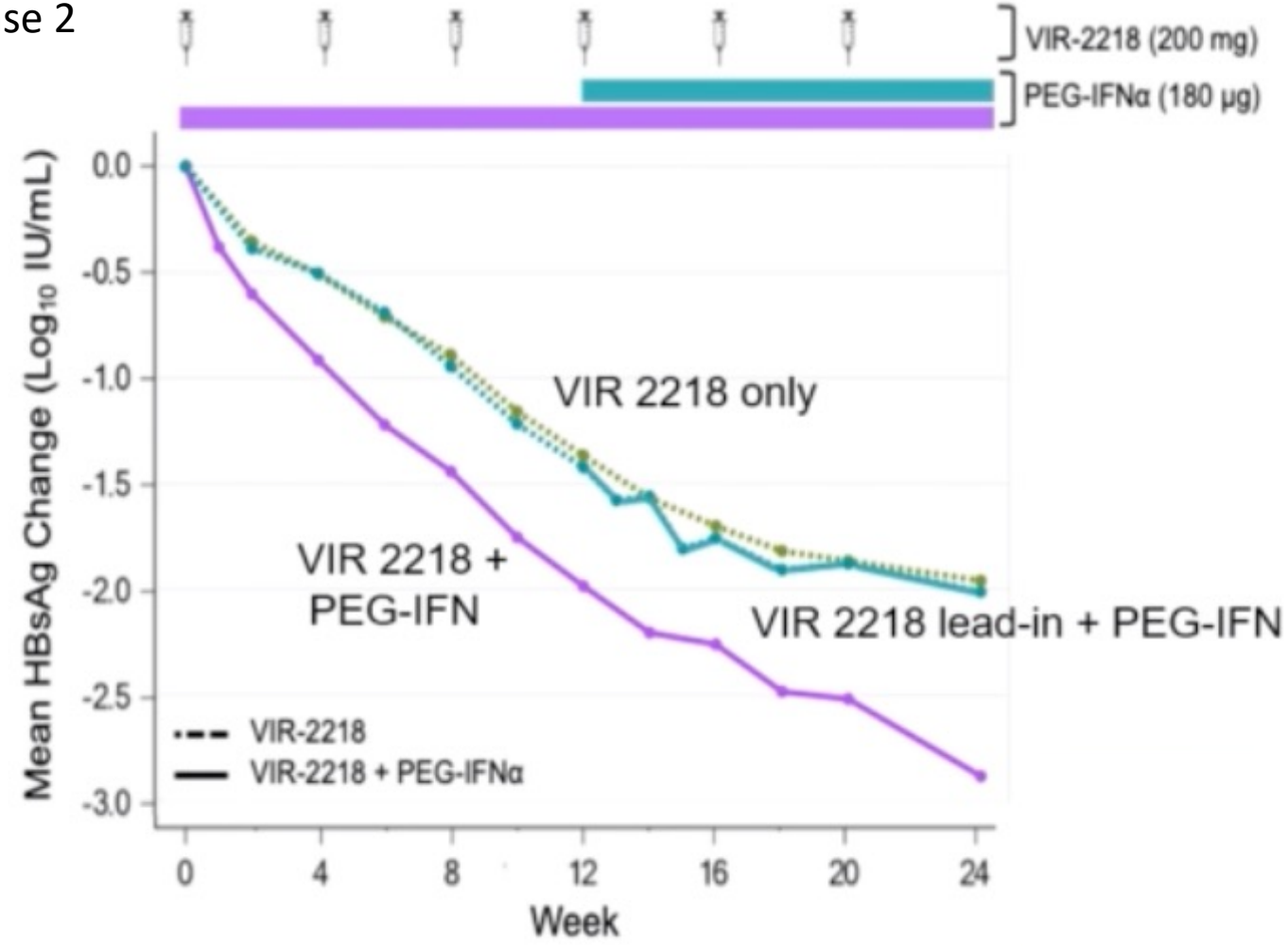
Outcomes after 24 weeks treatment of ASC22	ASC22 + NAs (Baseline HBsAg ≤ 10000 IU/mL , N =33)	PBO + NAs (N = 11)	*P* value
Mean HBsAg change from baseline (log_{10} IU/mL)	-0.38	0	0.0639
HBsAg reduction ≥ 0.5 log_{10} IU/mL	7 (21%)	0 (0%)	
HBsAg Loss	3 (9%)	0 (0%)	
Outcomes after 24 weeks treatment of ASC22	**ASC22 + NAs (Baseline HBsAg ≤ 500 IU/mL , N =16)**	**PBO + NAs (N = 11)**	***P* value**
Mean HBsAg from change baseline (log_{10} IU/mL)	-0.7	0	**0.0084**
HBsAg reduction ≥ 0.5 log_{10} IU/mL	7 (44%)	0 (0%)	
HBsAg Loss	3 (19%)	0 (0%)	



Wang GQ, AASLD 2021, Abst LB12

Triple Antiviral Therapy: NA + siRNA + Peg-IFN

Phase 2

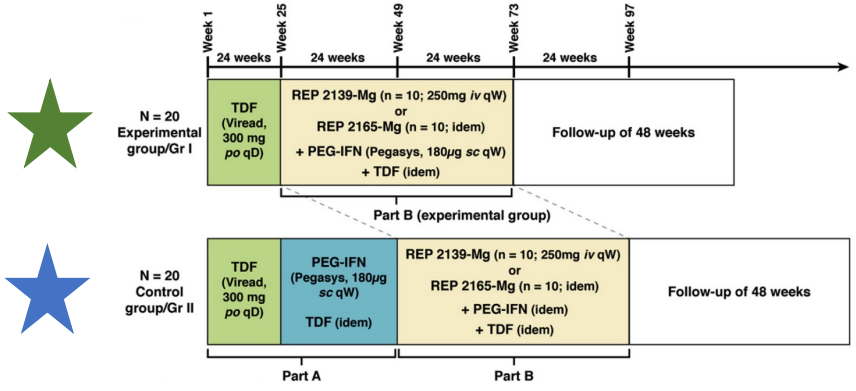


- siRNA **knocks down production of HBV genes** → reduce virion and Ag production
- N=48 patients on NA therapy
- Peg-IFN combination for 12 or 24 weeks
- Combo of VIR-2218 and Peg-IFN leads to greater reductions in HBsAg
  - 3 participants become HBsAg negative (2 also had anti-HBs)
- AEs consistent with those of peg-IFN

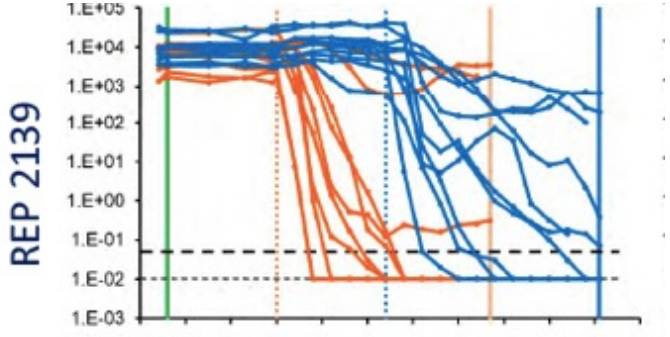
Yuen MF, AASLD 2021, Abstract 93

Triple Therapy: NA + NAPs + Peg-IFN

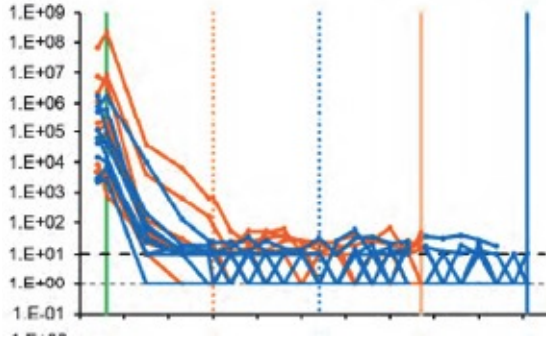
Phase 2



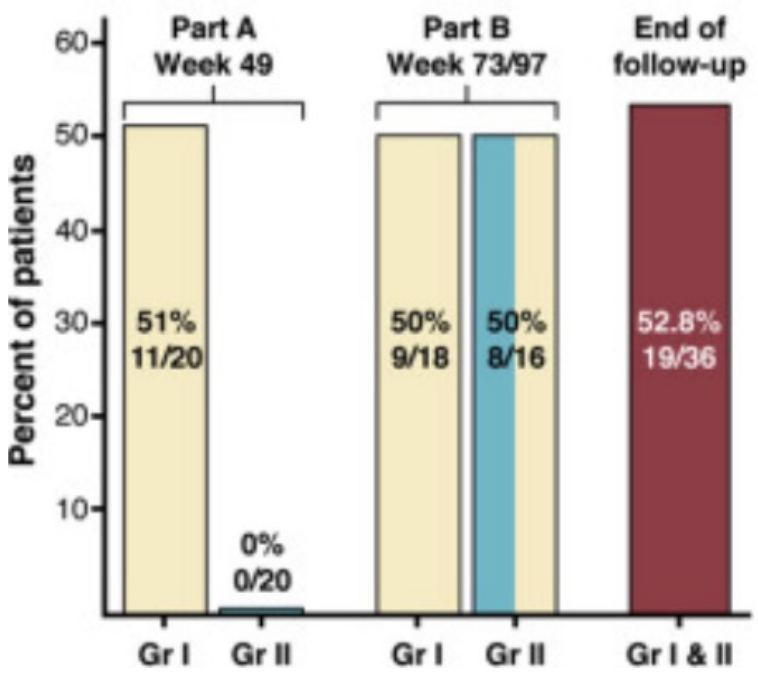
HBsAg



HBV DNA



NAP: nucleic acid polymers that **block viral release**
REP 2139/2165 given as IV infusion weekly X 48 wks



- **ALT/AST elevations common during treatment**
- **No associated with bilirubin elevations**

Bazinet M, Gastroenterology. 2020;158:2180-2194
Durantel D, Gastroenterology, 2020; 158:2051-2054

Summary 1

Novel HBV Therapies

- **There is a rich pipeline of novel HBV drugs under development**
  - Largely can be divided into drugs that (i) inhibit viral replication; (ii) reduce viral antigens; and (iii) boost the immune response
  - CAMs and siRNA are the most prevalent classes of drugs under study
- **Combination therapy is likely needed**
  - Many studies use NA-suppressed with 1 or 2 drug classes added
  - How best to combine drugs requires much more exploration
- **Increasing recognition of importance of immune-modifying compound to achieve cure with finite therapy**
  - Peg-IFN is being used for finite periods with new drugs

Strategies to Get to Functional Cure with Current Therapies

- NA withdrawal in HBeAg-negative CHB
- Peg-IFN add-on or switch in NA-treated patient

Stopping NA Therapy in HBeAg-Negative CHB

AASLD

- Treat i**ndefinitely** (or until **HBsAg loss**), unless strong competing rationale to stop *(patient preference, cost, toxicity)*
- **Indefinite if cirrhosis**

EASL

- Treat until **HBsAg loss ,** with or without HBs seroconversion
- Treat for at least 3 years with **undetectable HBV DNA for at least 18 months** (non-cirrhotic only)
- **Indefinite if cirrhosis**

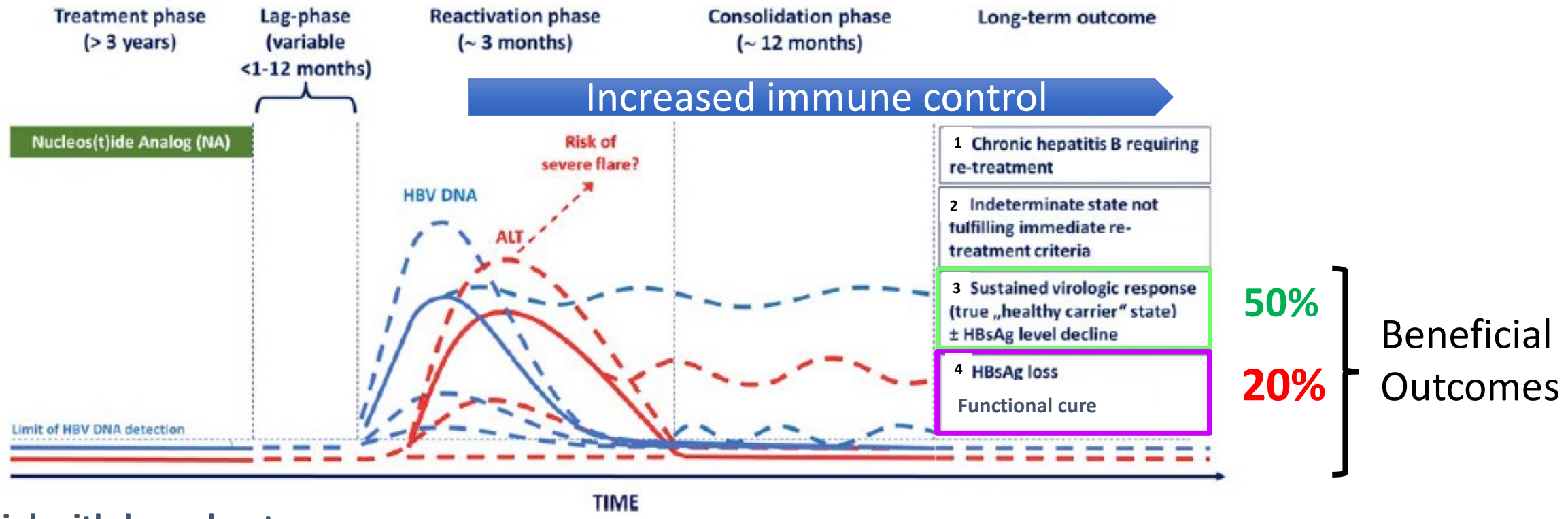
APASL

- Treat until **HBsAg loss** following either anti-HBs seroconversion or *at least 12 months of consolidation*
- Treat for at least 2 years with **undetectable HBV DNA** documented on three separate occasions, 6 months apart
- May **consider in compensated cirrhosis** with close monitoring

HBsAg loss 1-3 years after stopping NAs varies widely from low of ≤5% -- ≥

Withdrawal of NA Therapy to Enhance HBsAg Loss

Eligible HBeAg-Neg CHB: HBV DNA negative on NAs for ≥3 years and no cirrhosis

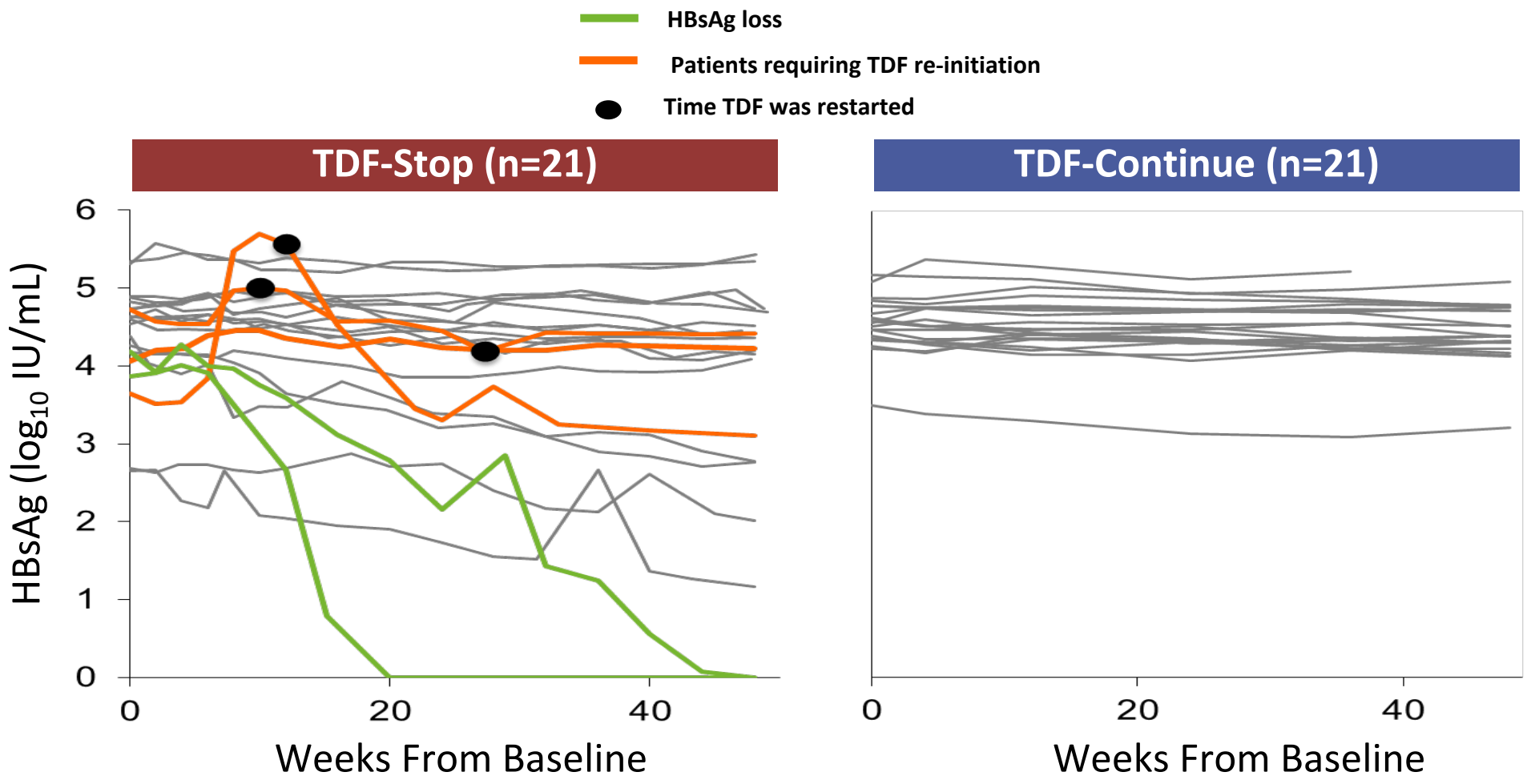


Beneficial withdrawal outcomes:

- **HBsAg loss at higher rate than continued NA treatment**
- **Identification of inactive CHB (no need for retreatment)**

Adapted from Lampertico and Berg, Hepatology 2018

HBsAg Profiles in HBeAg-Negative Patients Stopping and Continuing NA



Berg T, J Hepatol 2017;67:918-92

Summary of NA Withdrawal in HBeAg-negative CHB

Author	N	Median Follow-up	NA used	% HBsAg Loss	% Remaining off Treatment
Berg	21	33	TDF	19%	62%
Pan	30	115	TBV or LMV	9%	NR
Patwardhan	33	36	LMV, ADV, ETV, TDF	0%	52%
Hadziyannis	33	66	ADV	39%	55%
Kang	60	67	LMV	18%	75%
Hung	73	67	LMV, ETV, TBV	27%	NR
Liu	85	60	LMV, ADV, TBV, ETV	14%	NR
Yao	119	60	LMV or ETV	55%	76%
Jeng	671	36	ETV	**6%**	59%

***only studies with median ~3 y or more follow-up included**

Wide range of reported rates of HBsAg loss: 0-55% - median= 18% at 3-5 years

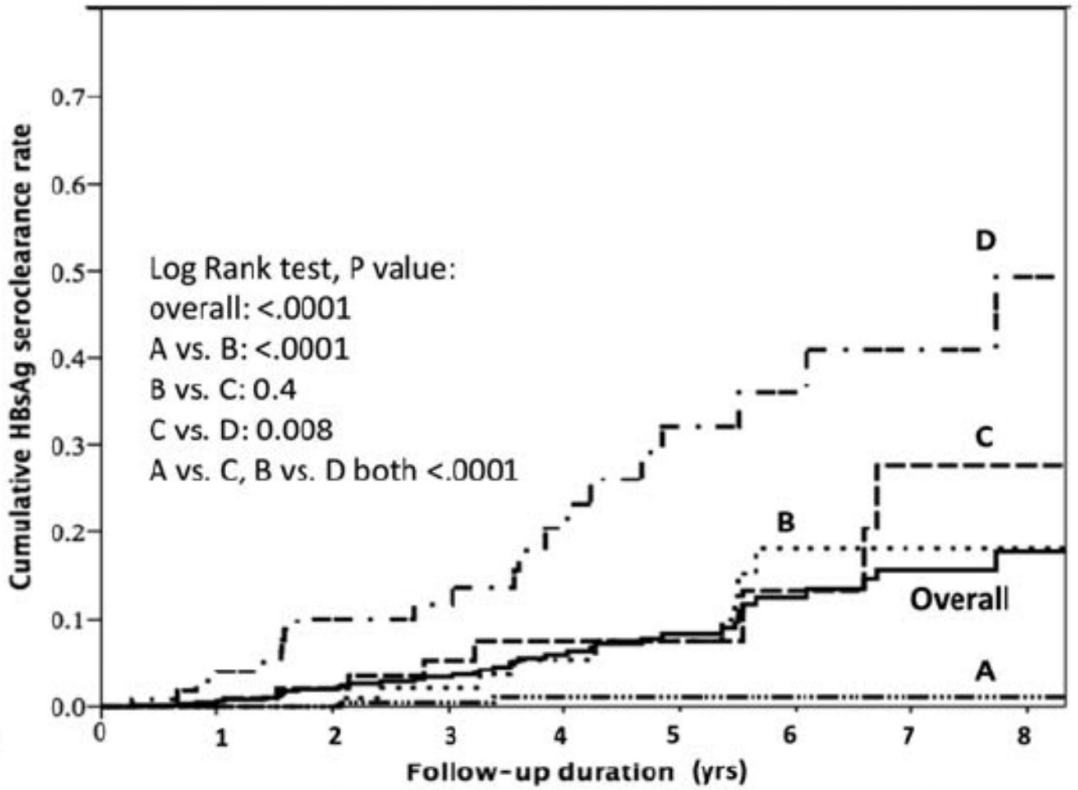
Less variability in remaining off treatment: 50-75%

Berg T, J Hepatol 2017;67:918-92
Jeng WJ, Hepatology 2018;68:425-434
Yao CC, Sci. Rep. 2017, 7, 1839.
Hung CH, J. Viral Hepat. 2017, 24, 599–607
Kang SH, J. Med. Virol. 2017, 89, 849–856.
Pan HY Clin. Microbiol. Infect. 2015, 21, 1123.e1–1123.e9.
Patwardhan VR< Aliment. Pharmacol. Ther. 2014, 40, 804–810
Liu F, J. Dig. Dis. 2018, 19, 561–571.

Heterogeneity in "Success" of NUC Discontinuation in HBeAg-Negative Patients

- **Differences in patient characteristics**
  - Genotype
  - Age, sex etc.
- **Different NA therapies**
  - Time and duration of NA therapy
  - Duration of HBV DNA undetectability
- **Criteria for restarting treatment**
  - Virologic versus clinical
- **Duration of follow-up after stopping NUCs**

How Essential are ALT Flares in Achieving HBsAg Loss?



Patient at risk

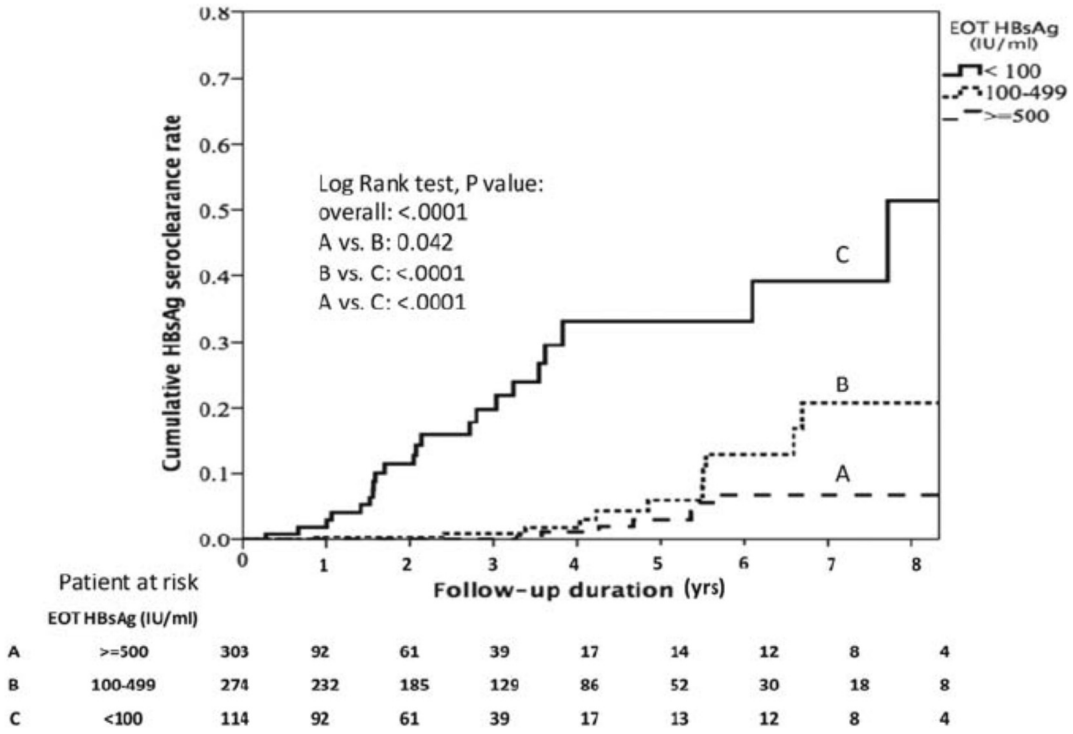
Overall			691	595	472	351	237	150	101	61	31
A	CR+	reTx	269	262	226	179	126	77	47	29	13
B	CR+	reTx-	150	135	107	77	49	36	25	15	9
C	CR-	VR+	128	109	76	47	33	17	15	8	6
D	CR-	VR-	144	89	63	48	29	20	14	9	3

Highest rate of HBsAg loss was among those **WITHOUT** virologic or clinical (ALT) relapse

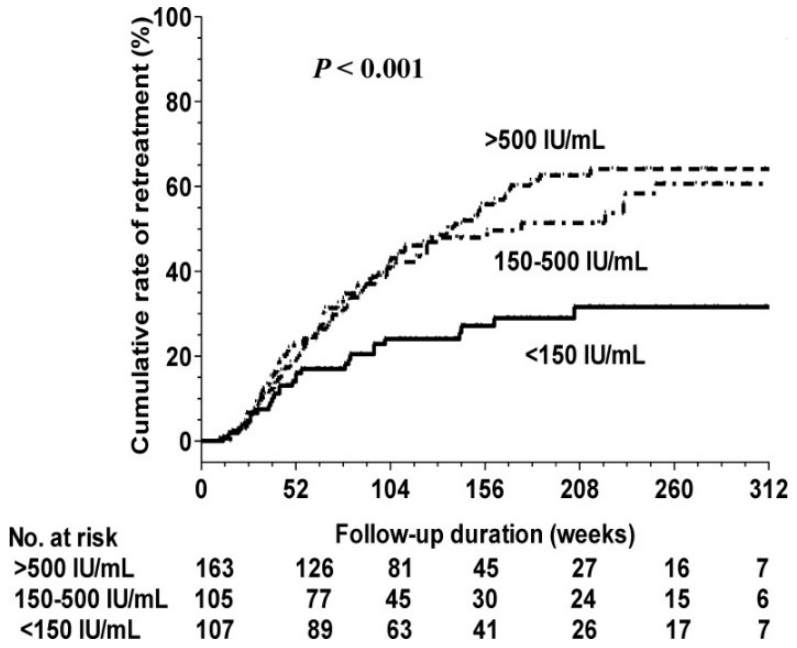
Jeng WJ, Hepatology 2018;68:425-434

Predictors of HBsAg Loss

- qHBsAg is most consistent predictor of HBsAg loss



Liu J, Hepatology 2019;70(3):1045-1055



Ma TH, PLoS One. 2019 Oct 4;14(10):e0222221

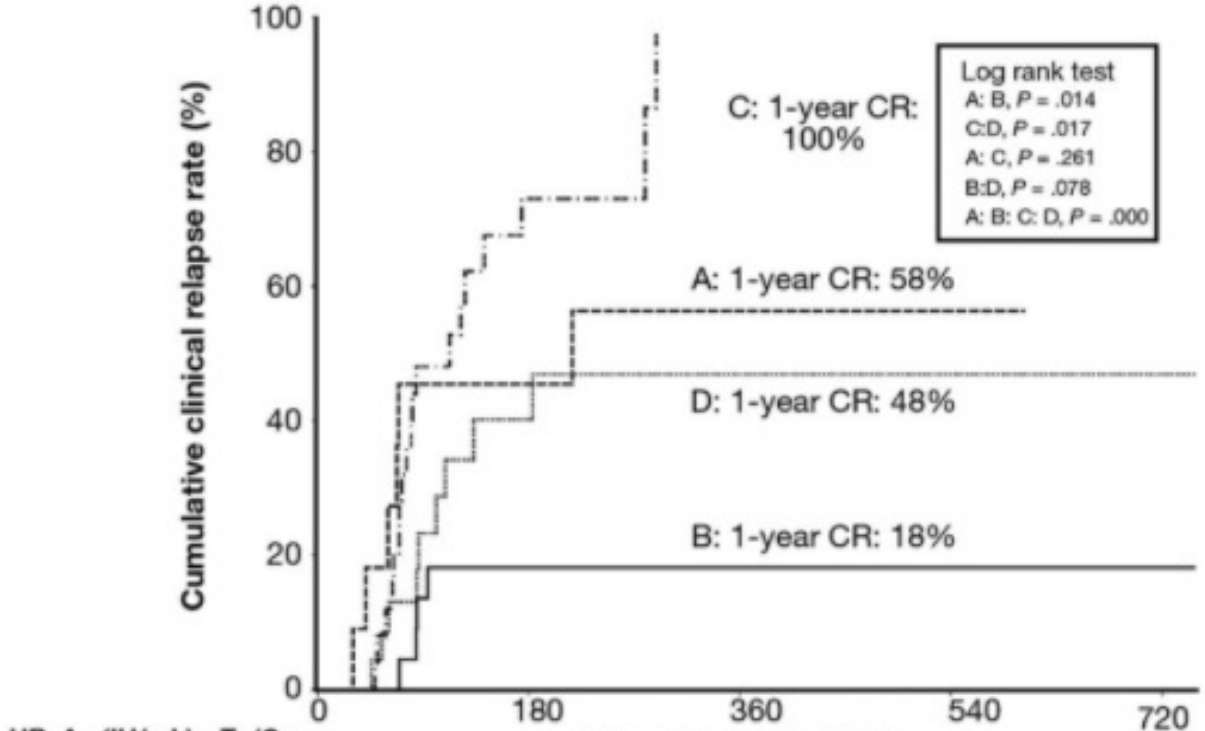
Systematic Review of 11 studies with 1,716 Asian patients

Outcome: **off-therapy clinical relapse rate** at ≥12 months off therapy

- 15.4%-29.4%(range) HBsAg at EOT was **<100 IU/mL**
- 48.1%-63.6% (range) if HBsAg at EOT was >100 IU/mL

Integrating sHBsAg, treatment duration and consolidation

HBeAg-negative CHB



	HBsAg (IU/mL)	Tx/Cx					
A	< 1000	< 144 wks and or < 108 wks	11	5	3	1	0
B	< 1000	≥ 144 wks + ≥ 108 wks	23	16	10	4	3
C	≥1000	< 144 wks and or < 108 wks	25	4	0	0	0
D	≥1000	≥ 144 wks + ≥ 108 wks	23	9	2	1	1

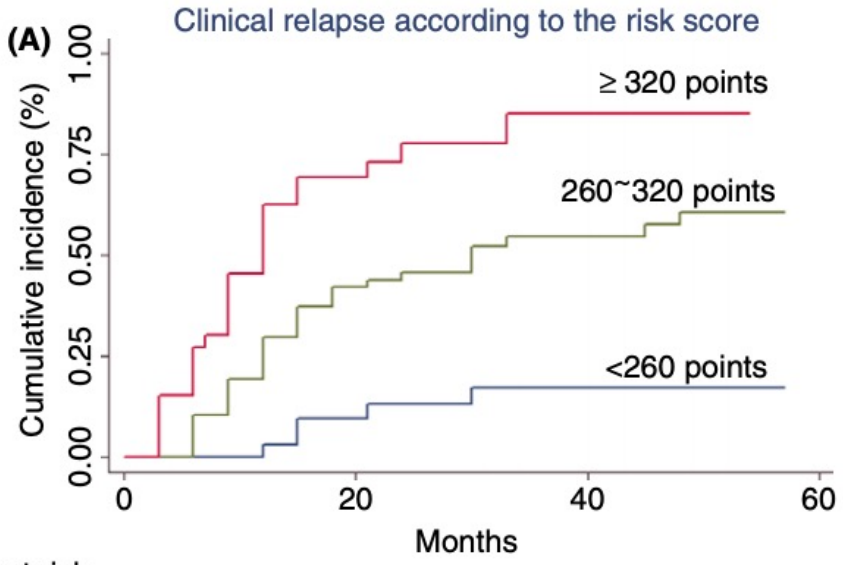
Highest rate of clinical relapse:
qHBsAg>1000, duration TDF <3 yrs or consolidation <2.25 yrs

Lowest rate of clinical relapse:
qHBsAg<1000, duration TDF ≥3 yrs + consolidation ≥ 2.25 yrs

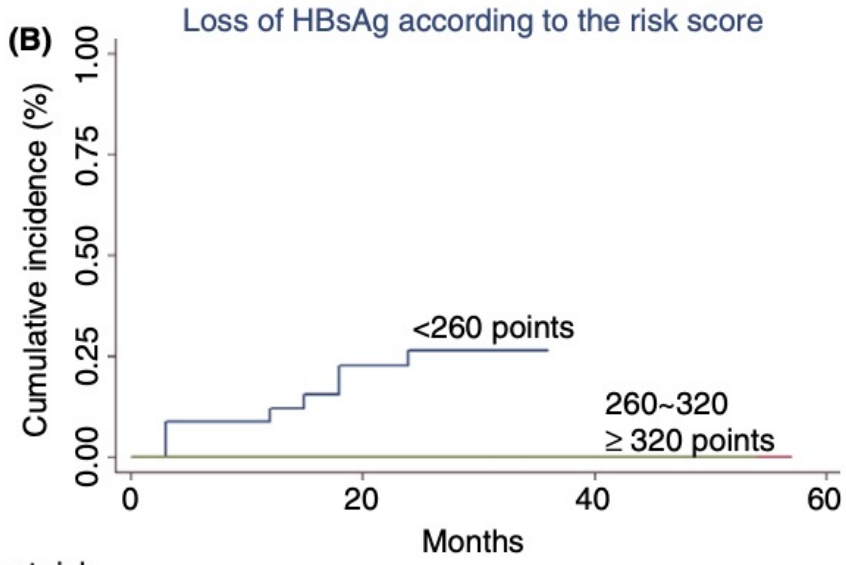
Jeng W, CGH 2016;14:1813-1820

HBCrAg and prediction of outcomes after NA discontinuation: SCALE-B

- 35*__HBsAg__ (log IU/mL) + 20*__HBcrAg__ (log U/mL) + 2* __age__ (year) + __ALT__ (U/L) + 40 for use of __tenofovir__.



Number at risk				
<260 points	34	26	15	3
260~320 points	68	34	15	2
≥ 320 points	33	8	1	0



Number at risk				
<260 points	34	22	0	0
260~320 points	68	36	7	1
≥ 320 points	33	11	2	0

Hsu YC, APT 2019;49:107-115

Summary 2

NA Withdrawal as Strategy to Achieve HBsAg Loss

- **NA withdrawal can achieve modest rates of functional cure**
  - ~20% (at 3-5 years follow-up) but higher than continued NA therapy (<1% per year)
  - Decompensation reported – caution withdrawing NAs if advanced fibrosis
- **Main drivers of heterogeneity in outcomes include duration of NA therapy and HBV DNA suppression, retreatment criteria**
- **qHBsAg remains the most consistent predictor of HBsAg loss after discontinuation**
  - Highest rates of HBsAg loss if HBsAg <100 IU/mL
  - HBcrAg may offer additional benefit in refining HBsAg loss

Strategies to Get to Functional Cure with Current Therapies

- NA withdrawal in HBeAg-negative CHB
- Peg-IFN add-on or switch in NA-treated patient

Using Peg-IFN to Enhance Functional Cure in Patients on NA Therapy

Strategy 1
De Nov Combined Peg-IFN + NAs

HBsAg loss 5% (1-yr) - **10%** (2.5 yrs) follow-up

Marcellin P, 2016 Gastroenterology;150:134-144
Ahn S, Dig Dis Sci, 2018,63:3487–3497
Terrault N, AASLD 2021

Strategy 2
NA Treated with Peg-IFN Add-on

Strategy 3
NA Treated with Switch to Peg-IFN

HBsAg loss Switch (14%) vs Add-on (8%) (p=0.012)

Qiu K, Aliment Pharmacol Ther 2018;47(10):1340-1348

Strategy 4
Peg-IFN Treated Switch or Add-on NA

HBsAg loss 12.5% switch and 4.9% add-on

(but not compared head-to-head and not significantly different than peg-IFN alone)

Liu J, Hep International 2020;14:958-972

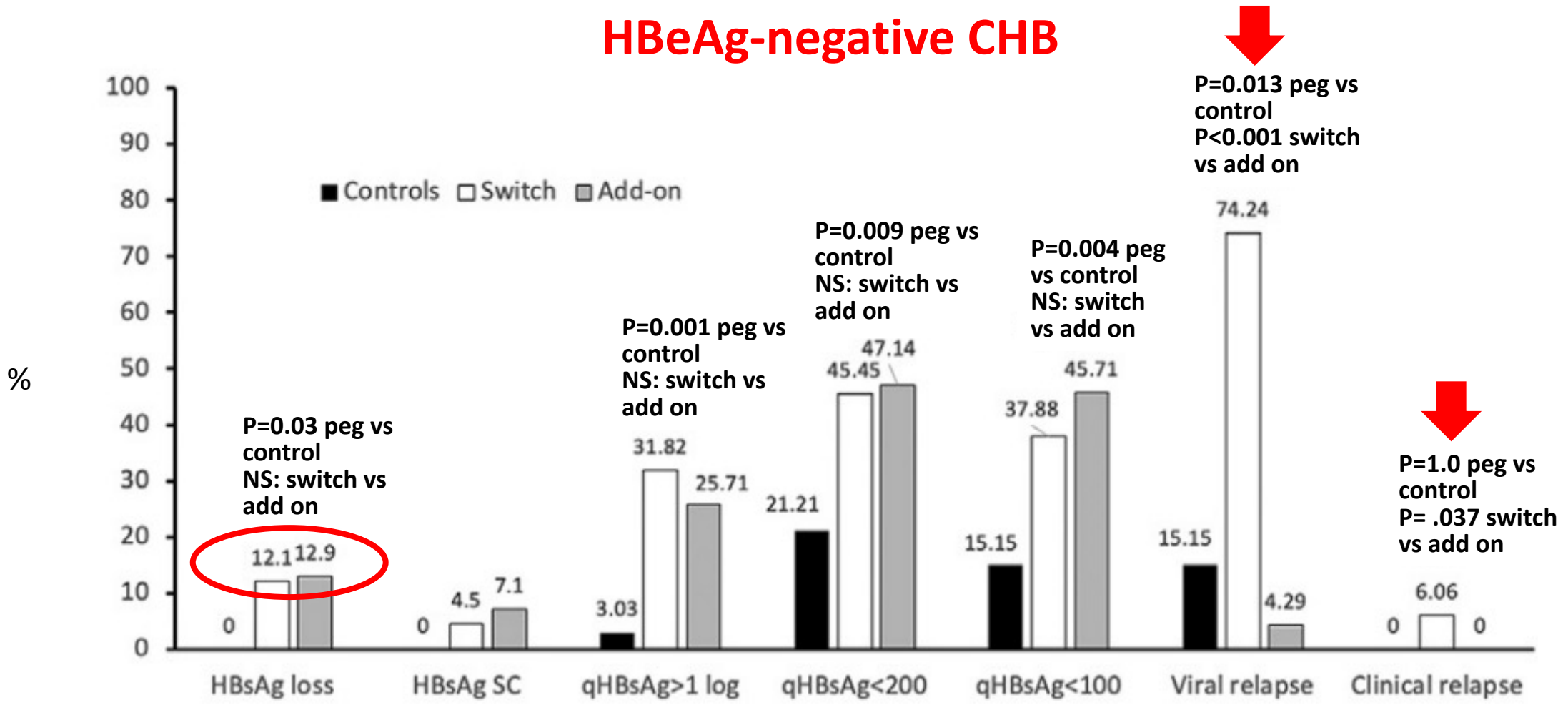
SWAP Study: Peg-IFN Add-on vs Switch in Patients on NA Therapy

RCT of CHB patients on NA >12 months with HBV DNA (–) randomized to switch or add-on peginterferon-alpha2b (1.5 mg/kg/weekly) for 48 weeks versus continuing NA (controls)

Variables	Control (n = 51)	Switch (n = 103)	Add-on (n = 99)	Total (n = 253)
Age (*y*)	50 (42–58)	47 (40–56)	51 (42–58)	49 (42–57)
Male (n, %)	40 (78.4)	84 (81.5)	80 (80.8)	204 (80.6)
Ethnicity				
Chinese	46 (90.2%)	94 (91.3%)	87 (87.9%)	227 (89.7%)
Malay	0	1 (1%)	4 (4%)	5 (2%)
Indian	1 (2%)	1 (1%)	0	2 (0.8%)
Others	4 (7.8%)	7 (6.8%)	8 (8.1%)	19 (7.5%)
Cirrhosis (n, %)	2 (3.9)	8 (7.8)	5 (5.0)	15 (5.9)
HBeAg positive (n, %)	16 (34.0)	37 (35.9)	29 (29.3)	82 (32.9)
qHBsAg (*IU/mL*)	726.22 (445.47–2251.25)	1064.11 (443.12–2154.65)	707.24 (181.3–2115.59)	816.12 (335.26–816.12)
DNA undetectable	49 (96.1)	99 (96.1)	93 (93.9)	241 (95.3)
High genetic barrier NUC (n, %)	39 (76.5)	82 (79.6)	80 (80.8)	201 (79.4)
Years of NUC therapy	6 (3–7)	5 (3–7)	6 (3–7)	6 (3–7)

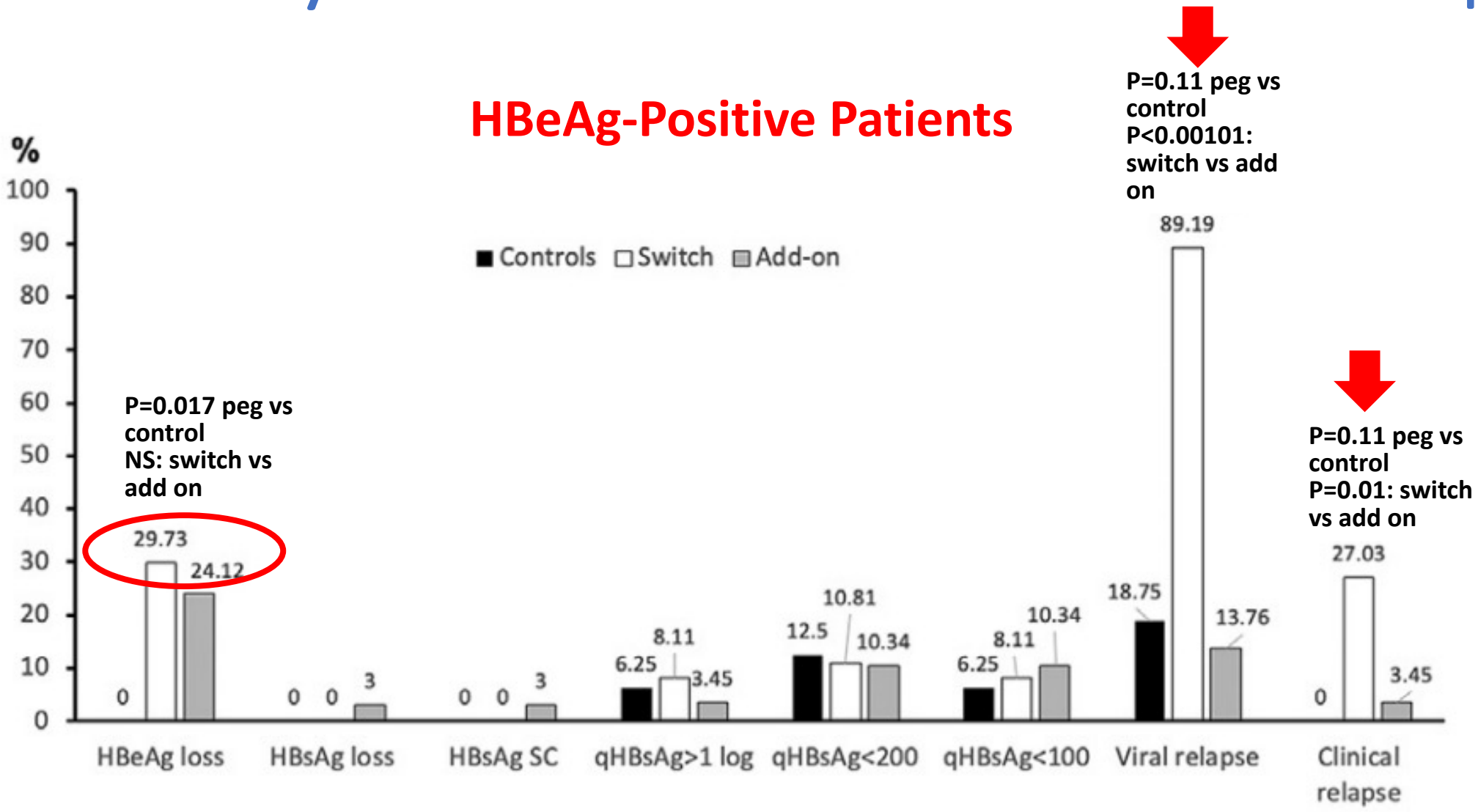
Lim SG, CGH, 2021, in press.

SWAP Study: Outcomes at Week 72 Follow-up



Peg-IFN increases rates of HBsAg loss: Add-on preferred strategy as less harm

SWAP Study: Outcomes at Week 72 Follow-up



Peg-IFN increases rates of HBsAg loss: Add-on preferred strategy as less harm

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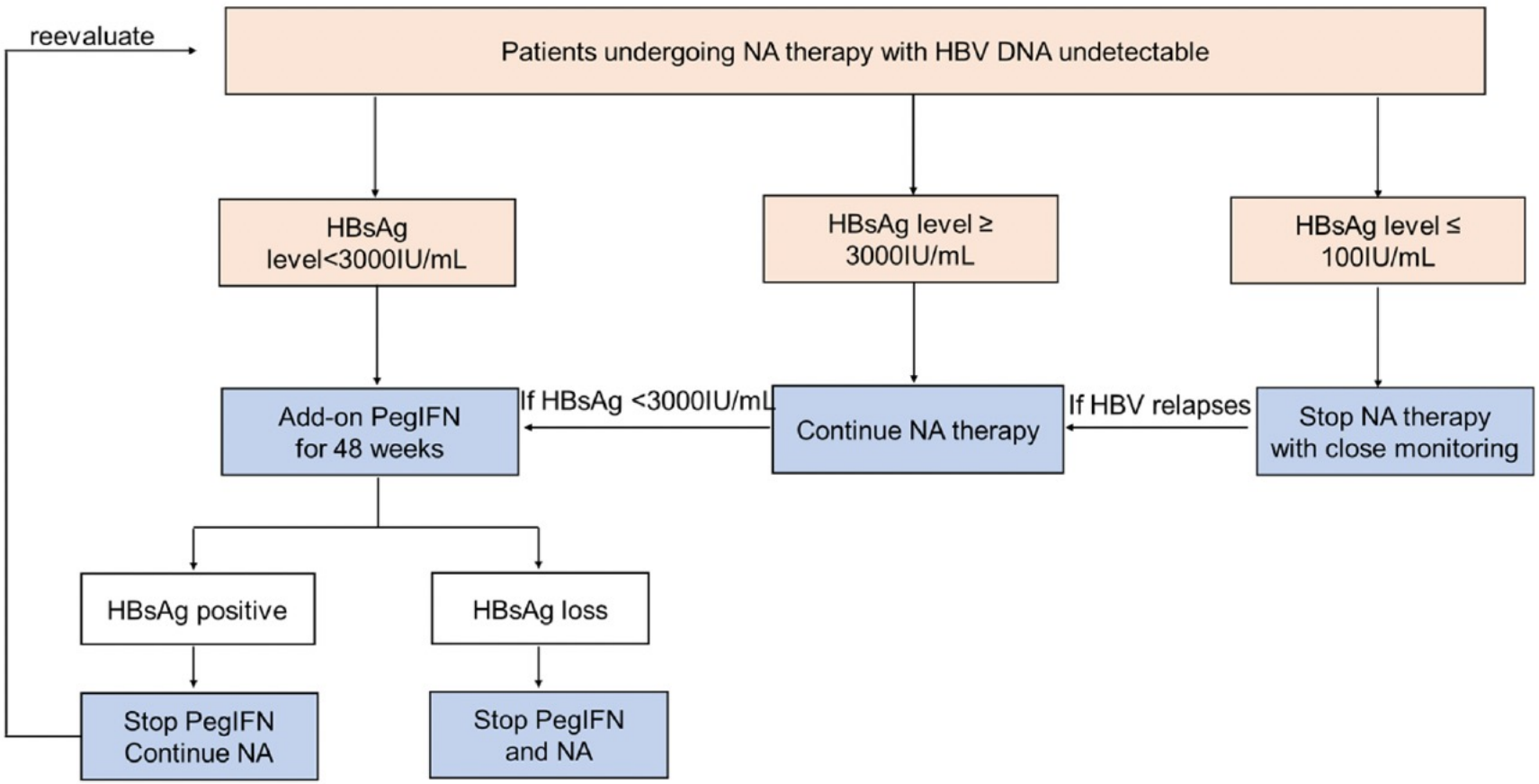
GUIDELINES

APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients

Jia-Horng Kao[1,2,3] · Wen-Juei Jeng[4,5] · Qin Ning[6] · Tung-Hung Su[1] · Tai-Chung Tseng[3] · Yoshiyuki Ueno[7] · Man-Fung Yuen[8]



Summary 3

Peg-IFN Add-on as Means to Achieve HBsAg Loss

- **Peg-IFN significantly increases rates of HBsAg loss in the short term (compared to NA alone)**
- **Add-on strategy is safest (less ALT flares) and achieves equivalent rates of HBsAg loss to switch strategy**
- **Areas of uncertainty remain:**
  - **Optimal duration of NA therapy and HBV DNA undetectability prior to peg-IFN add-on**
  - **Minimal duration of peg-IFN needed to achieve increased rates of HBsAg loss**

Hepatitis B Cure: Are We Close?

- New drug therapies are still several years away but phase 2 studies are encouraging
- There are strategies to enhance HBsAg loss among NA-treated patients:
  - NA withdrawal
  - Peg-IFN add-on
- Both these strategies offer modest increases in HBsAg loss but with some risks – particularly ALT flares
  - Patient selection can help minimize risk and maximize benefits
    - Those with advanced fibrosis are not candidates