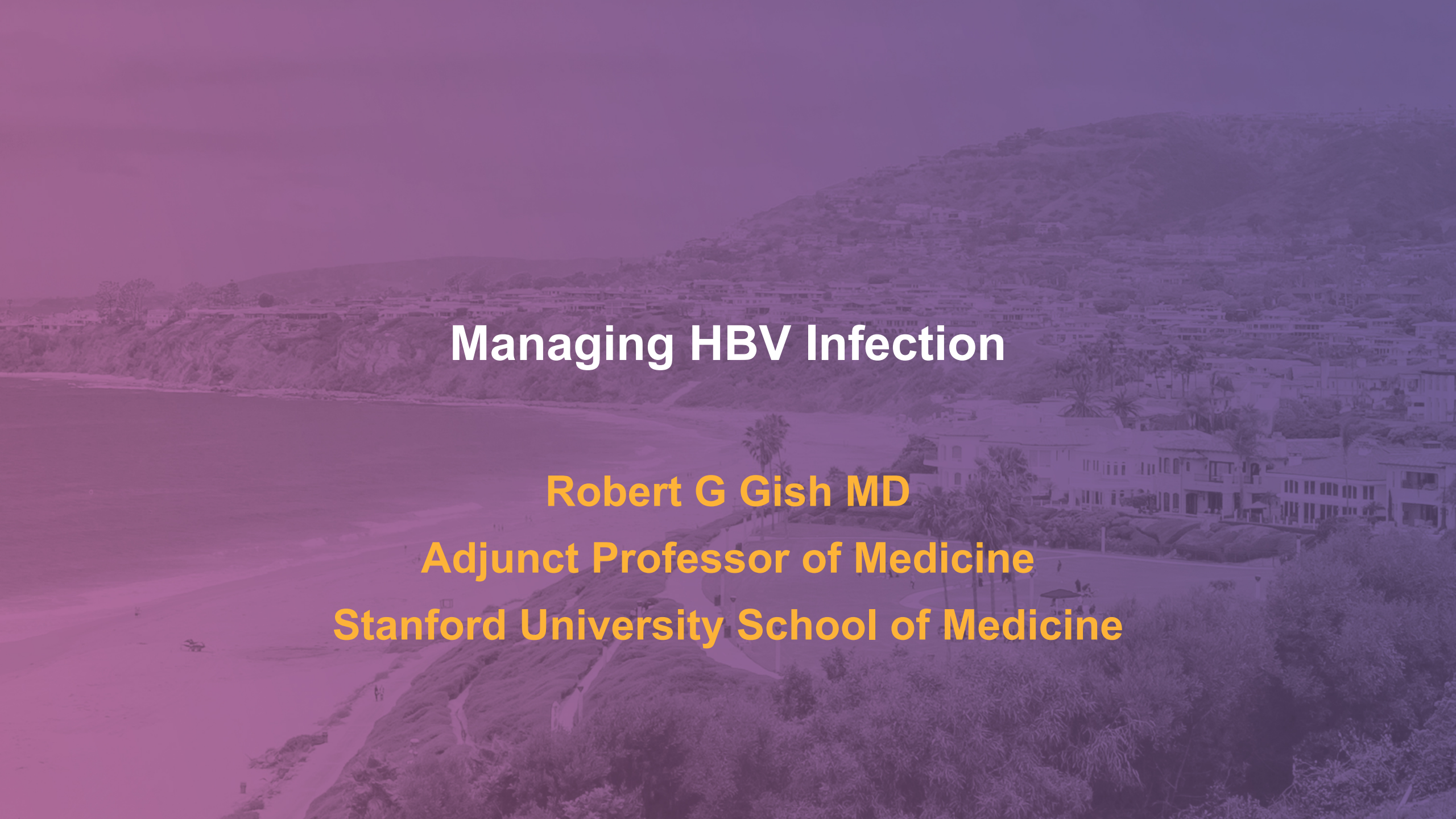
2018 SCSG POST-AASLD SYMPOSIUM

Annenberg Center For Health Sciences at Eisenhower
Imparting knowledge. Improving patient care.

Jointly provided by the Annenberg Center for Health Sciences at Eisenhower and Southern California Society of Gastroenterology.

Southern California Society of Gastroenterology



Managing HBV Infection

Robert G Gish MD
Adjunct Professor of Medicine
Stanford University School of Medicine

Disclosures

HBV Relevant Disclosures

Consultancy: Arrowhead, Dynavax, Enyo, Gilead

DSMB: Ionis

Speaker: Gilead

Are the guidelines too conservative?

Eligible HBeAg-negative non-cirrhotic CHB (n=2,322)
ALT ULN = 19 F and 30 M

Pre-active phase (n = 1370)
HBV DNA ≥ 2000 IU/mL
and ALT < 2 × ULN

HBeAg (-) hepatitis (n = 952)
HBV DNA ≥ 2000 IU/mL
and ALT ≥ 2 × ULN

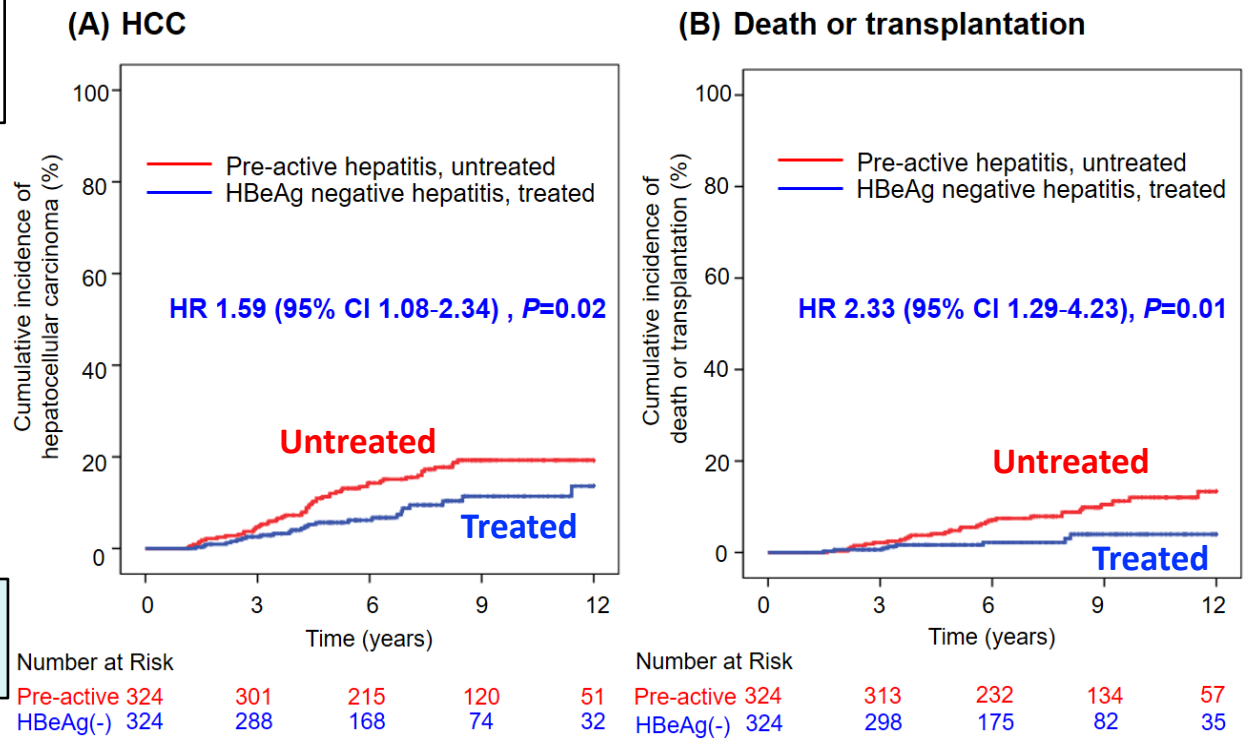
Exclusions (n=158)
Transition to HBeAg-negative hepatitis within 6 months

Exclusions (n=427)
Refused or did not receive antiviral treatment

Pre-active hepatitis, untreated (n=1,212)

HBeAg (-) hepatitis, treated (n=525)

Cumulative Incidence of HCC and Death/Transplantation in Matched cohorts (13,164 PY, median 4.7 yr F/U)



Elevated HBV DNA with minimal ALT elevation associated with worse outcomes…
should we lower the threshold for treatment?

Choi et al. AASLD 2018, Abstract 2146

TORONTO CENTRE FOR LIVER DISEASE

Excluding cirrhosis in CHB

Enrolled patients with CHB with biopsy for study entry

- Derivation n=2,926. Cirrhosis 340 (12%)
- Validation n=1,034. Cirrhosis 155 (15%)

APRI

- Of 340 with cirrhosis → 153 (45%) classified as no cirrhosis

FIB-4

- Of 340 with cirrhosis → 139 (41%) classified as no cirrhosis

APRI					
Dataset	Cut-off	N identified	Cirrhosis	NPV	Misclassification*
Derivation	< 0.45	627 (21.4%)	29 (4.6%)	95.4%	29/340 (8.5%)
Validation	< 0.45	407 (39.4%)	22 (5%)	94.6%	22/155 (14.2%)
	FIB-4				
Dataset	Cut-off	N identified	Cirrhosis	NPV	Misclassification*
Derivation	< 0.70	925 (31.6%)	31 (3.4%)	96.6%	31/340 (9.1%)
Validation	< 0.70	337 (32.6%)	9 (2.7%)	97.3%	9/155 (5.8%)

- Standard APRI and FIB-4 values estimate fibrosis poorly in CHB
- New thresholds of **APRI <0.45** or **FIB4<0.70** accurately exclude cirrhosis in CHB

TORONTO CENTRE FOR LIVER DISEASE

Sonneveld et al, AASLD 2018, Abstract 2072

HBsAg Seroclearance in Untreated Patients With CHB

- Retrospective cohort study of untreated patients with CHB in North America (n = 1635) and Asia (n = 8979)
- Male sex, higher age or ALT level, HBeAg negativity predicted spontaneous HBsAg seroclearance in multivariable analysis
- Annual HBsAg seroclearance rate: 1.33% (95% CI: 1.26% to 1.40%)
  - CIR: 4.92% at 5 yrs, 11.27% at 10 yrs, 19.36% at 15 yrs, 25.42% at 20 yrs

BL Characteristic		aHR* (95% CI)	*P* Value
Sex	▪ Female	1	
	▪ Male	1.17 (1.04-1.33)	.012
Age, yrs	▪ < 35	1	
	▪ 35-44	1.25 (1.06-1.48)	.009
	▪ 45-54	1.52 (1.28-1.80)	< .001
	▪ > 55	1.79 (1.49-2.15)	< .001
HBeAg status	▪ Negative	1	
	▪ Positive	0.25 (0.19-0.32)	< .001
ALT	▪ Every 10 U/L increase	1.01 (1.00-1.01)	< .001

*Adjusted for age, sex, race, study setting, BL cirrhosis, ALT level, and HBeAg status.

Yeo. AASLD 2018. Abstr 212.

Slide credit: clinicaloptions.com

The natural history of CHB – HBsAg loss

Retrospective study of 1 North American & 8 Asian cohorts – n=10,614 untreated CHB

Follow-up (yrs)	0	5	10	15	20
Patients (n)	10317	6882	5012	1655	550
CIR (%)	**0**	**4.92**	**11.27**	**19.36**	**25.42**

Annual seroclearance rate:
1.33% (95% CI: 1.26-1.40)

Subgroups		aHR (95% CI)*	*P*-value
Sex	**Female**	1	
	Male	1.17 (1.04-1.33)	0.012
Age	**<35**	1	
	35-44	1.25 (1.06-1.48)	0.009
	45-54	1.52 (1.28-1.80)	<0.001
	>55	1.79 (1.49-2.15)	<0.001
Baseline HBeAg status	**HBeAg (-)**	1	
	HBeAg (+)	0.25 (0.19-0.32)	<0.001
Baseline ALT	**Every 10 U/L increase**	1.01 (1.00-1.01)	<0.001

TORONTO CENTRE FOR LIVER DISEASE

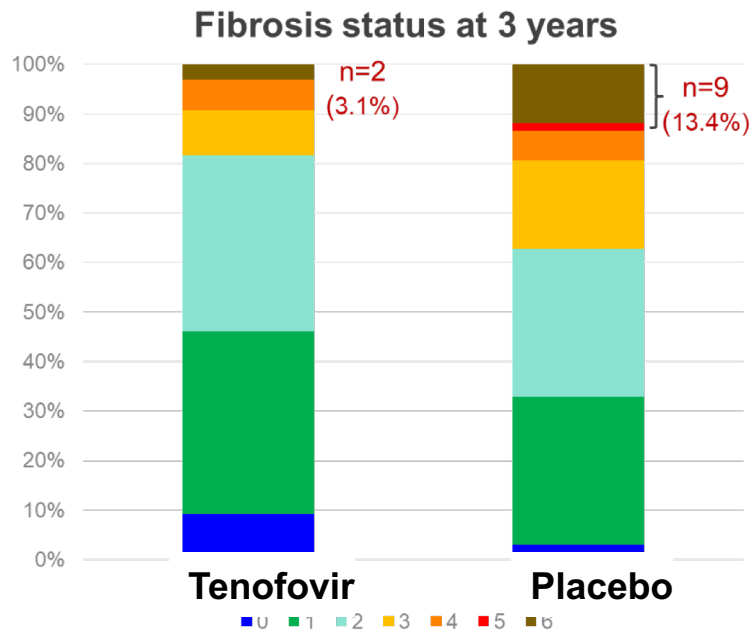
*Adjusted for sex, age, race, study setting, and baseline HBeAg status, cirrhosis, and ALT level

Given low HBsAg loss with or without current treatments, we need improved therapy

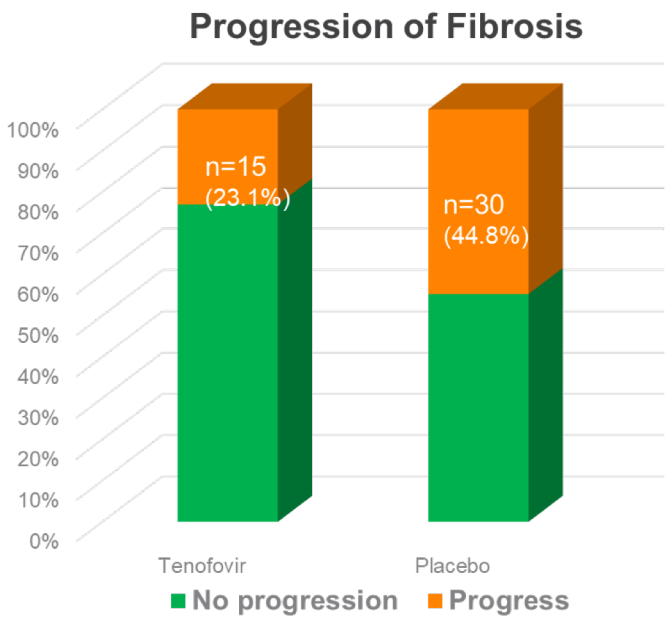
Yeo AASLD 2018, Abstract 0212

RCT of TDF for minimal ALT elevation

Double blind RCT of CHB with HBV DNA>2,000 IU/mL and ALT 40-80 (1-2x ULN) with paired liver bx @ 0 & 3 y



For cirrhosis (Ishak 5 or 6), RR: 0.23 (95% CI, 0.06~0.88; *P*=0.05)



For any increase in Ishak fibrosis; RR: 0.52 (95% CI, 0.31~0.85; *P*=0.01)

Findings

- **TDF treatment associated with:**
  - **Less fibrosis progression (RR 0.52**
  - **Less development of cirrhosis (RR 0.23)**
  - **Reduced inflammatory score, ALT and HBV DNA**

Caveats

- **More advanced fibrosis (Ishak 3/4) in placebo arm 27% vs 12%**
- **Entecavir used for 'flares' (ALT>2xULN)…10 placebo patients**

Intriguing…need a closer look but may support use of NA therapy with ALT<2x ULN

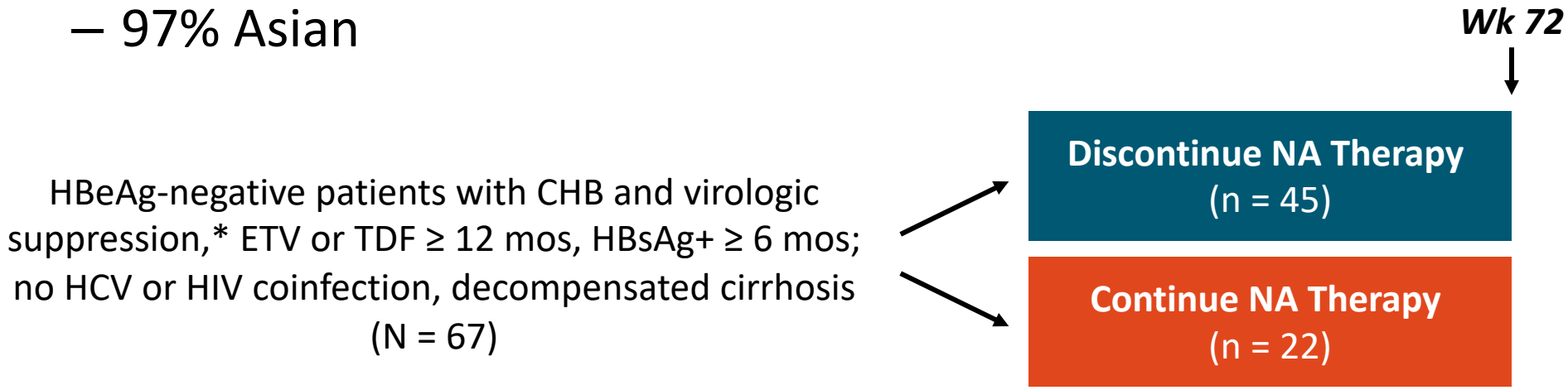
Hsu YC et al., AASLD 2018, Abstract 0264

TORONTO CENTRE FOR LIVER DISEASE

STOP ? Nucs ?

STOP: Nucleos(t)ide Analogue Cessation in HBeAg-Negative Patients With CHB

- Prospective, randomized, controlled, open-label phase IV trial
  - 97% Asian



*If HBeAg+ at NA start, HBeAg seroconversion + undetectable HBV DNA ≥ 12 mos; if HBeAg-, undetectable HBV DNA ≥ 36 mos.

- Primary endpoint: HBV DNA < 2000 IU/mL at Wk 48

Patients retreated for HBeAg seroreversion, HBV DNA > 2000 IU/mL + (ALT > 5 x ULN at 2 consecutive visits or > 15 x ULN at any visit), or HBV DNA > 20,000 IU/mL at 2 consecutive visits; ALT ULN: 40 IU/mL.

Liem. AASLD 2018. Abstr 268.

Slide credit: clinicaloptions.com

STOP: Virologic and Safety Outcomes

Outcome, n (%)	Stop (n = 45)	Continue (n = 22)
HBV DNA < 2000 IU/mL		
▪ Wk 48*	11 (24)	21 (95)
▪ Wk 72	12 (27)	NR
ALT		
▪ Grade 3 (> 5 x ULN)	22 (49)	0
▪ Grade 4 (> 20 x ULN)	7 (16)	0

*Primary endpoint.

- Limited HBsAg decline across arms

Outcome, %	Stop (n = 45)			
	Wk 0	Wk 24	Wk 48	Wk 72
Retreatment	0	27	29	38
Clinical relapse†	0	7	4	13
Virologic relapse‡	0	33	40	20
Sustained response§	100	31	24	27
HBsAg loss	0	2	2	2

†HBV DNA > 2000 IU/mL + ALT > 1.5 x ULN.
‡Lone HBV DNA > 2000 IU/mL.
§HBeAg negative + HBV DNA < 2000 IU/mL + ALT < 1.5 x ULN.

Liem. AASLD 2018. Abstr 268.

Slide credit: clinicaloptions.com

Stopping therapy – a prospective RCT

Inclusion

HBeAg-neg with DNA neg:

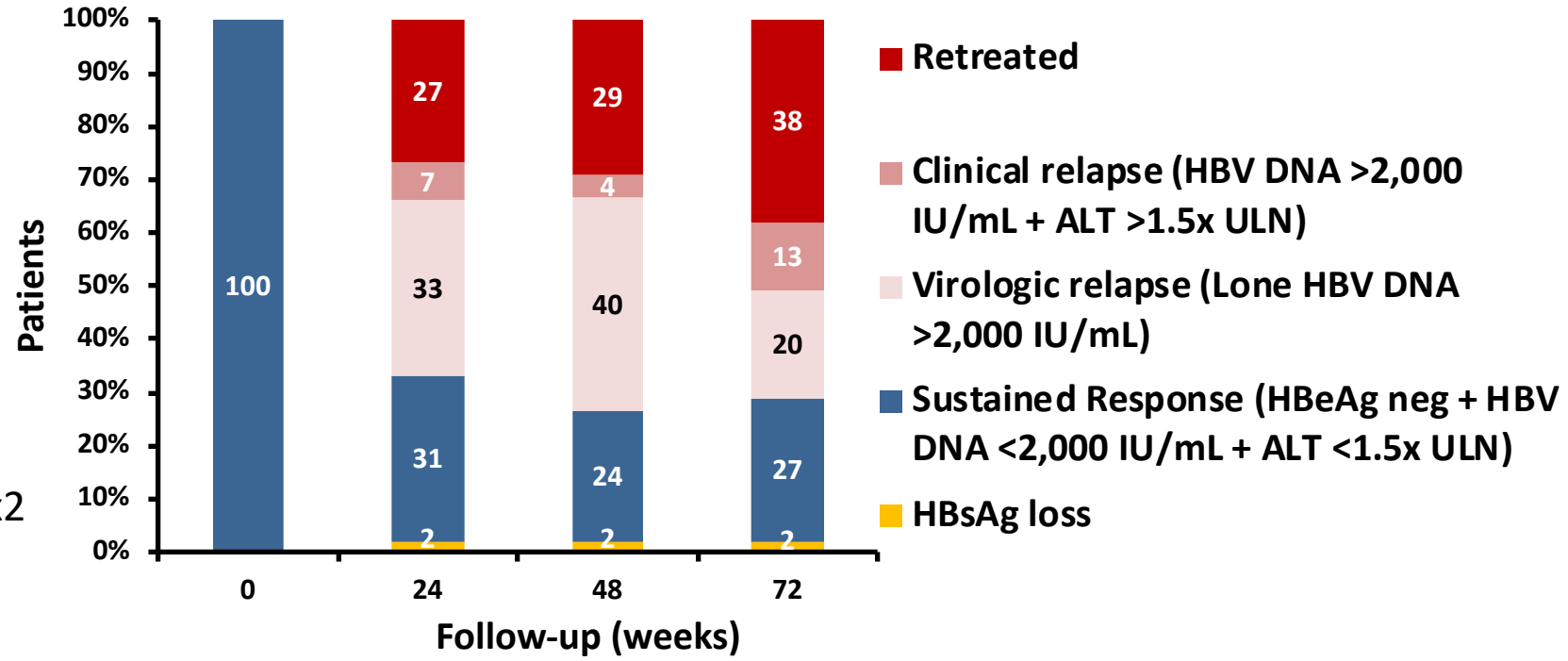
- > 3 yrs (start HBeAg-neg)
- >1 yr post HBeAg loss (start HBeAg+)

Intervention

- Randomized 2:1 stop vs continue NA
- F/u x 72 weeks

Retreatment criteria

1. HBeAg seroreversion
2. HBV DNA>2000 IU/mL + ALT>5xULN x2
   or ALT >15xULN x 1
3. HBV DNA >20,000 x 2



- Clinical relapse or retreatment in >50% and only ~30% with sustained off-treatment response
- Minimal effect on HBsAg levels…**not very effective approach in predominantly Asian patients**

Liem et al AASLD 2018, Abstract 268

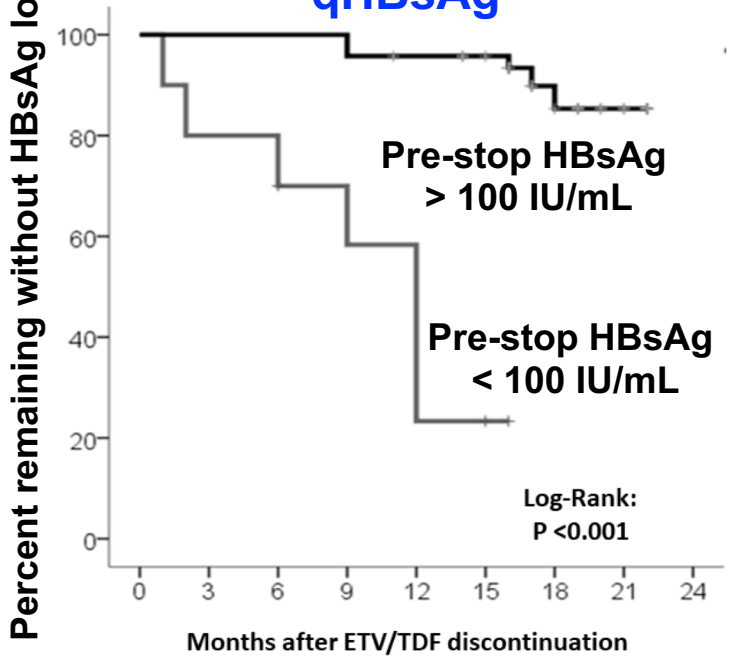
TORONTO CENTRE FOR LIVER DISEASE

Can we predict who will need retreatment?

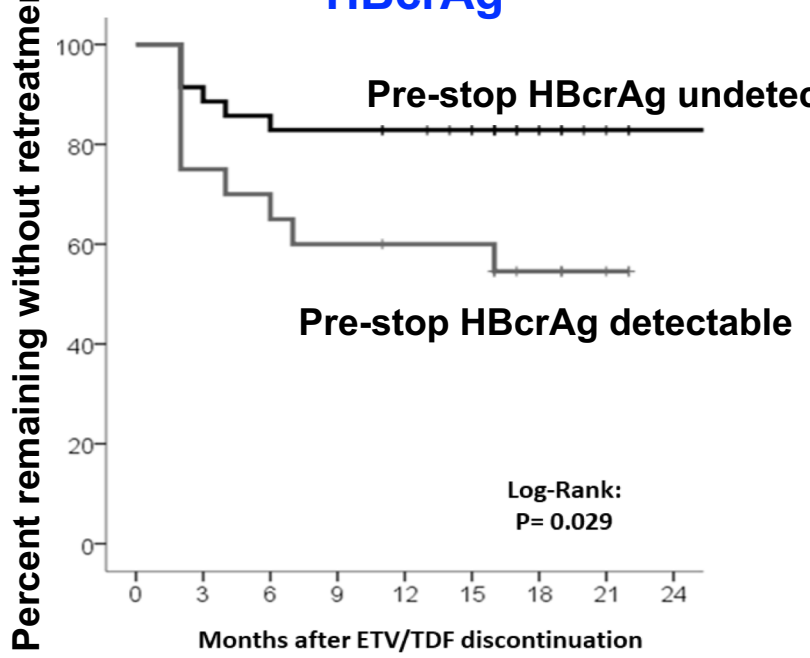
Prospective RCTs of stopping long-term NA therapy

DARING-B (n=60)

qHBsAg

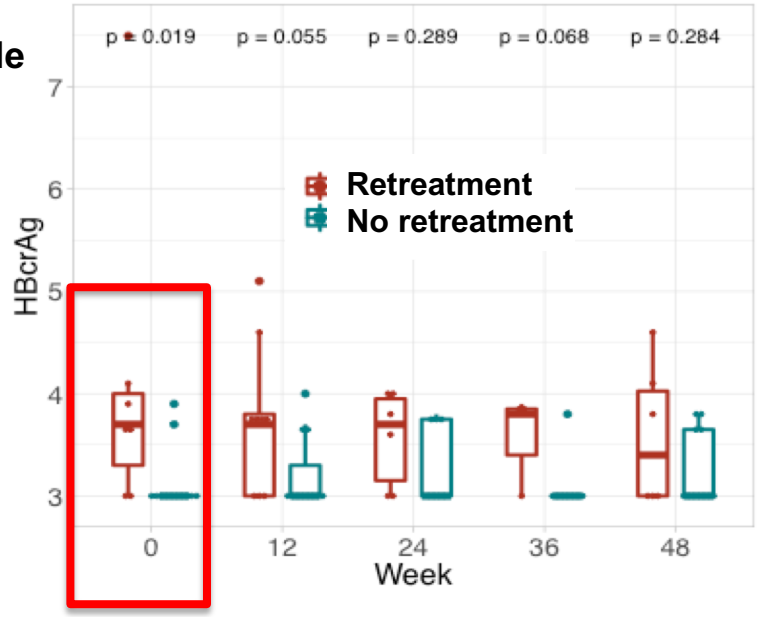


HBcrAg



FINITE Study (n=40)

HBcrAg



- **Multiple small studies showing undetectable HBcrAg and/or low qHBsAg at the time of stopping = lower risk of relapse & increased chance of HBsAg loss**
- **Need more data but could be promising predictive tools**

TORONTO CENTRE FOR LIVER DISEASE

Papatheodoridis, Abst 408, Van Bommel et al, Abst 458D, Hsu YC et al, Abst 0397, Seto et al, Abst 0417

Predictors of Relapse After NA Cessation in CHB

Unmet need for biomarkers to assess risk of treatment withdrawal

- Data from multiple small prospective studies support use of HBcrAg and/or HBsAg to predict risk of relapse

Prospective Study	Findings
(N = 135)[1]	▪ HBcrAg, HBsAg independently predict off-treatment clinical relapse, can be combined with age, ALT, and TDF use in novel risk score
DARING-B (N = 60)[2]	▪ HBsAg loss associated with lower levels of HBsAg at ETV/TDF d/c ▪ HBcrAg levels at d/c, 1 mo before retreatment predict probability of retreatment
(N = 103)[3]	▪ Significantly lower HBV reactivation rate in patients with BL HBsAg ≤ vs > 10 IU/mL ▪ Lower BL HBcrAg level associated with reduced HBV reactivation rate in patients with BL HBsAg > 20 IU/mL
(N = 15)[4]	▪ HBcrAg or pregenomic HBV RNA at TDF d/c may predict significant ALT flares necessitating retreatment

1. Hsu. AASLD 2018. Abstr 397. 2. Papatheodoridi. AASLD 2018. Abstr 408.
3. Seto. AASLD 2018. Abstr 417. 4. Carey. AASLD 2018. Abstr 530.

Slide credit: clinicaloptions.com

Summary of studies HBsAg seroclearance after stop NA

Study	N	Tx duration	HBsAg loss	Incidence
Chan	53	27 mo	11/53	23% - 5 yrs
Hadziyannis	33	4-5 yrs	13/33	39% - 3 yrs
Chen	105	93 wks		30% - 6 yrs
Patwardhan	33	5.3 yrs	?	30% - 6 yrs
Hung	73	30 mo	20/73	46% - 6 yrs
Yao	119	151 wks	44/119	55% - 6 yrs
Berg *	21 (42)	>4 yrs	4/21	19% - 144 wks
Jeng	691	156 wks	42/691	13% - 6 yrs
Papatheodoridis	57	5.3 yrs	12/57	25% 1.5 yrs

*** Estimated "Natural" Annual HBsAg loss of 1.78%**

Courtesy F. Zoulim EASL PCG 2018; adapted from Jeng WJ et al. Hepatology 2018;68:425

Outcome Predictors of NA Discontinuation

- Age, Race, HBV Genotype
- Time to undetectable HBV DNA
- Duration of viral suppression under NA
- HBsAg levels at NA baseline and at NA stop
- Type of NA: Tenofovir vs Entecavir?
- HBV-DNA levels during reactivation
- Re-treatment strategy

Most studies: HBsAg level at stop below 100-1000 IU/mL

Lampertico & Berg Hepatology 2018

Implications for Clinical Practice

- Male sex, higher age or ALT level, HBeAg negativity predict spontaneous HBsAg seroclearance
- High rates of relapse and retreatment after cessation of long-term ETV or TDF in Asian patients with HBeAg-negative CHB
- HBcrAg and/or HBsAg may have utility in predicting off-treatment relapse in patients with CHB who discontinue long-term NA therapy
  - More research needed for optimal risk stratification

Lower HCC Risk with TDF vs. ETV

HCC					
Groups	Patient-years	No. of events	No./100 patient -years (95% CI)	HR (95% CI)	P
Nationwide cohort					
Entecavir	11,464	590	**1.06**	Reference	<0.001
Tenofovir	12,692	394	**0.64**	**0.61** (0.54-0.70)	
AMC hospital cohort					
Entecavir	1560	115	**2.26**	Reference	0.03
Tenofovir	1141	39	**1.31**	**0.66** (0.46-0.96)	

Death or transplantation					
Groups	Patient-years	No. of events	No./100 patient -years (95% CI)	HR (95% CI)	P
Nationwide cohort					
Entecavir	11,464	281	0.50	Reference	0.004
Tenofovir	12,692	228	0.36	0.77 (0.65-0.92)	
AMC hospital cohort					
Entecavir	1,560	68	1.29	Reference	0.33
Tenofovir	1,141	23	0.76	0.79 (0.48-1.28)	

Choi J, Lim YS. JAMA Oncol 2018 Sep 27 [Epub ahead of print]

Randomized, double-blind, placebo-controlled trial of TDF in children 2 to <12 years with chronic hepatitis B

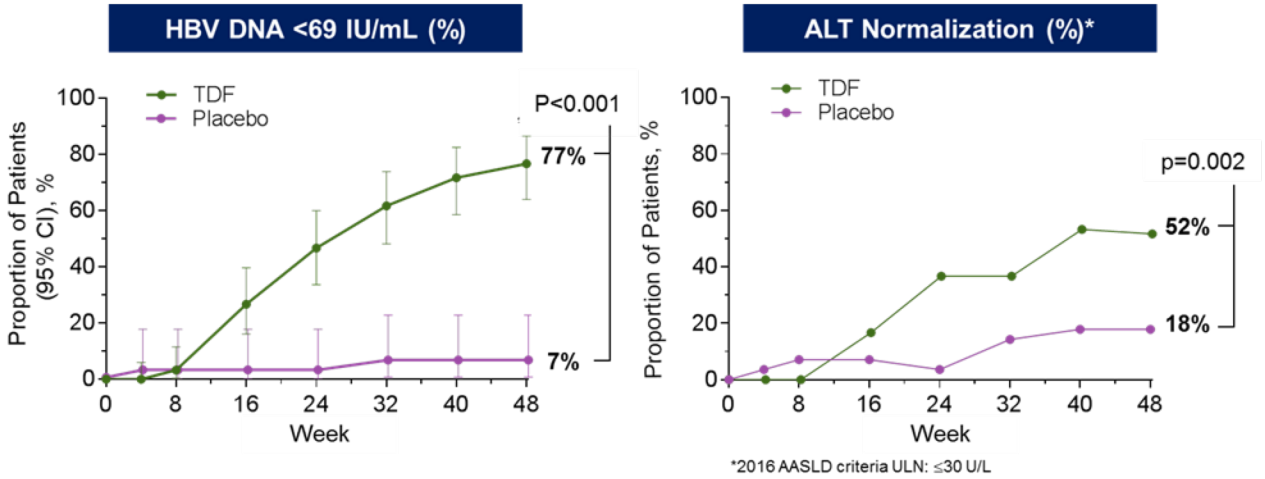
Aim: Evaluate the efficacy and safety at Week 48 of tenofovir DF (TDF) relative to placebo (PBO) in children 2 to <12 years of age with chronic HBV (CHB)

Methods:

- Double-blind, randomized (2:1), placebo-controlled trial comparing TDF 8 mg/kg QD to PBO QD in children with CHB
- Screening HBV DNA ≥4.2 $\log_{10}$ IU/mL (≥10^5 copies/mL); ALT ≥1.5 x ULN; HBeAg-positive or -negative; creatinine clearance (eGRF [Schwartz formula]) ≥80 mL/min/1.73 m^2

Main findings:

- Mean % change in bone mineral density (BMD) at Week 48:
  - Spine: TDF +3.80%; PBO +7.56% (*p*=0.007)
  - Whole body: TDF +4.53%; PBO +8.88% (*p*<0.001)
- Median change in eGFR at Week 48:
  - TDF -8.7 mL/min/1.73 m^2; PBO -0.1 mL/min/1.73 m^2 (*p*=0.047)
  - No TDF patients had a confirmed eGFR <50 mL/min/1.73 m^2



Conclusions:

- Children treated with TDF (n=60) showed higher rates of viral suppression and ALT normalization vs PBO (n=29) with no resistance at Week 48.
- TDF was safe and well tolerated vs PBO; however, increases in BMD were smaller with TDF treatment.

Chang M-H, et al., Abstract 76

HBV Flares

HBV Flares: Definition and Summary

- An abrupt elevation in serum ALT >5X ULN AND more than twice the baseline value is a proposed definition of an ALT flare
- ALT flares occur naturally during the course of CHB and are more frequent in those who are older, male, Asian, HBeAg positive and infected with HBV genotype C
- Among HBeAg positive patients, an ALT level >5XULN is associated with ~50% chance of HBeAg seroconversion
- ALT flares may be associated with hepatic decompensation and death
- Patients with cirrhosis or features of decompensation should receive immediate therapy with a first line nucleos(t)ide analogue
- Currently no biomarkers that can distinguish a good from a bad flare

After Marc Ghany AASLD 2018

Management of ALT Flares in HBV Infection:
increasing ALT in the setting of a rising or falling DNA

- Exclude other etiologies for flare
- Monitor weekly or biweekly for clinical deterioration or hepatic decompensation
- Consider monitoring for 3-6 months for HBeAg loss if HBeAg positive and:
  - No cirrhosis, no evidence of decompensation
  - Age <30 years
  - HBV DNA declining at time of flare
- Consider early treatment if:
  - Age >30 years
  - HBV DNA stable or increasing
  - HBeAg negative/anti-HBe positive
- Treat immediately if:
  - Cirrhosis present
  - Signs/symptoms of decompensation present

After Marc Ghany AASLD 2018

HBV Biomarkers

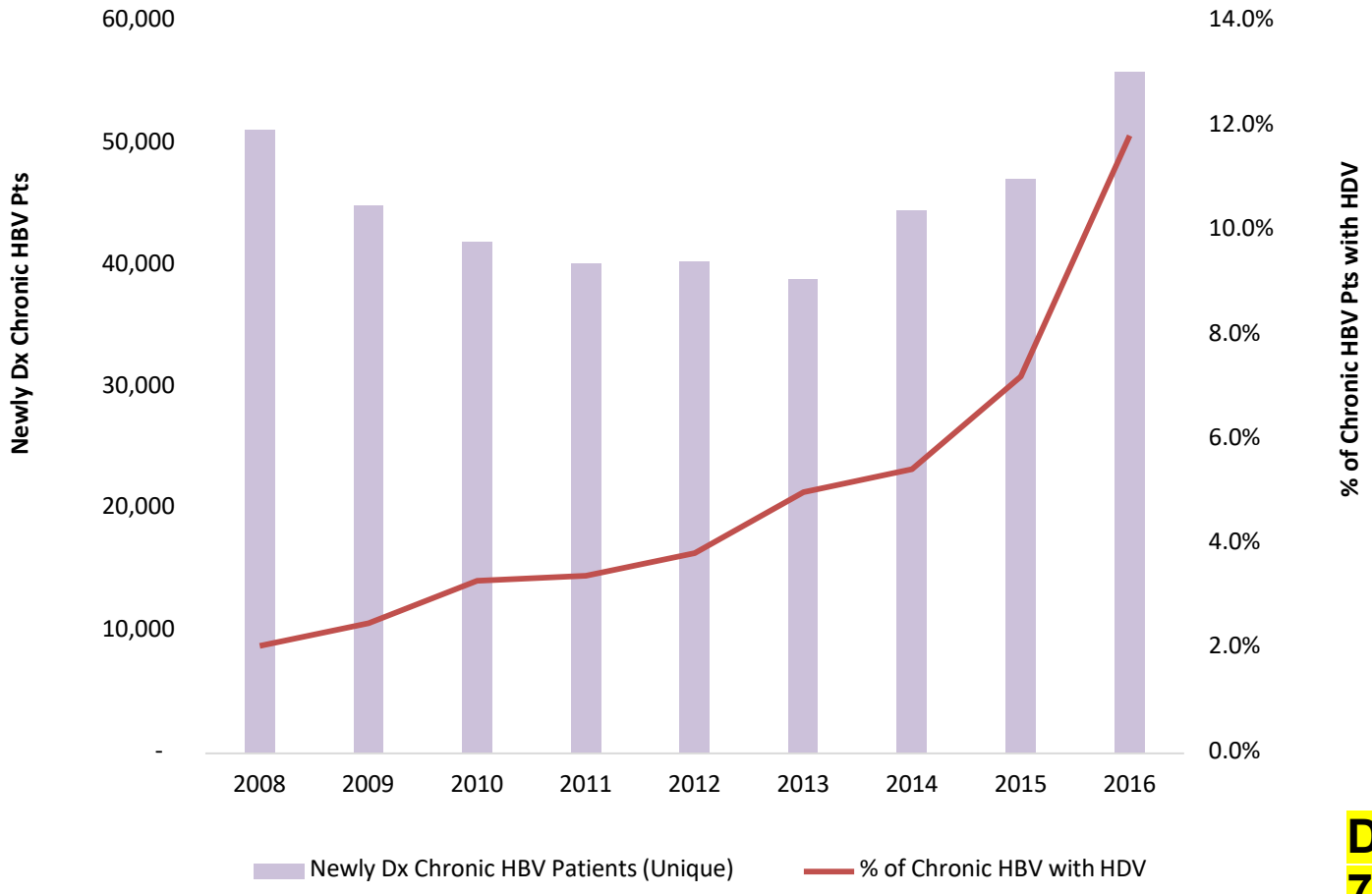
HBV Markers what is old/current and what is new ?

- Markers to define HBV cure
  - HBsAg loss <0.05 *IU*
    - WITH
  - HBV DNA < loq
- New markers
  - qHBsAg
  - qHBcrAg
  - qHBV RNA

- Change in quantitative HBsAg (qHBsAg) concentration at various time points on-treatment
- HBeAg concentration
- HBV RNA
- HBV core-related antigen (HBcrAg)
- cccDNA quantification
- HBsAg fragments
- HBsAg-anti-HBs immune complex

DELTA Hepatitis

Newly-Diagnosed Chronic HBV Patients and % with HDV Incidence Appears Higher Than Previous Estimates

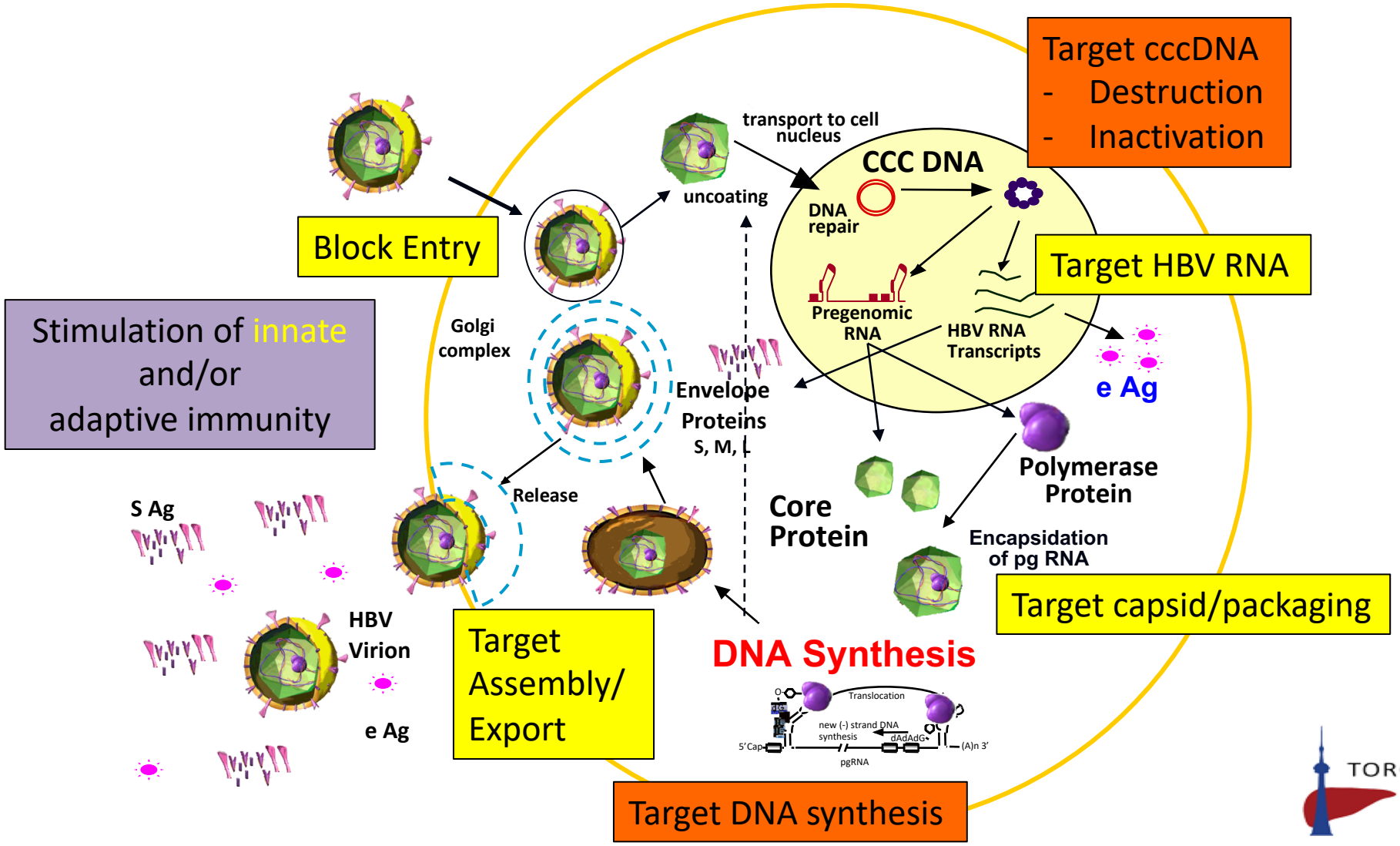


Delta Hepatitis has a 70% mortality Rate

Franco, Gish and Glenn, J. Prevalence of Hepatitis Delta Virus (HDV) Infection in the United States: Results from an ICD-10, Review. Poster AASLD 2018

Future Therapies Hepatitis

Potential targets in the lifecycle



TORONTO CENTRE FOR LIVER DISEASE

C-PAMS Capsid Modulator Capsid Inhibitors
Summary of clinical data through EASL '18/AASLD '18*

	NVR 3-778 (Novira)	GLS4-JHS (HEC Pharm)	JNJ-6379 (JNJ)	JNJ-0440 (JNJ)	RO-7049389 (Roche)	ABI-H0731 (Assembly)	
Company	JNJ	HEC	JNJ	JNJ	Roche	Assembly	
Dose (28 days)	600 mg BID	240 mg QD	100mgx1; 25 mg QD; 75 mg QD 150 mg QD; 250 mg QD* (n=8-9)	50, 150, 300, and 900 mg – HV SINGLE DOSE ONLY*	200 mg BID	100 mg QD; 200 mg QD; 300 mg QD (n=10/arm)	400 mg QD (n=2)
Mean DNA reduction (log)	1.72	2.13	2.16 – 2.89	N/A	2.7 (median)	1.7 - 2.8	3.9
Mean RNA reduction (log)	0.86	NR	1.67 - 2.3	N/A	NR	NR	NR
eAg/sAg	0.25/NR	0.30/ 0.14	-	N/A	NR/NR	NR/NR	NR/NR
Other		sAg Decline at 24 weeks	1 Gr 4 ALT – d/c (150 mg) T1/2 ~ 93-110 hrs	Gr 2 rash (900mg)*; 900 mg had 24-hour post-dose >EC90 for cccDNA inh (373nM)*; T½ ~10-13 hrs*	OATP substrate Liver:Plasma>100	T109M in 1 subj (300 mg) 1 other "poor responder"	1 d/c for Gr 3 rash (400mg)

*AASLD data based on abstracts

Some take home messages from AASLD 2018

1. Test all HBsAg+ patients for qHBsAg
2. There is a hope for a functional cure in 40% of patient in < 5 years with new combination therapies
3. Use the new thresholds of 25 IU women and 35IU men for ALT “healthy” for HBV treatment
4. Test all HBV + patient for delta antibody
5. TDF (?TAF) many have a lower risk of HCC than ETV
6. ETV has no renal or bone toxicity, no HCC risk or any cancer risk
7. HBV patients need to stop alc use and attain a normal BMI
    1. 24 Caucasian, 22 Asian
8. Stop NUCS in HBsAg+ patients ? Done by liver specialists under careful considerations?
    1. Never stops Nucs in HBsAg+ patients with cirrhosis

Thank you SCGIS, CCO, AASLD, Jordan Feld and Toronto Liver Center and Focusmed/CLDF

Simplified: 5 Pillars of HBV

- Test all adults for HBV including all immigrants, all patients with unknown HBV vaccine status
- Anti-HBc+ = exposure to HBV, do not vaccinate, do educate about reactivation risk (anti-HBc false + rate is 2/1000 in low risk patients)
- Vaccinate all adults who are triple panel negative
- ALT over ULH (upper limits of healthy) or
  - + fibrosis (APRI, FIB4, TE or bx) and + DNA over 2000 = Nuc treatment,
  - cirrhosis and any HBV DNA = Nuc treatment
- Treat all patients until HBsAg loss + 12 months consolidation