2018

NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Rehoboth McKinley Christian Health Care Services

Northern California Society for Clinical Gastroenterology

Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Northern California Society for Clinical Gastroenterology.

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Update on Viral Hepatitis
EASL and DDW

Norah Terrault, MD
Professor of Medicine and Surgery
Director, Viral Hepatitis Center
University of California San Francisco

HCV: Key Areas

- DAA therapy: Shorter duration of therapy
- Special treatment populations
  - Genotype 3 with cirrhosis
  - DAA failures
  - PWIDs
  - Incarcerated persons
- DAAs and liver cancer

Current Therapies for HCV: The 8 Week Option

Non-cirrhotic patients, treatment naive

	SOF-LDV	GLE-PIB	SOF-VEL	EBR-GZR
G1	YES*	YES		
G2		YES		
G3		YES		
G4		YES		
G5/6		YES		

* HCV RNA <6 million IU/mL, no HIV, non-AA

AASLD/IDSA. HCV guidance. June 2018

STREAGER: Elbasvir/Grazoprevir for 8 Wks in Patients With GT1b HCV and Nonsevere Fibrosis

- Interim analysis of an international, open-label, single-arm phase III study

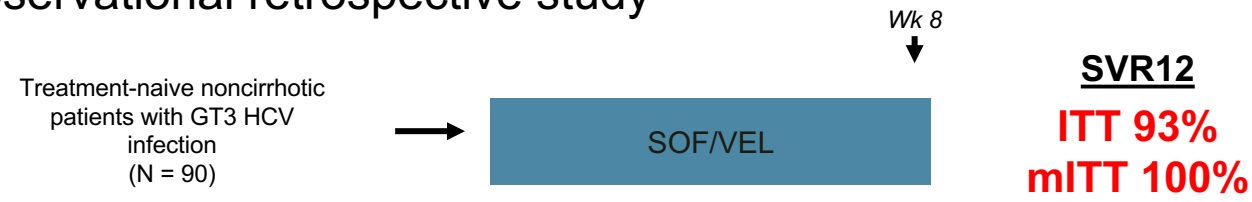
*Nonsevere fibrosis defined as *FibroScan* < 9.5 kPa and *FibroTest* < 0.59. Planned N = 120.

- SVR12 in GT1b: 98% (87/89; excludes 1 patient with GT1e HCV)
  - 4 relapses (3 at posttreatment Wk 12, 1 at posttreatment Wk 24 after achieving SVR12), including 1 patient with GT1e HCV
  - RAS detected in 3 of 3 relapsers
- No grade 3/4 AEs

Abergel A, et al. EASL 2018. Abstract LBP-010.

Sofosbuvir/Velpatasvir for 8 Wks in Treatment-Naive Patients With GT3 HCV and F2-F3 Fibrosis

- Observational retrospective study

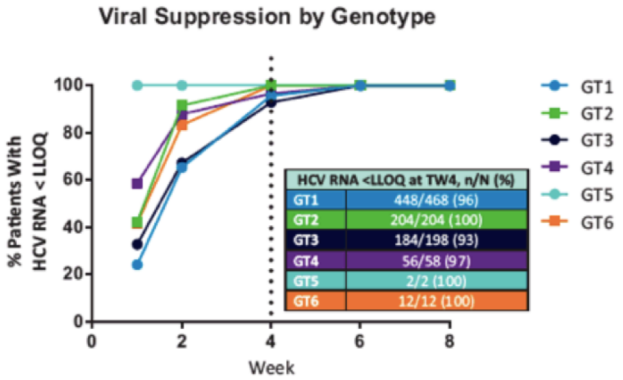


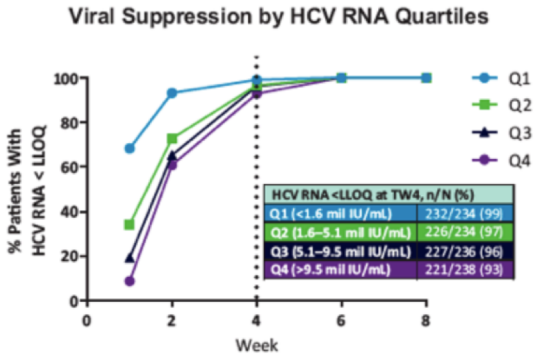
- 91% receiving OST; 42% receiving daily supervised OST
- Fibrosis: 67% F2; 31% F3
- 84 of 90 (93%) achieved SVR12 (ITT population)
  - 2 lost to follow-up, 2 d/c, 1 death, 1 reinfection
  - 100% SVR12 after excluding loss to follow-up, d/c, death, reinfection (mITT)

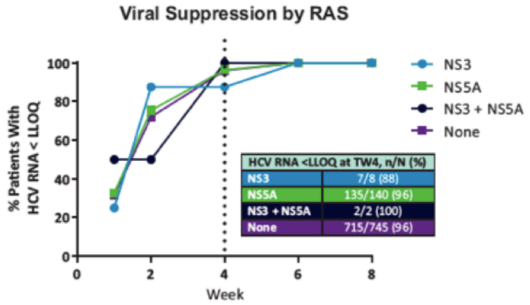
Boyle A, et al. EASL 2018. Abstract PS-034.

Time to Negativity Does not Influence SVR with 8-Wk Glecaprevir-Pibrentasvir Regimen

- **4% of patients treated with G/P for 8 weeks had quantifiable HCV RNA at Wk 4 → should these patients have treatment extended?**







- **N=960 patients treated: 17 variables evaluated as predictors of quantifiable HCV RNA at week 4: only high baseline VL associated**
- **All those quantifiable at week 4 achieved SVR –not predictive**

Sarrazin C, EASL, THU-384

Take Home Messages: 8 Week Options

- Treatment naïve, non-cirrhotic patients are easy to treat group
  - Several DAA combination may be effective as 8 week regimens
- Guidelines have not embraced any other 8-week regimens options
  - Important for groups where adherence to 12 wks is challenging
- No need for on-treatment HCV RNA monitoring

	SOF-LDV	GLE-PIB	SOF-VEL	EBR-GZR
G1	YES*	YES	(YES)	YES, 1b only
G2		YES	(YES)	
G3		YES	YES	
G4		YES	(YES)	
G5/6		YES	(YES)	

* HCV RNA <6 million IU/mL, no HIV, non-AA

Genotype 3 with Cirrhosis: Most Difficult to Cure Genotype in DAA Era

AASLD/IDSA Guidelines:

No Cirrhosis	Compensated Cirrhosis
GLE/PIB 8 wks SOF/VEL 12 wks	GLE/PIB 12 wks **SOF/VEL 12 wks***

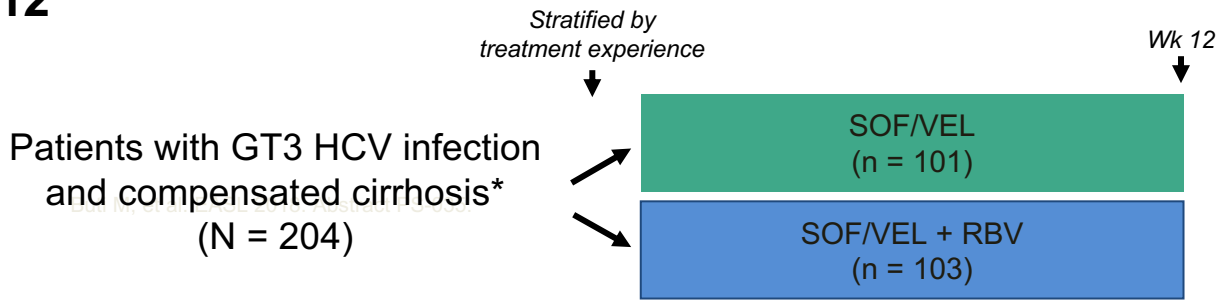
*** If treating with SOF/VEL, need to do baseline RAS testing -→ if Y93H present, add RBV or choose alternative regimen (consider SOF/VEL//VOX)**

- **ASTRAL-3 study: SVR12 if Y93H =84% versus 97% if no Y93H**

AASLD/IDSA. HCV guidance. September 2017.
Foster G, N Engl J Med N Engl J Med 2015;373:2608-17.

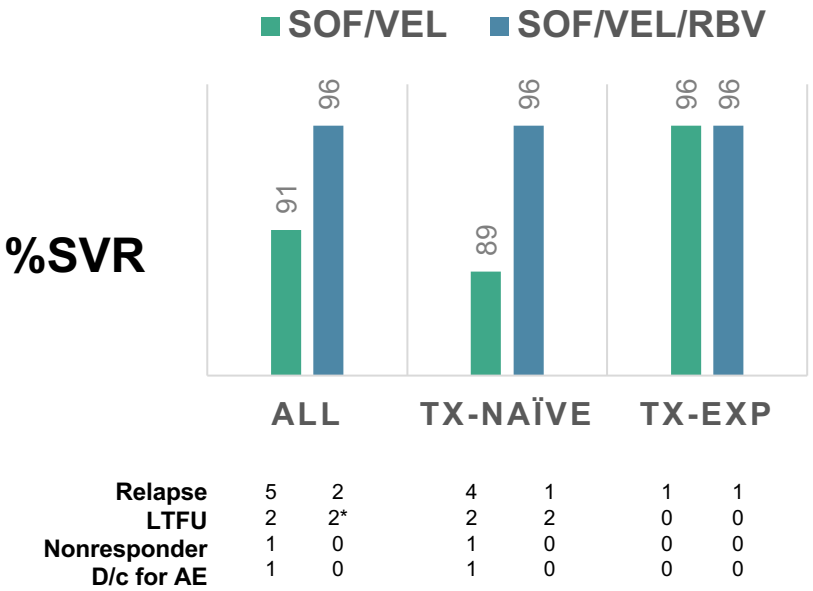
Sofosbuvir/Velpatasvir ± RBV for 12 Wks in Patients With GT3 HCV Infection and Cirrhosis

- **Randomized, open-label study**
  - Patients eligible if treatment naive or experienced, including previous use of NS3/4 PI or NS5B inhibitor.
  - All patients were NS5A inhibitor naive.
  - HIV coinfection permitted.
- Dosing: SOF/VEL 400/100 mg QD plus weight-based RBV.
- **Primary endpoint: SVR12**



Buti M, et al. EASL 2018. Abstract PS-035.

Efficacy of Sofosbuvir/Velpatasvir ± RBV for GT3 HCV With Cirrhosis



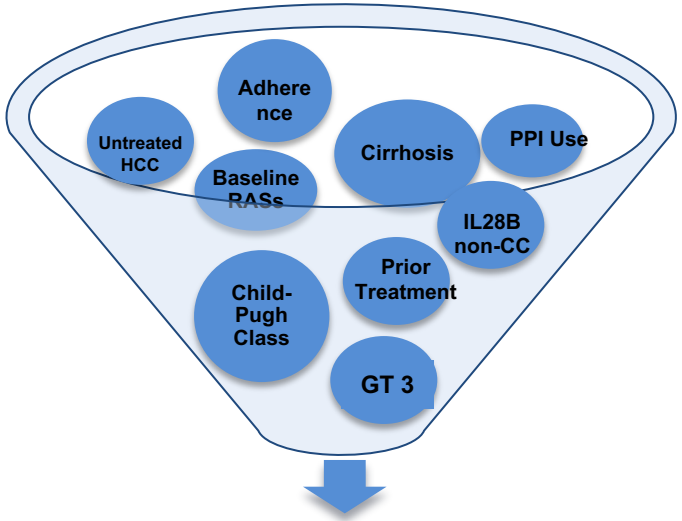
RAS Analysis, n/N (%)	SOF/VEL	SOF/VEL + RBV
Detection of BL RAS		
▪ No	79/98 (81)	79/101 (78)
▪ Yes	19/98 (19)	22/101 (22)
SVR12		
▪ No BL RAS	76/79 (96)	78/79 (99)
▪ BL RAS	16/19 (84)	21/22 (96)
▪ BL Y93H	2/4 (50)	8/9 (89)

Bottomline: AASLD/IDSA guidance should remain unchanged. If using SOF/VEL in GT3 with cirrhosis, need to do RAS testing

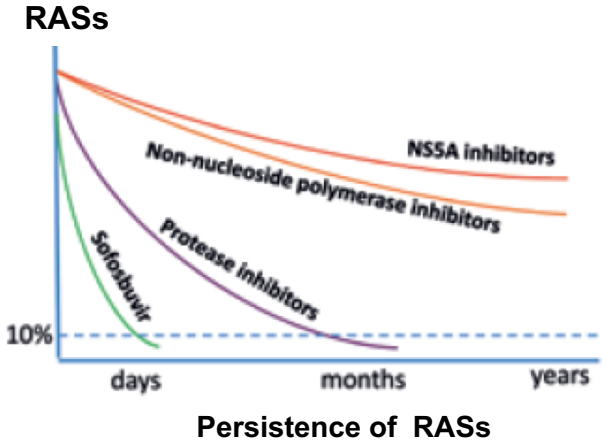
Buti M, et al. EASL 2018. Abstract PS-035.

DAA Treatment Failures: "Dealing with the 5%"

- **Multiplicity of negative factors increases risk of treatment failure**



Treatment failure typically associated with emergence of resistance-associated substitutions **(RASs)**



Adapted from Soriano V, AIDS Rev. 2016

AASLD/IDSA Guidance: Recommended Regimens for DAA-Exp'd Patients

- **No RAS testing recommended in this setting with recommended regimens**

HCV GT	Duration, Wks	Previous DAA Experience		
		NS3/4AI Only	NS5BI (SOF w/o NS5AI)	**NS5AI (± NS3/4AI, NS5BI)**
1	12	LDV/SOF (no cirrhosis) SOF/VEL GLE/PIB	SOF/VEL/VOX (1a) GLE/PIB SOF/VEL (1b)	**SOF/VEL/VOX**
2*	12	NA	SOF/VEL GLE/PIB	**SOF/VEL/VOX**
3	12	SOF/VEL/VOX	SOF/VEL/VOX	**SOF/VEL/VOX ± RBV†**
4, 5, 6	12	SOF/VEL/VOX	SOF/VEL/VOX	**SOF/VEL/VOX**

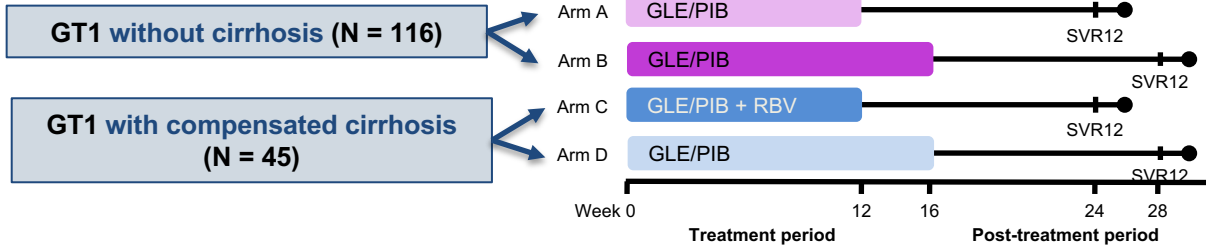
*Recommendations for any SOF + RBV experienced pt. †RBV if NS5AI failure and cirrhosis.

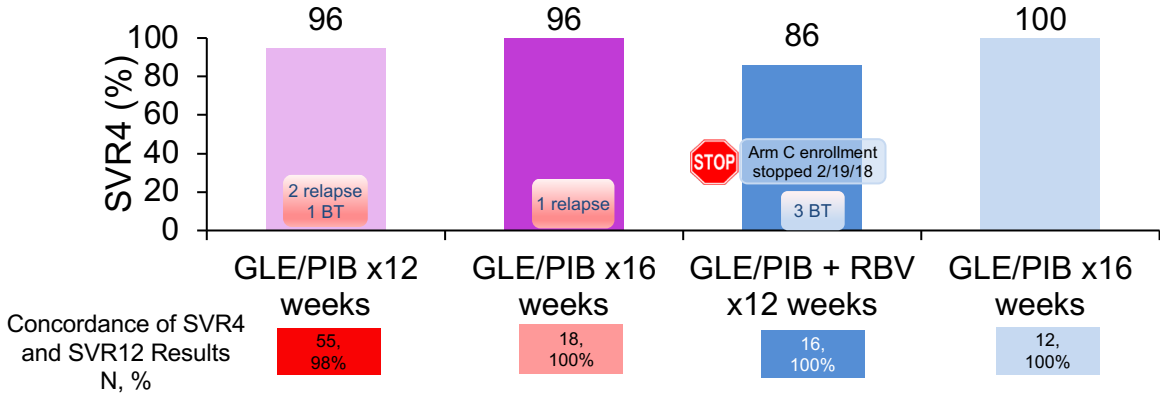
AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

Glecaprevir/Pibrentasvir ± RBV for GT1 HCV After Failing NS5A inhibitor + SOF therapy

Interim analysis of Phase 3b, multi-center, randomized, open-label, pragmatic study





*PI-experienced patients randomized to 12-wk →16 wks of treatment and subsequent analysis in respective 16-wk arms (5 noncirrhotic, 1 cirrhotic).

Lok A, et al. EASL 2018. Abstract LBO-008.

Glecaprevir/Pibrentasvir ± RBV for GT1 HCV After Failing NS5A inhibitor + SOF therapy

Virologic Failures

Arm	Prior Tx & days since exp	Response	NS3 RAS		NS5A RAS	
			Baseline	Failure	Baseline	Failure
No cirr G/P 12 wk	LDV/SOF 470	BT	none	R155W + A156G	Q30N + Y93H	M28T + Q30N + Y93H
No cirr G/P 12 wk	LDV/SOF 711	REL	none	A156V (21%)	Q30R + L31M	Q30R + L31M + H58D (70%); Q30R + L31M + H58D + E62D (30%)
No cirr G/P 12 wk	VEL/SOF 284	REL	none	none	Q30H + Y93H	Q30H + L31V + Y93H (60%); Q30N + Y93H (40%)
Cirr, G/P+ RBV 12 wk	LDV/SOF 425	BT	none	A156V	M28T + Q30R + E62D (28%)	M28T + Q30R + H58D + E62D
Cirr, G/P+ RBV 12 wk	LDV/SOF 580	BT	none	R155W + A156G	Q30H + L31M + Y93H	Q30H + L31M + Y93H
Cirr, G/P+ RBV 12 wk	LDV/SOF 684	BT	none	none	L31M	L31M + P32-del

All 8 failures in GT1a. Sequencing data pending in 2 failures.
All RAS are >95% abundance unless specified; "+" = RAS linkage; RED = Treatment Emerging RAS

Cirr, cirrhosis; REL, relapse; Tx, treatment; exp, exposure

Interim analysis of Phase 3b, multi-center, randomized, open-label, pragmatic study

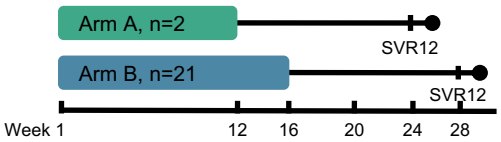
HCV-TARGET

Lok A, et al. EASL 2018. Abstract LBO-008.

Retreatment with GLE/PIB + SOF + RBV in Patients who failed GLE/PIB: MAGELLAN-3

- **12 or 16 weeks of GLE/PIB + SOF + RBV in patients who previously failed GLE/PIB treatment**

Study design:



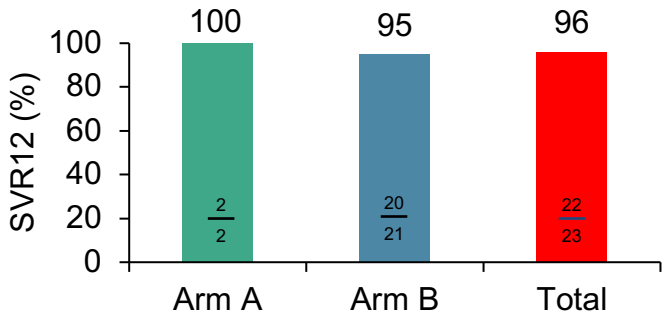
Treatment arm	GT	Cirrhosis status	Prior NS5Ai and/or PI*
A	1, 2, 4, 5, 6	NC	No
B	3	Any	Any
B	Any	C	Any
B	Any	Any	Yes

- **30% cirrhosis**
- **26% failed PI and/or NS5Ai before GLE/PIB treatment failure**
- **65% had ≥2 NS5A RASs at baseline**

Outcomes:

- **One GT 1a cirrhotic patient with prior experience of SOF/LDV relapsed**
- **100% (14/14) SVR12 in GT 3 patients**
- **No D/Cs and no DAA-related SAEs**

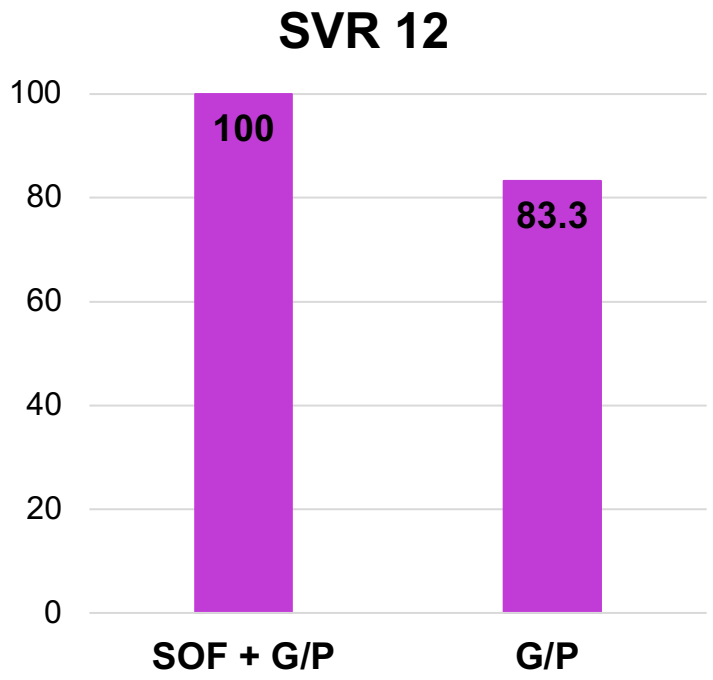
Efficacy of GLE/PIB + SOF + RBV



Wyles D, et al, et al. ILC 2018, #2563 (PS-040)i

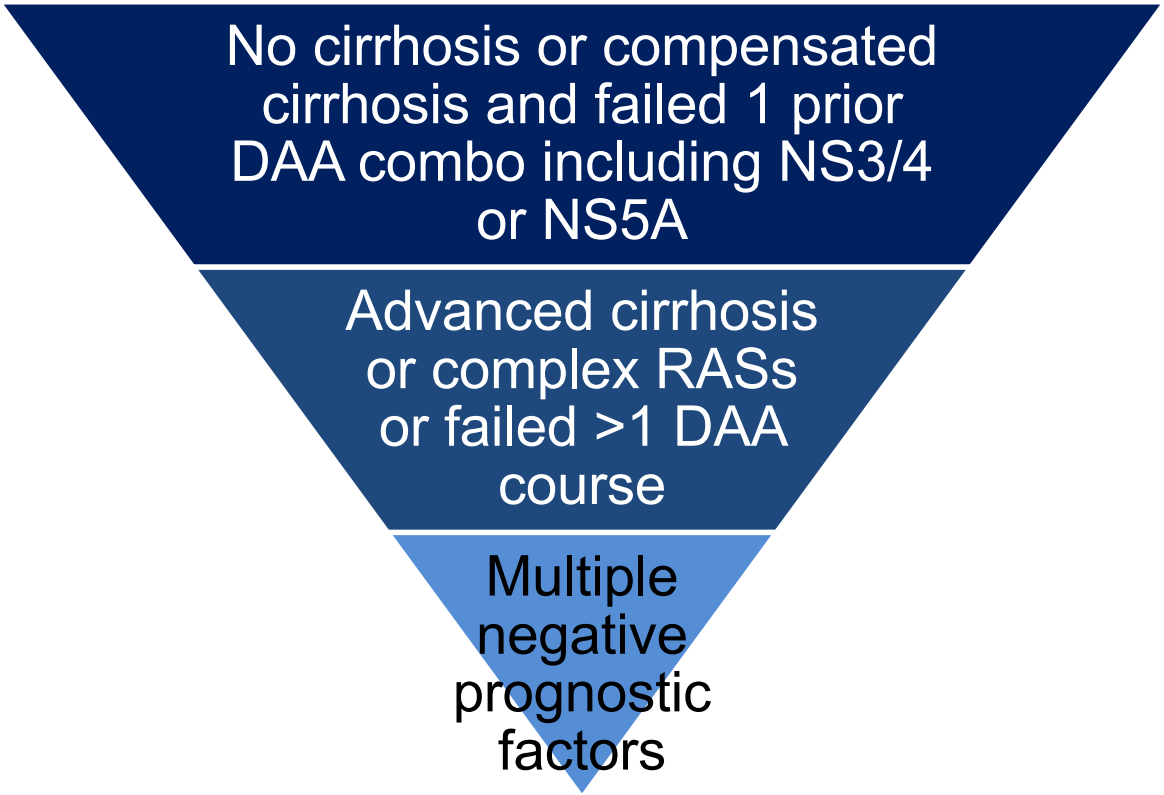
Glecaprevir/Pibrentasvir + SOF therapy for 12 Weeks in Patients with Prior DAA failures

- **Multicenter, compassionate access study from France**
- **Compensated liver disease**
- **N=36, prior DAA therapies**
  - 18 SOF/LDV
  - 18 SOF + DCV ± SMV
  - 2 SOF/Vel
  - 4 PrOD
  - 2 EBR/GZR
  - 1 G/P
- **N=26 → treated with SOF + G/P**
- **N=10 → treated with G/P**



De Ledinghen V, DDW, Abstract 791

Treatment of DAA Failures: Emerging Themes

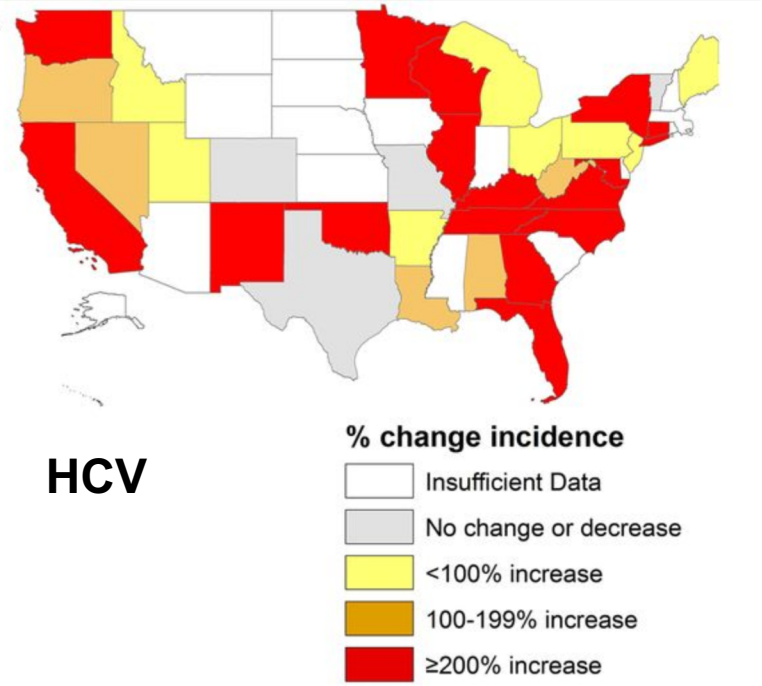


SOF/VEL/VOX for 12 wks
G/P for 16 wks if NS5A exp'd only

SOF + G/P ± RBV for 12 wks

SOF + G/P + RBV for 16-24 wks

Treatment of HCV in Special Populations: PWIDs



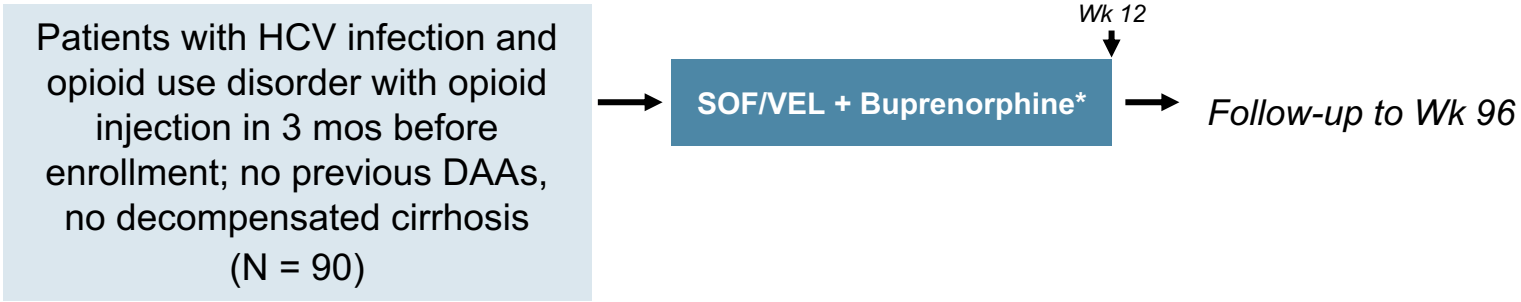
- Incidence infections spurred by the opioid epidemic
- Increases in 20-40 year old's; rural and urban
- Treat-to-prevent is strategy advocated in PWID population

- Novel models of care needed to address treatment in drug-using population

Suryaprasad AG, CID 2014;59:1411-9

ANCHOR Substudy: Colocation of HCV and Buprenorphine Treatment

- **Substudy of single-arm HCV treatment trial in Washington, DC**
  - **Endpoints: adherence to SOF/VEL, SVR12 rate; risk behaviors, HCV reinfection, HIV acquisition**

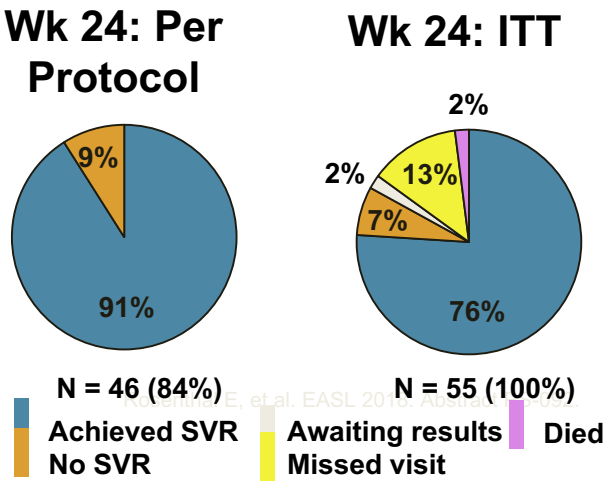


***Buprenorphine started between Wk 0-24 of SOF/VEL treatment initiation with follow-up for 1 yr at same center and with same provider as HCV treatment.**

Rosenthal E, et al. EASL 2018. Abstract PS-092.

ANCHOR Substudy: Efficacy of Colocalized Buprenorphine and HCV Treatment

- **HCV treatment visit adherence high: 77% to 87% over 24 wks**
  - 90% to 95% received study drug



- **39 patients started MAT with 26 (67%) retained**
  - MAT patients significantly more likely to receive second SOF/VEL bottle vs those not receiving MAT
- **HIV risk behavior decreased significantly**
  - From Day 0 to Wks 4, 12, and 24 of MAT

Rosenthal E, et al. EASL 2018. Abstract PS-092.

HCV Among Incarcerated Populations

The Washington Post

Health & Science

State Prisons Fail To Offer Cure To 144,000 Inmates With Deadly Hepatitis C

By Siraphob Thanthong-Knight July 9

HCV prevalence in state correctional departments, 2000-2012

State	Sex	Period of Observation	Median HCV Seroprevalence, %
Indiana	M & F	2003-2011	12.3
New Mexico	M/F	2010-2011	44.0/ 35.4
New York	M & F	2000-2007	12.8
North Dakota	M & F	2008-2011	10.7
Oregon	M & F	2000-2005	26.7
Pennsylvania	M & F	2004-2010	18.3

Varan AK, et al. Public Health Rep. 2014;129:187-195.

SToP-C: HCV Treatment as Prevention Trial in 4 Australian Correctional Centers

- **2 maximum security prisons in Australia**
- **Surveillance phase analysis includes 482 participants at risk of HCV (primary or reinfection) who had ≥ 1 follow-up visit; 388 py of follow-up**
- **Plan: treatment with SOF/VEL for 12 wks**
- **IDU in prisons is primary driver of new HCV infections**

HCV Infection	Incidence/100 PY	95% CI
Overall	7.9	5.6-11.3
Primary infection	6.4	4.0-10.1
Reinfection	12.3	7.2-21.2
In those w/IDU history but not during current imprisonment	11.4	5.4-23.9
In those injecting in current imprisonment*	**21.5**	**14.1-32.6**

Conclusion:
Both harm reduction AND HCV treatment will be needed to reduce HCV infection burden

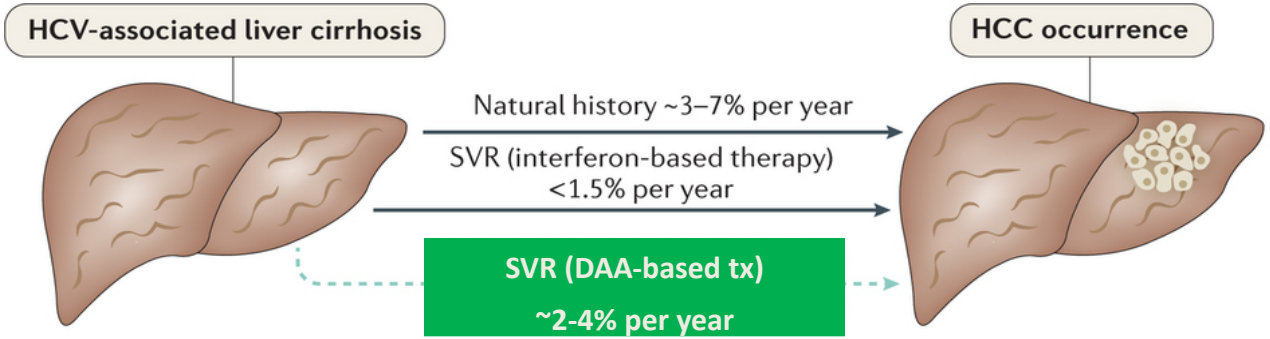
* sharing needle/syringe was the main factor associated with HCV transmission.

Hajarizadeh B, et al. EASL 2018. Abstract THU-134.

Take Home Messages: Special Populations

- Genotype 3 with cirrhosis: need RAS testing or use SOF/VEL/VOX
- DAA-experienced: higher complexity of RASs with each treatment course → triple therapy best option (SOF/VEL/VOX or SOF + G/P)
- For PWIDs and incarcerated populations: harm reduction plus DAAs needed

Risk of De Novo HCC After DAA Therapy



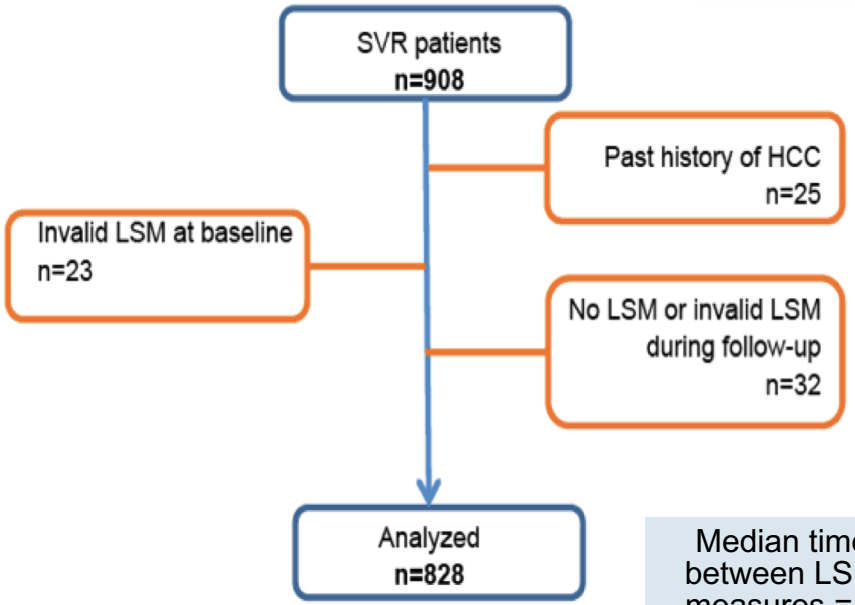
Patients differ in DAA era:

- **Older**
- **More advanced cirrhosis (longer duration of cirrhosis)**
- **Coexistent risks for NAFLD**

Adapted from Llovet JM, et al. *Nat Rev Gastroenterol Hepatol* 2016;13:561-2

Post-treatment liver stiffness measurement is not useful to predict HCC after SVR

- Prospective study from France of HCV patients prior to and after DAA-induced cure
- Endpoints: HCC and decompensation
- At baseline:
  - Median age 61 yrs
  - BMI 25 (IQR:23-28)
  - 15% diabetes, 13% MS
- 40% LSM ≥12.5kPa at baseline



Median time between LSM measures = 6 mos

Shilil, S, EASL, 2018

Baseline but NOT Change in LSM Predict Risk of HCC

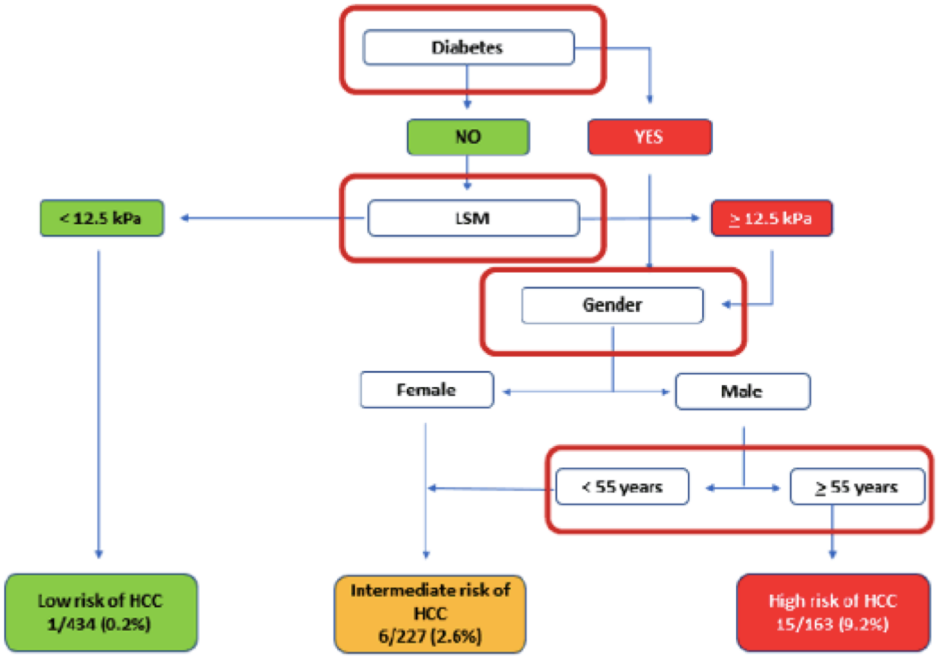
Complications after SVR

Event	Frequency (%)
Death	2 (0.2)
Variceal bleeding	5 (0.6)
Ascites	7 (0.9)
HCC	22 (2.8)

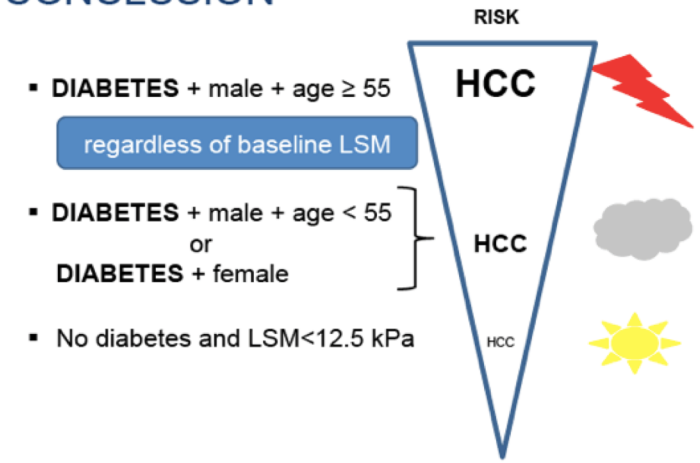
Multivariate predictors of HCC

	Multivariate analysis	
Parameter	HR [95% IC]	P value
Male sex (versus female)	3.04 [1.10-8.41]	0.032
Age (/year)	1.06 [1.02-1.10]	0.005
Age ≥ 55 years versus <55 years	4.35 [1.58-19.26]	0.040
Metabolic syndrome (yes versus no)	1.06 [0.64-1.75]	0.816
Diabetes (yes versus no)	2.70 [1.12-6.51]	0.026
LSM at baseline (/kPa)	1.05 [1.02-1.07]	<0.0001
Qualitative LSM at baseline:		0.005
-LSM [8-12.5] versus LSM < 8 kPa	1.59 [0.14-17.59]	
-LSM ≥ 12.5 versus LSM <8 kPa	10.44 [1.38-78.63]	
Delta LSM (/kPa)	0.99 [0.94-1.04]	0.705

Diabetes is Key Risk Factor of HCC after Cure



CONCLUSION



- **DIABETES** + male + age ≥ 55
  regardless of baseline LSM
- **DIABETES** + male + age < 55
  or
  DIABETES + female
- No diabetes and LSM<12.5 kPa

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

HBV

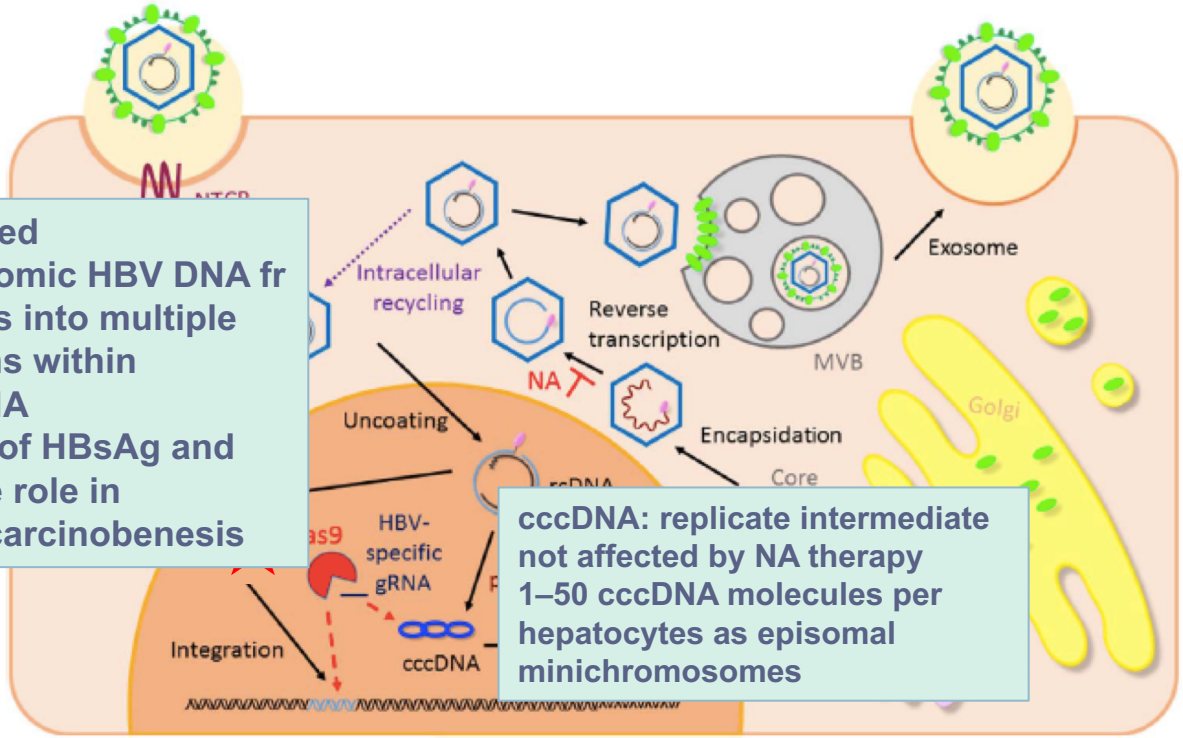
Goals of Therapy in HBV Patients

- **Undetectable HBV DNA levels in serum**
- **Reduced liver inflammation and fibrosis progression**
- **Prevention of cirrhosis, hepatic failure, liver cancer**
- **Improved quality and quantity of life**

Cure is not a term we use in treatment of CHB (in contrast to HCV)

Terrault N, Hepatology 2016;63;261-83
AASLD HBV Treatment Guideline 2016

Why Is Cure Rare With Current Therapies



Integrated subgenomic HBV DNA fragments into multiple locations within host DNA
Source of HBsAg and putative role in hepatocarcinobenesis

cccDNA: replicate intermediate not affected by NA therapy
1–50 cccDNA molecules per hepatocytes as episomal minichromosomes

Yang HC, Chen PJ, Virus Research 2018;244:304-310

Hepatitis B Cure: Emerging Definitions

- **Partial Cure:** HBsAg positive but HBV DNA persistently undetectable off treatment
  - = subgroup of those within active CHB
- **Functional Cure:** HBsAg loss and HBV DNA undetectable ± anti-HBs
- **Complete sterilizing cure:** Absence of cccDNA and integrated HBV DNA
  - No risk for reactivation
  - Elimination of HCC risk

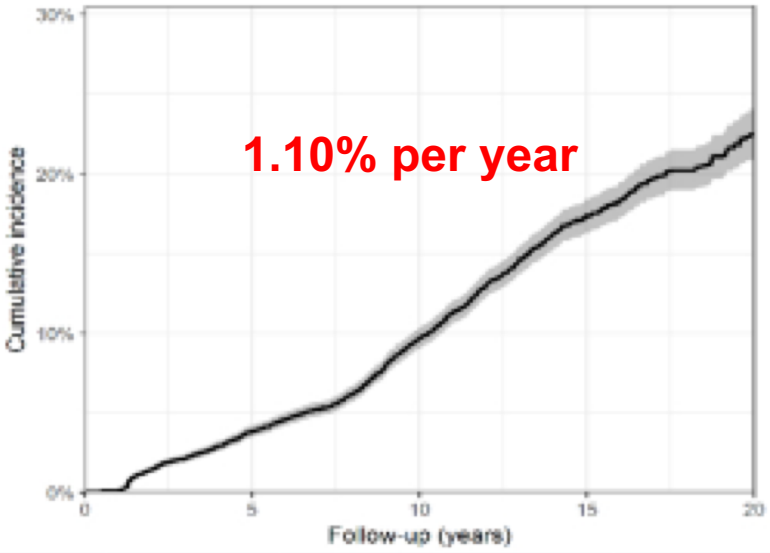
EASL The Home of Hepatology
THE INTERNATIONAL LIVER CONGRESS™ 2018
APRIL 11-15 PARIS FRANCE

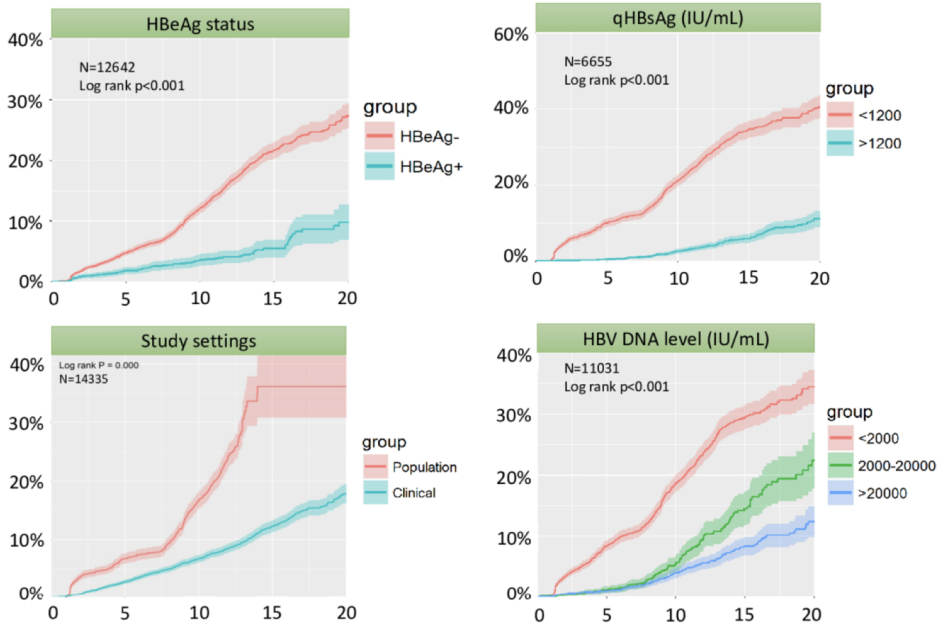
Real-world rates of hepatitis B surface antigen (HBsAg) seroclearance in patients with chronic hepatitis B: a systematic review, conventional aggregated data meta-analysis (ADMA) and individual patient data meta-analysis (IPDMA)

Yeo YH[1], Ho HJ[2], Yang HI[3], Tseng TC[4], Kwak MS[5], Park YM[6], Fung JYY[7], Buti M[8], Rodriguez M[9], Preda CM[10], Ungtrakul T[11], Charatcharoenwitthaya P[12], Li X[13], Le MH[1], Wei B[1], Zou B[1], Le A[1], Jeong D[1], Chien N[14], Kam L[14], Hosaka T[15], Suzuki F[15], Kobayashi M[15], Sriprayoon T[12], Chong Y[13], Tanwandee T[12], Yuen MF[7], Lee HS[5], Kao JH[4], Lok AS[16], Wu CY[2], Nguyen MH[1]. 1. Stanford University, United States. 2. Taichung Veterans General Hospital, Taiwan. 3. Academia Sinica, Taiwan. 4. National Taiwan University Hospital, Taiwan. 5. Seoul National University Hospital, Korea. 6. Bundang Jesaeng General Hospital, Korea. 7. The University of Hong Kong, China. 8. Hospital Universitario Valle Hebron, Spain. 9. Hospital Universitario Central de Asturias, Spain. 10. Clinic Fundeni Institut, Romania. 11. HRH Princess Chulabhorn College of Medical Science, Thailand. 12. Siriraj Hospital, Mahidol University, Thailand. 13. The Third Affiliated Hospital, Sun Yat-sen University, China. 14. Kaohsiung Medical University, Taiwan. 15. Toranomon Hospital, Japan. 16. University of Michigan, United States.

Cumulative Incidence of HBsAg Seroclearance

(treated and untreated patients)





Systematic review: 31 studies pooled

Strategies to Increase Rates of HBsAg

- Use of peg-IFN: Switch or add
- Withdrawal of NA therapy in patients on long-term suppressive therapy
- New drugs!

SWAP Clinical Trial (Switch vs Add on Peg-IFN) and Novel Markers of HBsAg Seroclearance

W.W. Phyo[1], G. Cloherty[6], E.K. Butler[6], M.C. Kuhns[6], A. McNamara[6], V. Holzmayer[6], J. Gersch[6], W.L. Yang[3], J. Ngu[4], J. Chang[4], J. Tan[5], T. Ahmed[6], Y.Y. Dan[1,2], Y.M Lee[1,2], G.H. Lee[1,2], P.S. Tan[2], C.Y. Tan[2], C. Lee[1], A. Tay[1], E. Chan[7], S.G. Lim[1,2]
[1]National University of Singapore, [2]National University Health System, [3]Tan Tock Seng Hospital, [4]Singapore General Hospital, [5]Changi General Hospital, [6]Khoo Teck Puat Hospital, [7]Singapore Clinical Research Institute, [8]Abbott Diagnostics

N=111 HBeAg ±, on NA therapy for >12 mos randomized to:

1) Continued NA
2) Add peg-IFN X 48 wks
3) Switch to peg-IFN X 48 wks

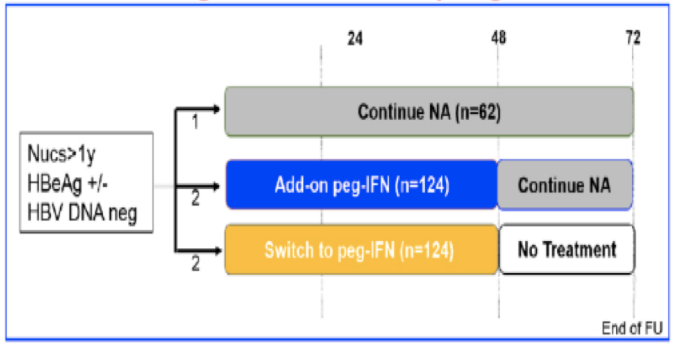


Table 1. Baseline characteristics

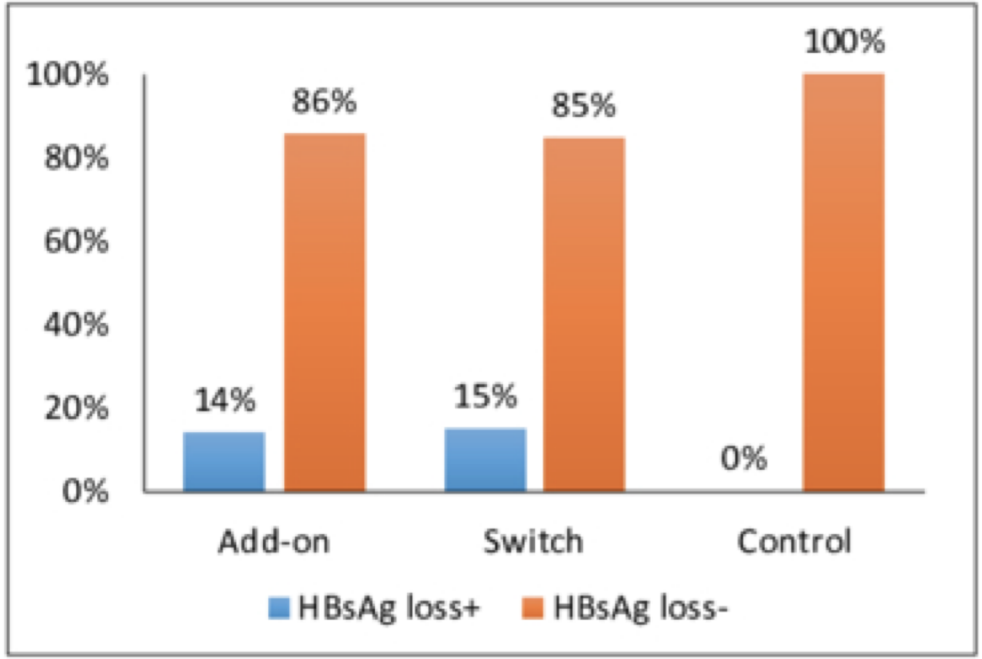
	Add-on (n=42)	Switch (n=46)	Control (n=23)	Total (n=111)
Age	50±1	49±2	50±3	49±1
Male	38 (90.5)	39 (84.8)	18 (78.3)	95 (85.6)
e-Ag positive	11 (26.2)	17 (37.0)	7 (30.4)	35 (31.5)
Cirrhosis	2 (4.8)	3 (6.5)	0	5 (4.5)
Number of years of NA	5.2±0.4	4.7±0.4	5.4±0.3	5.0±0.3
Baseline qHBs (IU/ml) (n=110)	1667 (959-2374)	3038 (1566-4509)	2138 (652-3623)	2325 (1609-3042)
Baseline crAg (log U/ml) (n=86*)	3.7 (3.4-3.9)	3.8 (3.5-4.2)	4.0 (3.6-4.3)	3.8 (3.6-4.0)
Baseline RNA				
Positive	22 (52.4)	24 (52.2)	8 (34.8)	54 (48.6)
LLOQ	13 (31.0)	13 (28.3)	13 (56.5)	39 (35.1)
Negative	7 (16.7)	9 (19.6)	2 (8.7)	18 (16.2)

*Patients with negative HBeAg
Categorical variables in percent. Continuous variables in range. Continuous variable in mean±S.E

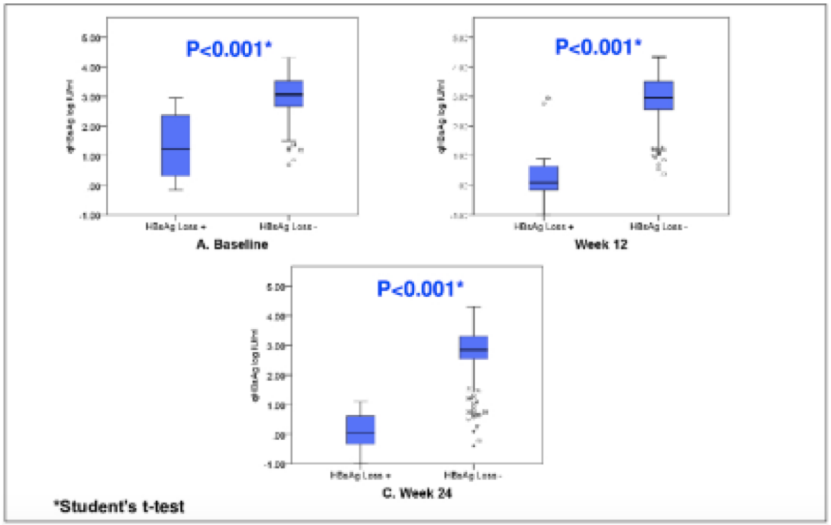
Study endpoint: HBsAg loss at 72 wks

SWAP Study Outcomes and Predictors

~15% of peg-IFN treated patients lost HBsAg



qHBsAg at baseline and WK12 predicts HBsAg loss

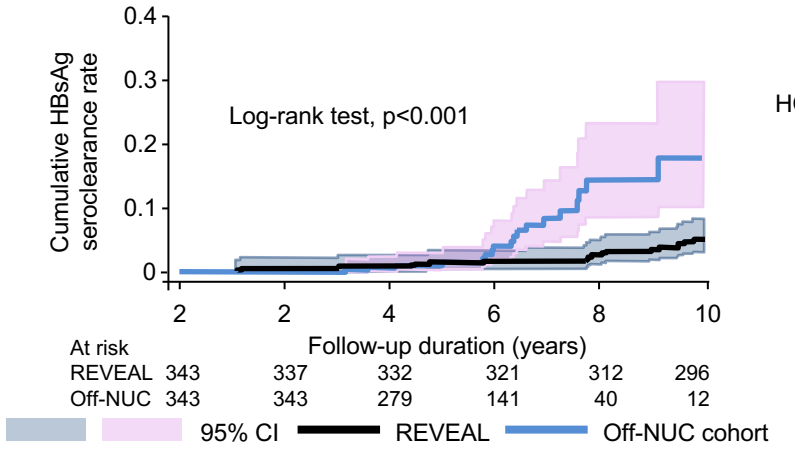


12/13 who lost HBsAg were HBeAg negative at baseline

Increased HBsAg seroclearance in HBeAg-negative CHB patients who discontinued NUC therapy vs. natural course

- HBsAg seroclearance is rare during NUC therapy but may increase after NUC cessation in HBeAg– CHB patients
- **Aim:** propensity score matched (PSM) study to examine whether the increase in HBsAg loss is real
- **Methods:**
  - Long-term course of 764 HBeAg– CHB patients with finite NUC therapy (Off-NUC cohort) was compared with untreated controls from REVEAL-HBV cohort (2916 HBeAg–subjects)
  - PSM on age, gender, serum HBV DNA and quantitative HBsAg levels at 1:1 ratio was applied
  - 343 patients in each cohort

Cumulative incidence of HBsAg seroclearance after PSM



- **Higher HBsAg seroclearance in Off-NUC cohort (p=0.0002)**
- **Off-NUC cohort had decreased overall mortality and no increase in**

Conclusions: the increase of HBsAg seroclearance in HBeAg– patients with finite NUC therapy reflects the real effect of finite NUC therapy, in which the risk of adverse outcome(s) is not increased

Jeng WJ, et al. ILC 2018, #PS-158

DARING-B: HBsAg Loss After Long-term ETV or TDF in HBeAg-Negative CHB Without Cirrhosis

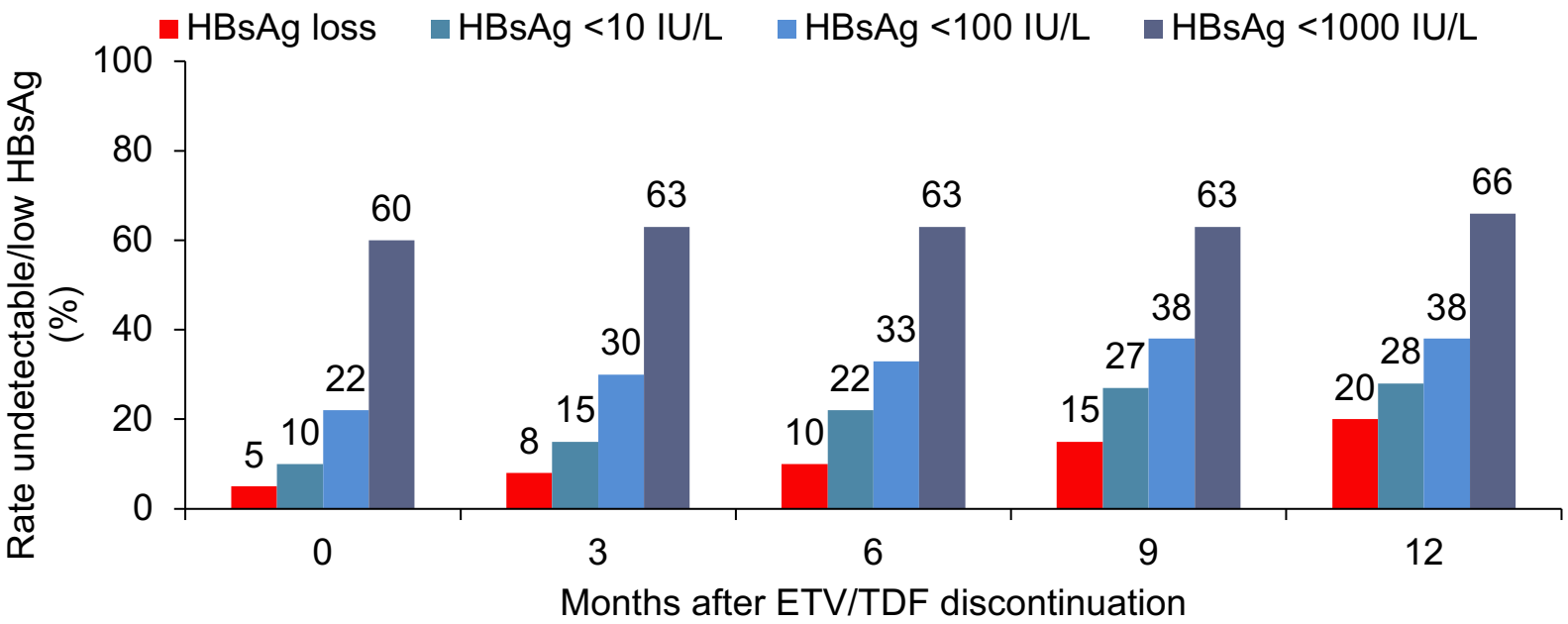
- Prospective study of 60 noncirrhotic patients who received ETV or TDF for ≥ 4 yrs with undetectable HBV DNA for ≥ 3 yrs
- No cirrhosis: all had Ishak stage ≤4 or elastrography <10 kPa
- Mean duration of on-therapy (ETV:18, TDF:42) virological remission was 5.6 ± 2.3 years.
- Mean follow-up: 19 mos

- Cumulative viral relapse (HBV DNA > 2000 IU/mL) rates 62%, 68%, and 70% at 6, 12, and 18 mos
- No deaths, jaundice or decompensation
- Cumulative HBsAg loss rates 5%, 10%, and 20% at 0, 6, and 12 mos after NA discontinuation

Papatheodoridi M, et al. EASL 2018. Abstract PS-159 ad EASL 2017 PS-043

Discontinuation of effective ETV/TDF therapy in patients with HBeAg-negative CHB

Cumulative rates of undetectable or low levels of HBsAg



Papatheodoridis M, et al. ILC 2018, #PS-159

DARING-B: HBsAg Loss After Long-term ETV or TDF in HBeAg-Negative HBV Without Cirrhosis

Independent predictors of HBsAg loss

(at or post NA discontinuation)

Factor	aHR (95% CI)	P Value
Serum HBsAg (per 100 IU/L)	0.738 (0.590-0.923)	.008
ALT 1 mo post (per 10 IU/L)	1.134 (1.026-1.253)	.0013
IP10 1 mo post (per 10 pgIU/L)	1.103 (1.022-1.191)	.0012

IP10:interferon-induced protein 10

Papatheodoridi M, et al. EASL 2018. Abstract PS-159.

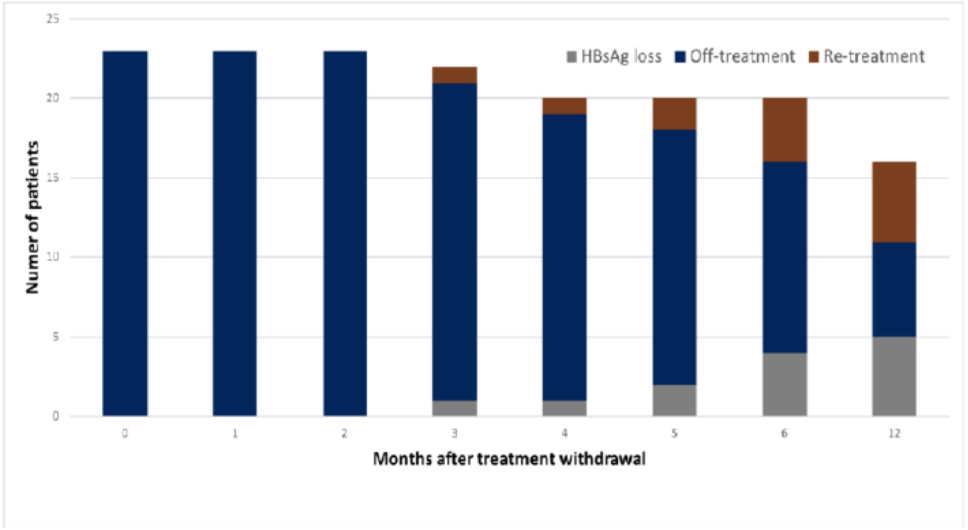
Clinical and virological predictors of response after antiviral therapy interruption in HBeAg-negative chronic hepatitis B

Sabela Lens[1], Mireia García-López[1], Zoe Mariño[1], Martín Bonacci[1], Sergio Rodríguez-Tajes[1], Elena Perpiñán[1], Barbara Testoni[3], Francisco Rodríguez-Frias[2], Giorgios Koutsoudakis[1], María Buti[2], Fabien Zoulim[3], Sofía Pérez del Pulgar[1], Xavier Forns[1]

1 Liver Unit Hospital Clínic Barcelona. IDIBAPS. CIBERehd. University of Barcelona. Spain

2 Internal Medicine, Hepatology Section, Hospital Vall Hebron, Barcelona. CIBERehd. Spain

3 INSERM, U1052, Cancer Research Center of Lyon (CRCL), University of Lyon, France



Variable	HBsAg Loss	No HBsAg Loss	P Value
qHBsAg	52 (0.05-914)	2122 (556-3786)	<0.01
Intra-hepatic HBV DNA	0.03 (.01-0.26)	0.91 (0.35-1.27)	<0.01
HBcrAg	0 (0-3.5)	2.8 (2.6-3.1)	0.09

Age, duration NA therapy and ALT not predictive

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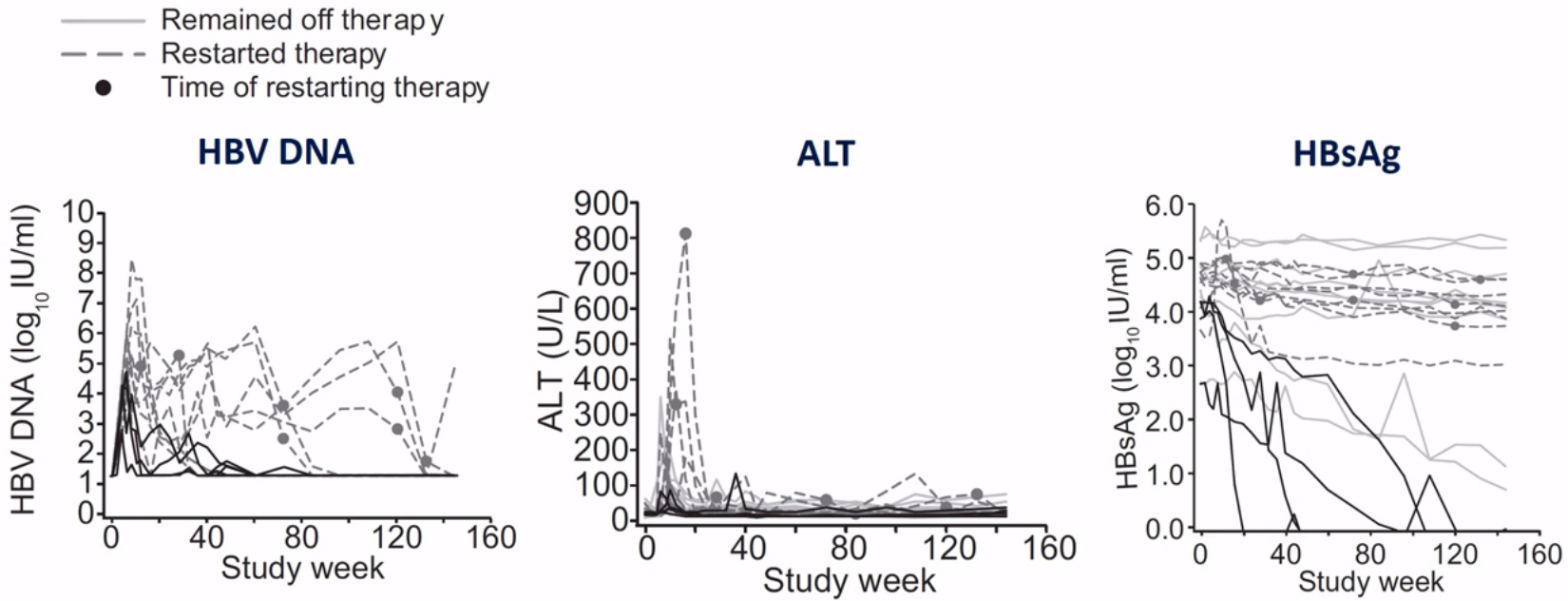
Take-Home Message
HBeAg-Negative CHB Treated with NA Therapy

1. **Switch or add-on peg-IFN can increase HBsAg loss → may be acceptable strategy for some patients**
2. **NA withdrawal strategies – appear promising**
   - Achieves functional cure in up to 20% (with 3 years follow-up)
   - Achieves partial cure (inactive CHB) in additional proportion (at maximum 30%)
   - Predictors: duration of NA therapy; qHBsAg may be helpful but more studies needed

Dynamics of HBV DNA , ALT and HBsAg Levels After NA Discontinuation



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Berg T, J Hepatol 2017

AASLD Guidance on Discontinuing NA Therapy in HBeAg-Negative CHB

- "***A decision to discontinue therapy for HBeAg-negative adults without cirrhosis requires careful consideration of risks and benefits for health outcomes.***
  - **Risks:** virologic relapse, hepatic decompensation and death
  - **Benefits:** burden of continued therapy, HBsAg loss
- **Close monitoring after discontinuation essential to monitor for relapse/flares**
  - **Requires adherent patient and dedicated provider**

AASLD. HBV guidance. 2018.

Preferred Oral Therapies for CHB

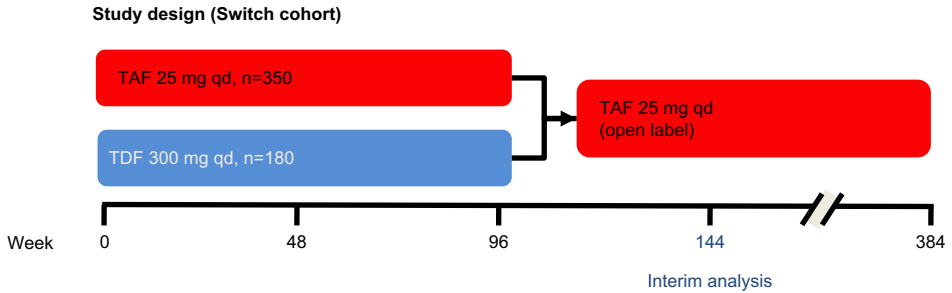
Nucleos(t)ide Analogue	Antiviral Potency	Side Effects	Risk of Resistance	Dose Adjustment CrCl (mL/min)	Subgroups of Importance
Entecavir 0.5 mg daily	+++	Lactic acidosis No renal or bone toxicity	Very Low if no prior LMV exposure	<50	Not recommended in pregnant women
Tenofovir disoproxil fumarate 300 mg daily	+++	Lactic acidosis Some risk renal and bone toxicity	Very Low	<50 (no dosing info at < 10 ml/min without dialysis)	Approved for HIV Safe in pregnant women
Tenofovir alafenamide 25 mg daily	+++	Lactic acidosis Minimal risk renal and bone toxicity	Very Low	<15 (not recommended at <15 ml/min)	Approved for HIV Not studied in pregnant women or patients with decompensated cirrhosis

Entecavir [package insert]. 2017. Tenofovir disoproxil fumarate [package insert]. 2017. Tenofovir alafenamide [package insert]. 2017.

Switch From TDF to TAF in Patients With Chronic HBV Infection and TDF Risk Factors

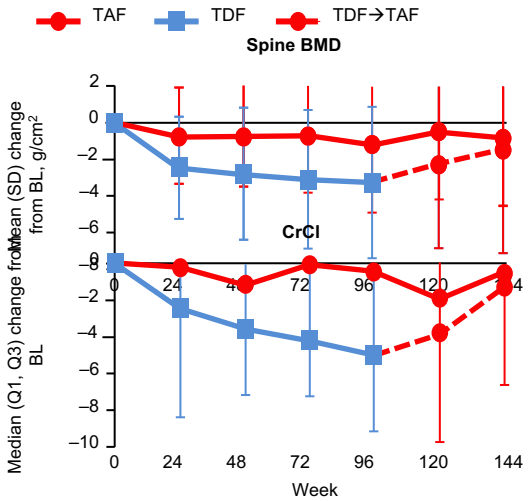
- **Objective: to assess 1 year renal and bone safety, antiviral efficacy (HBV DNA <29 IU/ml) and ALT normalization in a subset of patients with CHB and baseline risk factors for TDF* switching to open-label TAF at Week 96**

***TDF risk factors:** age >60 years, osteoporosis of hip/spine, ≥stage 2 CKD, albuminuria (UACR >30 mg/g), hypophosphataemia (PO_4 <2.5 mg/dl), or comorbidities associated with CKD (e.g. HTN, DM, obesity)



- **1298 patients randomized and treated, 540 switched to OL TAF at Week 96; 284 (53%) had ≥1 TDF risk factor**
- **HBV DNA suppression 1 year following switch were similar for both groups**
- **Switch patients had increased rate of ALT normalization and improved bone and renal safety parameters**

Bone/renal parameters in patients ≥TDF risk factor



Gane E, et al. EASL 2018. Abstract PS-156.

How to Choose Among Nucleos(t)ide Analogues for CHB Treatment

If no comorbidities (for most pts) → **Monotherapy with ETV, TDF, or TAF**

If risk of or preexisting bone or renal disease, prioritize ETV or TAF

- Age > 60 yrs
- Bone disease
  - Chronic steroids or other meds that affect bone
  - History of fragility fracture
  - Osteoporosis
- Renal abnormalities
  - eGFR < 60 min/mL/1.73 m^2
  - Albuminuria > 30 mg or moderate proteinuria
  - Low phosphate (< 2.5 mg/dL)
  - Hemodialysis

When to prioritize TAF over ETV

- Previous nucleoside exposure[2]
  - Lamivudine with or without adefovir resistance
- HIV/HBV coinfection
- No dose adjustment for CrCl ≥ 15 mL/min

When to prioritize ETV over TAF

- If less expensive (generic available)
- No prior nucleoside exposure and HIV uninfected
- CrCl < 15 mL/min (with dose adjustment)

Adapted from: Terrault N, Hepatology 2018
EASL. J Hepatol. 2017;67:370-398.

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM