Hepatitis Debrief
The Liver Meeting 2019

Marc Ghany, MD, MHSc, FAASLD
Liver Diseases Branch, NIDDK, NIH
Bethesda, Maryland

Overview

HBV

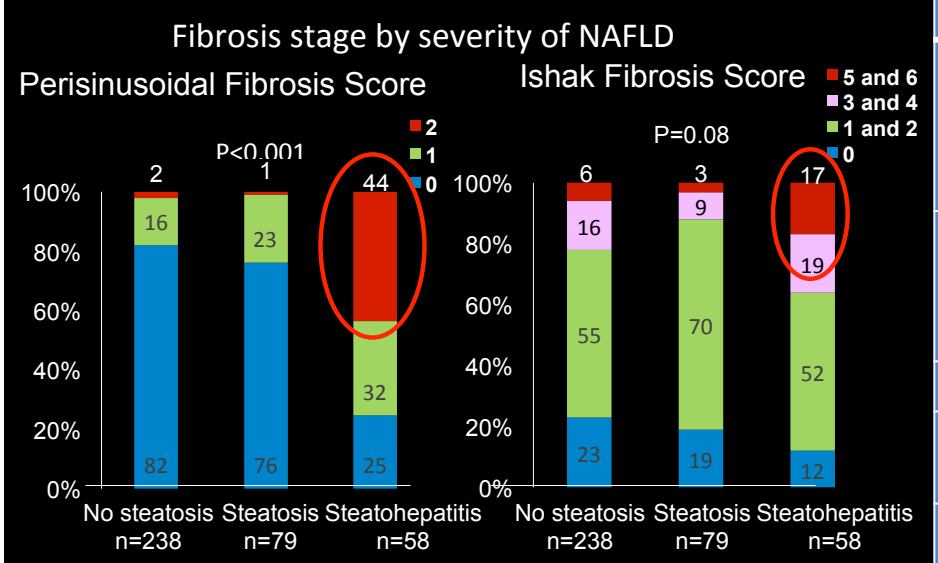
- Natural history
- Novel therapies to achieve functional cure
- Prevention
  - Vaccination
  - Screening
- Co-infection with HDV

HCV

- Models of elimination
  - Treatment
  - Vaccination
- Therapy
  - Unique populations
  - Challenging populations
- Benefits of SVR
- Organ transplantation

Steatohepatitis Worsens HBV Liver Injury

Liver biopsies from 420 adults enrolled in North American cohort study scored for inflammation, fibrosis and NAFLD



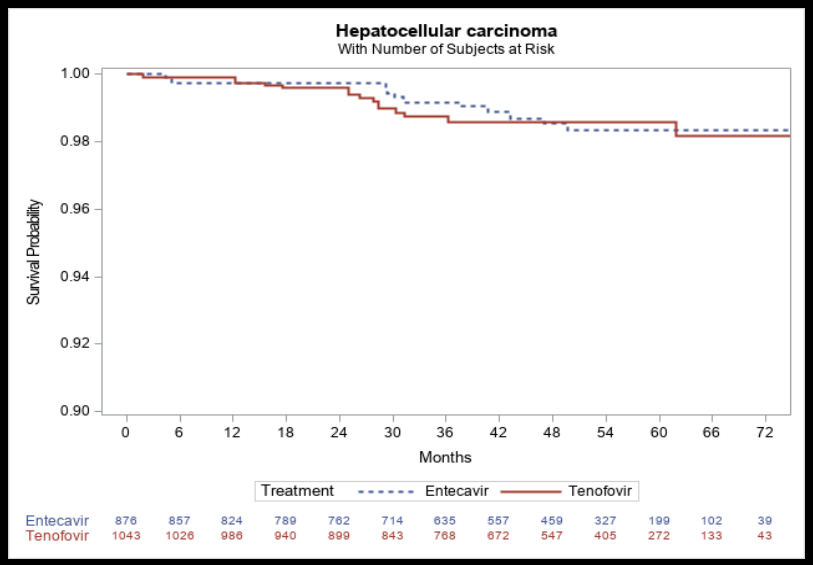
Variables	N	Advanced Fibrosis (score≥3) Unadjusted Risk Ratio (95%CI) N=366	P	Adjusted Risk Ratio (95%CI) N=342	P
No steatosis	249		0.003		0.002
Steatosis	71	0.6 (0.3, 1.1)		0.5 (0.3, 0.9)	
Steatohepatitis	55	1.7 (1.1, 2.5)		1.6 (1.1, 2.4)	
Age, per 10 years	375	1.1 (1.0, 1.3)	0.1	1.2 (1.1, 1.4)	0.003
Sex (versus Female)	141		0.02		0.08
Male	234	1.7 (1.1, 2.6)		1.4 (1.0, 2.1)	
HBV DNA, per log10 IU/mL	375	1.1 (1.0, 1.2)	0.02	1.2 (1.1, 1.3)	0.004
ALT, per log2 U/L	342	1.3 (1.2, 1.5)	<0.001	1.3 (1.1, 1.5)	<0.001

Implications for clinical practice: Important to screen and manage metabolic abnormalities to prevent liver disease progression

Khalili et al Abstract 0162

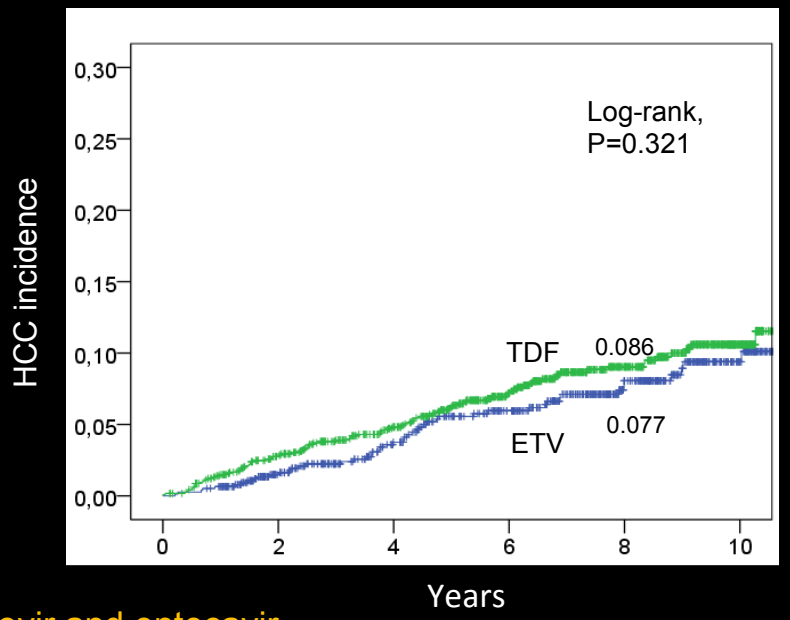
Is There a Difference in HCC Risk between Tenofovir and Entecavir?

ANRS CO22 Cohort:1960 (all races) HBeAg+/- patients who received tenofovir (1075) or entecavir (885) followed-up for a mean of in 45 months



Pol et al Abstract 0197

PAGE-B Cohort: 1935 Caucasian adults HBeAg +/-with or without compensated cirrhosis on ETV (n=772) or TDF (n=1163)

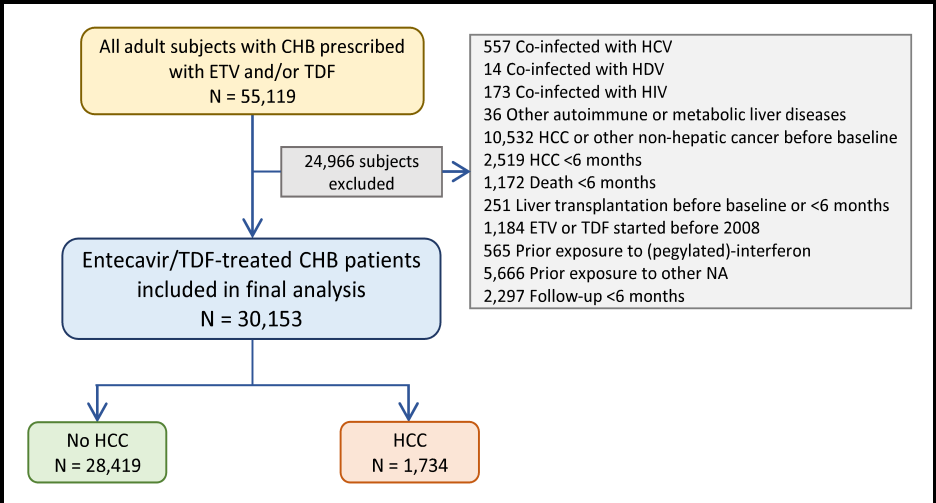


Papatheodoredis et al Abstract 0454

No difference in HCC risk between tenofovir and entecavir

Association Between Anti-Platelet Therapy and HCC Risk

Retrospective cohort study in patients receiving entecavir or tenofovir for ≥6 months



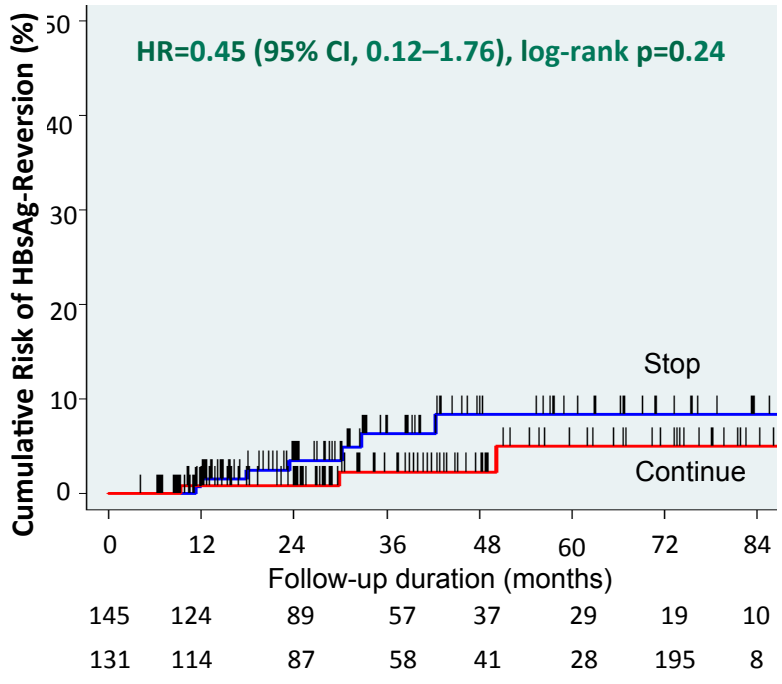
Parameters	Multivariable analysis^		
	Adjusted HR	95% CI	*P* value
Antiplatelet#	0.83	0.72 – 0.95	0.007
Aspirin monotherapy#		Referent	
Non-user#	1.12	0.96 – 1.30	0.152
DAPT#	0.72	0.54 – 0.97	0.029

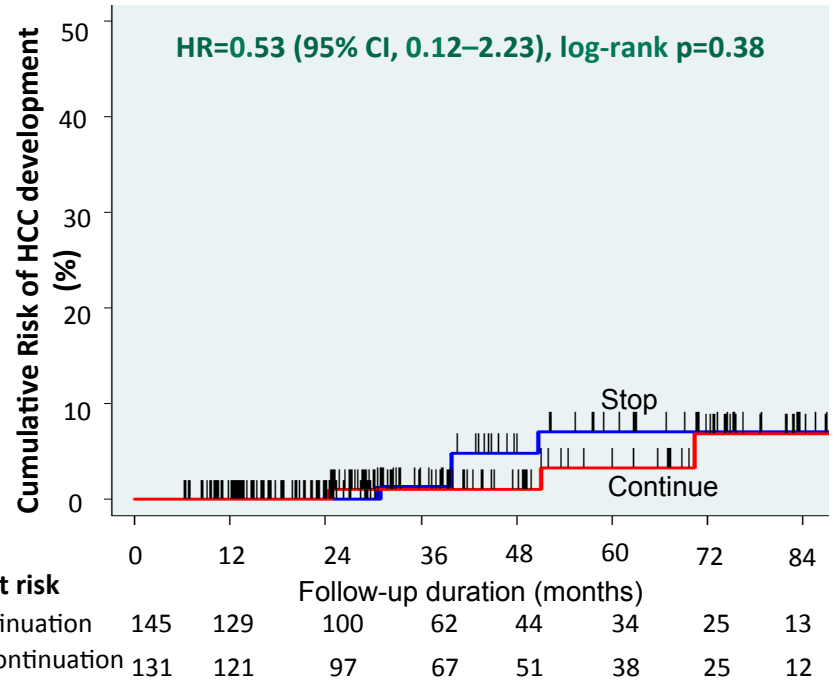
Implications for clinical practice: Provocative findings, need further confirmation

Yip et al Abstract 0934

NA-Induced HBsAg Loss is Durable

Retrospective analysis of patients who stopped or continued NA after HBsAg loss
Evaluated incidence of HBsAg sero-reversion and HCC

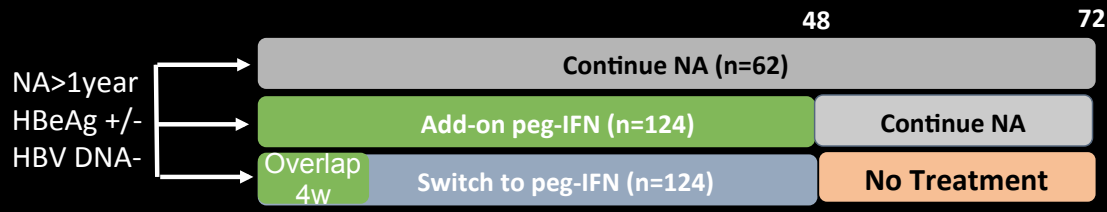




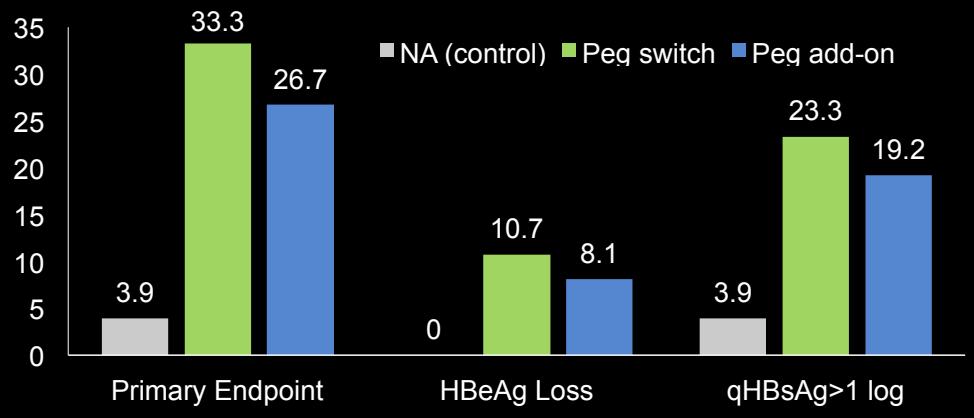
Implications for clinical practice: HBsAg loss is a durable and safe endpoint for stopping therapy

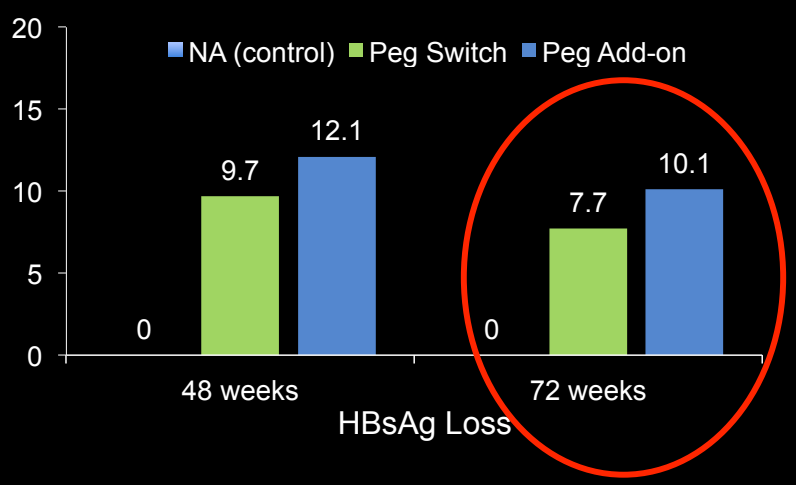
Kim et al Abstract 0198

Switch or Add-on Peginterferon to NA Therapy



Primary endpoint
- HBeAg loss at week 72
- Reduction in qHBsAg>1log





Implications for clinical practice: Little benefit to add-on or sequential approach to induce HBsAg loss

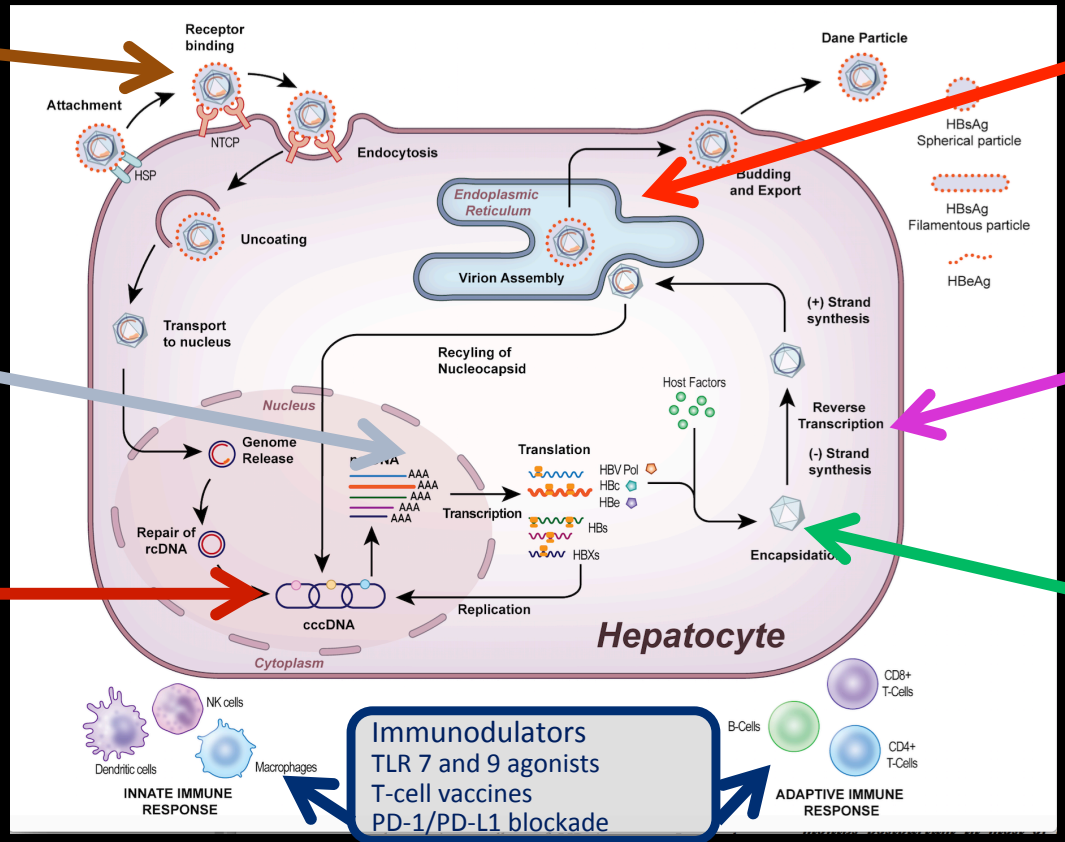
Lim et al Abstract 0193
Farag et al Abstract 0195

HBV Lifecycle and Many Drug Targets

Entry Inhibitors
- Myrcludex
- Cyclosporine
- Ezetimibe

Inhibit viral transcripts by:
- siRNA
- Antisense oligonucleotides
- Ribozymes

cccDNA silencing



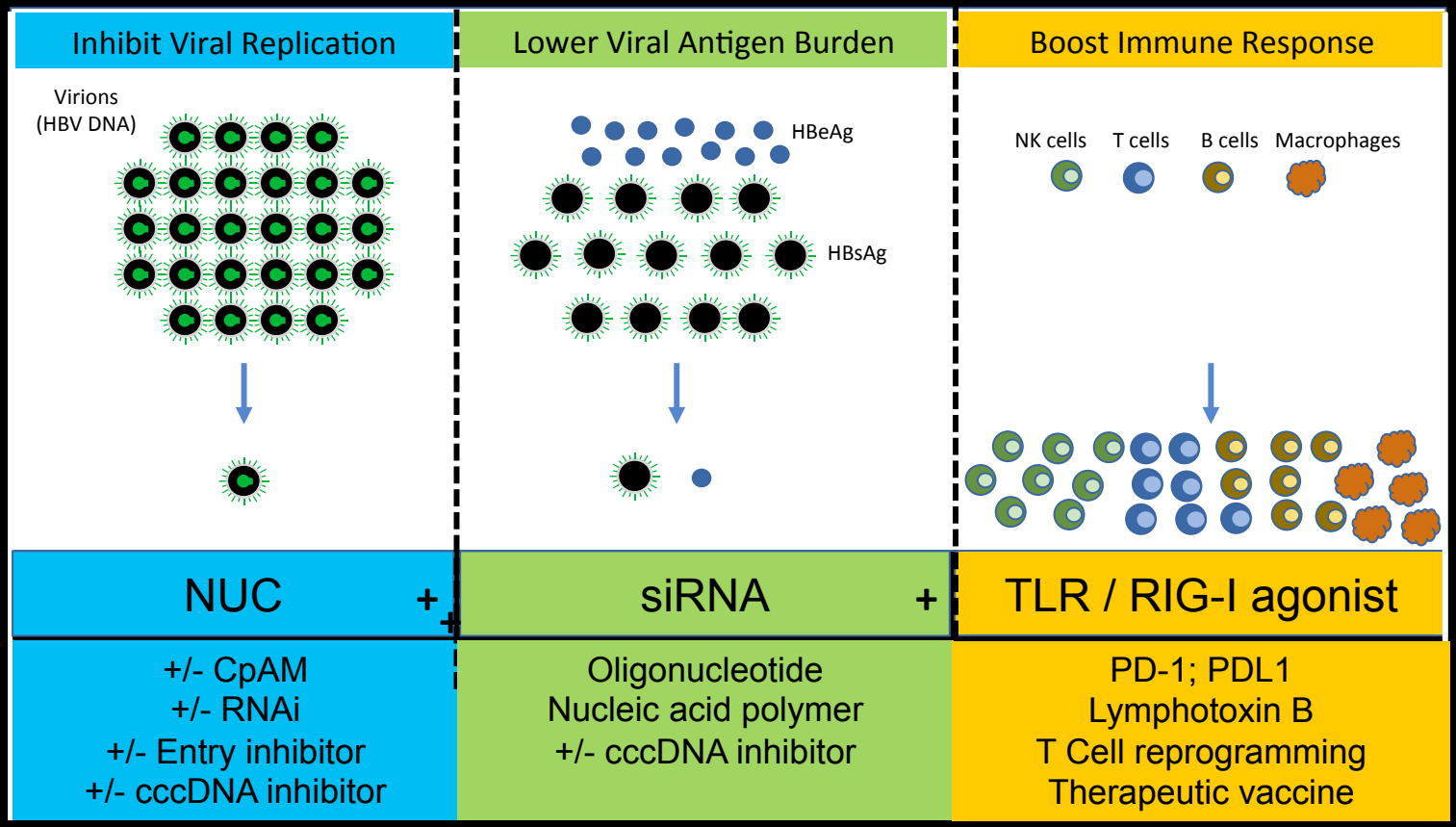
Immunodulators
TLR 7 and 9 agonists
T-cell vaccines
PD-1/PD-L1 blockade

HBsAg release Inhibitor
- NAP

RT Pol Inhibitors
- Nucleotide analogues
- Non-Nuc analogues
- RNAseH inhibitors

Core inhibitors
- Heteroaryldihydropyrimidines
- Phenylpropenamides
- Sulfamoyl benzamides
- Aminothiazole

Pathways to Achieving Functional Cure



Core Assembly Modulator (CAM) JNJ-0440

Two cohorts of 10 treatment-naïve HBeAg +/- patients randomized to JNJ-0440 or placebo x 28 days

Efficacy

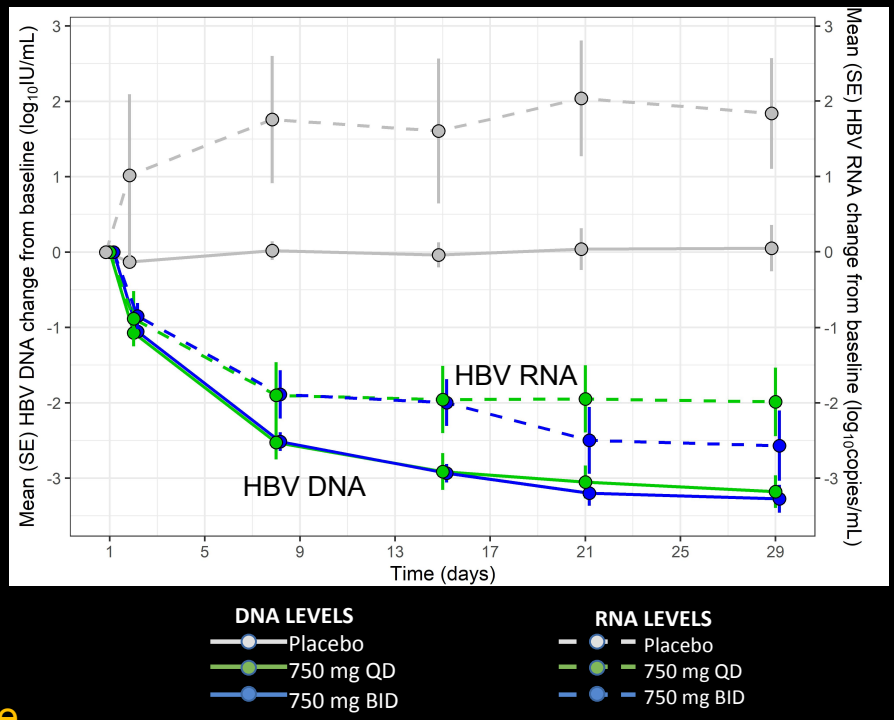
	750 mg QD	750 mg BID
Mean change in HBV DNA vs. BL $\log_{10}$ IU/mL	-3.2	-3.3
Mean change in HBV RNA vs. BL $\log_{10}$ copies/mL	-2.0	-2.6

- Mean change in HBeAg vs. BL $\log_{10}$ IU/mL -0.2
- No relevant changes in HBsAg levels

Safety

No treatment discontinuations/serious AEs

Potent inhibition of viral replication ?functional cure



Gane et al Abstract 0089

GSK3389404 (antisense oligonucleotide) in NUC Suppressed Patients

Phase 2a, multicenter, randomized, double-blind, placebo-controlled study in HBeAg+/-, n=66

Mean change from baseline in HBsAg (log_{10} IU/mL) over time by treatment group

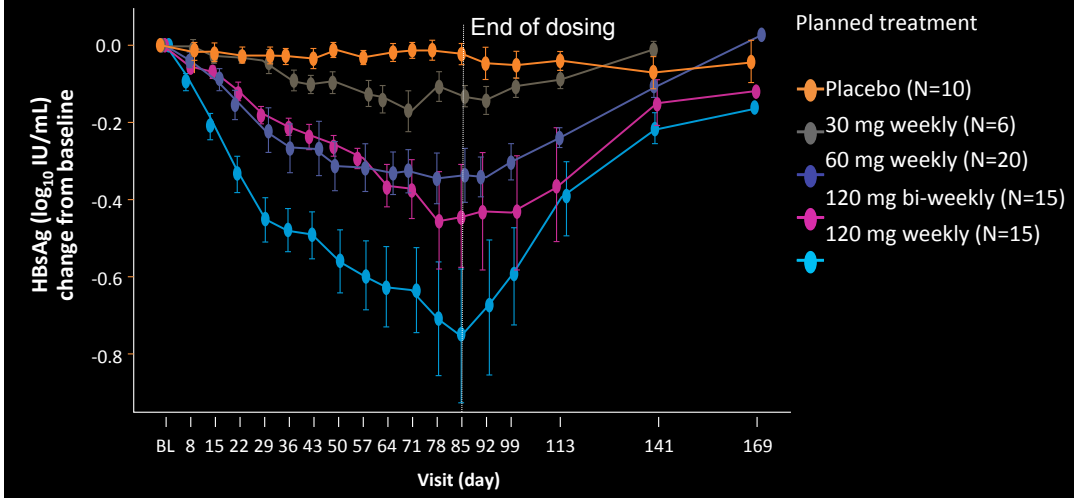


Table 1. Summary of AEs

		GSK3389404				
	Placebo (N=10)	30 mg weekly (N=6)	60 mg weekly (N=20)	120 mg weekly (N=15)	120 mg bi-weekly (N=15)	Total GSK3389404 (N=56)
Any AEs, n (%)	8 (80)	3 (50)	15 (75)	11 (73)	8 (53)	37 (66)
Mild (Grade 1)	2 (20)	2 (33)	7 (35)	4 (27)	4 (27)	17 (30)
Moderate (Grade 2)	4 (40)	0	8 (40)	6 (40)	2 (13)	16 (29)
Severe (Grade 3)	0	1 (17)	0	1 (7)	2 (13)	4 (7)
Potentially life-threatening (Grade 4)	2 (20)[a]	0	0	0	0	0
Treatment-related AEs, n (%)	4 (40)	3 (50)	10 (50)	8 (53)	7(47)	28 (50)
Serious AEs, n (%)	0	0	0	0	1 (7)	1 (2)
AEs leading to study withdrawal or treatment discontinuation, n (%)	0	0	0	0	1 (7)[b]	1 (2)

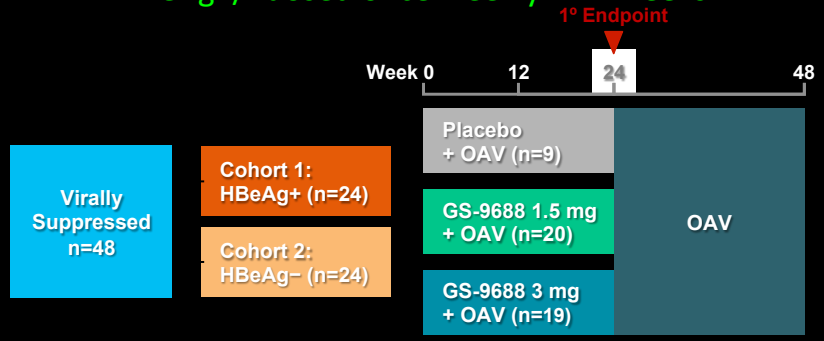
[a]Both Grade 4 lab abnormality of creatine kinase increase attributed to physical activity. [b]Grade 1 pruritus on the neck.
AEs, adverse events.

Proof of principle that antisense oligonucleotides can decrease HBsAg levels

Yuen et al Abstract 0695

Toll-Like Receptor 8 Agonist (TLR8) GS-9688 in NA Suppressed Patients

HBeAg+/- dosed once weekly x 24 weeks

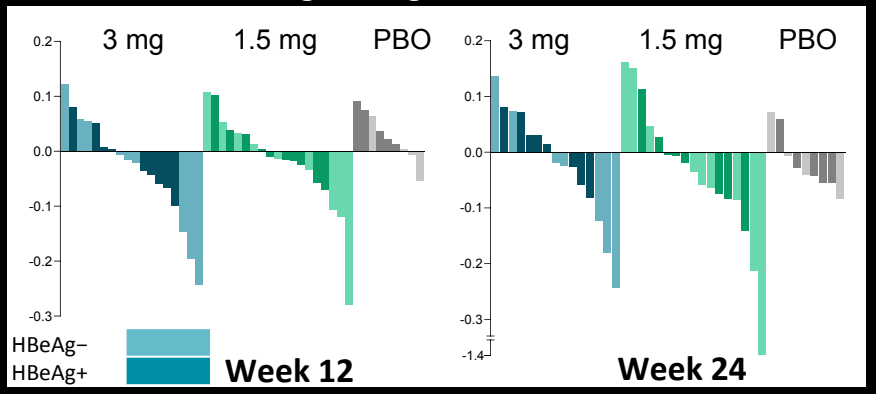


- HBsAg loss in 2 HBeAg- patients (one from each treatment arm at Weeks 24, 48)
- HBeAg loss in 1 patient (Week 24)
- Dose-dependent increases in serum cytokines observed in GS-9688 treatment groups

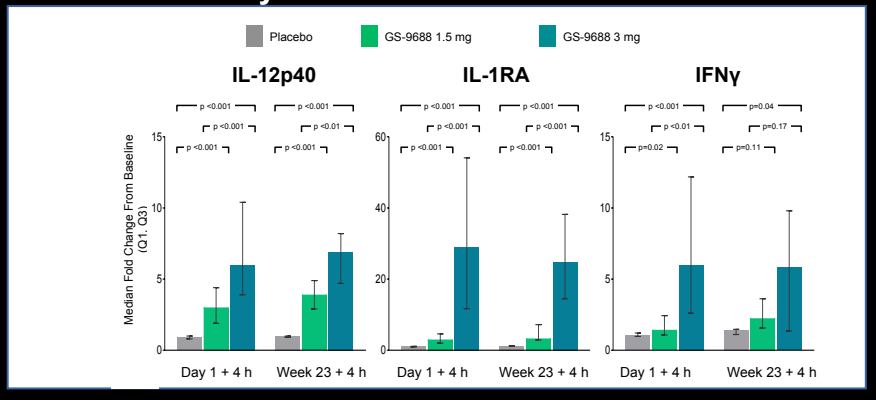
Promising approach, await further studies

Gane et al Abstract 0697

HBsAg Change from Baseline



Cytokine Induction With GS-9688



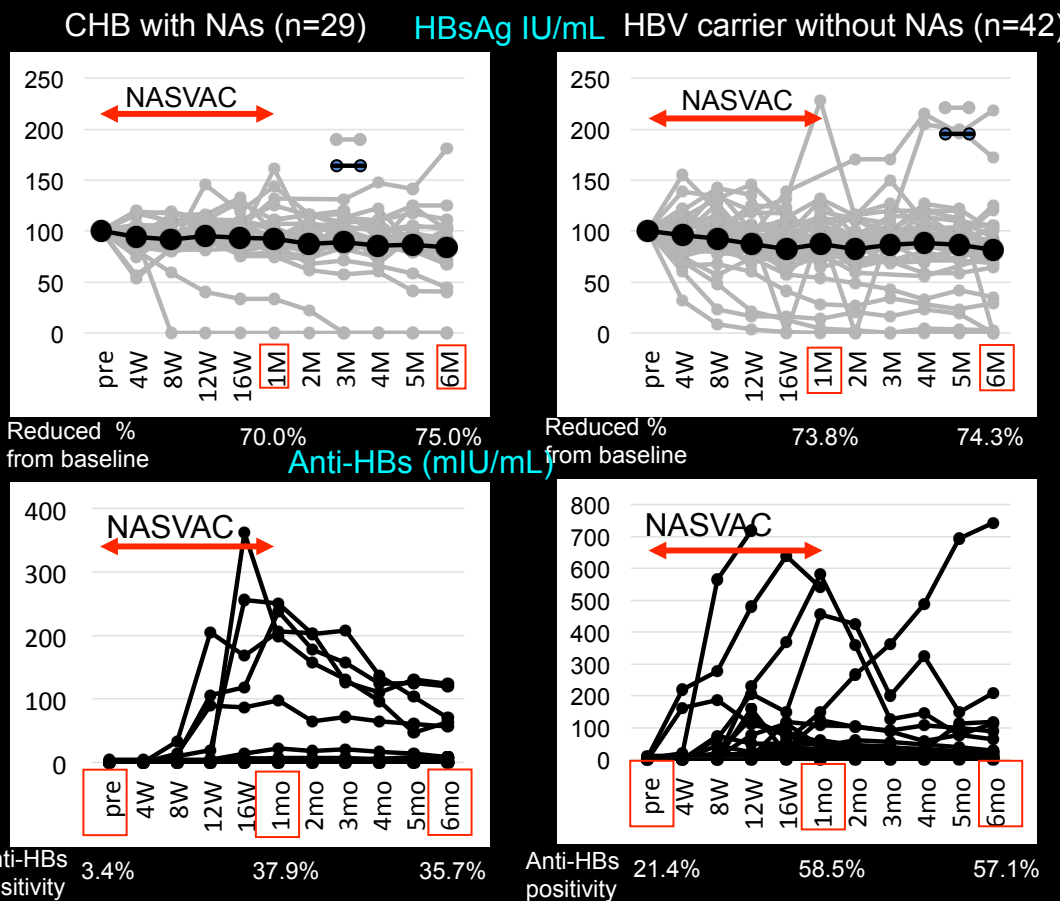
Therapeutic HBV Vaccine

- NASVAC: contains HBsAg and HBcAg
- Administered intranasally 10 times, bi-weekly to NA-suppressed patients and inactive carriers

Efficacy
- ~3/4 had 20% decline in HBsAg
- ~1/3 developed anti-HBs
- 2 patients in each group lost HBsAg

Promising immune therapy for achieving functional cure

Yoshida et al Abstract 0088



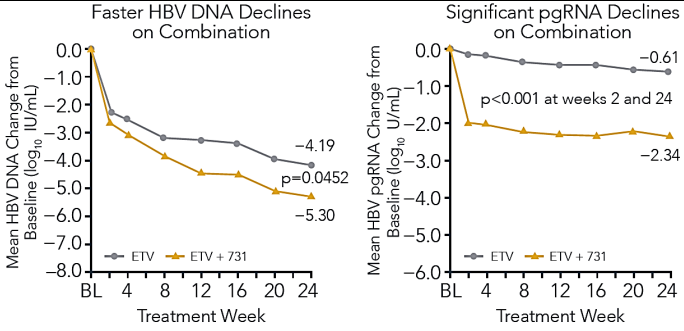
Dual Therapy CAM (ABI-H0731) plus NA

Study 202
HBeAg+
Rx-naive

- ETV + Pbo (n=12)
- ETV + 731 300 mg (n=13)

0 — Double blind — 24

Study 202



- Superior reductions in DNA/pgRNA

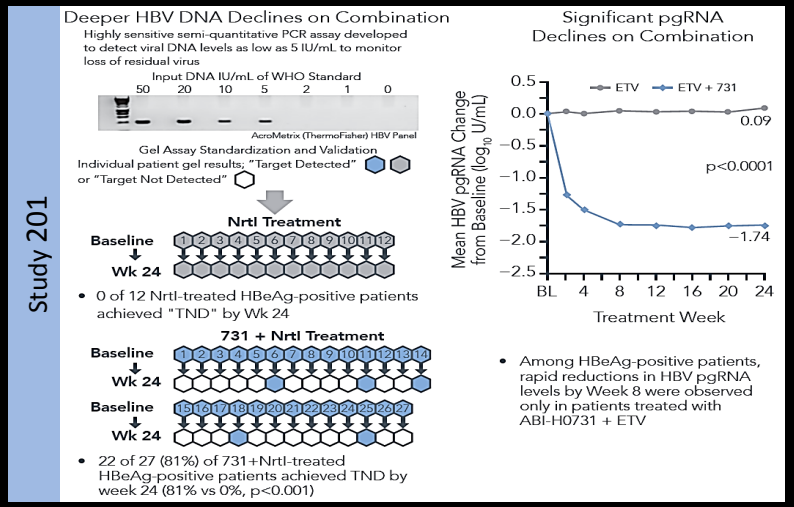
Deeper HBV DNA and HBV RNA suppression with combination. Await data on HBeAg and HBsAg loss

Study 201
HBeAg+
On NA suppressive therapy

- NA + Pbo (n=18)
- NA + 731 300 mg (n=29)

0 — Double blind — 24

Study 201



Higher % of patients with DNA TND and pgRNA <35 IU/mL

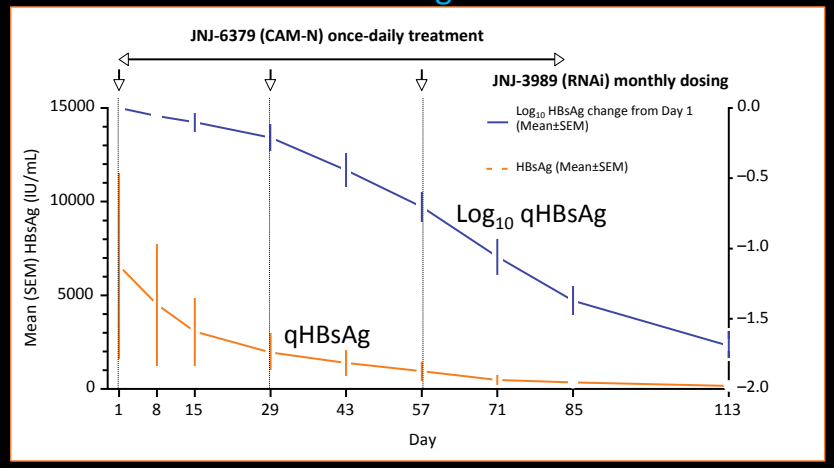
Sulkowski et al Abstract LP1

Triple Therapy: RNAi + CAM + NA

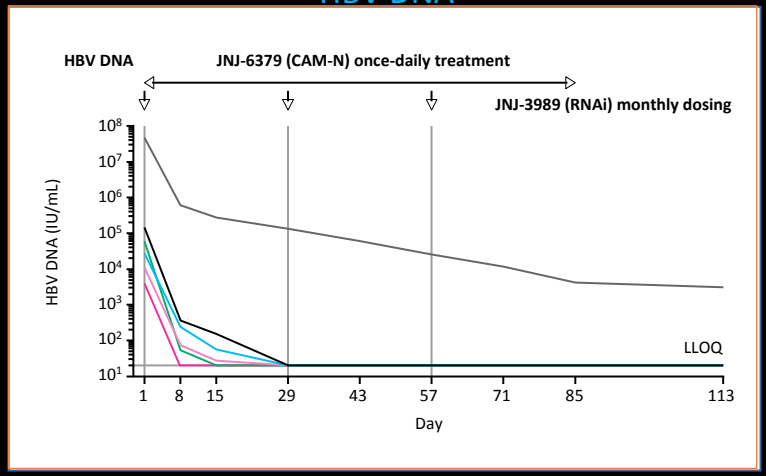
HBeAg+ n=4 / HBeAg- n=8, NA-naïve n=5 / experienced n= 7, All 12 Asian

- Three 200 mg JNJ-3989 subcutaneous doses on Days 1, 29 and 57
- Oral JNJ-6379 250 mg once daily for 12 weeks (until Day 85)
- Started or already on ETV or TDF treatment on Day 1 to beyond the end of JNJ-6379 dosing
- Response rates similar between HBeAg+ and HBeAg-

HBsAg



HBV DNA

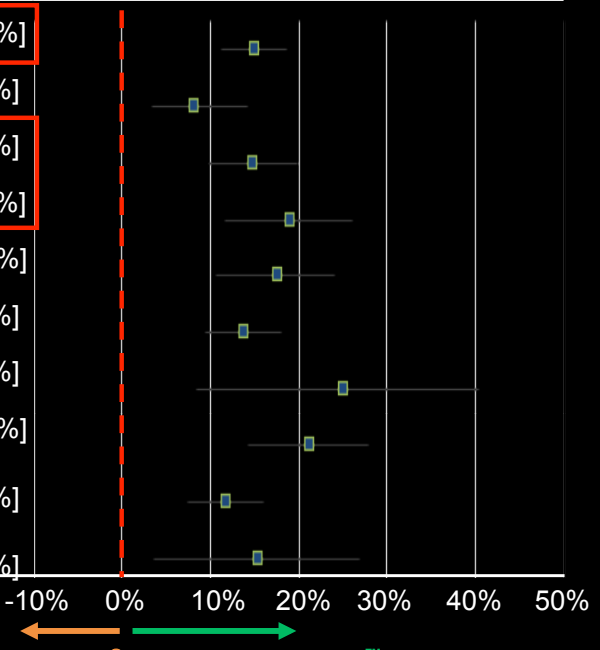


Triple therapy resulted in marked decline in HBsAg levels …?Functional cure

Yuen et al Abstract LP4

Trivalent HBV Vaccine Superior to Monovalent Vaccine

Population	Engerix-B® N	Engerix-B® SPR (%)	Sci-B-Vac™ N	Sci-B-Vac™ SPR (%)	Difference in SPR (%) [95% Confidence Interval]
All subjects	723	76.5%	718	91.4%	14.9% [11.2%, 18.6%]
18-44 years	135	91.1%	125	99.2%	8.1% [3.4%, 14.2%]
45-64 years	322	80.1%	325	94.8%	14.7% [9.8%, 19.8%]
65+ years	266	64.7%	268	83.6%	18.9% [11.6%, 26.1%]
Men	269	69.5%	282	86.9%	17.4% [10.6%, 24.2%]
Women	454	80.6%	436	94.3%	13.7% [9.5%, 18.0%]
Diabetics	60	58.3%	54	83.3%	25.0% [8.4%, 40.4%]
Obese (BMI > 30)	254	68.1%	269	89.2%	21.1% [14.3%, 28.0%]
Non-Obese (BMI ≤ 30)	469	81.0%	449	92.7%	11.6% [7.4%, 16.0%]
Current Smokers	95	70.5%	92	85.9%	15.3% [3.5%, 27.0%]

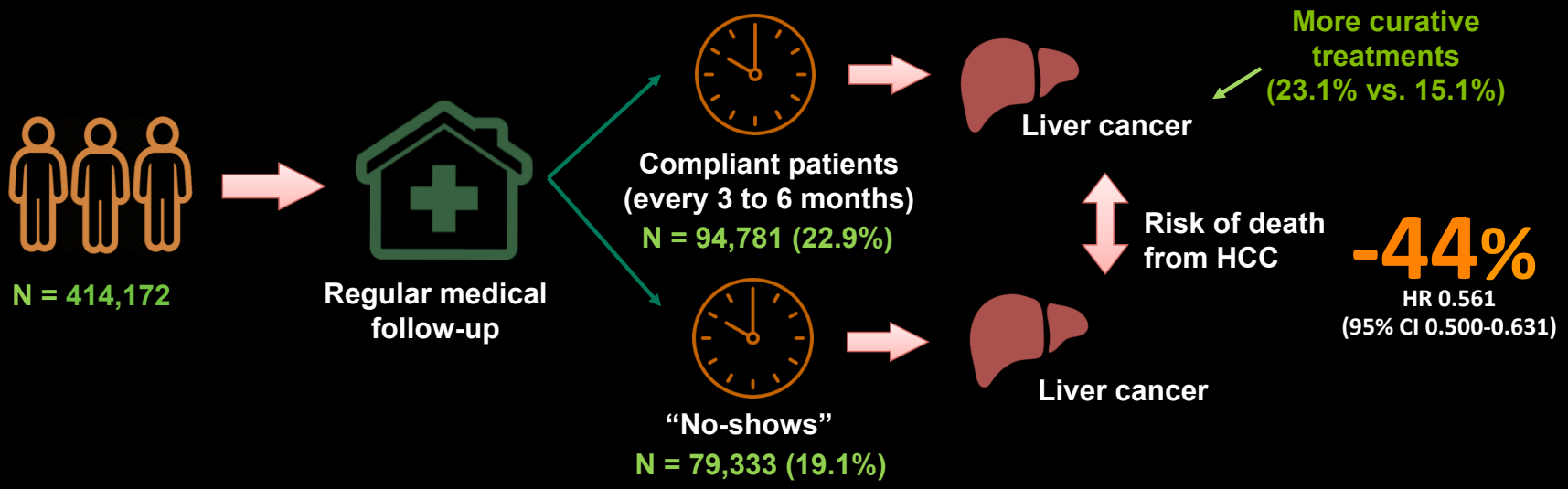


Promising HBV vaccine with higher response rates in difficult to vaccinate populations

Langley et al Abstract LP13

Impact of Regular Follow-up on Liver Cancer Mortality in Patients with Chronic Hepatitis B

National Health Insurance Cohort Study in Korea

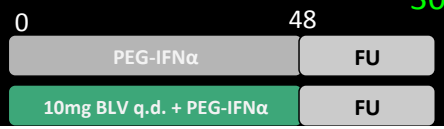


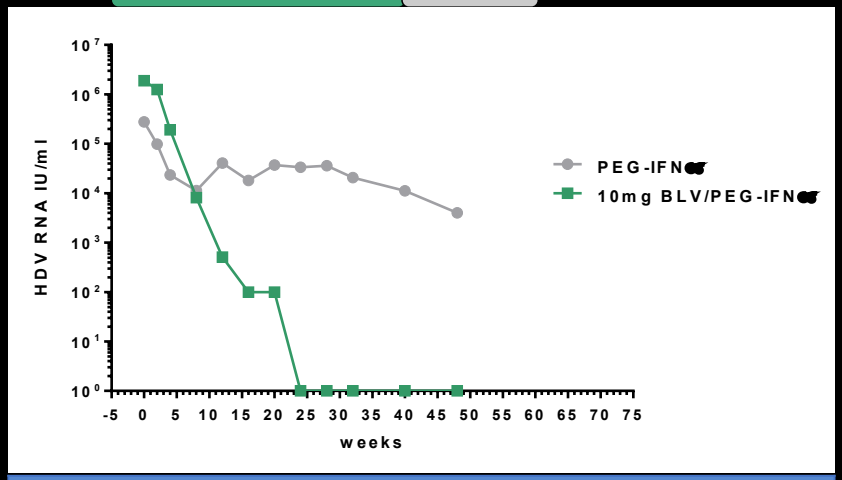
Implications for clinical practice: Reinforce need to screen patients with chronic hepatitis B

Shim et al Abstract 0159

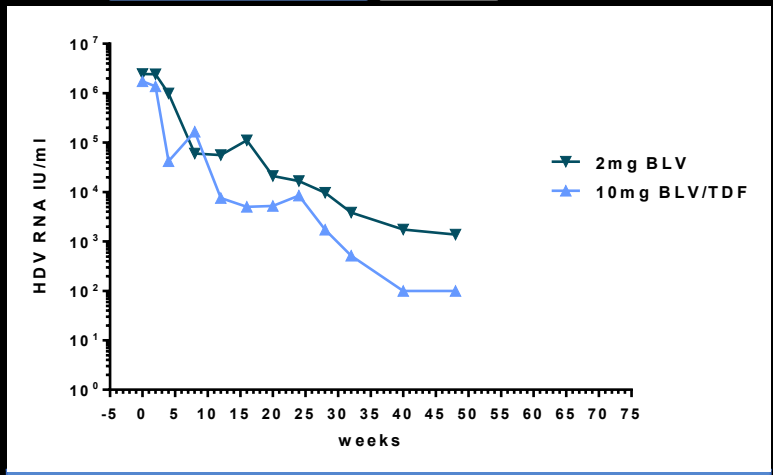
Bulevirtide (Myrcludex B) plus Peginterferon alfa-2a or Tenofovir for Delta Hepatitis

30 HBeAg-neg CHB/CHD patients





Virological response: week 48	Median HDV RNA reduction [log]	undetectable HDV RNA
PEG-IFNα	-1.29	13.3%
10mg BLV + PEG-IFNα	-6.09	86.7%



Virological response: week 48	Median HDV RNA reduction [log]	undetectable HDV RNA
2mg BLV	-2.84	13.3%
10mg BLV + TDF	-4.58	40.0%

Promising results; May require long-term administration

Wedemeyer et al Abstract 0085

Lonafarnib, Ritonavir and Peginterferon Lambda for Delta Hepatitis

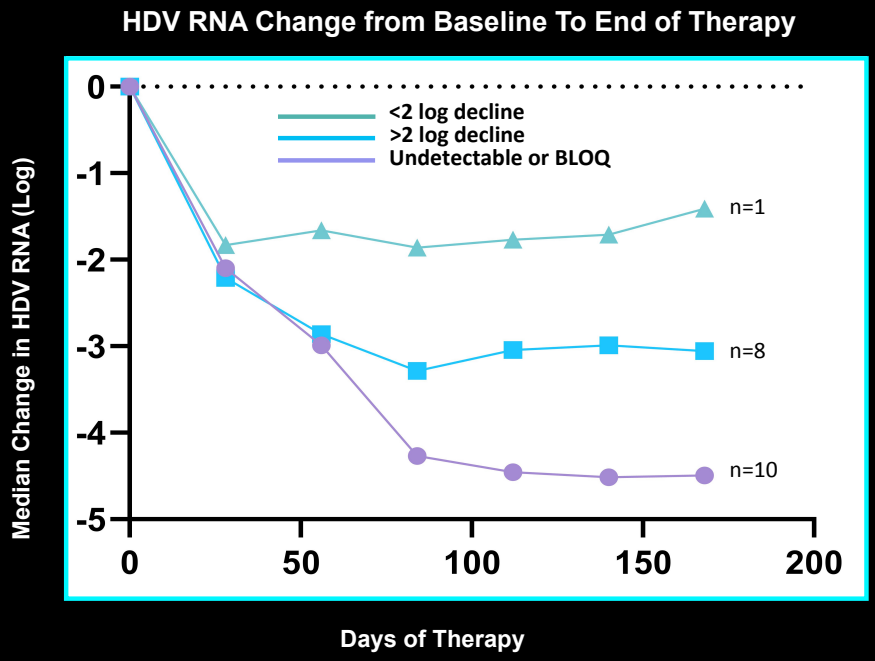
Phase 2a, open-label, prospective treatment trial x 24 weeks

Efficacy

- At the end of therapy (n=19), median HDV RNA decline was 3.4 log IU/mL (p<0.0001)
  10/19 (53%) patients achieved HDV RNA undetectable or below LLOQ in serum

Safety

- GI symptoms most common AEs
- Hyperbilirubinemia
- Dose reduction occurred in 3 patients
- Discontinuation of therapy occurred in 4 patients



Promising results, await longer follow-up

Koh et al Abstract L08

HBV Summary

- Steatohepatitis worsens HBV liver disease
- Many promising therapeutic approaches to achieve functional cure
  - Combination therapy will be needed
  - Optimal combination unknown
- HCC surveillance reduces HCC mortality
- Antiplatelet therapy may lower HCC risk in NA-suppressed patients
- More effective vaccine for difficult to vaccinate populations
- Promising therapies for delta virus

Overview

HBV

- Natural history
- Therapy
  - Current
  - Novel therapy
- Prevention
  - Screening
  - Vaccination
- Co-infection with HDV

HCV

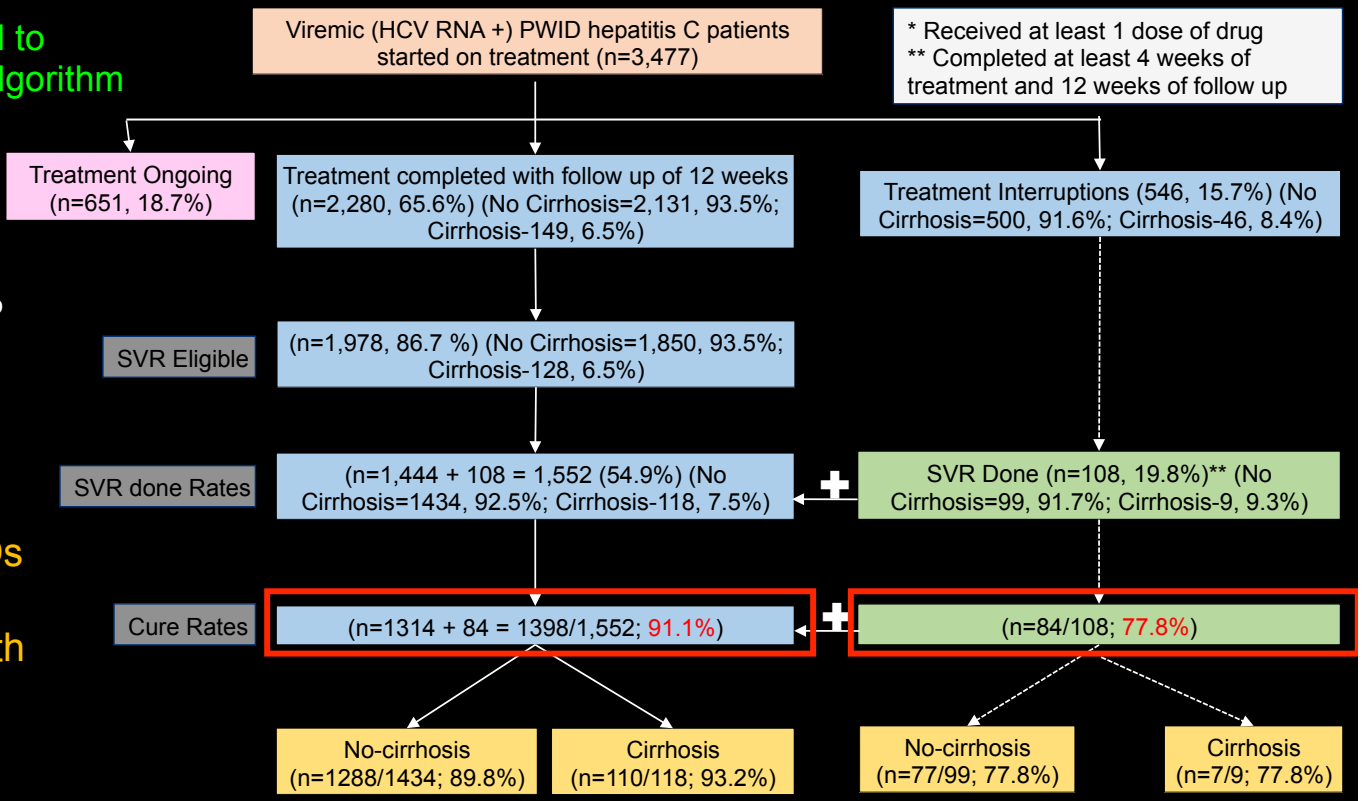
- Models of elimination
  - Treatment
  - Vaccination
- Therapy
  - Unique populations
  - Challenging populations
- Benefits of SVR
- Organ transplantation

Feasibility of Treating PWIDs in Public Health Setting

Primary care providers trained to provide care using standard algorithm

- 3477 PWIDs initiated treatment
- 7% cirrhosis
- SVR_{12} was achieved in 91% in a modified ITT analysis
- Treatment interruptions were common and reduced SVR rate to 78%

Decentralized care of PWIDs using DAA regimens is safe and effective even those with cirrhosis.



Dhiman et al Abstract 0165

Schmidbauer Abstract 1561; Sulkowski1554; Nallapeta 1589

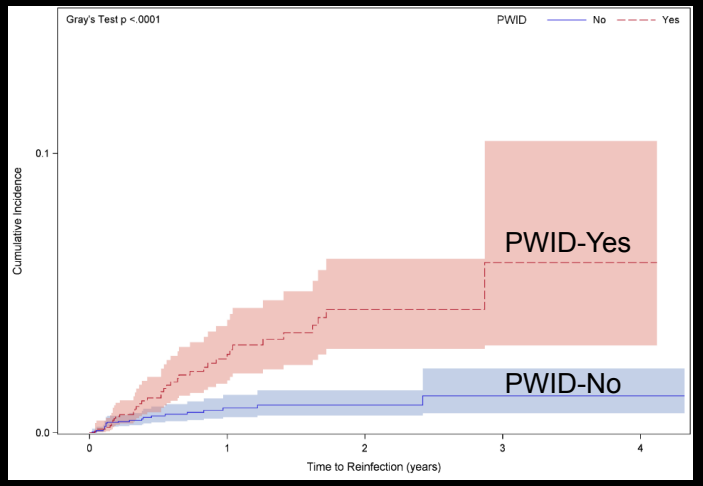
Reinfection Rate After Curative Therapy

Population-based cohort study estimated HCV reinfection rates among all DAA-treated individuals in British Columbia, Canada

Total participants	5,702
Total reinfections, n	64
Follow-up time, person-years (PY)	4,834.5 PY
Reinfection rate/100 PY, overall	1.28
Reinfection rate/100 PY, PWID	2.36

	All N= 5,702	PWID N= 1,613
	AdjHR (95% CI)	AdjHR (95% CI)
Birth cohort ≥ 1975 (ref: < 1965)	3.81(2.01-7.23)	4.69(2.07-10.62)
Male (Ref: Female)	1.47(0.83-2.59)	4.2(1.59-11.08)
PWID (Ref: No)	3.28(1.37-7.87)	
OAT, Regular use, (ref: non-user)		NE/ 0 re-infections
OAT, Non-regular use, (ref: non-user)		2.09(1-4.39)
Illicit opioid use history (ref: no)		1.65(0.72-3.81)
Major mental illness (ref: no)	1.46(0.83-2.57)	1.78(0.79-4.02)
HIV Co-infection (Ref: No)	1.69(0.94-3.02)	1.86(0.92-3.75)
Antipsychotic treatment (Ref: No)	0.92(0.5-1.67)	0.55(0.27-1.12)

Cumulative incidence curve by IDU history



PWIDs have a ~3-fold higher reinfection rate that non-PWIDs

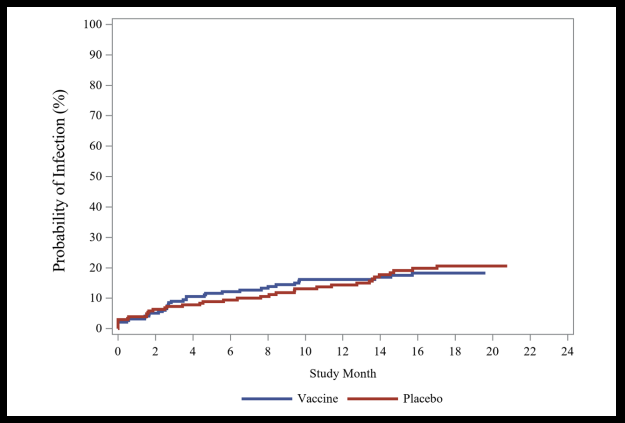
Implications for clinical practice: Consider opioid agonist therapy before and after HCV treatment in PWIDs

Janjua et al Abstract 0282 Grebely 1584

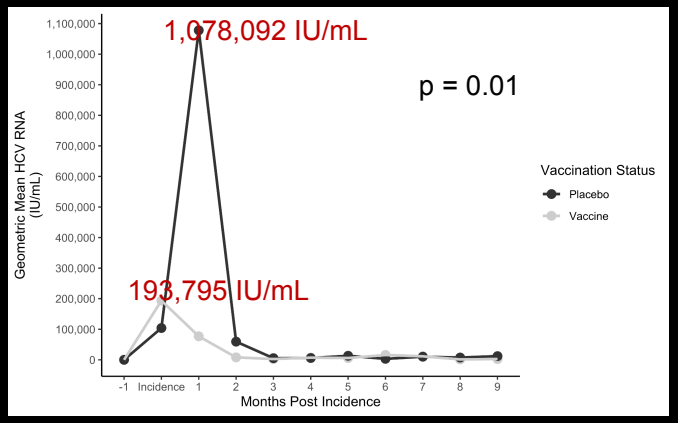
HCV Vaccine to Prevent HCV Infection

Double blind, randomized, placebo controlled phase I/II trial of prime (chimpanzee derived Adenovirus: ChAd3) /boost (modified vaccinia virus Ankara) HCV vaccine among actively using PWIDs

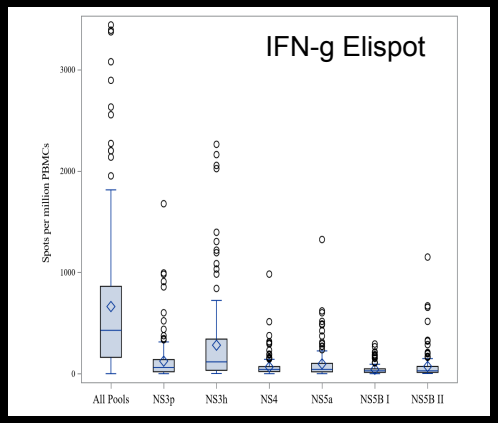
Incidence of Infection



Peak HCV RNA levels



Immunogenicity



Demonstrated feasibility of vaccine studies among PWIDs. More efforts are needed on vaccine development

Page et al Abstract LP17

Pangenotypic Therapy for Children: Glecaprevir /Pibrentasvir (G/P)

Safety and efficacy of the pediatric formulation of G/P for 8 weeks in children aged 3- <12 years, n=81,GTs 1-6

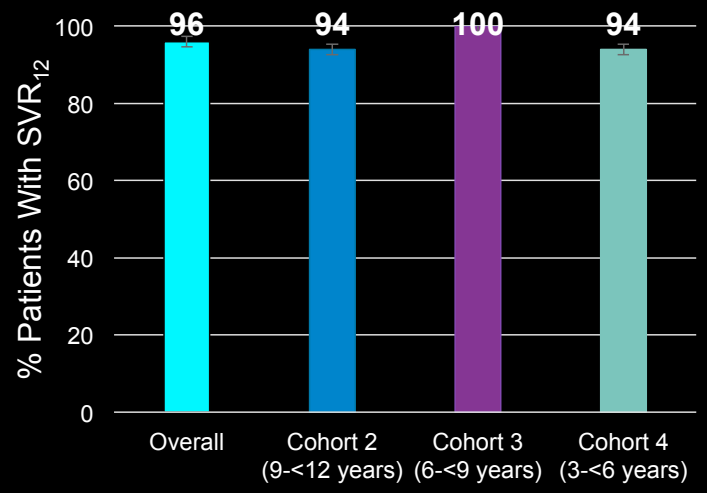
Dosing

Group	Weight Range	Dose (GLE + PIB)
Cohort 2 (9-<12 years)	≥30 to <45 kg	250 mg + 100 mg
Cohort 3 (6-<9 years)	≥20 to <30 kg	200 mg + 80 mg
Cohort 4 (3-<6 years)	≥12 to <20 kg	150 mg + 60 mg

Safety

Treatment-emergent Adverse event (AE), n (%)	Total N = 48
Any AE	33 (69)
Any AE with a reasonable possibility of being related to G/P	13 (27)
Any AE with a Grade 3 or higher	0
Any AE leading to treatment discontinuation	0
AEs in ≥10% of all patients Headache, vomiting, diarrhea, fatigue, cough upper abdominal pain	

Efficacy



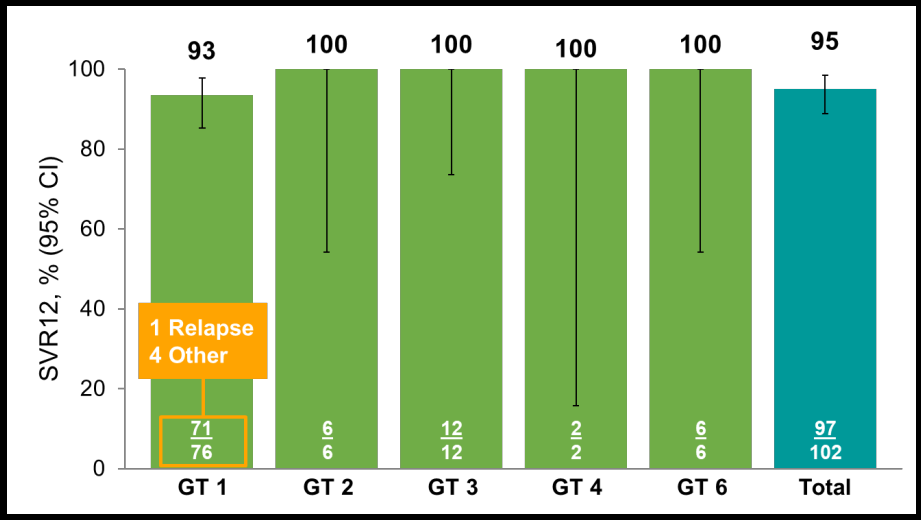
Jonas et al Abstract 1551

Pangenotypic Therapy for Children with CHC

204 children, 70% Caucasian, genotypes 1-4 & 6, no cirrhosis

Aged 6–11 Years (n-102)
SOF + VEL 200mg + 50 mg x 12 weeks

Aged 12–17 Years (n=102)
SOF + VEL 400mg + 100 mg x 12 weeks



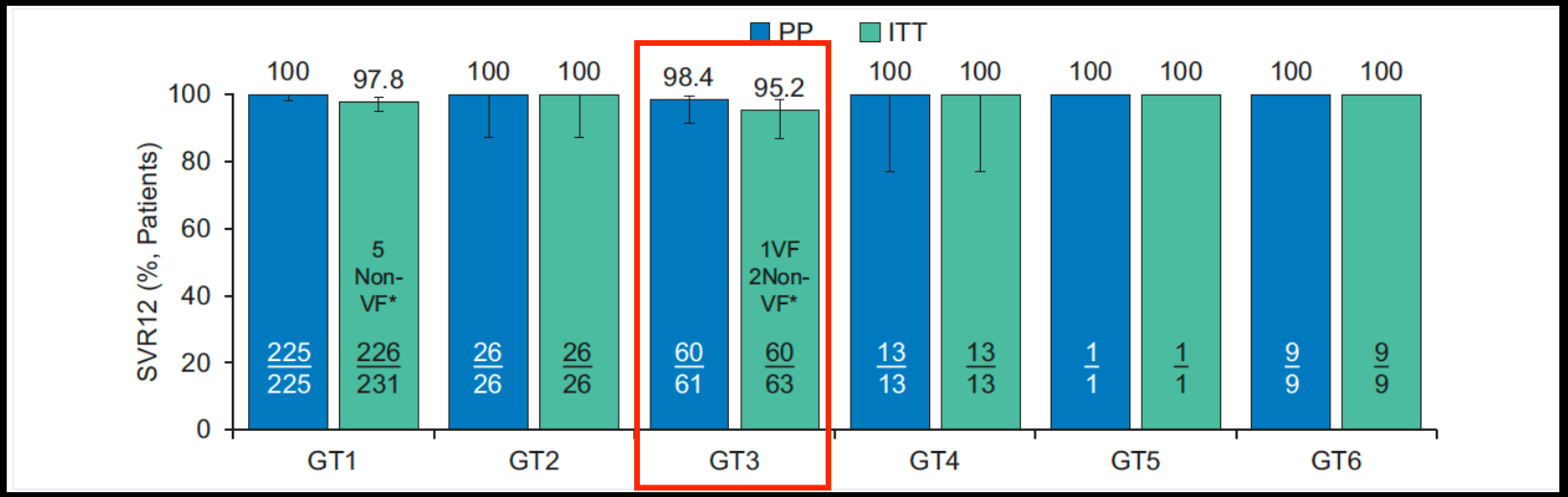
Study ongoing in children 3-<6 years

Implications for clinical practice: In the near future we should have have a safe and effective, pangenotypic regimen for children 3 year or older

Jonas et al Abstract 0748

Short Course Therapy for Compensated Cirrhosis and HCV GT 3

61 treatment-naïve patients with GT3 and compensated cirrhosis received glecaprevir/pibrentasvir x 8 weeks



- 1 patient relapsed
- NS5A RASs: A30K was present at 4.8% at 2% and 15% NGS detection thresholds
  Y93H was present at 8.1% and 6.5% using a detection threshold of 2% or 15%
- All GT3-infected patients with A30K or Y93H at baseline achieved SVR12

Implications for clinical practice: Effective short duration therapy approved for previously difficult to treat population

Brown et al Abstract LP9

Impact of SVR on Liver-related Mortality

VA database of CHC patients
Treated patients propensity score matched untreated controls

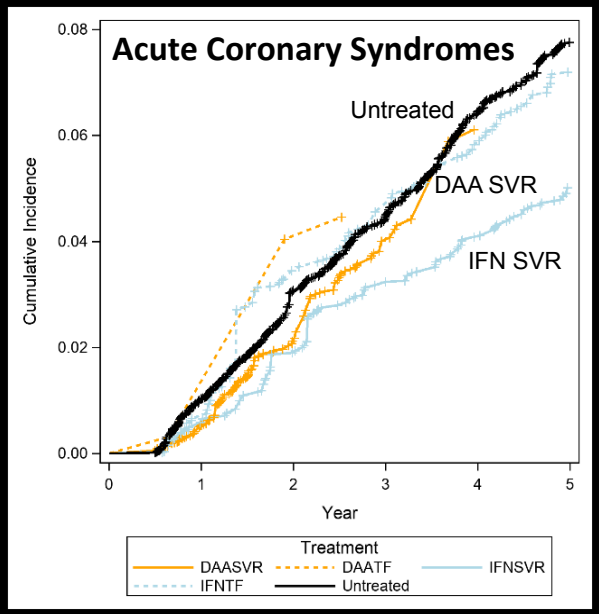
	Liver-related deaths		
	N	Rate/100PY (95% CI)	P-value
Overall			
HCV+ treated	1057	0.68 (0.64,0.72)	--
HCV+ untreated	1921	1.29 (1.23,1.35)	<.0001
Among those treated			
By treatment response			
SVR achieved	127	0.14 (0.12,0.17)	--
SVR not achieved	930	1.40 (1.31,1.49)	<.0001
By treatment regimen			
PEG/RBV treated	963	0.76 (0.72,0.81)	--
DAA treated	73	0.31 (0.24,0.38)	<.0001
By regimen and SVR			
PEG/RBV SVR achieved	84	0.13 (0.10,0.16)	--
PEG/RBV SVR not achieved	879	1.44 (1.35,1.54)	<.0001
DAA SVR achieved	40	0.20 (0.14,0.27)	0.02
DAA SVR not achieved	33	0.81 (0.54,1.09)	<.0001

Further evidence of the benefits of SVR

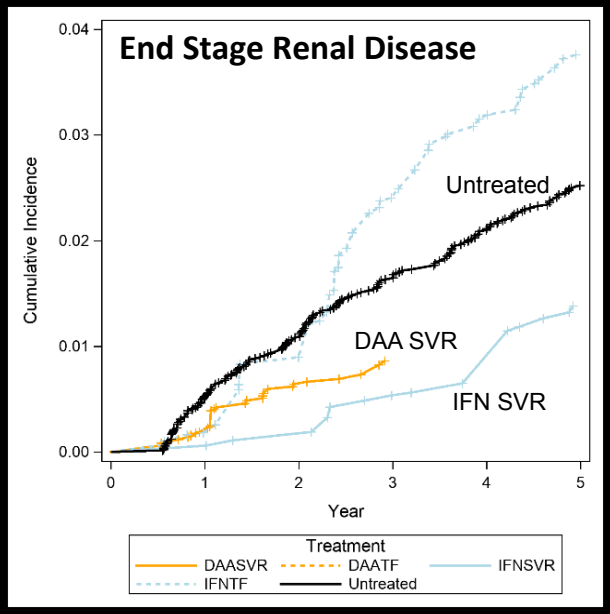
Butt et al Abstract 0039

Impact of SVR on Extra-Hepatic Outcomes

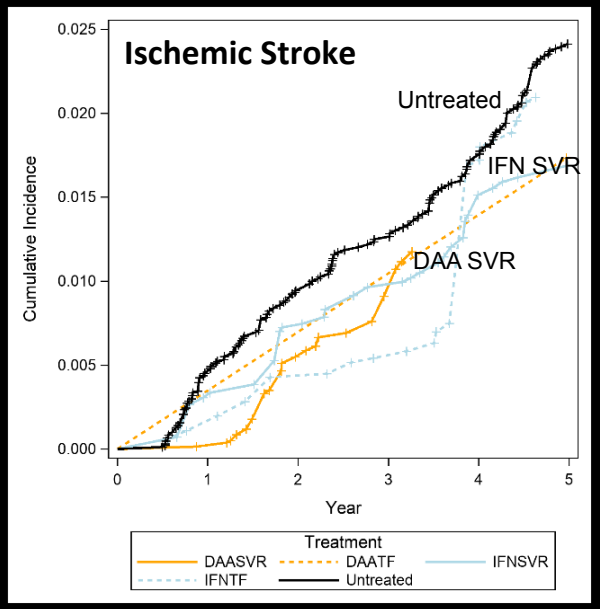
Chronic Hepatitis Cohort 15,999 HCV patients under routine care at four US health care systems



- SVR was associated with significantly reduced risk of ACS, regardless of treatment type.
- IFN SVR was associated with a significantly lower risk of ACS than DAA SVR.



- SVR was associated with significantly reduced risk of ESRD, regardless of treatment type.



- SVR associated with significantly reduced risk of ischemic stroke, regardless of treatment type

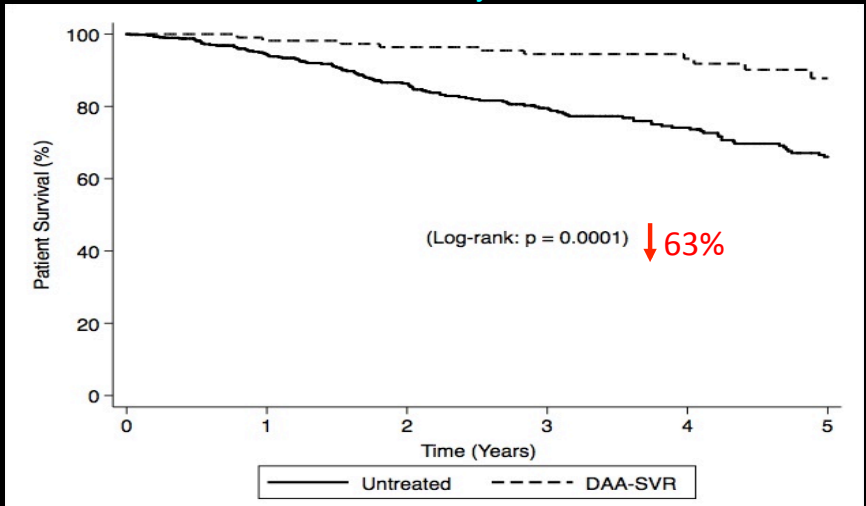
Extra-hepatic benefits to SVR

Li et al Abstract 0037

SVR Improves HCC Survival

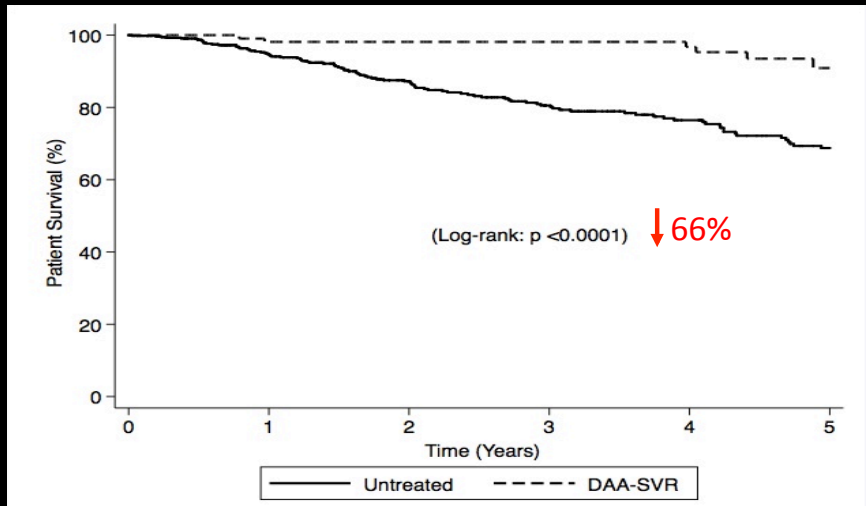
Multi-national, propensity score matched analysis of impact of HCV eradication on HCC survival

All-cause Mortality



Type of Mortality	HCV treatment status	Adjusted HR* (95%CI)	P-value
All-cause	Untreated for HCV	Reference	Reference
	SVR	0.37 (0.16-0.83)	0.016

Liver-related Mortality



Type of Mortality	HCV treatment status	Adjusted HR* (95%CI)	P-value
Liver-related	Untreated for HCV	Reference	Reference
	SVR	0.34 (0.13-0.88)	0.026

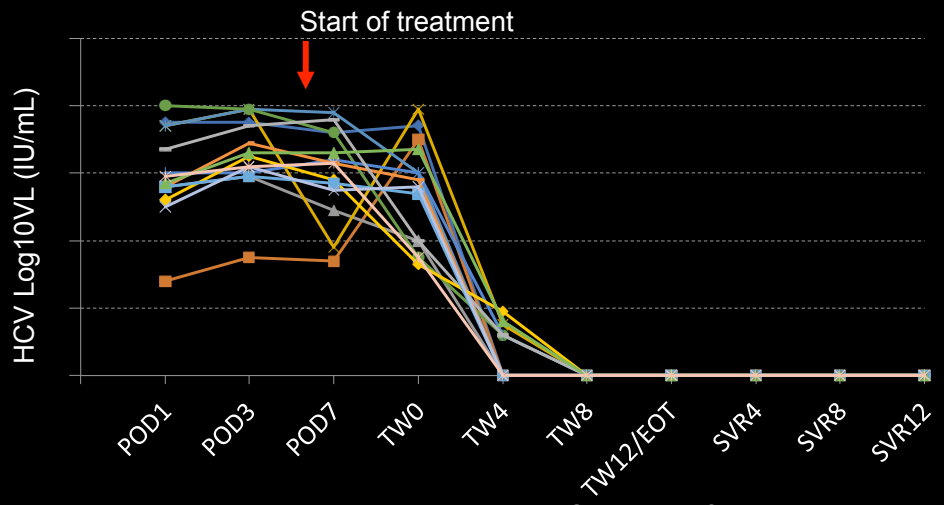
Implications for clinical practice: HCC patients who are candidates for HCC therapy should also be considered for DAA therapy.

Dang et al Abstract 0040

Use of HCV-Seropositive Donors in HCV-Seronegative Liver Transplant Recipients

Retrospective analysis of 24 HCV-seropositive to HCV-seronegative Liver transplants (10 NAT neg; 14 NAT+)

- Viremic documented within 5 days after LT
- Mean pre-treatment viral load 24,955,159 IU/ml (range 3,230 to 97,500,000)
- Median time to start DAA treatment 27.5 days (range 6-67)
  - G/P x 12 weeks,
  - Sof/Vel x 12 weeks,
  - SOF/LDV+/-RBV x 12-24 weeks
- All achieved SVR12



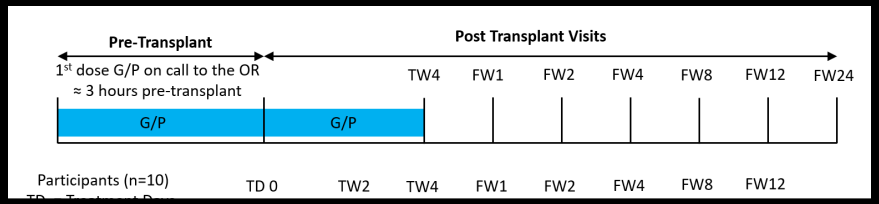
POD = post-operative day; TW = treatment week; EOT = end of the treatment; SVR = sustained virologic response

Implication for Clinical Practice: LT using grafts from HCV-viremic donors to HCV negative recipients had excellent short-term outcomes

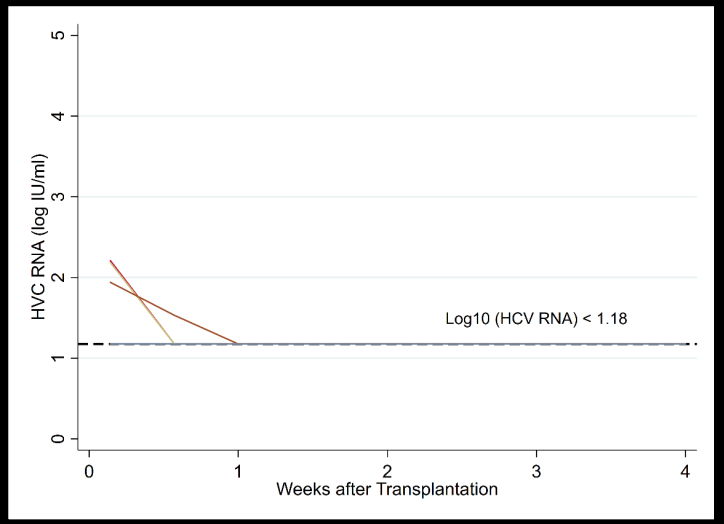
Wijarnpreecha et al Abstract 0003

Short Duration, Prophylactic Therapy to Prevent Post-transplant HCV Infection from HCV-Infected Donors to HCV-Uninfected Recipients

10 HCV D+/R- kidney transplants



HCV RNA levels post-transplant



Outcome

5/10 never had detectable HCV RNA
5/10 low level (peak 161 IU/mL) first week
9/9 achieved SVR

Safety

No AEs related to DAA prophylaxis
No deaths, graft failures or rejections
No significant elevations in AST, ALT, or bilirubin

Implications for clinical practice: Short duration prophylactic therapy appears effective at preventing post-transplant infection from HCV Donor+ to -recipients

Durand et al Abstract 0042

Pre-emptive Combination DAA and Entry Blocker Therapy to Prevent Post-transplant HCV Infection from HCV-Infected Donors to HCV-Uninfected Recipients

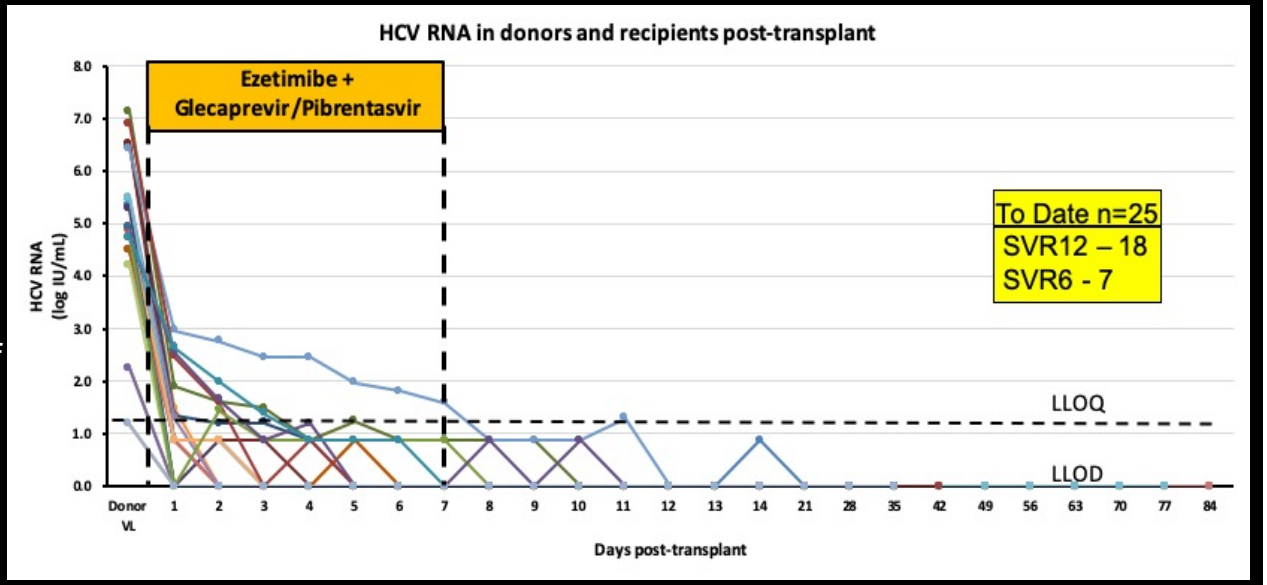
Ezetimibe (HCV entry blocker) + Glecaprevir/Pibrentasvir given 1 dose before and for 7 days post-transplant to prevent HCV infection from 16 HCV+ organ donors to 25 HCV-negative recipients 12lung, 8 kidney, 1 K-P, 4 heart

Outcome

- 9 had quantifiable HCV RNA (max 2.96 log IU/mL)
- 9 had HCV RNA that was detectable but <LLOQ (15 IU/mL)
- 7 never had detectable viremia
- All HCV RNA negative at last F/U
- Donor VL was the only predictor of transient post-transplant viremia

Safety

- Reversible ALT and CK elevations with no other safety concerns



Implications for clinical practice: Pre-emptive Ezetimibe + glecaprevir/pibrentasvir for 7 days, prevented or rapidly cured post-transplant HCV infection

Feld et al Abstract 0038

HCV Summary

- Feasible to treat PWIDs. Overcoming adherence issues is a challenge
- Treatment
  - Pangenotypic regimens will be available for children
  - Short course pangenotypic therapy available for treatment-naïve compensated cirrhotics
- Multiple benefits of SVR
  - Lower liver-related mortality
  - Lower cardiovascular and renal outcomes
  - Improved survival after HCC treatment
- Pre-emptive 7-28 day therapy appears to prevent or cure HCV infection post-transplant