Updates in Liver Disease

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Viral Hepatitis

All First Line Treatment Options Lead to Sustained response rates ≥ 95%

HCV genotype	No Cirrhosis		Compensated Cirrhosis	
1	EBR/GZR* GLE/PIB LDV/SOF SOF/VEL	12 W 8 W 8 or 12 W 12 W	EBR/GZR* GLE/PIB LDV/SOF SOF/VEL	12 W 12 W 12 W 12 W
2/3	GLE/PIB SOF/VEL	8 W 12 W	GLE/PIB SOF/VEL	12 W 12 W
4	EBR/GZR GLE/PIB LDV/SOF SOF/VEL	12 W 8 W 12 W 12 W	EBR/GZR GLE/PIB LDV/SOF SOF/VE	12 W 12 W 12 W 12 W
5/6	GLE/PIB LDV/SOF SOF/VEL	8 W 12 W 12 W	GLE/PIB LDV/SOF SOF/VEL	12 W 12 W 12 W

GLE/PIB
SOF/VEL
are pan-genotypic options

https://www.hcvguidelines.org

Almost All Unique Populations Achieve High SVR rates

Population	SVR Rate	Comments
DAA failures	>95%	SOF/VEL/VOX pangenotypic option
HIV/HCV Coinfection	>95%	Must do drug drug interactions
Post Orthotopic Liver Transplant	>95%	Must do drug drug interactions
With Renal Impairment/Dialysis	>95%	GLE/PIB pangenotypic option
Kidney Transplant Patients	>95%	Must do drug drug interactions
Management of Acute HCV Infection	>95% if treated for 8 weeks	20-50% of acute infections clear
HCV in Pregnancy	No treatment during pregnancy	Screen at risk women, treating before pregnancy preferred
HCV in Children	>95%	Treatment approved for those≥ 12 years of age

- Drug-Drug interactions are essential to evaluate, particularly with HIV/HCV coinfection and transplant patients
- use available resources (https://aidsinfo.nih.gov/guidelines/htmltables/1/5536 is an example for HIV)
- Antiretroviral drug switches, when needed, should be done in collaboration with the HIV practitioner

First Line Treatment Options lead to good SVR rates (>85%) in Childs B/C patients

HCV genotype	Decompensated Cirrhosis, RBV tolerant		Decompensated Cirrhosis, RBV intolerant	
1,4	LDV/SOF/RBV SOF/VEL/RBV SOF/DAC/RBV	12 W 12W 12 W	LDV/SOF SOF/VEL SOF/DAC	24 W 24 W 24W
2/3	SOF/VEL/RBV SOF/DAC/RBV	12W 12 W	SOF/VEL SOF/DAC	24 W 24W
5, 6	LDV/SOF/RBV SOF/VEL/RBV	12 W 12 W	LDV/SOF SOF/VEL	24 W 24 W

- Those with decompensated cirrhosis who have failed therapy remain one of the final special populations in need
- of additional therapies
- Protease inhibitors cannot be given in decompensated cirrhosis

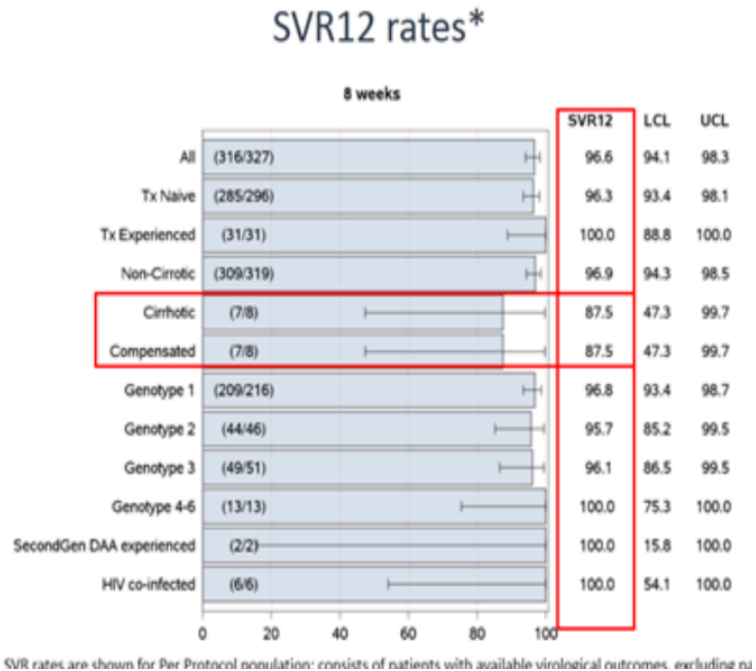
SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR FOR THE TREATMENT OF HCV GENOTYPE 1-6: RESULTS OF THE HCV-TARGET STUDY

Patients enrolled in HCV-TARGET were treated according to the local standards of care at academic (n=45) and community medical centers (n=19) in North America (n=60) and Europe (n=4)

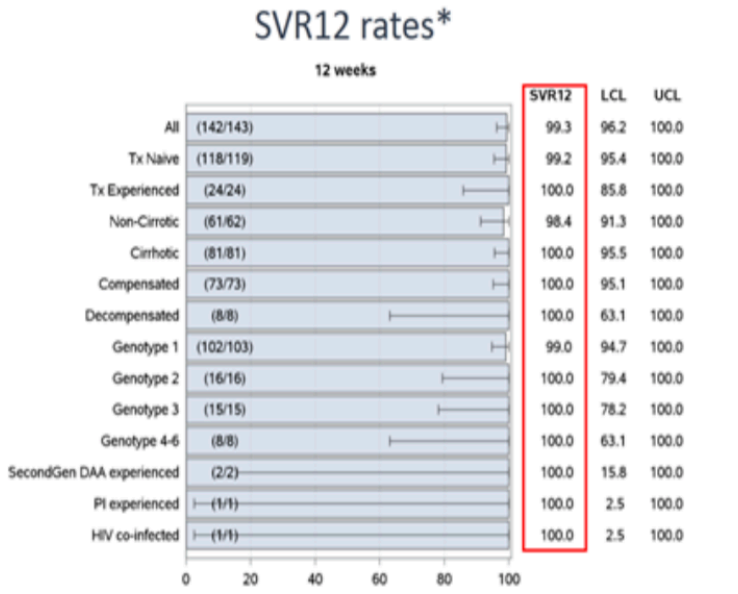
	Treatment duration				
	8 weeks N=430	12 weeks N=184	16 weeks N=25	Other N=30	Total N=726
Male	237 (55)	131 (71)	18 (72)	16 (53)	433 (60)
Age 60+	123 (29)	85 (46)	11 (44)	6 (20)	243 (34)
Genotype: 1	294 (68)	132 (72)	18 (72)	22 (73)	512 (71)
2	59 (14)	20 (11)	1 (4)	3 (10)	88 (12)
3	63 (15)	21 (11)	5 (20)	1 (3)	96 (13)
4-6	13 (3)	10 (5)	.	2 (7)	25 (3)
Nos	1 (0)	1 (1)	1 (4)	2 (7)	5 (1)
Tx Experienced	36 (8)	28 (15)	17 (68)	3 (10)	88 (12)
Cirrhotic	18 (4)	97 (53)	14 (56)	4 (13)	137 (19)
Liver Transplant	.	8 (4)	2 (8)	.	10 (1)
History of Decomp.	3 (1)	9 (5)	1 (4)	1 (3)	14 (2)
Dialysis	6 (1)	9 (5)	1 (4)	.	16 (2)
Prior SecondGen DAA	2 (1)	3 (2)	12 (48)	2 (7)	19 (3)
PI Experience	.	2 (1)	2 (8)	.	4 (1)
HIV co-infection	7 (2)	3 (2)	1 (4)	.	12 (2)
NS5A RAS Tested	44 (10)	20 (11)	6 (24)	5 (17)	78 (11)
RAS Present	11 (3)	7 (4)	2 (8)	3 (10)	23 (3)

DDW 2019 #951

SAFETY AND EFFICACY OF GLECAPREVIR/PIBRENTASVIR FOR THE TREATMENT OF HCV GENOTYPE 1-6: RESULTS OF THE HCV-TARGET STUDY



SVR rates are shown for Per Protocol population: consists of patients with available virological outcomes, excluding pa



SVR rates are shown for Per Protocol population: consists of patients with available virological outcomes, excluding patients wi
arly except for whom lack of efficacy was recorded. 95% CIs were calculated by Clopper-Pearson method.

HIGH EFFICACY AND IMPROVEMENT IN CPT CLASS WITH SOFOSBUVIR/VELPATASVIR PLUS RIBAVIRIN FOR 12 WEEKS IN PATIENTS WITH CPT C DECOMPENSATED CIRRHOSIS

Open-label, single-arm study conducted in France and the US.
Patients had CPT score 10-12 at screening and infected with any HCV genotype

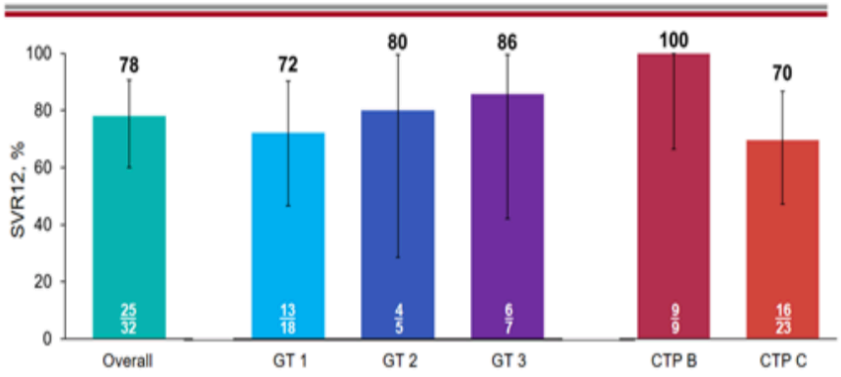
All subjects were treated with SOF/VEL (400mg/100 mg) and RBV (starting dose of 600 mg/day regardless of weight) for 12 weeks

		SOF/VEL + RBV 12 wk: N=32
HCV GT, n (%)*	1	18 (56)
	2	5 (16)
	3	7 (22)
	Indeterminate	2 (6)
Mean HCV RNA, log_{10} IU/mL (SD)		5.2 (1.2)
HCV RNA ≥800,00 IU/mL, n (%)		9 (28)
IL28B CC, n (%)		15 (47)
HCV treatment experienced, n (%)		4 (13)
Mean $eGFR_{CG}$, mL/min (SD)		113 (41)
Mean platelets, $x10^3$/uL (SD)		89 (31)
Mean albumin, g/dL (SD)		2.7 (0.5)
Mean INR (SD)		1.5 (0.3)
Mean hemoglobin, g/dL (SD)		12.0 (1.3)
Mean bilirubin, mg/dL (SD)		3.4 (1.6)
CTP class, n (%)	B (7–9)	9 (28)
	C (10–15)	23 (72)
MELD score, n (%)	10–15	13 (41)
	16–20	17 (53)
	21–25	2 (6)
Ascites, n (%)	None	3 (9)
	Mild/moderate	20 (63)
	Severe	9 (28)
Encephalopathy, n (%)	None	5 (16)
	Medication controlled	27 (84)
	Medication refractory	0

HIGH EFFICACY AND IMPROVEMENT IN CPT CLASS WITH SOFOSBUVIR/VELPATASVIR PLUS RIBAVIRIN FOR 12 WEEKS IN PATIENTS WITH CPT C DECOMPENSATED CIRRHOSIS

SVR12: Overall and by Key Subgroup

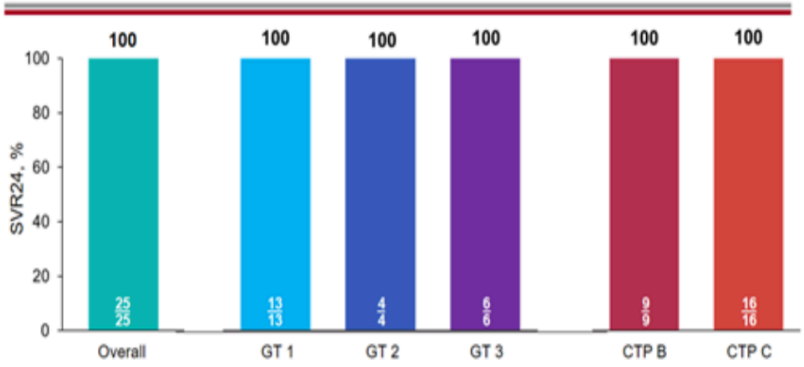
Intent-to-Treat



- No patients experienced virologic failure at FU-12
  - 7 had no FU-12 assessment due to investigator discretion (n=1) and death (n=6); all unrelated to study drugs

SVR12: Overall and by Key Subgroup

Per Protocol



- 1 HCV GT3 CTP C patient with SVR12 did not achieve SVR24
  - No baseline NS5A or NS5B resistance-associated substitutions (RASs) detected; NS5A RAS Y93H emerged at Week 24

HIGH EFFICACY AND IMPROVEMENT IN CPT CLASS WITH SOFOSBUVIR/VELPATASVIR PLUS RIBAVIRIN FOR 12 WEEKS IN PATIENTS WITH CPT C DECOMPENSATED CIRRHOSIS

Shift in CTP Class From Baseline

		Baseline CTP Class, n/n (%)*	
		B n=8	C n=16
Posttreatment Week-24 CTP Class	A (5–6)	1/6 (17)	0/13
	B (7–9)	5/6 (83)	7/13 (54)
	C (10–15)	0/6	6/13 (46)

- Of the 19 patients who achieved SVR24, did not have a liver transplant, and were assessed at posttreatment Week 24, there were improvements in CTP class in 8 (42%)
- Changes in liver function were primarily due to improvements in laboratory parameters

*Only patients with assessments at posttreatment Week 24 and without on-study liver transplant were included.

DDW 2019, May 18-21, I

Study Day of Death	Duration of Study Treatment, d	Cause of Death
Posttreatment Day 8	6	Colitis*
Posttreatment Day 1	3	Sepsis*
Posttreatment Day 53	84	Cardiac arrest
Posttreatment Day 80	84	Sepsis
Posttreatment Day 90	84	Liver failure
Posttreatment Day 103	84	Acute pancreatitis
Posttreatment Day 123	84	Liver failure
Posttreatment Day 164	84	Variceal hemorrhage

Changes in MELD Score at Posttreatment Week 24 in Patients Who Achieved SVR24

- Of the 19 patients who achieved SVR24, did not have a liver transplant, and were assessed at posttreatment Week 24, there were improvements in MELD score in 10 (53%)

*Only patients with assessments at posttreatment Week 24 and without on-study liver transplant were included.

DDW 2019, May 18-21, San Diego, Califo

Treat Childs B/C with caution, they are sick
Or refer to liver center

EFFECTIVENESS OF ELBASVIR/GRAZOPREVIR IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFFECTION WHO RECEIVE OPIOID AGONIST THERAPY: TREATMENT UTILIZATION AND THE IMPACT OF CONCOMITANT PSYCHIATRIC MEDICATIONS

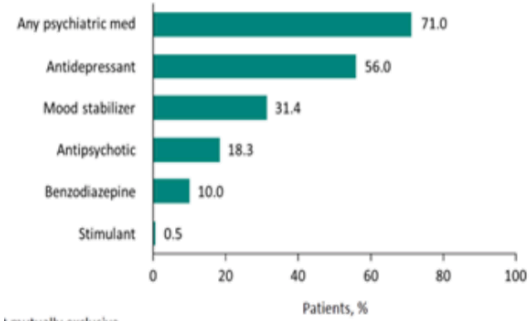
Retrospective observational cohort study of patients with chronic HCV infection in the VA

Received EBR/GZR >11 weeks with diagnosis of opioid use or ≥1 prescription for OAT (including methadone, buprenorphine, levomethadone, naloxone, and naltrexone) within 1 year

Characteristic	EBR/GZR regimens N = 611
Age, mean (SD), years	61.6 (7.5)
Race/ethnicity, n (%)	
Black	326 (53.4)
White	227 (37.2)
Other	58 (9.5)
Sex, n (%)	
Male	586 (95.9)
Female	25 (4.1)

Characteristic	EBR/GZR regimens N = 611
Treatment history, n (%)	
Treatment-naive	549 (89.9)
Treatment-experienced	62 (10.1)
HCV genotype, n (%)	
GT1a	286 (46.8)
GT1b	303 (49.6)
GT1-unknown	22 (3.6)
Baseline viral load, n (%)	
<800,000 IU/mL	163 (26.7)
≥800,000 IU/mL	416 (68.1)
Missing	32 (5.2)

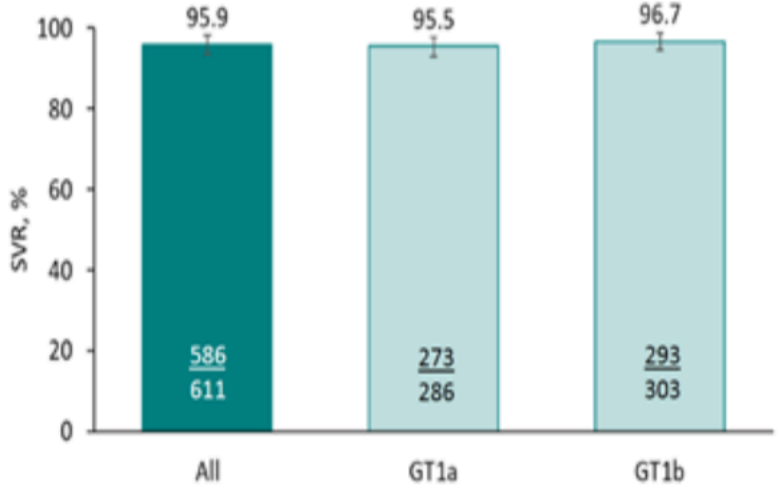
71% of patients were receiving ≥1 concomitant psychiatric medication*



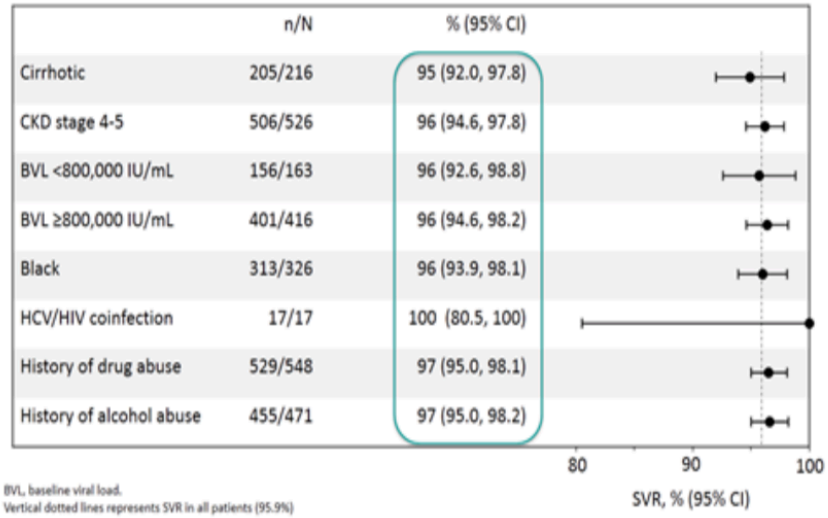
DDW 2019 #955

EFFECTIVENESS OF ELBASVIR/GRAZOPREVIR IN PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 1 INFFECTION WHO RECEIVE OPIOID AGONIST THERAPY: TREATMENT UTILIZATION AND THE IMPACT OF CONCOMITANT PSYCHIATRIC MEDICATIONS

SUSTAINED VIROLOGIC RESPONSE (N = 611)



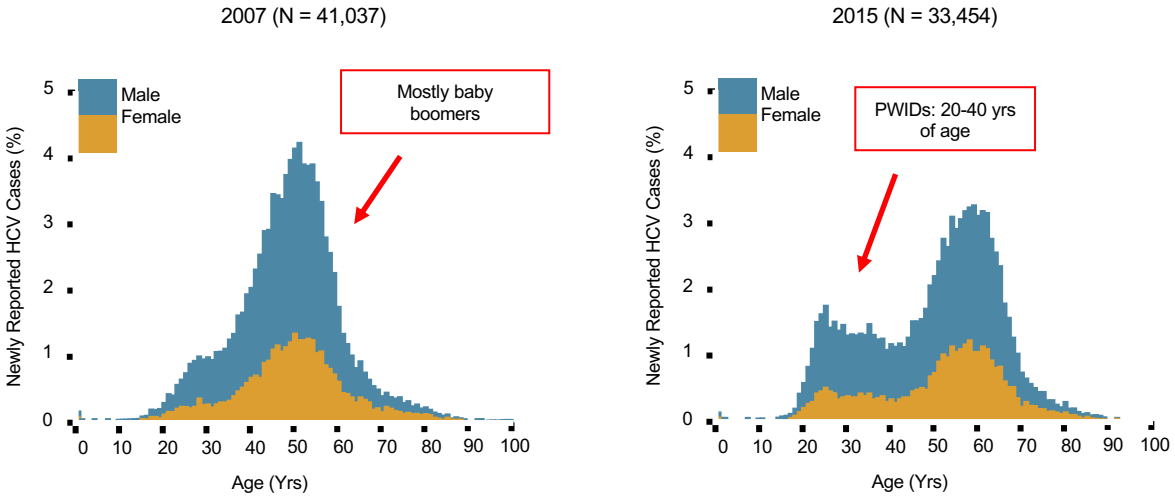
Note: excluded 22 patients with GT1 unknown subtype



BVL, baseline viral load.
Vertical dotted lines represents SVR in all patients (95.9%)

HCV infected individuals on opiate agonist therapy should be treated

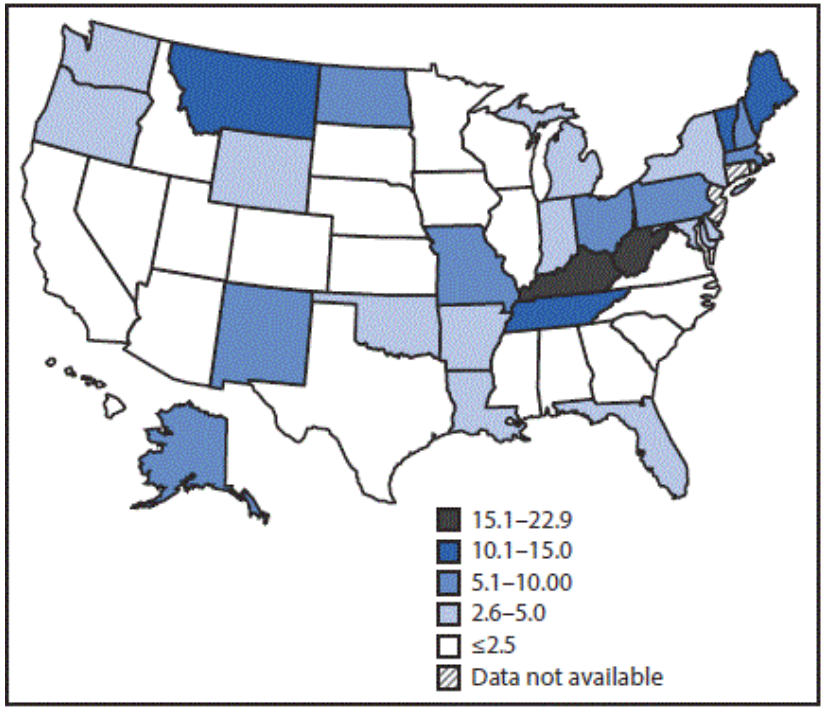
Changing Epidemiology of HCV in California Similar to rest of US



- Screening → linkage to HCV care → DAA treatment cascade must be operative in all those at risk
- Treatment of PWIDs plus harm reduction efforts essential part of elimination efforts

California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

Rate of hepatitis C infection among pregnant women per 1,000 live births, by state — United States, 2014



https://www.cdc.gov/mmwr/volumes/66/wr/mm6618a3.htm

HCV Screening During Pregnancy

- **CDC and the American College of Obstetricians and Gynecologists** recommend selective screening at high risk (i.e., history of IDU use or long-term hemodialysis)

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA
Infectious Diseases Society of America

Testing

Recommendation for Universal Hepatitis C Screening in Pregnancy	
RECOMMENDED	RATING
All pregnant women should be tested for HCV infection (see Recommendations for Initial HCV Testing and Follow-Up), ideally at the initiation of prenatal care.	IIb, C

AASLD/IDSA. HCV guidance**. May 24 2018**.

Treatment of HCV in Pregnancy Clears Virus

— Both mothers and infants do well in pilot study

Characteristics for the nine women in the study were as follows:

- Median age was 31
- All were white
- Eight had public insurance, and one was insured through the military
- Two of the women had less than a high school education, and six had more than a high school education
- Eight of the women had been infected with hepatitis C infection through intravenous drug use, and one had been infected perinatally

Genotypes 1, 4, 5, 6
All received ledipasvir/sofosbuvir for 12 weeks
All the patients were cured of hepatitis C virus infection and all infants are negative to date."

CROI

Source Reference: *Chappell C, et al "A Phase 1 study of ledipasvir/sofosbuvir in pregnant women with hepatitis C virus" CROI 2019.*

Treatment of HCV in Pregnancy

- Recruitment was the largest challenge in this study and not because of a lack of HCV prevalence.
- Over the 2 year recruitment period over 170 HCV viremic pregnant women were identified,
  - only 29 women screened for the study with 20 failed to enroll, most commonly due to having HCV genotype 2 or 3 infection, 4 due to ongoing IV drug use or use of cocaine, 3 declined to participant due to social reasons
  - We enrolled 9 participants, all have completed the study medication and delivered. One is currently between delivery and the SVR assessment. Of the 9 infants enrolled, 5 have reach one year of age and completed the study, while 4 others are still in follow-up
- Not yet ready from prime time
- But, this is an opportune time to engage woman who are HCV infected to link to appropriate care and treatment

HCV eradication in patients with hepatocellular carcinoma and cirrhosis improves tumour management and survival: The ANRS CO12 CirVir cohort

BACKGROUND & AIMS

- Assess impact of HCV eradication on:
  - HCC recurrence, liver decompensation, overall survival (OS) following curative treatment

METHODS

- Data were collected from 1,323 patients
  - With compensated cirrhosis*
  - Curatively treated for incidental HCC (resection or percutaneous ablation)
- Recruited 2006–2012 in 35 centres and followed up prospectively
  - SVR and HCC occurrence
- Primary outcomes
  - HCC recurrence, decompensation and OS from time of HCC treatment

RESULTS

- During a median FU of 67.5 months
  - 218 patients developed HCC
  - 128 received a curative procedure
- At HCC† diagnosis
  - Most patients were male (58.7%)
  - Mean age 63.9 years
  - 52.5% Child–Pugh A
- Attainment of SVR‡
  - Never: 71 patients (52.9%)
  - Before HCC occurrence: 27 patients (20.7%)
  - After HCC occurrence: 23 patients (18.1%)
- After a median 27.1 months post-HCC treatment
  - 55 (43.0%) experienced HCC recurrence
  - 48 (37.6%) patients died

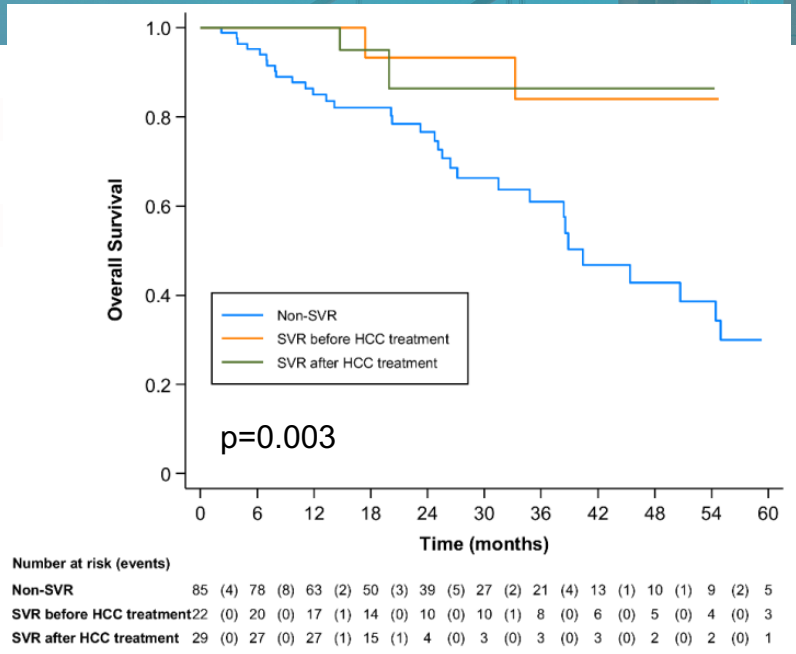
*Compensated Child–Pugh A biopsy-proven; †Mostly uninodular (75.7%), <20 mm (66.7%), and BCLC 0/A (93.7%); ‡Data missing in 7 patients.

Nahon P, et al. ILC 2019; PS-118

HCV eradication in patients with hepatocellular carcinoma and cirrhosis improves tumour management and survival: The ANRS CO12 CirVir cohort

RESULTS (Cont.)

- SVR did not significantly associate with reduced risk of HCC recurrence*
- In univariate (*Figure*) and multivariate analysis, SVR did associate with improved OS (HR=0.19 [0.07–0.48], p=0.001)
  - Survival benefit was explained by lower incidence of liver decompensation with SVR and higher rates of HCC recurrence re-treatment using sequential percutaneous ablation
- DAA intake associated with improved OS but not risk of HCC



CONCLUSIONS SVR is not associated with risk of HCC recurrence after a curative procedure in patients with cirrhosis. However, HCV eradication prevents potential liver function deterioration and improves OS by increasing HCC recurrence re-treatment

*Whether considering final SVR status (HR=0.94 [0.51; 1.73], p=0.84) or according to its time to achievement (before or after HCC emergence, global p=0.29).

Nahon P, et al. ILC 2019; PS-118

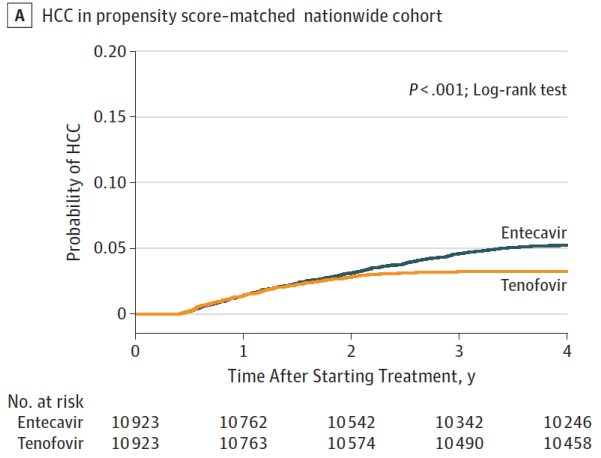
Hepatitis B

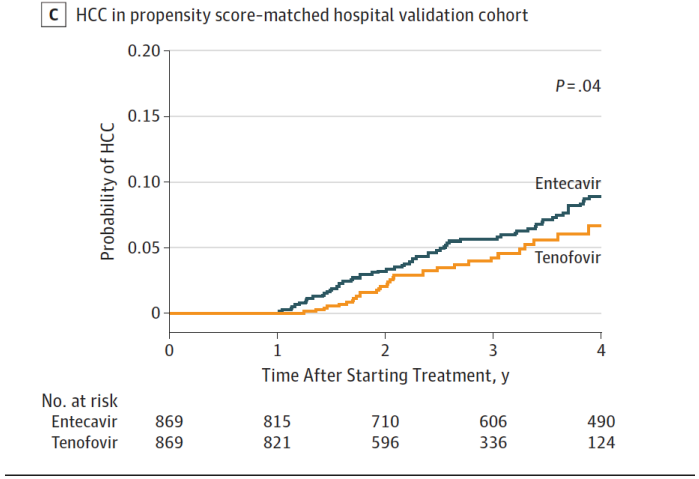
HBV Treatments: Dose Adjustments in CKD

eGFR (ml/min)	> 50	30-49	10-29	<10 HD, PD
Tenofovir disoproxil	300 mg daily	300 mg q48	300 mg q72-96	300 mg q 7 days
Entecavir	0.5 mg daily	0.5 mg q48 0.25 mg q24	0.5 mg q72 -.15 mg q24	0.5 mg q 7 days 0.05 mg daily
Entecavir (decompensated)	0.5 mg daily	1 mg q48 0.5 mg q24	1 mg q72 .3 mg q24	1 mg q 7 days 0.1 mg daily
Tenofovir alafenamide	25 mg daily	25 mg daily	25 mg daily but do not use GFR < 15 ml/min*	*25 mg

EMA, no dose adjustment for TAF in HD, GFR < 15 ml/min on HD
In US hemodialysis TAF dose is 25 mg daily, give after dialysis , not recommended for GFR<15 ml/min not on HD

Cumulative Incidence of Hepatocellular Carcinoma (HCC) and Death or Transplant in Propensity Score–Matched Pairs of Patients With Chronic Hepatitis B Infection Treated With Entecavir or Tenofovir





Corrected HRs for HCC in the tenofovir treatment group in the entire cohort and the propensity-score matched cohort are changed from 0.61 (95% CI, 0.54-0.70) to 0.68 (95% CI, 0.59-0.77), and from 0.62 (95% CI, 0.54-0.70) to 0.68 (95% CI, 0.60-0.78), respectively. The corrected HRs remain statistically significant.

JAMA Oncol. 2019;5(1):30-36. doi:10.1001/jamaoncol.2018.4070 *JAMA Oncol.* Published online April 25, 2019. doi:10.1001/jamaoncol.2019.0576

Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

BACKGROUND & AIMS

- TDF and ETV have potent hepatitis B antiviral effects and are recommended first-line for CHB
- **Aim:** To compare TDF and ETV on HCC risk in a territory-wide CHB cohort

METHODS

- Adult CHB patients initially treated with ETV or TDF for ≥6 months between 01/2008–06/2018
  - In/out-patient data from all Hong Kong public hospitals and clinics
  - Exclusions: patients with cancers or LT before or within first 6 months of treatment
  - Missing data replaced by MI by chained equations, then PS weighted to balance BL clinical characteristics

RESULTS

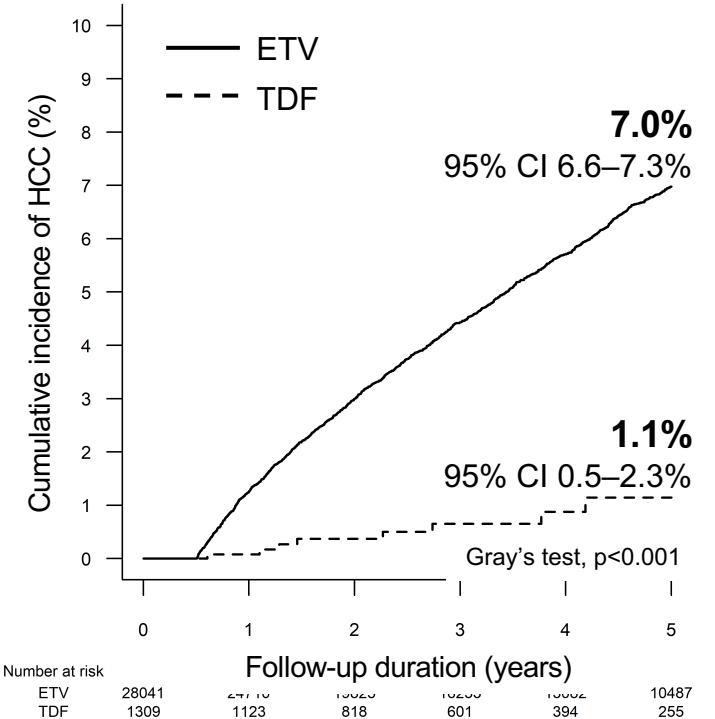
- 29,350 CHB patients identified (mean age 52.9 ± 13.2 years; 63.7% male)
  - 1,309 (4.5%) and 28,041 (95.5%) first received TDF and ETV, respectively
- At a median 3.6 years FU, 8 (0.6%) TDF and 1,386 (4.9%) ETV-treated patients developed HCC
  - TDF associated with lower HCC risk than ETV*

*Before (aHR 0.36, p=0.042) and after MI, with (weighted HR 0.36, p=0.013) and without (aHR 0.32, p=0.002) PS weighting.

Yip TCF, et al. ILC 2019; LB-03

Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir in patients with chronic hepatitis B

FIGURE 5-year cumulative HCC incidence



*Log-transformed in the model; †p=0.002 for TDF vs. ETV; ‡p=0.003 for TDF vs. ETV; All others p<0.001.

Yip TCF, et al. ILC 2019; LB-03

TABLE HCC risk analysis

Parameters	Univariate analysis†		Multivariable analysis†	
	SHR	95% CI	Adjusted SHR	95% CI
TDF vs. ETV	0.15	0.07–0.29	0.32	0.16–0.65
Age	1.06	1.06–1.06	1.05	1.04–1.05
Male sex	2.17	1.90–2.47	2.42	2.11–2.76
Cirrhosis	5.73	5.16–6.36	2.30	2.01–2.64
Platelet*	0.35	0.31–0.40	0.54	0.49–0.60
Albumin	0.91	0.91–0.92	0.97	0.97–0.98
ALT*	0.81	0.77–0.84	0.87	0.83–0.91
Total bilirubin*	1.48	1.41–1.56	–	–
HBeAg+‡	0.82	0.73–0.93	1.44	1.26–1.65

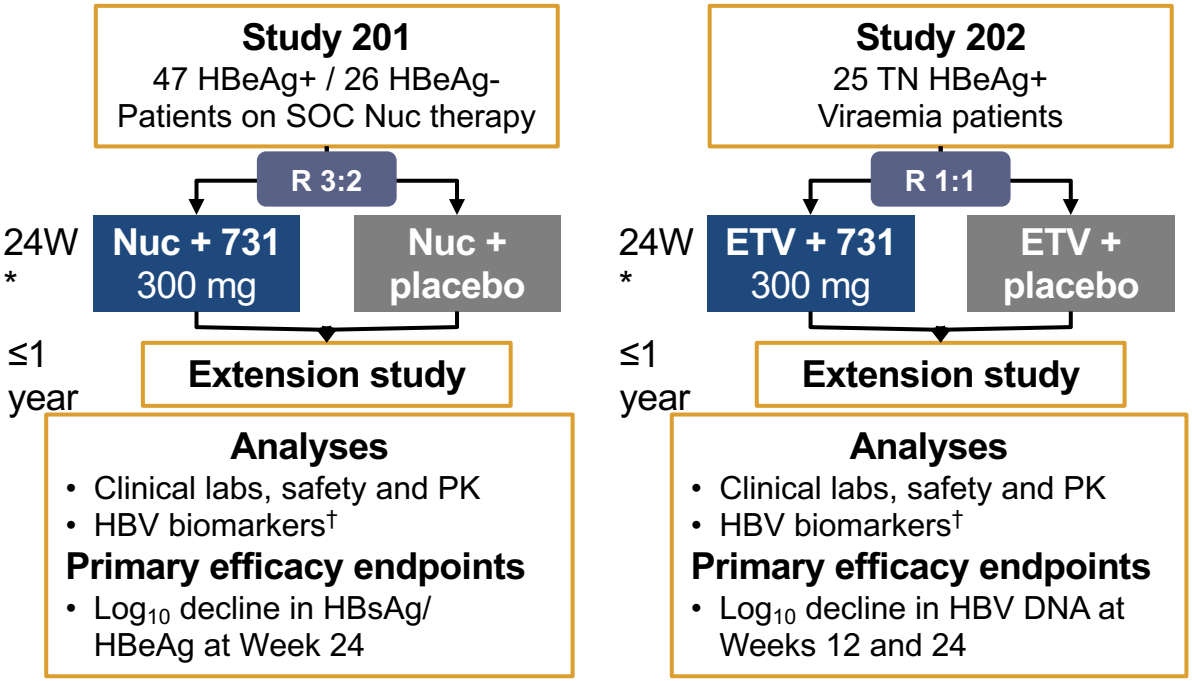
CONCLUSIONS TDF treatment associated with lower HCC risk than ETV in a territory-wide CHB cohort

Interim safety and efficacy results of the phase 2a program of ABI-H0731 + Nuc therapy in treatment-naïve and treatment-suppressed patients with CHB

BACKGROUND & AIMS

- Nucs are the standard of care (SOC) for CHB
  - But achieve low rates of sustained response off therapy
- The novel core inhibitor ABI-H0731 (731) exhibited potent anti-HBV activity over 28 days as monotherapy
- 731 + Nuc combo is being evaluated in two double-blind, placebo-controlled phase 2a trials in patients with CHB and F0–2 fibrosis

METHODS



*Including follow-up at Weeks 2, 4 and then monthly; †Including HBV DNA, HBV RNA, HBsAg and HBeAg.

Ma X, et al. ILC 2019; LB-06

Interim safety and efficacy results of the phase 2a program of ABI-H0731 + Nuc therapy in treatment-naïve and treatment-suppressed patients with CHB

RESULTS

- Enrolment complete in both studies
- Few TEAEs or laboratory abnormalities; generally mild or moderate
  - 3 AEs (rash) “possibly related” or “related” to treatment
  - None had associated systemic symptoms and none required treatment interruption
  - No discontinuations due to AE or ALT flares
- Significantly greater declines in HBV viremia (DNA/RNA) seen on combination therapy
- Individuals have shown decreases in HBeAg and HBsAg, but no meaningful conclusions can be drawn on antigen reductions at this early interim time point

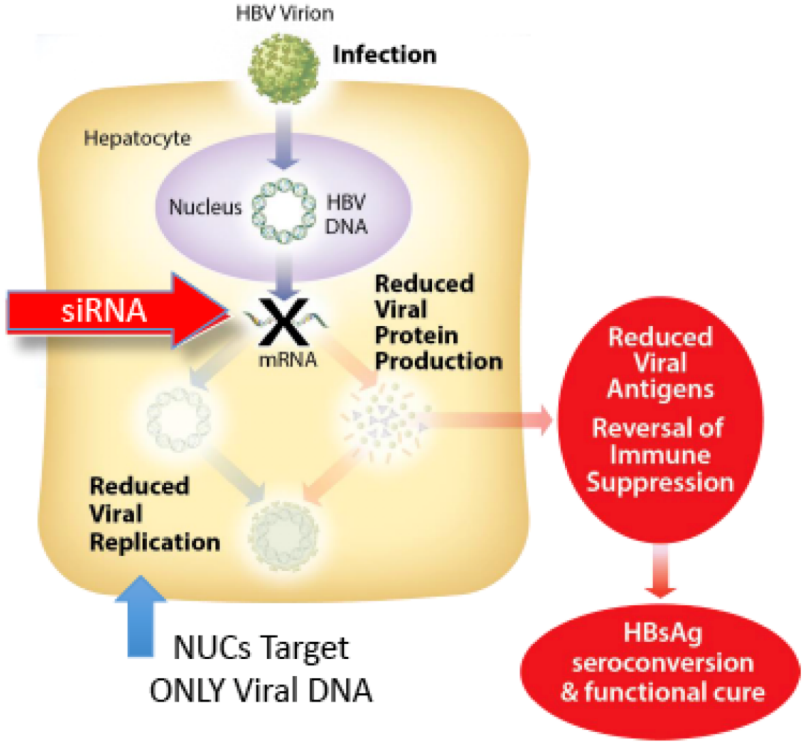
Study 202 (TN HBeAg+ subjects), mean log_{10} declines				
Marker	Week	ETV (n)	731+ETV (n)	P values
RNA, copies/mL	12	0.44 (12)	2.27 (12)	<0.005
	24	0.61 (5)	2.54 (6)	<0.005
DNA, IU/mL	12	3.29 (12)	4.54 (12)	<0.011
	24	3.99 (6)	5.94 (6)	<0.005
Study 201 (Nuc-suppressed HBeAg+ subjects), mean log_{10} declines				
Marker	Week	Nuc (n)	731+Nuc (n)	P values
RNA, copies/mL	12	0.05 (18)	2.34 (23)	<0.001
	24	0.15 (4)	2.20 (6)	0.012
Study 201 (Available subjects at Week 24), HBV DNA (+/-)				
DNA, PCR TND*	24	0 (4)	5 (6)	N/A

CONCLUSIONS Interim data suggest ABI-H0731+Nuc was well tolerated over the dosing period and exhibited early and enhanced antiviral benefit in suppressing HBV DNA and HBV RNA levels to a greater extent than seen with Nuc therapy. These interim data support the use of CIs in a next-generation regimen as potential advance in treatment

*Target not detected using ASMB <5 copies/mL semi-quantitative PCR assay.

Ma X, et al. ILC 2019; LB-06

Short term RNA interference (RNAi) therapy in chronic hepatitis B (CHB) using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold



Silence Entire HBV Genome

1. "HBsAg Theory"
   - Reducing HBsAg enables host immune system de-repression and long term control of virus
2. Destabilizing Viral Function
   - Silencing all antigens and reducing pgRNA could destabilize normal viral function
   - Enable host immune system de-repression and long term control of virus

Short-term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

AIMS

- To explore the effect of 3 doses of JNJ-3989 (formerly ARO-HBV) on HBsAg reductions below certain thresholds

METHODS

- Patients with chronic HBV received 3 SC doses of JNJ-3989 weekly to monthly together with ETV or TDF
- HBsAg levels were assessed in patients that had ≥24 weeks of HBsAg data (n=40)
- Safety and tolerability were assessed in all patients in these cohorts (n=56)

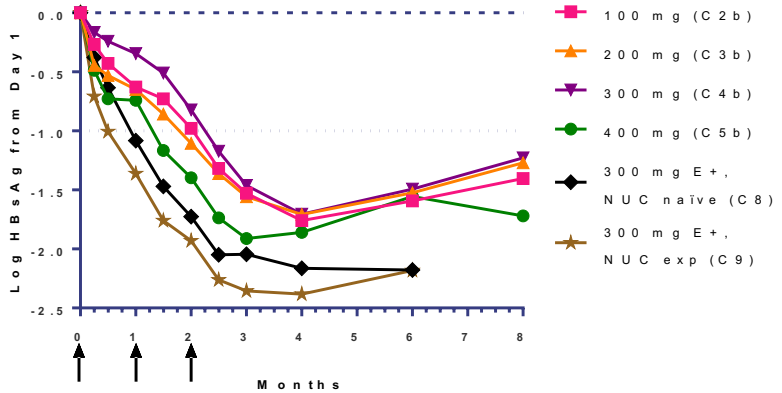
RESULTS

- JNJ-3989 was well tolerated
- JNJ-3989 reduced viral products in HBeAg+ and HBeAg-, NUC experienced or naïve patients
- HBsAg was reduced as follows:
  - To <100 IU/mL in 88%
  - By ≥1 Log_{10} IU/mL in 100%
  - Both thresholds have been associated with increased probability of HBsAg clearance when stopping NUC treatment[1]

1. Jeng WJ, et al. Hepatology 2018;68:425-34.
Yuen MF, et al. ILC 2019; PS-080

Short-term RNA interference therapy in chronic hepatitis B using JNJ-3989 brings majority of patients to HBsAg <100 IU/ml threshold

FIGURE **Mean HBsAg reductions from baseline**



Baseline HBsAg		
Threshold	N	Percent
>100 IU/ml	37 of 40	93%
NADIR HBsAg		
Threshold	N	Percent
≤100 IU/ml	35 of 40	88%
≤10 IU/ml	17 of 40	43%

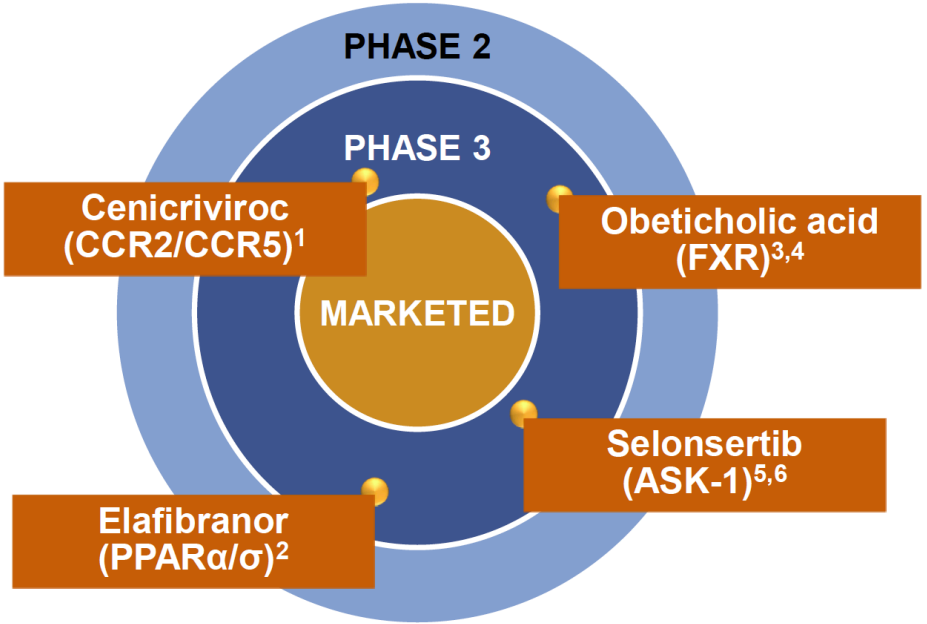
CONCLUSIONS

JNJ-3989 exhibits characteristics desirable for a cornerstone therapy in finite regimens aimed at HBsAg seroclearance in patients with chronic hepatitis B infection

Yuen MF, et al. ILC 2019; PS-080

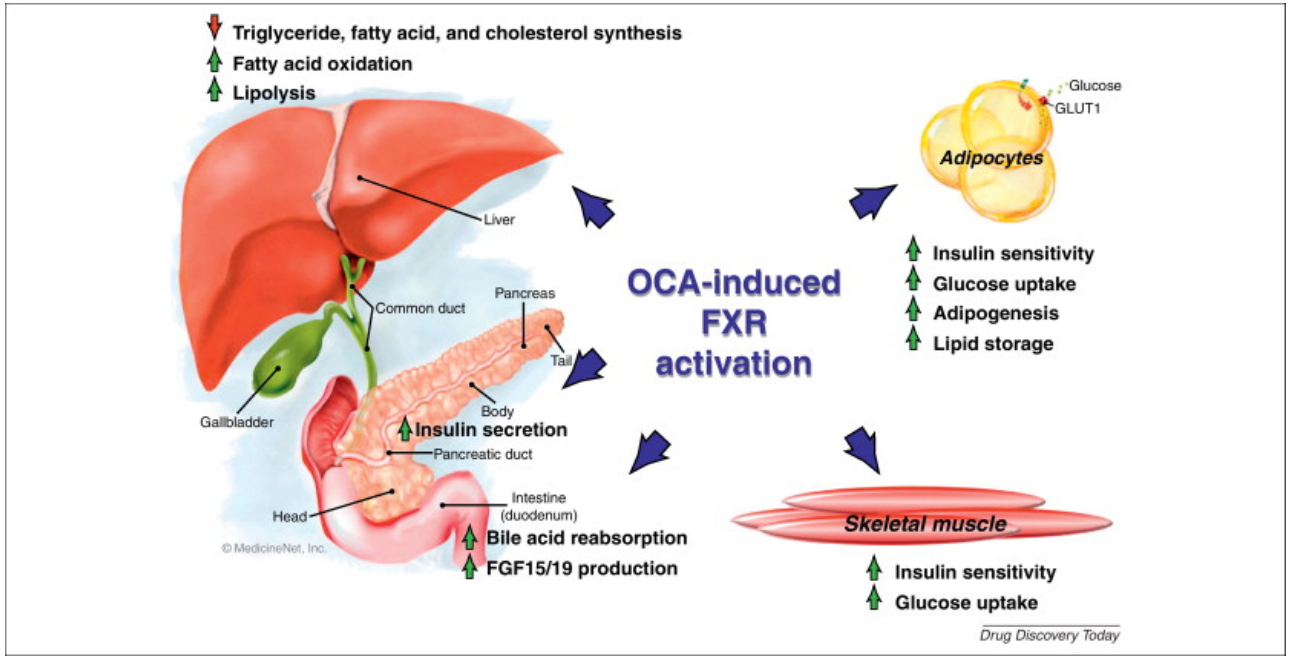
4 Regimens in Phase 3 of Development for Treatment of NASH

- Many drugs under evaluation for treatment of NASH
  - >85 clinical trials (active or planned)
  - 4 Phase 3 Clinical Trials



U.S. National Institutes of Health. ClinicalTrials.gov. Accessed June 11, 2018:
1. https://clinicaltrials.gov/ct2/show/NCT03028740. Last updated February 13, 2018; 2. https://clinicaltrials.gov/ct2/show/NCT02704403. Last updated May 14, 2018; 3. https://clinicaltrials.gov/ct2/show/NCT02548351. Last updated May 28, 2018; 4. https://clinicaltrials.gov/ct2/show/NCT03439254. Last updated May 24, 2018; 5. https://clinicaltrials.gov/ct2/show/NCT03053050. Last updated May 14, 2018;
6. https://clinicaltrials.gov/ct2/show/NCT03053063. Last updated February 26, 2018.

Obeticholic Acid



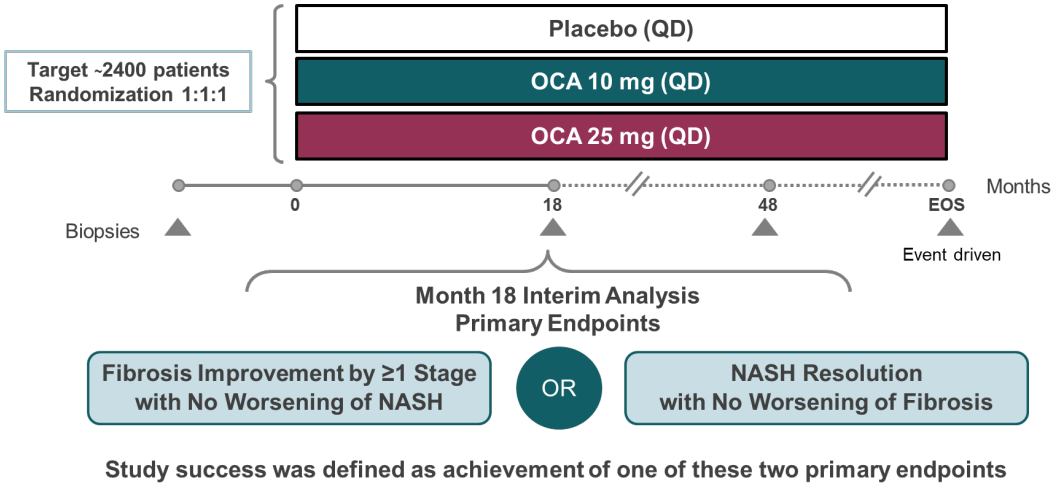
Adorini L, Drug Dis Today 2012;17:988-997

Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

BACKGROUND & AIMS

- OCA is a potent FXR agonist shown in preclinical models to have a direct antifibrotic effect in the liver[1]
- In the phase 2b FLINT study, OCA 25 mg for 72 weeks improved fibrosis and other histological features of NASH[2]
- OCA is the only investigational drug to have received Breakthrough Therapy designation by the US FDA for the treatment of NASH patients with liver fibrosis
- This Month 18 interim analysis of REGENERATE evaluated OCA on liver histology in NASH patients with F2/F3 fibrosis

METHODS



Study success was defined as achievement of one of these two primary endpoints

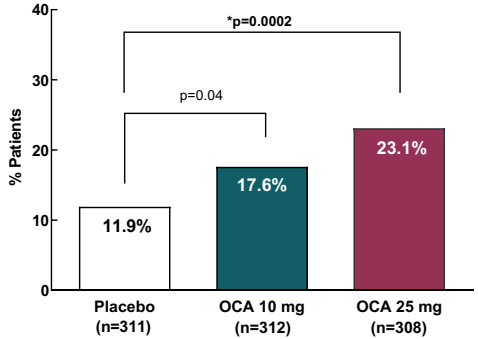
1. Albanis A, et al. AASLD 2005 (Hepatology 2005;42:1040A);
2. Neuschwander-Tetri BA, et al. Lancet 2015;385:956–65.
Younossi Z, et al. ILC 2019; GS-06

Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

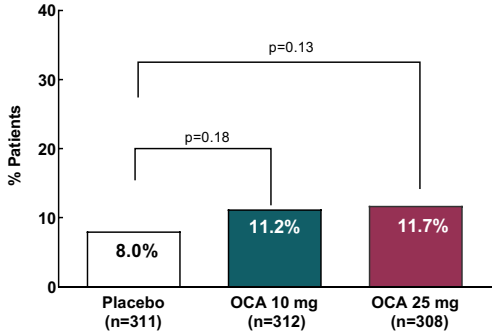
RESULTS

- OCA 25 mg QD met the primary endpoint of improvement in liver fibrosis with no worsening of NASH (p=0.0002* vs. placebo)
  - The antifibrotic effect of OCA was dose dependent and consistent across endpoints and key subgroups
- Although the additional primary endpoint of NASH resolution with no worsening of fibrosis was not met, OCA improved NASH disease activity based on key histological parameters including NAFLD activity score, hepatocyte ballooning and lobular inflammation

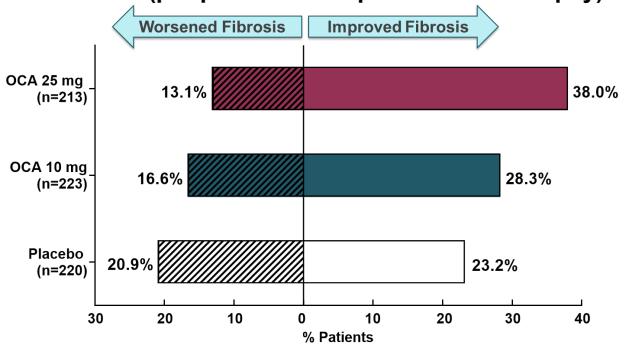
Primary endpoint (ITT): fibrosis improvement by ≥1 stage with no worsening of NASH



Primary endpoint (ITT): NASH resolution with no worsening of fibrosis



Fibrosis improvement or worsening by ≥1 stage (per protocol with post-baseline biopsy)



*Statistically significant in accordance with the statistical analysis plan agreed with the FDA. All other p values are nominal.

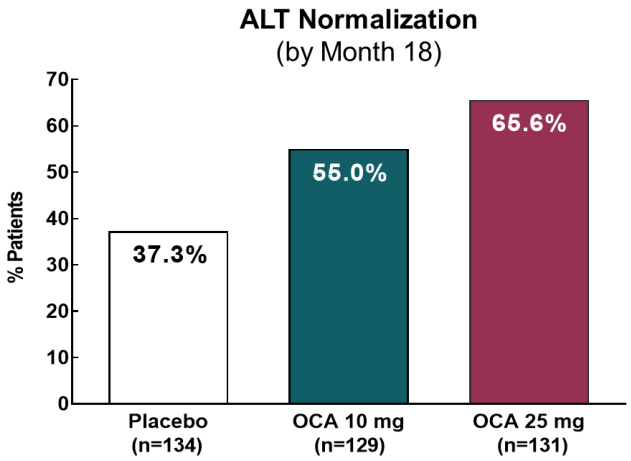
Younossi Z, et al. ILC 2019; GS-06

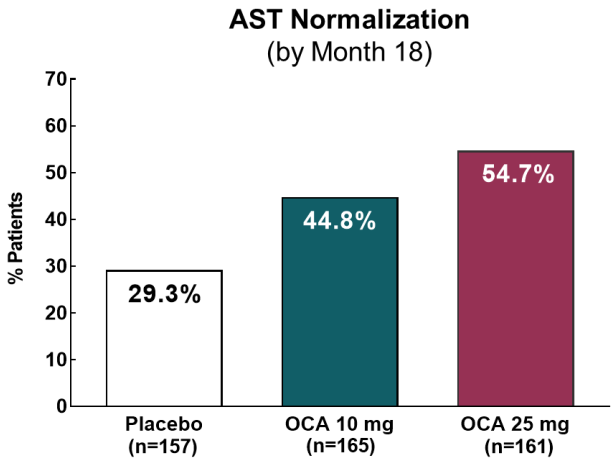
Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study of obeticholic acid treatment for NASH

RESULTS (Cont.)

- OCA rapidly decreased ALT, AST and GGT levels, which are routinely monitored by clinicians
- AEs were mostly mild to moderate in severity and the most common were consistent with the known profile of OCA

Normalization of aminotransferases in patients with elevated baseline levels

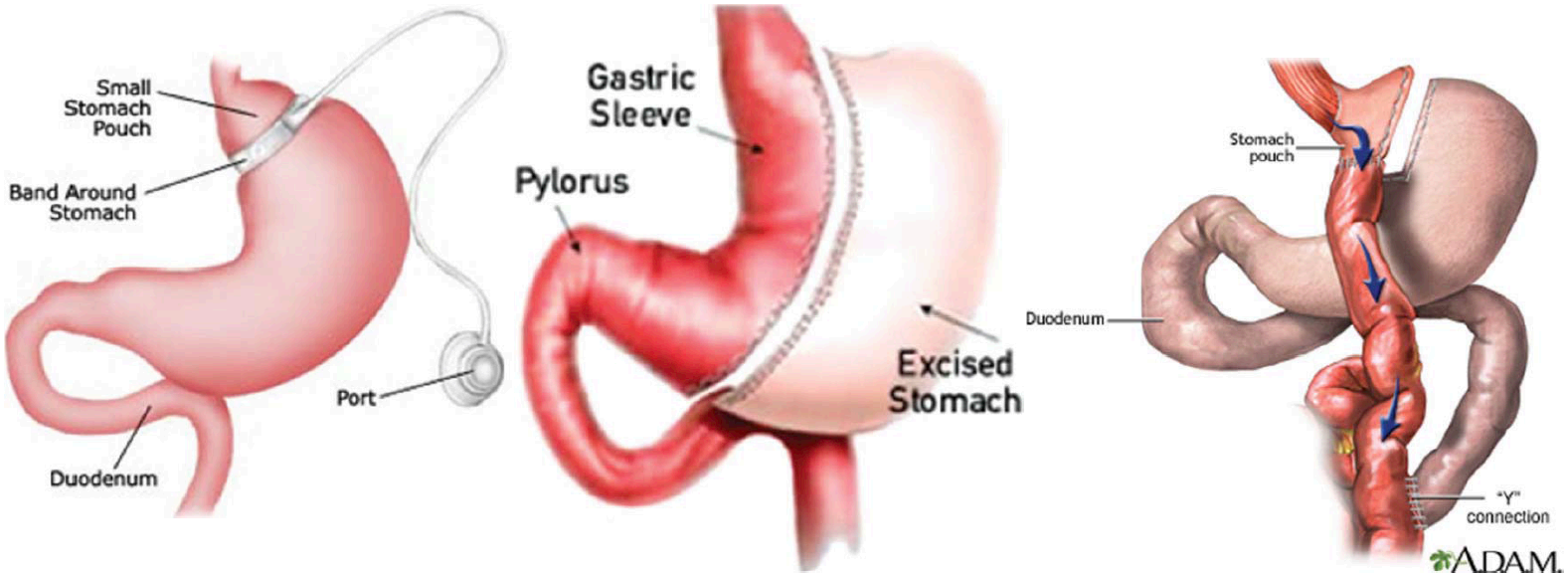




CONCLUSION REGENERATE is the first successful phase 3 study in NASH. These results are highly relevant because fibrosis is a strong predictor of liver-related morbidity and mortality in NASH.[1] The REGENERATE study is ongoing to confirm benefit on clinical outcomes

1. Dulai PS, et al. Hepatology 2017;65:1557–65.
Younossi Z, et al. ILC 2019; GS-06

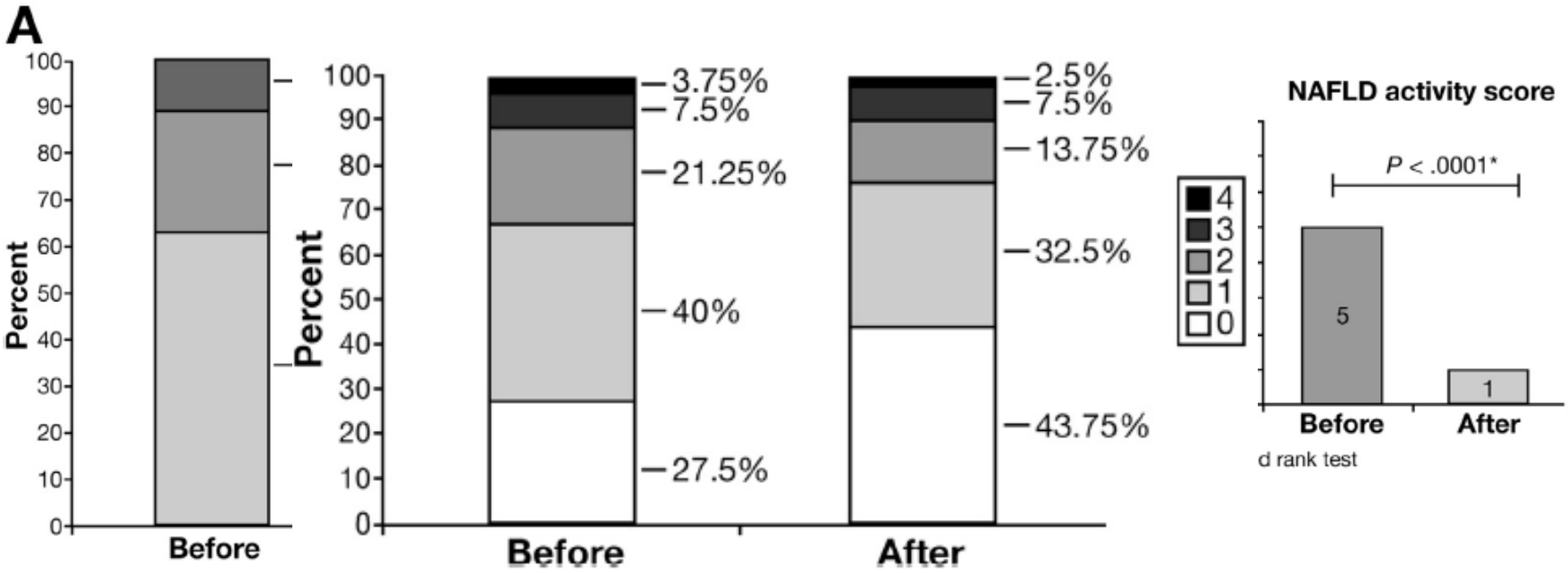
Surgical Procedures to Advance Weight Loss



Wachacheril JL, Chalasani N. Nonalcoholic fatty liver disease (NAFLD): Is it really a serious condition? Clinical Liver Disease 2012

Bariatric Surgery Improves Liver Biopsy Histology in Pts With NASH

- Prospective study of bariatric surgery in pts who are morbidly obese with biopsy-validated NASH, ≥ 1 comorbidity factor for > 5 yrs, no chronic liver disease (N = 109)



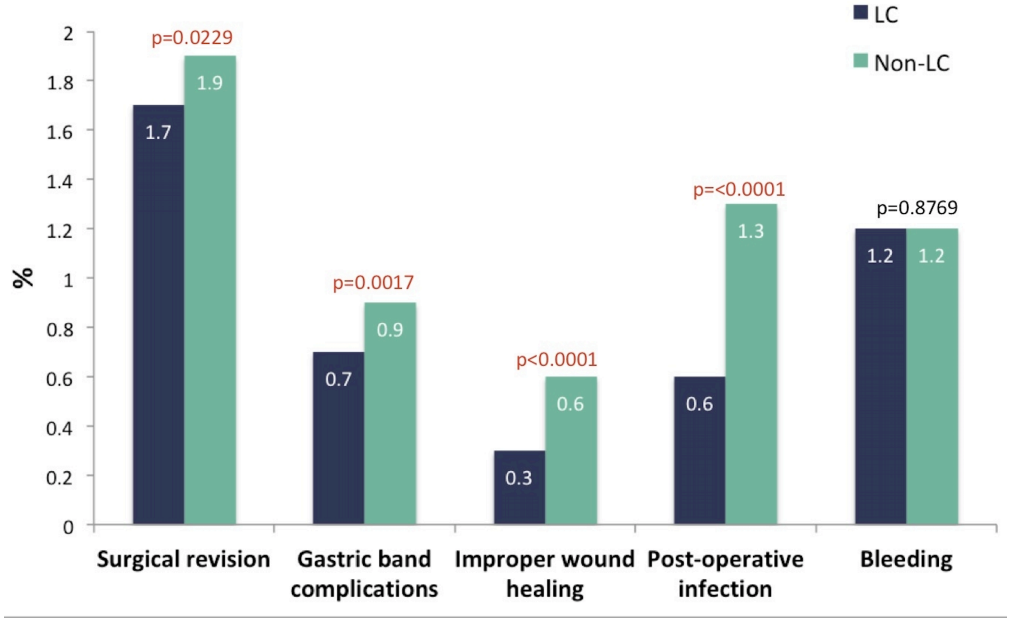
Lassailly G, et al. Gastroenterology. 2015;149:379-388.

LIVER CIRRHOSIS DOES NOT PREDICT WORSE OUTCOMES IN BARIATRIC SURGERY

- To determine outcomes for cirrhotic patients undergoing bariatric surgery (BS) compared to noncirrhotic patients
- Data from the National Inpatient Sample for 2012-2015, comprised of 44 states and 4,378 hospitals, accounting for over 7 million discharges were analyzed
- 302,306 patients underwent BS, of which 20,095 had LC and 282,211 did not (non-LC).

DDW 2019 #808

LIVER CIRRHOSIS DOES NOT PREDICT WORSE OUTCOMES IN BARIATRIC SURGERY



	LC n (%)	Non-LC n (%)	Chi square p-value	Adjusted OR (95% CI)
Inpatient mortality	218 (1.1)	1390 (0.5)	<0.0001	1.47 (1.24-1.73)
Mean LOS	3.3 days	3.7 days	<0.0001	-
Mean total charges	$32,040	$27,685	<0.0001	-

*All statistically significant values are noted in red text.

Slightly higher mortality rates among LC patients

These patients did not have worse postoperative outcomes compared to non-LC

LC should not be an exclusion criterion for BS.

DDW 2019 #808

Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor immunotherapy

BACKGROUND & AIMS

- Common liver immune-related AEs (LirAEs) resulting from CPi immunotherapy are poorly characterized
- **Aim:** To better understand the causes of liver enzyme elevation (LEE), frequency of LirAEs and the resulting impact on patient management

METHODS

Aug 2012–Dec 2018
Patients from phase 1/2 clinical trials (Tumor Immunotherapy Program*)

↓

Clinical records reviewed for patients with clinically significant LEE (ALT/AST >3x ULN and/or bilirubin >1.5x ULN)

RESULTS

Patient demographics	Patients (%) treated with CPi (N=472)
Therapy type	
Anti-PD-1	65.2
Combination CPi	6.1
Clinically significant LEE	21.6
Diagnostic evaluation	
Liver imaging	71.6
HBV/HCV serology	16.7
Autoimmune serology	13.7
Liver biopsy	2.9
LEE attributed to	
Disease progression	54.9
Other drugs/toxins	6.9
Surgery	4.9
Other	16.7
LirAE	16.7 of LEE (3.6% of total cohort)

*At the Princess Margaret Cancer Centre, Toronto, Canada.
Cunningham M, et al. ILC 2019; PS-139

Liver enzyme elevations and hepatotoxicity in patients treated with checkpoint inhibitor therapy

RESULTS (Cont.)

- LirAE associated with
  - Prior CPi exposure (in 41.2% of patients with vs. 15.4% without LirAE; p=0.011)
  - Other irAEs (in 76.5% of patients with vs. 19.2% without LirAE; p=<0.001)
- 15/17 patients with LirAE received steroids and liver enzymes normalized after a median of 37 days (IQR 21–52). 4 patients received further CPi with recurrent LirAE in 1 patient

Variable	Patients (N=472)
Follow-up, median (IQR)	7.5 months (3.6–16.2)
Total disease progression, n (%)	421 (89.2)
Patients with LirAE (%)	52.9
Patients without (%)	86.7
	p=0.001
Death, n (%)	292 (61.9)
Death due to complications from LirAE	0

CONCLUSIONS

LEE may be unrelated to cancer/CPi. LirAEs were more common in patients with previous CPi exposure and other irAEs. Lower incidence of disease progression seen in those with LirAE

Cunningham M, et al. ILC 2019; PS-139

Bezafibrate improves the effect of obeticholic acid on cholestasis in patients with primary biliary cholangitis

BACKGROUND & AIMS

- OCA is the 2nd-line treatment for patients with PBC and inadequate response/intolerance to UDCA[1]

  Bezafibrate has also been shown to improve biochemical responses in patients with PBC[2]
- **Aim:** To explore whether OCA + bezafibrate therapy normalized ALP and bilirubin levels (strongest predictor of improved outcome) and to explore the safety of this combination

METHODS

- 16 patients from the POISE* study who received OCA (5 or 10 mg QD) ± UCDA for 4–5 years
  - OCA terminated in 3 patients (pruritus n=2)
- After 5 years, bezafibrate 400 mg QD added to OCA + UCDA in 11 patients
  - 9 female; mean age 64 years; mean FibroScan 9.3 kPa (range 4.3–21.8)
  - Bezafibrate terminated in 1 patient due to myalgia
  - Effect on pruritus assessed with the PBC-40 questionnaire
- Primary endpoint: Normalization of ALP and bilirubin†

*PBC OCA International Study of Efficacy; †P-values calculated by per-protocol analysis.

1. Nevens F, et al. N Engl J Med 2016;375:631–43; 2. Corpechot C, et al. N Engl J Med 2018;378:2171–81.
Smets L, et al. ILC 2019; LB-05

Bezafibrate improves the effect of obeticholic acid on cholestasis in patients with primary biliary cholangitis

RESULTS

- After 6 months of OCA, ALP decreased in 73% of patients (p<0.01)*
- After 4–5 years of POISE, no patients reached the primary endpoint
  - Normal ALP: 0/11, normal bilirubin: 9/11 (*Table*)
- After 6 months of triple treatment, ALP further decreased in 100% of patients (p<0.001). Bilirubin further decreased in 100% of the patients (p=0.01)
  - Normal ALP in 5/10, normal bilirubin in 9/10 (primary endpoint met in 50% of patients)
  - Itching decreased in 5/8 with bezafibrate; mean PBC-40 score decreased from 5.6 to 4.4 (p=0.07)

TABLE Biochemical parameters (median [IQR])

	start UDCA (n=11)	start OCA (n=11)	6 m OCA (n=11)	4–5 y OCA (n=11)	6 m OCA + bezafibrate (n=10)
ALP (U/L)	1026 [403.0–1558.0]	315.0 [275.0–408.4]	233.2 [194.4–259.4]	190.2 [157.4–252.0]	108.5 [93.8–150.3]
BILI (µMOL/L)	12.3 [4.3–14.9]	7.7 [6.8–20.9]	8.6 [5.8–18.0]	7.7 [6.8–14.7]	5.8 [3.5–8.6]
AST (U/L)	71.0 [34.0–98.0]	37.2 [27.9–67.9]	35.9 [23.8–69.0]	29.3 [26.3–47.8]	37.0 [26.3–44.5]
ALT (U/L)	78.0 [26.0–118.0]	45.6 [27.2–67.8]	29.3 [17.4–46.0]	21.9 [15.5–32.0]	27.0 [16.8–35.0]
GGT (U/L)	260.0 [101.0–938.0]	274.7 [97.3–397.7]	71.0 [52.1–189.9]	37.2 [27.6–87.8]	35.5 [24.8–101.5]

*Bilirubin also decreased, but was not significant (p>0.05).

CONCLUSIONS

OCA + bezafibrate in patients with PBC had a strong positive effect on cholestasis, improved pruritus and is well tolerated

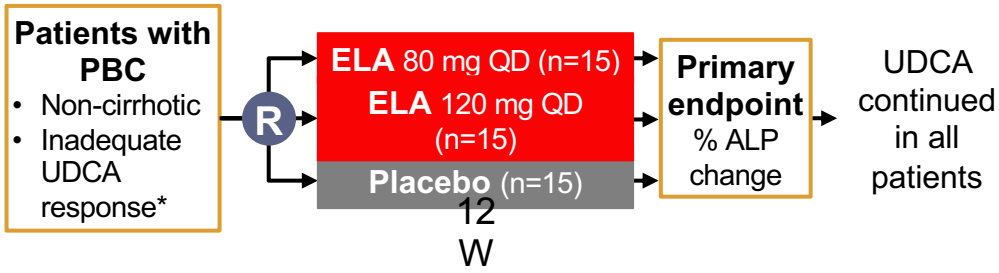
Smets L, et al. ILC 2019; LB-05

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

BACKGROUND & AIMS

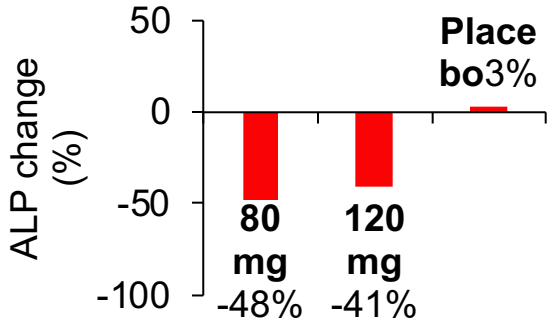
- Up to 40% of UDCA-treated patients have suboptimal response and are at high risk of disease progression
- **Aim:** This phase 2a, double-blind, placebo-controlled study investigated elafibranor (ELA), a dual PPARα/δ agonist, as a new anti-cholestatic treatment for PBC

METHODS



RESULTS

- **Primary endpoint:** ELA demonstrated significant decreases in mean ALP at Week 12



- Highly significant treatment effect vs. placebo (both p<0.001)
  - 80 mg: -52% (95% CI -62.5, -41.5)
  - 120 mg: -44% (95% CI -55.7, -32.1)

*Defined as ALP >1.67x ULN.

Jörn S, et al. ILC 2019; LB-02

Elafibranor demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to UDCA

RESULTS (Cont.)

- Composite endpoint of ALP <1.67x ULN + ALP decrease >15% + total bilirubin <ULN
  - 80 mg: 67% patients (p=0.002); 120 mg: 79% patients (p<0.001) vs. placebo: 6.7%
- GGT also highly significant vs. placebo
  - 80 mg: -39% (p=0.001); 120 mg -40% (p=0.002)
- ELA-treated patients showed improvement in lipid markers,* reduction of inflammatory markers,† and a decrease in C4 (an intermediate of bile acid synthesis)
- By self-reported VAS, patients with BL pruritus (10/group) showed improvement at Week 12
  - 80 mg: -24%; 120 mg: -49%; placebo: -7%
- Both doses of ELA were well tolerated

CONCLUSIONS ELA demonstrated a substantial anticholestatic effect in patients with PBC and inadequate response to UDCA. This was associated with anti-inflammatory and potential antipruritic effects, which make it a promising novel treatment candidate

*Including total cholesterol, low-density lipoprotein, and triglycerides; †IgM, CRP, haptoglobin, and fibrinogen.

Jörn S, et al. ILC 2019; LB-02

Long-term outcome in autoimmune hepatitis: The second 20 years of follow-up

BACKGROUND & AIMS

- Despite immunosuppressive therapy, liver disease can progress in AIH
- Follow-up data beyond 20 yrs are sparse
- Patient outcomes were compared over the second 20 yrs of follow-up with those in 327 patients followed up from initial diagnosis

METHODS

- Survival analysis with Kaplan–Meier comparisons, Cox regression analysis, calculation of standardized mortality ratios (SMR)

RESULTS

- 65 patients diagnosed 1971–1996 and already followed up for 20 yrs, followed-up for a further median 6.1 yrs (range 0.3–26)
- 40 patients remained on treatment until end of follow-up
- 5 patients (4 on treatment) relapsed for the first time after 20 yrs
- 22 patients had cirrhosis at diagnosis
  - Cirrhosis developed in a further 12 within 20 yrs
  - Cirrhosis developed in 5 more after 20 yrs
- 42 patients were alive at end of follow-up
  - 3 underwent liver transplantation
- 20 patients died
  - 3 liver related and 17 due to other causes*

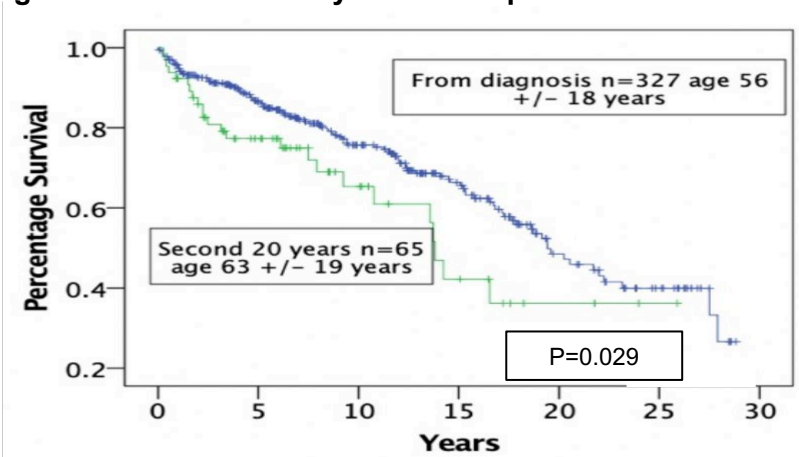
*7 malignancy, 6 infection and 4 other.

Harrison L, et al. ILC 2019; FRI-025

Long-term outcome in autoimmune hepatitis: The second 20 years of follow-up

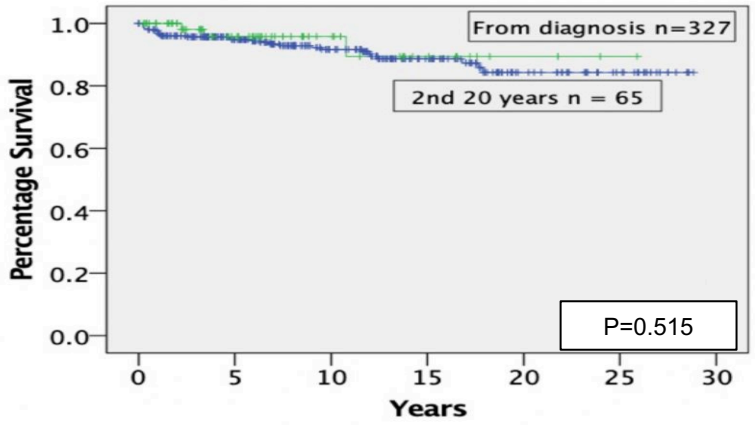
RESULTS (Cont.)

Figure 1. Survival from any death/transplant



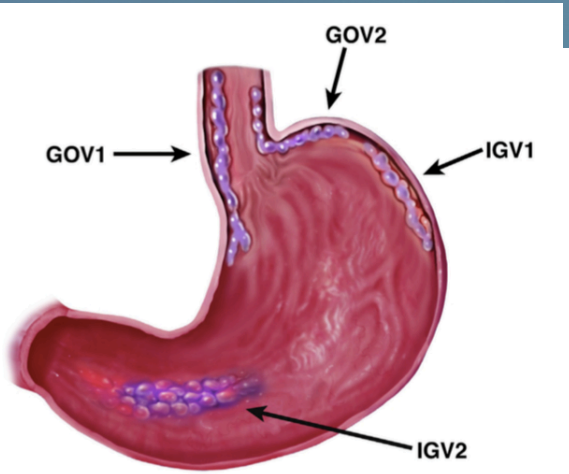
- SMRs did not differ significantly between those followed over the second 20 yrs (1.45 [0.84–2.65]) and those followed from diagnosis (1.60 [1.21–1.91])

Figure 2. Survival from liver-related death/transplant



CONCLUSIONS During the second 20 yrs of follow-up, patients with AIH continue to have disease relapse and to develop cirrhosis. They have similar age-adjusted survival to patients followed from initial diagnosis

Acutely bleeding Gastric varices

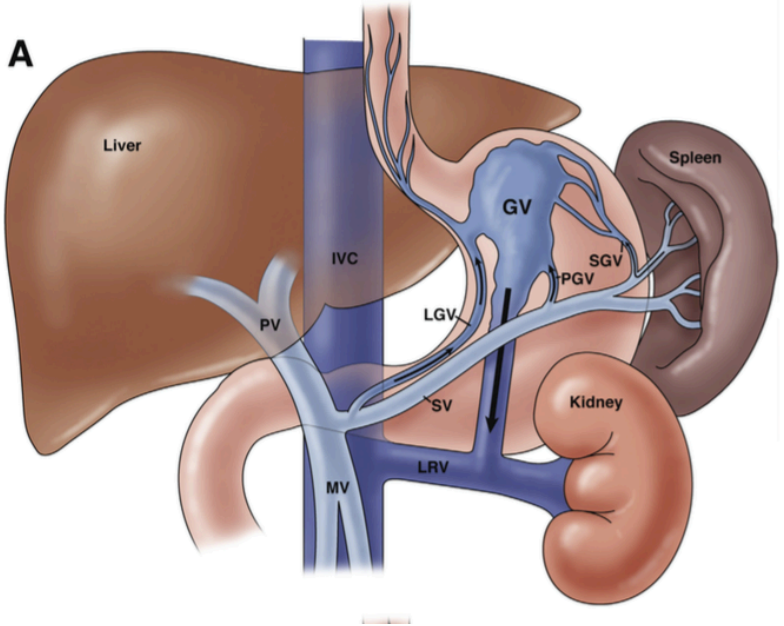


- GOV1: treat with ligation
- GOV2 and IGV1: Cyanoacrylate if available (2 octyl cyanoacrylate) and local expertise
- Otherwise TIPS or BRTO

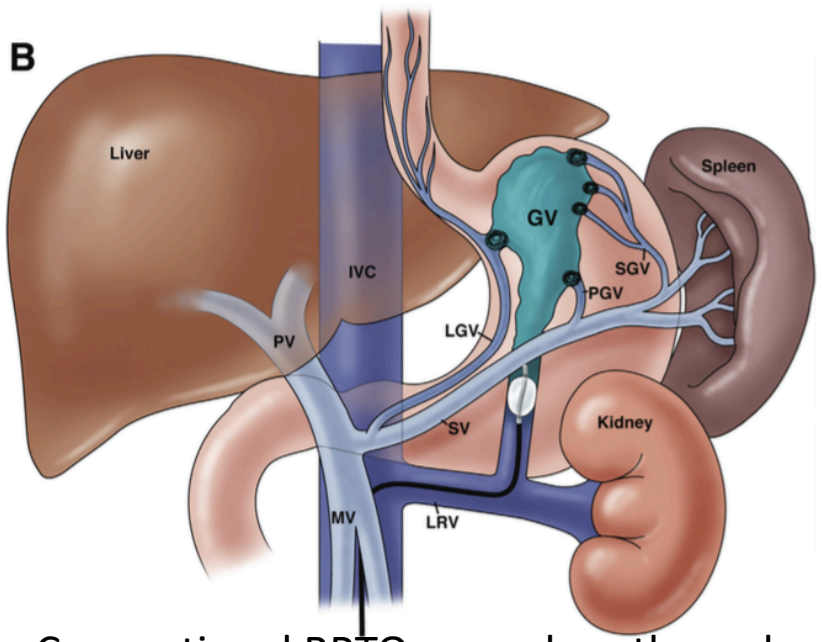
- Cyanoacrylate generally preferred over sclerotherapy
  - Complications include cyanoacrylate emboli
- If IGV1 found, assess for splenic vein thrombosis

Dig Dis Sci. 2014 Sep;59(9):2178-83

Balloon-occluded Retrograde Transvenous Obliteration For Gastric varices



porto- systemic venous anatomy of GV with the classic gastrorenal or splenorenal shunts.



Conventional BRTO procedure through transfemoral approach with balloon in the gastrorenal shunt

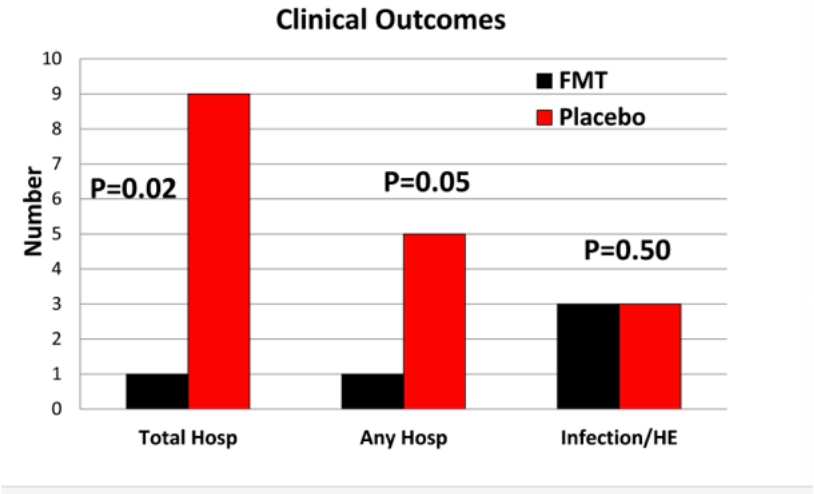
Clinical Gastroenterology and Hepatology 2014;12:919–928

RANDOMISED TRIAL OF BALLOON-OCCLUDED RETROGRADE TRANSVENOUS OBLITERATION VERSUS CYANOACRYLATE INJECTION FOR PREVENTION OF GASTRIC VARICEAL REBLEEDING

- 64 patients with variceal bleeding were randomly assigned either balloon-occluded retrograde transvenous obliteration (n = 32) or cyanoacrylate injection (n = 32)
- The mean duration of follow−up period was 20.9 months in the BRTO group and 22.6 months in the
- The cumulative probability of remaining free of all-cause rebleeding was significantly higher in the BRTO group than in the cyanoacrylate group; the probability at 2 years was 94.7% in the BRTO group and 66.9 % in the cyanoacrylate group (p = 0.005).
- no difference in survival with estimated 1-year survival rates for BRTO and cyanoacrylate injection treated patients of 93.3% and 90.6%, and 2-year survival rates of 82.3% and 86.5%, respectively.

FECAL MICROBIOTA CAPSULAR TRANSPLANT IS SAFE AND EFFECTIVE IN PATIENTS WITH RECURRENT HEPATIC ENCEPHALOPATHY: A RANDOMIZED, BLINDED, PLACEBO CONTROLLED TRIAL

- The safety and impact on brain function & mucosal/stool microbiota in recurrent HE of capsular FMT vs placebo.
- Cirrhotic outpts with recurrent HE on SOC were randomized 1:1 into receiving 15 FMT capsules vs placebo from a single donor enriched in beneficial Lachnospiraceae & Ruminococcaceae.
- 20 pts on lactulose/rifaximin were randomized 1:1. MELD score was similar at baseline (9.6 vs 10.2) & study end (10.2 vs 10.5).



Bajaj et al DDW 2019

LONG TERM USE OF PROTON PUMP INHIBITORS INCREASES MORTALITY AND HEPATIC DECOMPENSATION IN PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

- This study examined whether PPI use increases mortality and admissions for severe hepatic decompensation in patients with decompensated liver cirrhosis and to determine if dosage and duration of PPI has an impact on these findings
- Comparison between users and non-users was done after propensity score adjustment for 40 baseline characteristics, comorbidities and medication
- 511 patients were included, 334 were PPI users of which 3.9% (13/334) had HCC at baseline. 116 were non-users, of which 4.3% (5/116) had HCC.

DeRoza et al DDW 2019 #314

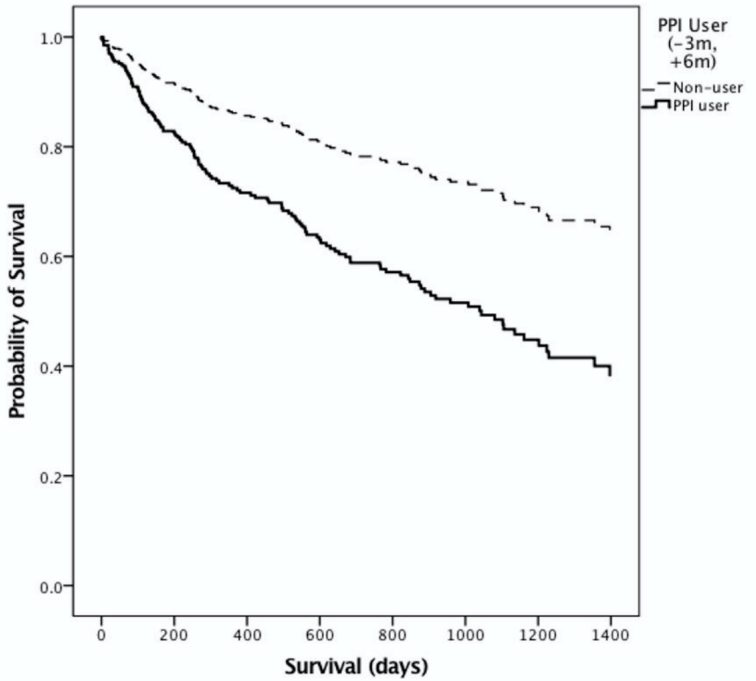
LONG TERM USE OF PROTON PUMP INHIBITORS INCREASES MORTALITY AND HEPATIC DECOMPENSATION IN PATIENTS WITH DECOMPENSATED LIVER CIRRHOSIS

Table 1: Mortality Risk for Proton Pump Inhibitor Users with Decompensated Cirrhosis

Overall Mortality Risk of PPI Users in Decompensated Cirrhosis Population*		
	Adjusted HR (95% CI)	**P value**
Landmark Period: -3 to +6 months *N=332*	2.159 (1.231- 3.787)	0.007
Period: -3 to + 3 months *N=295*	1.419 (0.935- 2.154)	0.100
Period: -3 to +9 months *N=263*	3.691 (1.605- 8.485)	0.002
Mortality Risk for PPI Exposure Using Cumulative Defined Daily Dose(cDDD)		
cDDD	**HR (95% CI)**	**P Value**
28 to 90	1.55 (0.547-4.401)	0.409
91 to 180	2.75 (1.245-6.075)	0.012
>180	2.15 (1.219-3.777)	0.008

HR: Hazard Ratio (with propensity score adjustment)
CI: Confidence Interval
*- Propensity Score Adjusted Cox Regression Analysis

Figure 1: Survival Analysis for Proton Pump Inhibitor User and Non-User with Decompensate Liver Cirrhosis, by Six Month Landmark Analysis



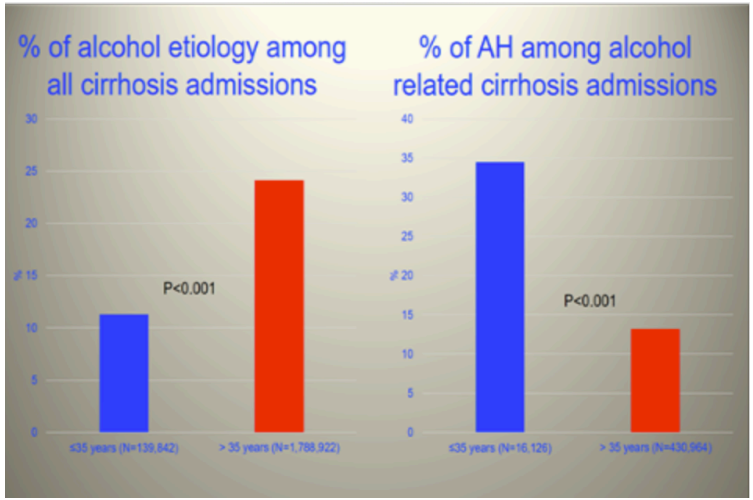
Annual age- standardized mortality rates for chronic liver disease in the United States from 2007 through 2016

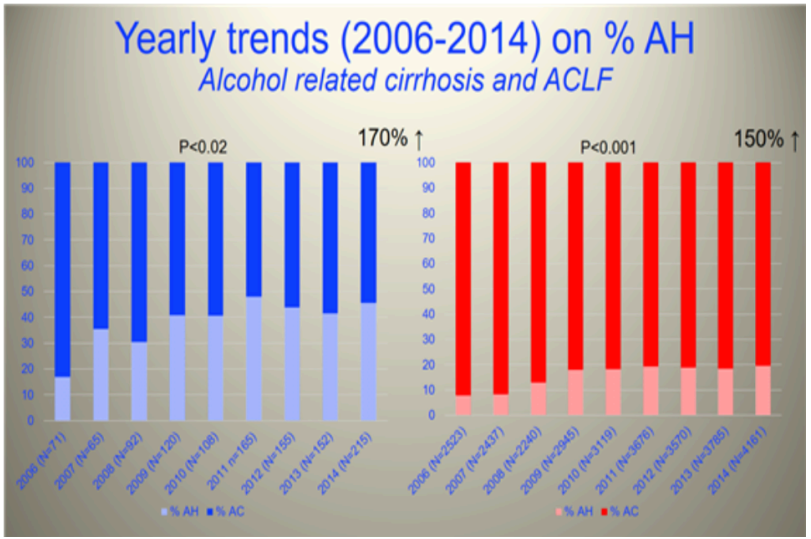
- Liver-related mortality rates for ALD have consistently increased over the past decade
- Annual percentage change in age-standardized mortality rates for alcoholic liver disease was +2.3% from 2007–2013 and accelerated to +5.3% from 2013–2016
- Currently alcoholic liver disease is the leading cause of all cause mortality and underlying cause of death in those with chronic liver disease

Gastroenterology 2018;155:1154–1163

INCREASING HOSPITALIZATIONS AND BURDEN OF ACUTE ON CHRONIC LIVER FAILURE AMONG ALCOHOL ASSOCIATED LIVER DISEASE IN YOUNG INDIVIDUALS IN THE US

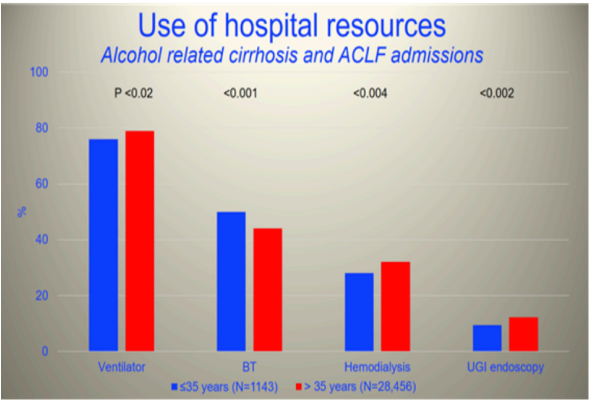
- National Inpatient Sample (2006-2014) was queried for hospitalizations with discharge diagnosis of cirrhosis using ICD-09 codes.
- ACLF was defined with ≥2 organ failures (OF) and its severity stratified to 1, 2, 3 with 2, 3, and >3 OF. Hospitalizations were stratified by age: young (≤35 yrs.) and old (>35 yrs.)
- Of 447,078 patients, admissions with discharge diagnosis of AALD between 2006 and 2014, 16,114 (3.7%) were ≤35 years

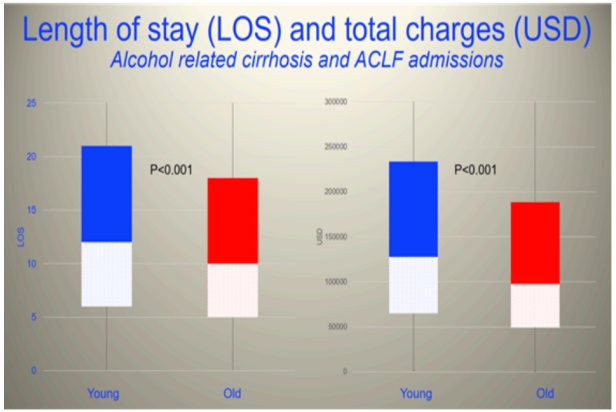


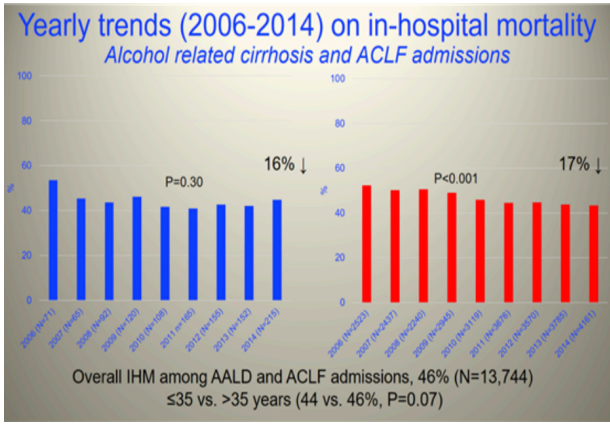


Singal et al DDW 2019

INCREASING HOSPITALIZATIONS AND BURDEN OF ACUTE ON CHRONIC LIVER FAILURE AMONG ALCOHOL ASSOCIATED LIVER DISEASE IN YOUNG INDIVIDUALS IN THE US







The disease burden in young individuals with ACLF is increasing with higher frequency of admissions with more severe ACLF and is associated with consumption of hospital resources.
Studies are needed to develop preventive strategies to reduce burden in young adults related to AALD and ACLF.

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