Clinical Impact of New Viral Hepatitis Data From San Francisco 2018

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Faculty

Paul Y. Kwo, MD
Professor of Medicine
Director of Hepatology
Stanford University School of Medicine
Palo Alto, California

Nancy Reau, MD
Professor of Medicine
Chief, Section of Hepatology
Associate Director, Solid Organ Transplantation
Richard B. Capps Chair of Hepatology
Rush University Medical Center
Chicago, Illinois

Faculty Disclosures

Paul Y. Kwo, MD, has disclosed that he has received consulting fees from AbbVie, Arrowhead, Bristol-Myers Squibb, Ferring, Gilead Sciences, Johnson & Johnson, Merck, Quest, and Surrozen; has received funds for research support from Assembly, Bristol-Myers Squibb, Gilead Sciences, and La Jolla; has served on data and safety monitoring boards for Durect and Johnson and Johnson; and has ownership interest in Durect.

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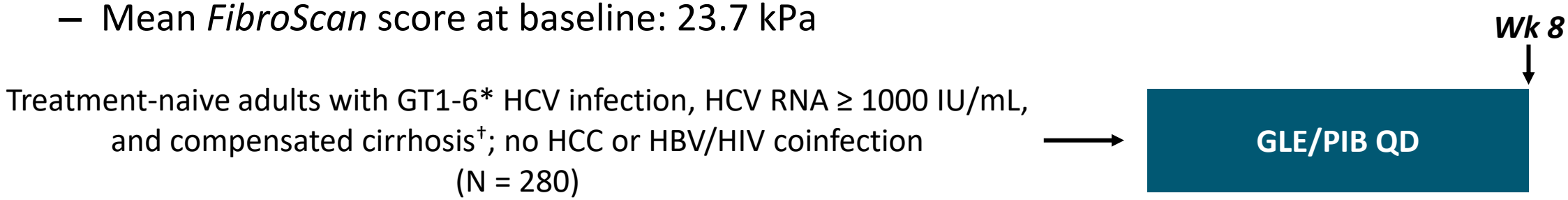
Treatment of HCV Infection

EXPEDITION-8: GLE/PIB for 8 Wks in Patients With GT1-6 HCV and Compensated Cirrhosis

- Multicenter, open-label, single-arm phase IIIb study
  - 83% HCV GT1; 90% CP5, 9% CP6, 1% CP7; 17% with platelet count < 100 x 10^9 cells/L
  - Mean *FibroScan* score at baseline: 23.7 kPa



*GT3 added in protocol amendment with enrollment ongoing; excluded from current analysis.
†*FibroTest* ≥ 0.75 and APRI > 2, *FibroScan* ≥ 14.6 kPa, or biopsy at screening.

- Primary endpoint: SVR12
  - ITT: includes all patients receiving ≥ 1 study drug dose; PP: excludes ITT patients with virologic breakthrough or discontinuation before Wk 8, missing data in SVR12 window

Brown. AASLD 2018. Abstr LB-7.

EXPEDITION-8: Efficacy and Safety With 8-Wk GLE/PIB

- In ITT and PP analyses, lower bounds of 95% CIs exceeded predefined efficacy thresholds
  - No virologic failures

SVR12, % (n/N)	GLE/PIB
ITT	98 (274/280)*
PP	100 (273/273)†

*Missing SVR12 data, n = 5 (all undetectable at last visit); premature d/c, n = 1. †Excludes ITT nonresponders, n = 6; patient achieving SVR12 with < 8 wks GLE/PIB, n = 1.

- No unexpected safety events

- No deaths, HCC, d/c for AEs, single AE in ≥ 10% of patients, notable ALT/AST or bilirubin elevations

AE	GLE/PIB (N = 280)
Any AE, n (%)	134 (48)
Serious AEs, n (%)	6 (2)*
AEs in 5% to < 10% of patients, %	
▪ Pruritus	9.6
▪ Fatigue	8.6
▪ Headache	8.2
▪ Nausea	6.4

*Atrial fibrillation, bronchitis, duodenal ulcer hemorrhage, peripheral edema, pneumonia, pyelonephritis; none related to treatment.

Brown. AASLD 2018. Abstr LB-7.

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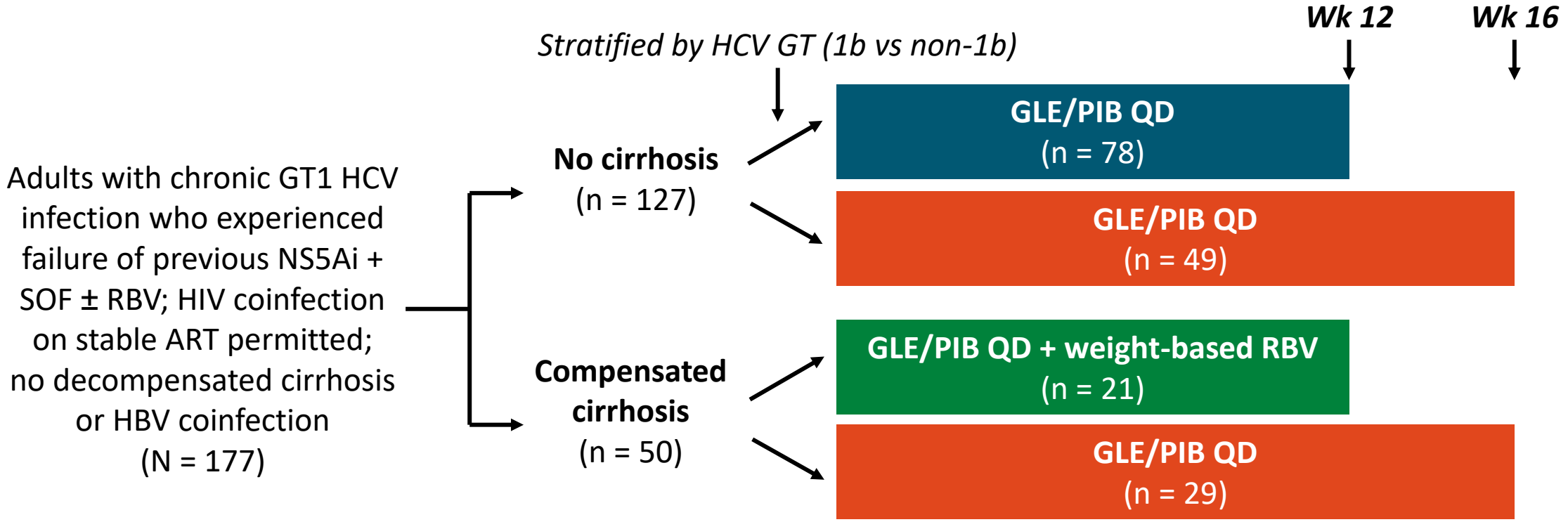
GLE/PIB ± RBV for GT1 HCV After Failure of NS5A Inhibitor + SOF ± RBV

- Multicenter, randomized, open-label phase IIIb study
  - Primary endpoint: SVR12



Sulkowski. AASLD 2018. Abstr 226.

Slide credit: clinicaloptions.com

Efficacy and Safety of GLE/PIB ± RBV for GT1 HCV After Failure of NS5A Inhibitor + SOF ± RBV

Virologic Outcome	12-Wk GLE/PIB ± RBV			16-Wk GLE/PIB		
	All (n = 99)	GT1b (n = 21)	GT1a† (n = 78)	All (n = 78)	GT1b (n = 13)	GT1a (n = 65)
SVR12, %	89	95	87	95	100	94
▪ Relapse, n	4	0	4	3	0	3
▪ Breakthrough, n	5	0	5	1	0	1
▪ Reinfection, n	1	0	1	0	0	0
▪ Death, n	1	1*	0	0	0	0

*HCC, not drug related. †Includes n = 4 non-GT1 patients.

- No VF in GT1b; VF in GT1a associated with treatment-emergent RASs
- RBV associated with increased toxicity but not increased efficacy

Sulkowski. AASLD 2018. Abstr 226.

Slide credit: clinicaloptions.com

VA HCV Case Registry: SOF/VEL/VOX in DAA-Experienced Patients With GT1-4 HCV

- Observational ITT cohort analysis of DAA-experienced patients with GT1-4 HCV initiating SOF/VEL/VOX in any VA center with EOT by March 31, 2018 (N = 573)
  - Primary endpoint: SVR where HCV RNA < LLOQ at least 12 wks after EOT

SVR,* % (n/N)		GT1	GT2	GT3	GT4
Overall		90.7 (429/473)	90.0 (18/20)	91.3 (42/46)	100 (12/12)
Cirrhosis	▪ No	91.5 (289/316)	92.9 (13/14)	91.3 (21/23)	100 (5/5)
	▪ Yes	89.2 (140/157)	83.3 (5/6)	91.3 (21/23)	100 (7/7)
History of decompensation	▪ No	90.5 (391/432)	88.9 (16/18)	91.7 (33/36)	100 (11/11)
	▪ Yes	92.7 (38/41)	100 (2/2)	90.0 (9/10)	100 (1/1)
Duration of SOF/VEL/VOX	▪ < 12 wks	46.5 (20/43)	100 (1/1)	0 (0/1)	--
	▪ 12 wks	95.1 (409/430)	89.5 (17/19)	93.3 (42/45)	100 (12/12)

*n = 22 patients excluded from analysis for lack of HCV RNA measurement ≥ 12 wks after EOT.

Belperio. AASLD 2018. Abstr 227.

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VA HCV Case Registry: Efficacy in Patients Receiving Full 12-Wk Course of SOF/VEL/VOX by Prior Treatment

SVR With 12-Wk SOF/VEL/VOX, % (n/N)		GT1	GT2	GT3
Class of prior treatment	▪ NS3/4A	94 (148/158)	100 (1/1)	--
	▪ NS5A	95 (409/430)	89 (16/18)	93 (37/40)
	▪ NS5B	95 (352/370)	90 (17/19)	93 (42/45)
	▪ NS3/4A + NS5A	95 (134/141)	100 (1/1)	--
	▪ NS5A + NS5B	96 (261/272)	88 (15/17)	93 (37/40)
	▪ PegIFN/RBV	95 (37/39)	100 (4/4)	100 (3/3)
Prior regimen	▪ GZR/EBR	96 (68/71)	--	--
	▪ LDV/SOF ± RBV	95 (286/300)	67 (2/3)	94 (16/17)
	▪ OBV/PTV/RTV/DSV ± RBV	96 (67/70)	100 (1/1)	--
	▪ SOF/VEL*	82 (14/17)	86 (12/14)	85 (11/13)
	▪ SOF + SMV	83 (5/6)	--	--

*$P < .05$

- In analysis restricted to patients receiving full 12 wks of SOF/VEL/VOX, lower SVR rates in GT2 with prior NS5A and/or NS5B experience, in GT1-3 with prior SOF/VEL

Belperio. AASLD 2018. Abstr 227.

French Compassionate Use Study: SOF/VEL/VOX in Patients With DAA Failure, Compensated Cirrhosis

- Real-world cohort of adults with GT1-5 HCV, compensated cirrhosis, and prior DAA failure of an NS5A inhibitor and/or PI receiving 12-wk SOF/VEL/VOX ± RBV (N = 44)
  - SVR12: 95% (38/40)
  - Serious AEs: n = 2 (liver decompensation, HCC in 1 patient with baseline Child B8 score)
  - Relapse: n = 2, both in patients with prior SOF + DCV

Pt With Relapse*	Age, Yrs	*FibroScan*, kPa	HCV GT	Baseline RASs	SOF/VEL/VOX	HCV RNA at EOT, IU/mL	Relapse RASs
Male	59	13	1a	NS3, NS5A	12 wks	< 15	Pending
Male	53	16	3a	Y93H	12 wks + RBV	< 12	Pending

*Among n = 40 with ≥ 12 wks of follow-up after d/c of treatment.

Hezode. AASLD 2018. Abstr 629.

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Additional Data on Real-World Efficacy of SOF/VEL/VOX

- Trio Health: examination of SOF/VEL/VOX initiation (± RBV) from July 2017 to April 2018 in US patients with chronic HCV infection (N = 196)[1]
  - 88% treatment experienced
  - 73% male, 60% GT1a HCV, 42% cirrhotic

SVR12 by Prior Regimen, % (n/N)	PP	ITT
LDV/SOF ± RBV	99 (88/89)	96 (88/92)
SOF/VEL ± RBV	95 (19/20)	95 (19/20)
GZR/EBR ± RBV	100 (17/17)	89 (17/19)
OBV/PTV/RTV/DSV	100 (10/10)	91 (10/11)
Other (SOF-based)	100 (16/16)	94 (16/17)

- DHC-R: examination of SOF/VEL/VOX retreatment (± RBV) as of February 2018 in German patients with chronic HCV infection and prior DAA failure (N = 86)[2]
  - Prior treatment experience
    - OBV/PTV/RTV/DSV ± RBV, 31%
    - LDV/SOF ± RBV, 30%
    - SOF/VEL ± RBV, 14%
  - 86% male, 64% GT1 HCV, 24% cirrhotic
- SVR12: 100% in 52 evaluable patients

1. Bacon. AASLD 2018. Abstr 706. 2. Vermehren. AASLD 2018. Abstr 676.

Slide credit: clinicaloptions.com

SHARED 2: LDV/SOF Without On-Treatment Laboratory Monitoring in Rwandan Patients With GT4 HCV

- Prospective, open-label, single-arm, single-site study in Rwanda
  - Primary endpoints: SVR12, grade 3/4 AEs, early d/c for AEs

DAA-naive adults with GT4 HCV infection, HCV RNA > 1000 IU/mL; no decompensated cirrhosis, HCC, active HBV/uncontrolled HIV (N = 60)

Laboratory Assessment	Screen	Entry	Wk 4	Wk 8	Wk 12	Wk 24
HCV GT, HCV/HIV Ab, HBsAg	X					
HCV RNA	X		X		X	X
CBC, CMP	X		X	X	X	X
PT/INR/albumin		X				

X = study physician blinded to results; labs reviewed in real time by independent monitor to ensure trial safety.

Grant. AASLD 2018. Abstr 54.

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SHARED 2: Efficacy and Safety

- SVR12: 88% (53/60)
  - Failures: n = 7 (all relapse)
  - Lower SVR12 rate (56%) in subtype GT4r due to more frequent RASs
- Adherence ≥ 90% by pill count at Wks 4, 8 in 58 evaluable patients
- In 3 cases, independent monitor released labs to study physician
  - Labs normalized without intervention
- No d/c for AEs or lab abnormalities, grade 4 AEs, or deaths

Grade 3 AE, n	LDV/SOF
Any	11*
▪ Hypertension	6
▪ Insomnia	2
▪ Hyperglycemia	1
▪ Knee pain	1
▪ Weakness	1

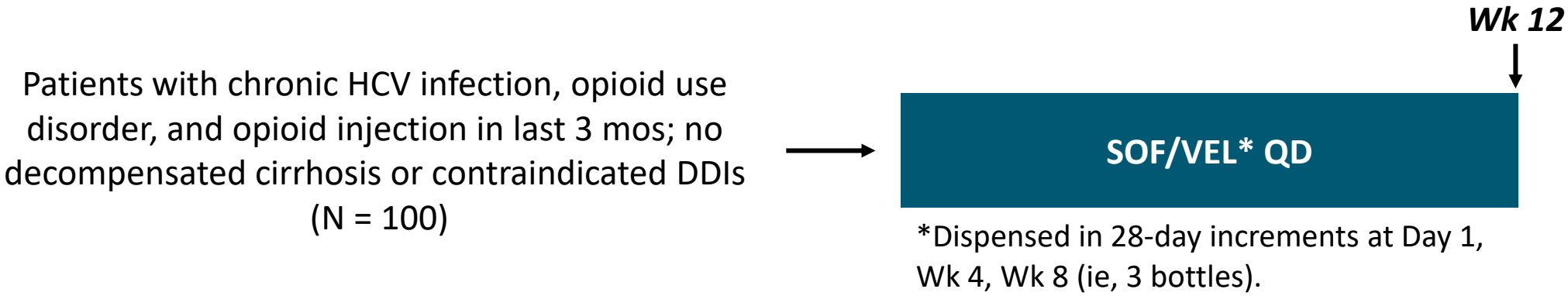
*Occurring in 7 patients; none drug related.

Grant. AASLD 2018. Abstr 54.

Slide credit: clinicaloptions.com

ANCHOR: SOF/VEL in PWID With Chronic HCV and Ongoing Injection Drug Use

- Single-center study at harm reduction organization in Washington, DC
  - 76% men, 93% black, 33% cirrhotic, 58% injected drugs at least daily



- Primary endpoint: SVR12
- Adherence assessments: Wk 4 HCV RNA, treatment interruptions, completion of study drugs, EOT timing vs Wk 12

Kattakuzhy. AASLD 2018. Abstr 18.

Slide credit: clinicaloptions.com

ANCHOR: Efficacy and Adherence

- SVR12 in ITT population: 78% (73/93)
  - Virologic success unaffected by BL demographics such as frequency of drug use, housing stability, MAT
- Through Wk 12 in full study population (N = 100)
  - SOF/VEL prescriptions dispensed: 92% to 97%
  - Visit attendance: 70% to 88%

Adherence Measure in ITT Population		SVR12, %	*P* Value
Wk 4 HCV RNA < 200 IU/mL	▪ Yes (n = 80) ▪ No (n = 8)	86 25	.0005
No treatment interruptions	▪ Yes (n = 76) ▪ No (n = 12)	86 67	**.22**
Completed 2 or 3 of 3 SOF/VEL bottles	▪ Yes (n = 87) ▪ No (n = 6)	84 0	.0001
Finished SOF/VEL on time (vs late)	▪ Yes (n = 20) ▪ No (n = 43)	95 88	**.65**

Kattakuzhy. AASLD 2018. Abstr 18.

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HCV Continuum of Care

HCV Linkage to Care in the United States: 2013 vs 2016

- Analysis of real-world demographic data, clinical test results from 2 large commercial labs in the United States
  - Limited to patients who underwent HCV antibody screening
- From 2013-2016, proportion with follow-up HCV RNA test increased

Care Step in HCV Ab+ Patients	2013 (N = 179,144)	2016 (N = 287,130)
HCV RNA test performed, %	45.0	76.5
▪ Positive result, %	63.8	63.9
• Saw a specialist,* % (n)	21.2 (10,903)	17.4 (24,358)

*Gastroenterology, hepatology, infectious disease.

Reau. AASLD 2018. Abstr 1567.

Slide credit: clinicaloptions.com

HCV Linkage to Care in the United States: Baby Boomers vs Young Adults

HCV RNA Positive, %	Baby Boomers*	Young Adults†
2013	66.1	58.9
2016	63.5	65.5

*48-71 yrs of age. †18-39 yrs of age.

- From 2013-2016, treatment rates rose in both groups, with highest increases in baby boomers across provider types
- In 2016, specialist vs PCP visit associated with greater likelihood of treatment

Patients Engaging in Care Step by Yr, %		Linked to Specialist		Linked to PCP	
		Baby Boomers*	Young Adults†	Baby Boomers*	Young Adults†
Saw provider	▪ 2013 ▪ 2016	25.4 23.4	17.1 9.2	37.7 40.9	32.6 40.3
Received treatment after provider visit	▪ 2013 ▪ 2016	10.6 32.0	15.4 22.6	2.9 8.1	4.2 4.5

Reau. AASLD 2018. Abstr 1567.

Slide credit: clinicaloptions.com

Age-Stratified Examination of HCV Continuum of Care for PWID in Philadelphia

- From 2013-2017, N = 29,820 HCV Ab+ labs reported to the Philadelphia Dept of Public Health
  - Subset interviewed as part of routine surveillance: n = 5184, 46% of whom self-identified as PWID
  - 76% white in younger cohort; 41% black, 40% white in older cohort
- Linkage to HCV care, treatment rates significantly lower in younger vs older cohort

Care Step in HCV Ab+ PWID, %	≤ 35 Yrs (n = 1239)	> 35 Yrs (n = 1151)
HCV RNA test performed	81	90
HCV RNA positive	75	85
Initiated HCV care*†	**41**	66
HCV tx initiated or infection resolved†	**8**	25

*Saw a specialist or had a subsequent HCV RNA measurement > 180 days after initial result.
†$P < .0001$ for difference between groups.

Addish. AASLD 2018. Abstr 1632.

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Posttreatment HCV Outcomes

C-EDGE CO-STAR: Assessment of HCV Reinfection Risk in Patients on OAT Who Received GZR/EBR

- Part A: GZR/EBR for 12 wks in patients with HCV GT1, 4, or 6 on OAT (N = 296)
  - SVR12: 91% in full analysis set; 97% of patients had > 95% adherence
- Part B: observational follow-up study in patients who received ≥ 1 dose of GZR/EBR; HCV reinfection, drug use assessed (n = 199)
- **10 reinfections** during 36 mos following end of HCV treatment
  - Occurred in first 6 mos post-treatment, n = 6
  - Spontaneous clearance, n = 2; persistent viremia, n = 8 (4/8 cleared with retreatment)

Parameter at Posttreatment Mo 36	All Patients (n = 296)	Part B*	
		IDU (n = 80)	No IDU (n = 119)
Reinfection rate/100 PY (95% CI)	1.8 (0.8-3.3)	2.8 (1.0-6.2)	0.3 (0-1.8)

*IDU self-reported after completion of HCV treatment.

Grebely. AASLD 2018. Abstr 52. NCT02105688.

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C-EDGE CO-STAR: Assessment of Drug Use Behavior in Patients on OAT Who Received GZR/EBR

- Stable drug use patterns through Mo 30 with 15% to 26% reporting IDU

Reported Drug Use in Part B, %		Mo 6 (n = 191)	Mo 12 (n = 178)	Mo 18 (n = 173)	Mo 24 (n = 155)	Mo 30 (n = 148)
Injection	▪ Previous mo	21	19	17	15	16
	▪ Previous 6 mos	25	26	21	20	22
Non-injection	▪ Previous mo	39	38	42	39	36
	▪ Previous 6 mos	45	40	42	38	39

Urine Drug Screen, %	Part A	Part B					
	Day 1 (n = 199)	Day 1 (n = 199)	Mo 6 (n = 190)	Mo 12 (n = 177)	Mo 18 (n = 172)	Mo 24 (n = 152)	Mo 30 (n = 142)
Any positive*	59	60	59	62	59	59	53

*Excludes buprenorphine, methadone.

Grebely. AASLD 2018. Abstr 52.

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HCC Recurrence Rate After HCV DAA Therapy Among Patients With HCC Complete Response

- Retrospective multicenter cohort study in North American patients achieving CR after ablation, radiation therapy, resection, or TACE/TARE for HCV-related HCC between January 2013 and December 2016 (N = 795)
  - Exclusion criteria: extrahepatic HCC, HCV DAAs before initial HCC, recurrent HCC within 30 days of CR, unknown HCC response
- Primary analysis: association between HCV DAA therapy and time to HCC recurrence by Cox regression
- Significant BL differences between HCV DAA-treated vs DAA-untreated cohorts in type ($P < .001$) and number ($P = .04$) of HCC treatments leading to CR, Child-Pugh at CR ($P < .001$)

Singal. AASLD 2018. Abstr 92.

HCC Recurrence After DAA Therapy: Outcomes

- HCC recurrence with median follow-up of 10.4 mos[1]
  - DAA treated: all, n = 128; early, n = 52
  - DAA untreated: all, n = 289; early, n = 228

HCC Recurrence[1]	aHR (95% CI)	
	Overall	Early
Time-dependent exposure*	**0.90 (0.70-1.16)**	**0.96 (0.96-1.33)**
DAA start time after HCC CR		
▪ ≤ 6 mos	0.90 (0.67-1.21)	1.04 (0.74-1.47)
▪ > 6 mos	0.90 (0.64-1.27)	0.55 (0.22-1.38)

Adjusted for age, sex, site, CP, AFP, tumor burden, HCC therapy.
*Stratified by receipt of DAA therapy.

- No increased risk of HCC recurrence (early or overall) in patients receiving DAA therapy after CR for HCV-related HCC[1]
  - Finding consistent across predefined subgroups
- In a separate, prospective evaluation of 163 Sicilians with HCV cirrhosis and CR by resection or ablation after early HCC[2]
  - No difference in HCC recurrence, improved OS (*P* = .03) and rate of hepatic decompensation (*P* = .02), with DAA initiation vs matched, DAA-untreated controls

1. Singal. AASLD 2018. Abstr 92. 2. Cabibbo. AASLD 2018. Abstr 95.

HCV D+R- Transplantation

HCV D+R- Liver Transplantation

- Retrospective analysis of **liver transplantation** from April 2014 to January 2018 in the Scientific Registry of Transplant Recipients; HCV treatment status unknown (N = 16,858)
- Increasing use of HCV NAT+ donors
  - 2014: 8 D+R+, 0 D+R- vs 2017: 269 D+R+, 46 D+R-
- Similar graft survival rates in HCV-negative pts receiving D+ vs D- livers

Graft Survival, %	D+R+ (n = 753)	D+R- (n = 87)	D-R+ (n = 4748)	D-R- (n = 11,270)
Yr 1	94.3	92.8	92.9	92.6
Yr 2	89.7	85.7	88.0	88.3

Paul. AASLD 2018. Abstr 249.

Slide credit: clinicaloptions.com

Preemptive DAAs in HCV D+R- Cardiac Transplantation

- Open-label, single-center, proof-of-concept trial in HCV-negative patients awaiting **cardiac transplantation** and willing to receive an HCV-positive donor heart (N = 25)
  - NAT+ donor heart, n = 20
  - VAD as bridge, n = 16; long-term inpatients, n = 13
- Pan-genotypic DAA therapy initiated preemptively immediately prior to transplantation if BL NAT+ or with return of HCV RNA if BL NAT-
  - GLE/PIB for 8 wks
  - All patients monitored to Wk 52 for HCV Abs, HCV RNA, and LFTs

Bethea. AASLD 2018. Abstr 7.

Slide credit: clinicaloptions.com

Efficacy of Preemptive DAAs in HCV D+R- Cardiac Transplantation

- Viral suppression achieved by posttransplant Day 9 in all NAT+ recipients

Median HCV RNA, IU/mL	NAT+ Heart Recipients (n = 20)
Donor	3,000,000
Peak recipient	500

- As of November 10, 2018, 12/25 patients have reached the SVR12 time point
  - HCV RNA undetectable in all
- No HCV/DAA-related AEs or serious AEs
- No lapse in or d/c of DAAs for drug reactions or interactions
- Reduced time to transplantation resulted in an estimated $3.4 million in cost savings

Outcome	HCV Protocol	Standard Protocol
Median pretransplant wait time,* days (IQR)	11.5 (5-35)	113.0 (40-366)

*P = .0001

Bethea. AASLD 2018. Abstr 7.

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HCV D+R- Lung Transplantation

- Prospective study of single or bilateral **lung transplantation** from HCV NAT+ donors to HCV- recipients (N = 20)
  - Ex vivo lung perfusion for 6 hrs to reduce HCV RNA; postoperative HCV RNA monitoring; SOF/VEL for 12 wks if HCV RNA > 1000 IU/mL
- 90-day survival: 100%
- 19/20 recipients infected with HCV within 1 wk after transplantation
  - Median time to DAAs: 21 days
  - Viral relapse after SVR12: 25% (2/8)

Feld. AASLD 2018. Abstr 223.

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