Viral Hepatitis Highlights from EASL and DDW 2016

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Viral Hepatitis Highlights

- HCV Cohort Studies
- Resistance, Relapse, and Retreatment
- Next Generation Antivirals

THE REAL WORLD: HCV COHORT STUDIES

What is the REAL WORLD effectiveness of current DAA regimens?

Background:

- Clinical trials show ≥95% SVR12 across many patient groups with all-oral DAAs
- IFN-based HCV therapy SVRs more modest in real world than clinical trials

Methods:

- Real-world cohorts
  - German Hepatitis C-Registry[1]
  - Trio Network (US)[2]
- Choice of treatment, f/u testing at physician's discretion

Aim:

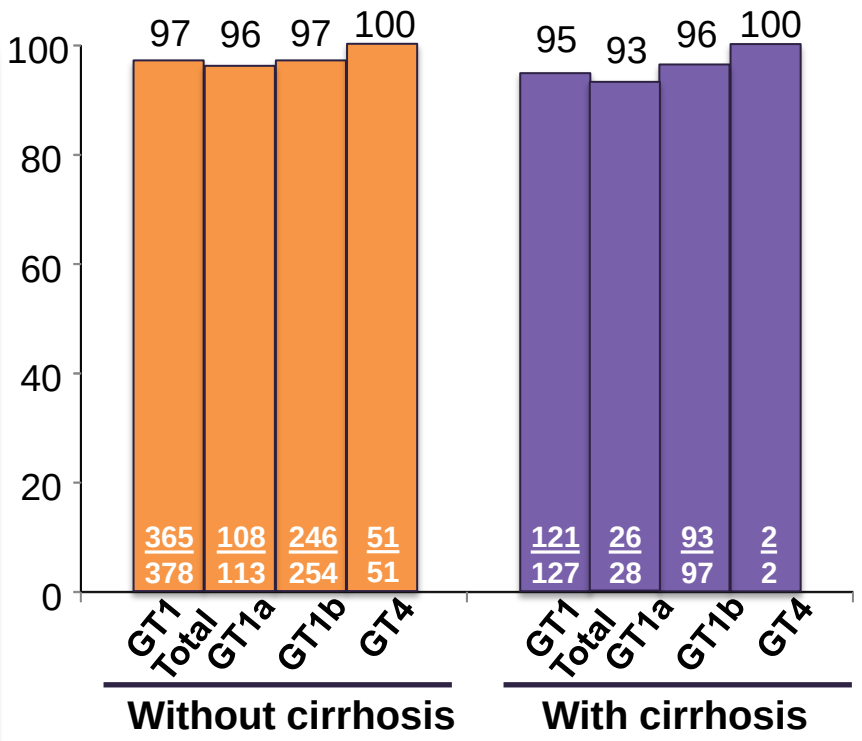
To evaluate safety and effectiveness of all-oral DAAs in routine clinical practice

[1]Hinrichsen EASL Abstract GS07, [2]Afdhal DDW Abstract Su1429

What is the REAL WORLD effectiveness of current DAA regimens?

German Hepatitis C Registry:

- GT1 or 4 pts, 254 sites
  - Ombitasvir/paritapervir/ritonavir +/- dasabuvir, +/- RBV
- Baseline characteristics
  - 95% Caucasian
  - 88% GT1
  - 22% Cirrhotic (7% decompensated)
  - 59% Tx experienced (12% prior PI)
- Label recommended regimen
  - 76-89% of GT1 patients
  - 92-94% of GT4 patients



- SAE in 2.1% (21/1017), more frequent w/RBV
- Total bilirubin ≥Grade 2 was rare in pts without cirrhosis (6-7% in pts with cirrhosis)
- ALT or AST elevations were infrequent

Hinrichsen EASL Abstract GS07

What is the REAL WORLD effectiveness of current DAA regimens?

Factors associated with all-oral DAA failure:

- German Hepatitis C Registry[1]: 99% SVR12 among those treated within guidelines vs 92% not treated within guidelines
- Trio Network[2]: cirrhosis, platelets <100k/mL, male sex, non-African American, treatment outside FDA guidelines

	LDV/SOF +/- RBV	SMV + SOF +/- RBV	OPr(D) +/- RBV	Total
Outside FDA label	87% (204/235)	80% (16/20)	60% (9/15)	85% (229/270)
Inside FDA label	95% (2347/2461)	83% (25/30)	88% (49/56)	95% (2421/2547)
Total	95% (2551/2696)	82% (41/50)	82% (58/71)	94% (2650/2817)

Clinical Implications:

- ❖Excellent SVR rates are achieved within routine practice
- ❖Consult and adhere to clinical treatment guidelines

[1]Hinrichsen EASL Abstract GS07, [2]Afdhal DDW Abstract Su1429

What is the impact of HIV on the effectiveness of current DAAs?

Background:

- High SVR rates among HIV/HCV-coinfected pts with all-oral DAAs in clinical trials
- Most HIV+ pts do not meet trial inclusion criteria[1]

Aim:

To compare DAA effectiveness among pts with and without HIV infection in routine clinical practice

Methods:

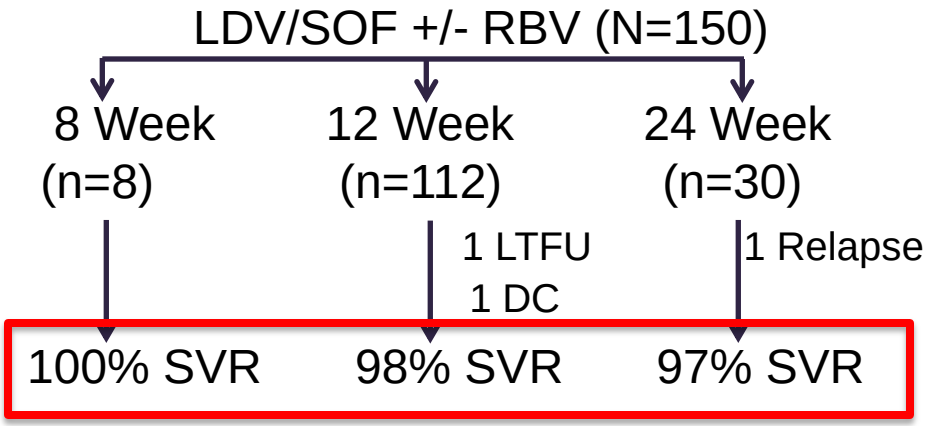
- Real-world cohorts
  - TRIO Network (US)[2]
  - VA Database(US)[3]
  - HEPAVIR-DAA & GEHEP-MONO (Spain)[4]
- Choice of regimen, f/u testing at physician's discretion

[1]Saeed et al. Clin Infect Dis 2016. [2]Dieterich DDW Abstract 606, [3]McGinnis EASL Abstract LBP514, [4]Neukam EASL Abstract LBP513

What is the impact of HIV on the effectiveness of current DAAs?

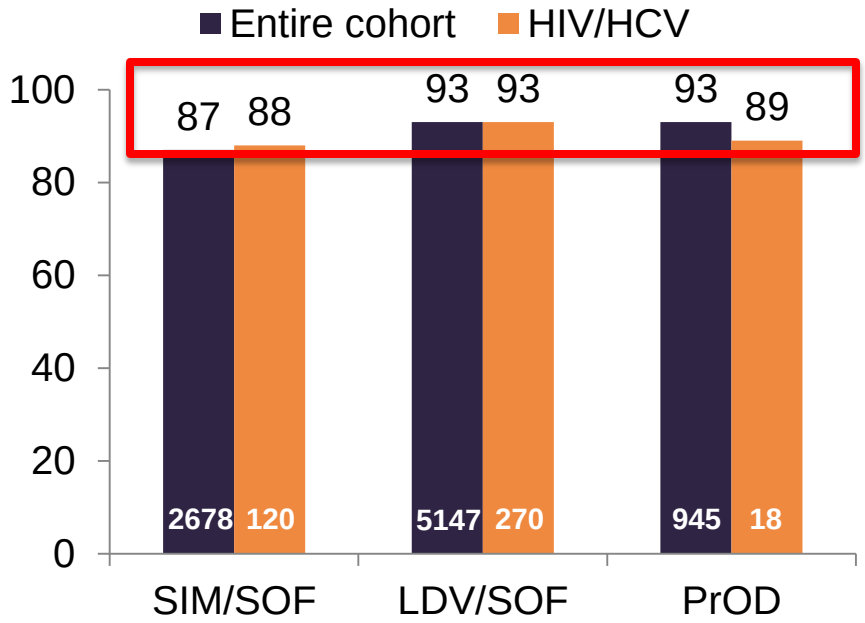
TRIO Network (US)[1]

- Baseline characteristics
  - 80% GT1a
  - 70% Male
  - 21% African American
  - 35% Cirrhotic
  - 10% Platelets <100K/mL



VA Database (US)[2]

- 9,604 treated pts before 9/2015
  - 408 (4.2%) HIV-coinfected
  - Majority G1 (75%) and male (96%)
  - More cirrhotics in SIM/SOF grp (69%)



[1]Dieterich DDW Abstract 606 , [2]McGinnis EASL Abstract LBP514

What is the impact of HIV on the effectiveness of current DAAs?

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  - 80% GT1a
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  - 21% African American

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- 9,604 treated pts before 9/2015
  - 408 (4.2%) HIV-coinfected
  - Majority G1 (75%) and male (96%)
  - More cirrhotics in SIM/SOF grp (69%)

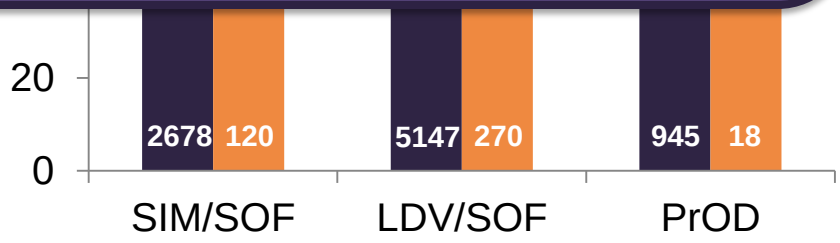
Clinical Implications:

❖High SVR rates are achieved in HIV+ patients in routine practice

❖Consult and adhere to clinical treatment guidelines especially for drug-drug interactions with ART

1 LTFU
1 DC
1 Relapse

100% SVR | 98% SVR | 97% SVR



[1]Dieterich DDW Abstract 606 , [2]McGinnis EASL Abstract LBP514

Can we shorten LDV/SOF to 8 weeks in some treatment naïve patients

Background:

- Post-hoc analysis of ION-3[1] demonstrated comparable relapse (2%) with 8 or 12 weeks of LDV/SOF in:
  - Treatment naïve
  - Non-cirrhotic
  - BL HCV RNA<6 million IU/mL

Aims[2]:

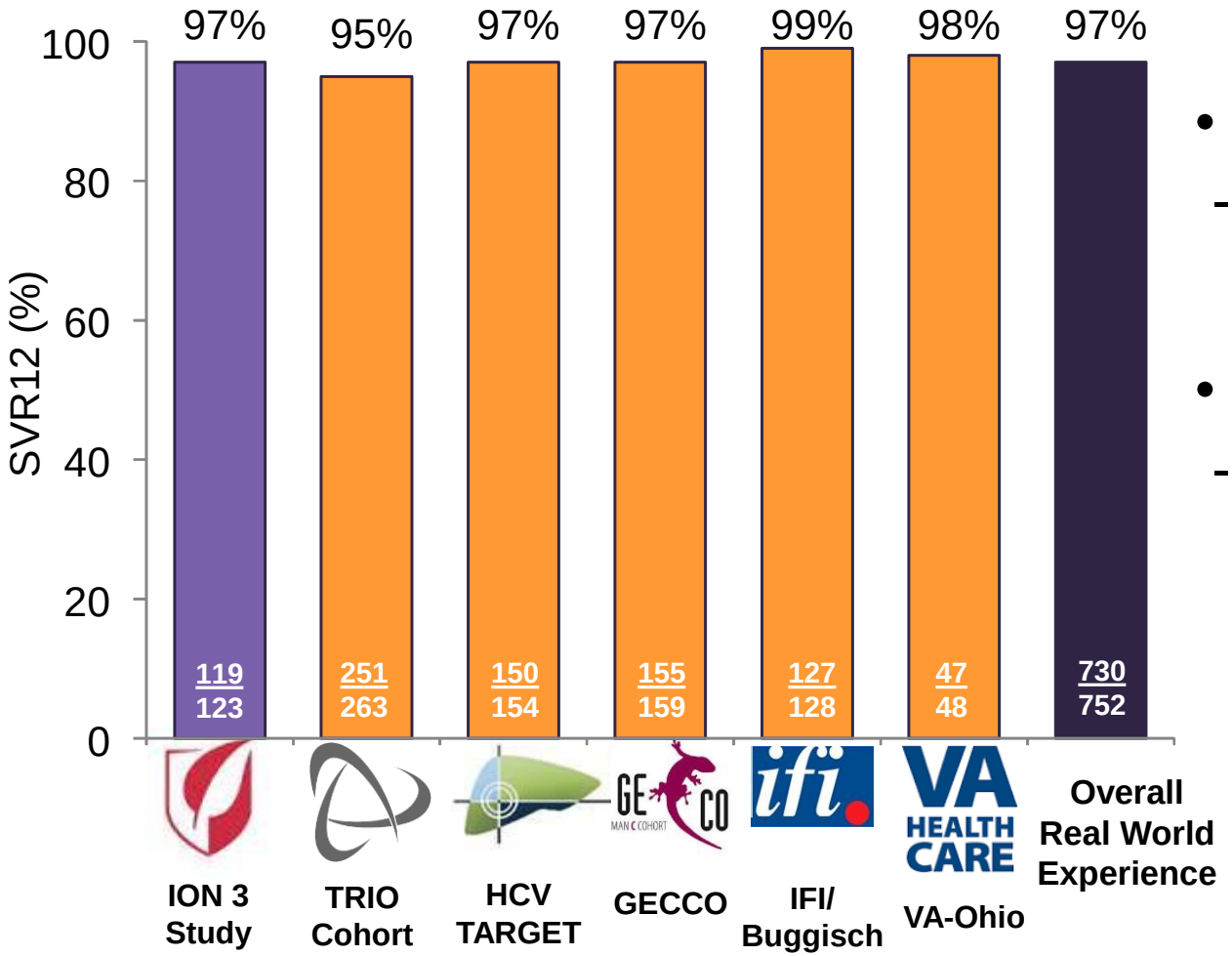
- To evaluate the effectiveness of LDV/SOF x 8wks in real-world
- Compare SVR data from ION-3 to real-world cohorts

Methods:

- ION-3 Study (N=123)
- 3 prospective multicenter real world cohorts
  - HCV-TARGET (US) (N=154)
  - TRIO Network (US) (N=263)
  - GECCO (Germany) (N=245)
- 2 retrospective single center real world cohorts
  - IFI/Buggisch(Germany) (N=130)
  - VA-Ohio (US) (N=60)

[1]Kowdley et al. NEJM 2014, [2]Buggisch EASL Abstract SAT-242, [2]Kowdley DDW Abstract 602

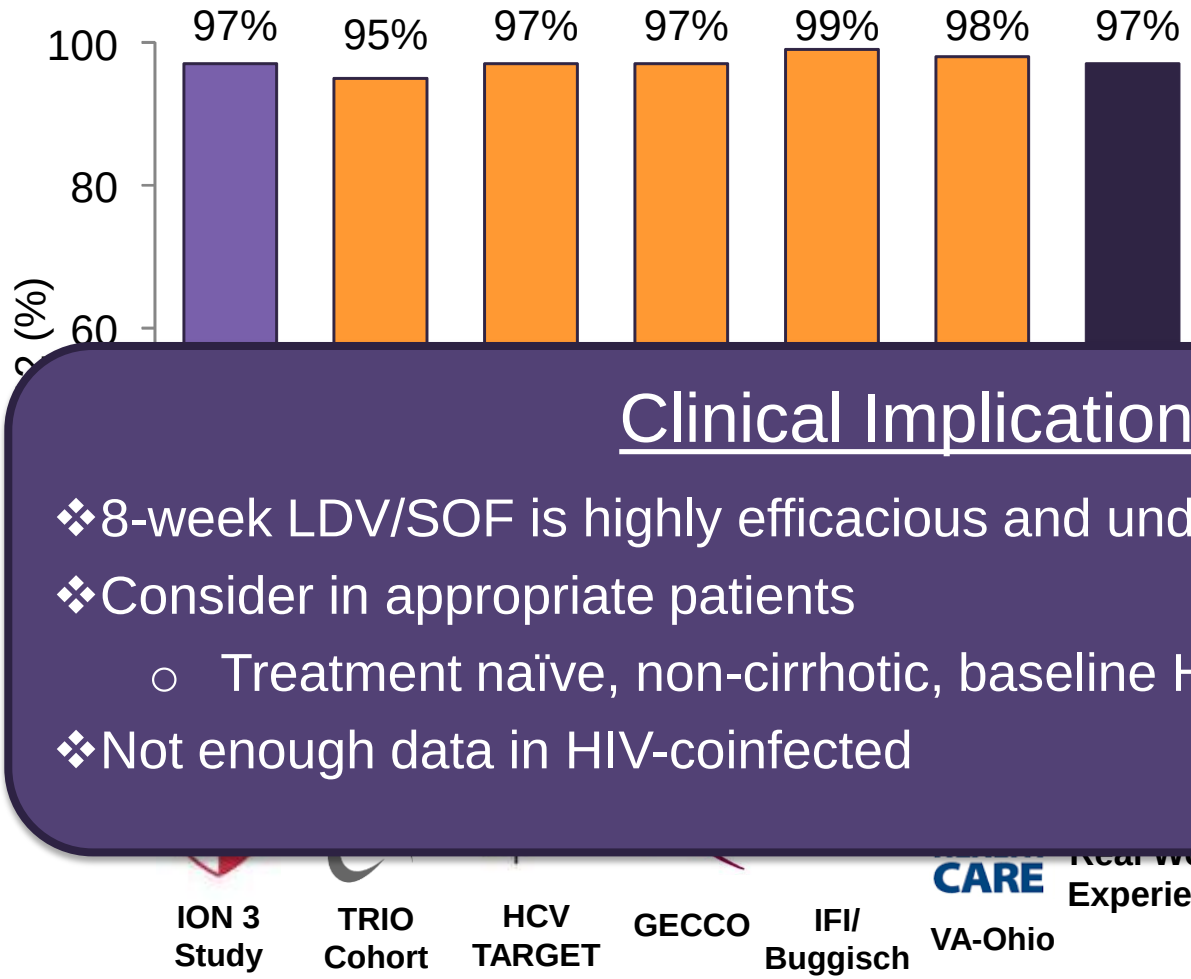
Can we shorten LDV/SOF to 8 weeks in some treatment naïve patients



- HCV-TARGET
  - 41% of 8-week eligible pts received 8 weeks
- IFI/Buggisch
  - 52% of 8-week eligible pts received 8 weeks

Buggisch EASL Abstract SAT-242, Kowdley DDW Abstract 602

Can we shorten LDV/SOF to 8 weeks in some treatment naïve patients



- HCV-TARGET
  - 41% of 8-week eligible pts received 8 weeks

Clinical Implications:

- 8-week LDV/SOF is highly efficacious and underutilized
- Consider in appropriate patients
  - Treatment naïve, non-cirrhotic, baseline HCV RNA <6 million IU/mL
- Not enough data in HIV-coinfected

Buggisch EASL Abstract SAT-242, Kowdley DDW Abstract 602

Do PPI's diminish the effectiveness of LDV/SOF?

Background:

- LDV solubility ↓ as pH ↑
- Recommend limiting PPI to equivalent of omeprazole 20mg[1]
- HCV-TARGET reported lower SVR (-4.3%, absolute) among pts on baseline PPI

Aim[3]:

To evaluate the impact of PPI type, dose, and duration on SVR in real world pts treated with LDV/SOF

Methods:

- TRIO Network (US)
- Prescription information through providers and specialty pharmacies
  - Capture PPI use at any point during HCV tx (23% of pts)
  - Most (62%) on low dose
  - Vast majority (94%) remained on PPI throughout treatment
  - Small number (6%) started PPI after HCV tx initiation, used intermittently, or d/c'd PPI

[1]Harvoni Package Insert, [2]Terrault AASLD 2015 Abstract 94, [3]Afdhal EASL Abstract LBP519

Do PPI's diminish the effectiveness of LDV/SOF?

Results[1]:

- No difference in SVR by PPI use
  - 96% in no PPI vs 94% in PPI (p=0.22)
- No difference in SVR by PPI use when stratified by tx duration
- Matched Propensity Analysis:

	PPI n=444	No PPI n=443	P value
Matched pop. (n=887)	97.3%	97.2%	0.99
8 weeks (n=82)	100%	97.5%	1.00
12 weeks (n=588)	96.6%	96.9%	0.81
24 weeks (n=217)	98.1%	98.1%	1.00

- Lower SVR with BID PPI (91.7%) on univariate analysis

[1]Afdhal EASL Abstract LBP519

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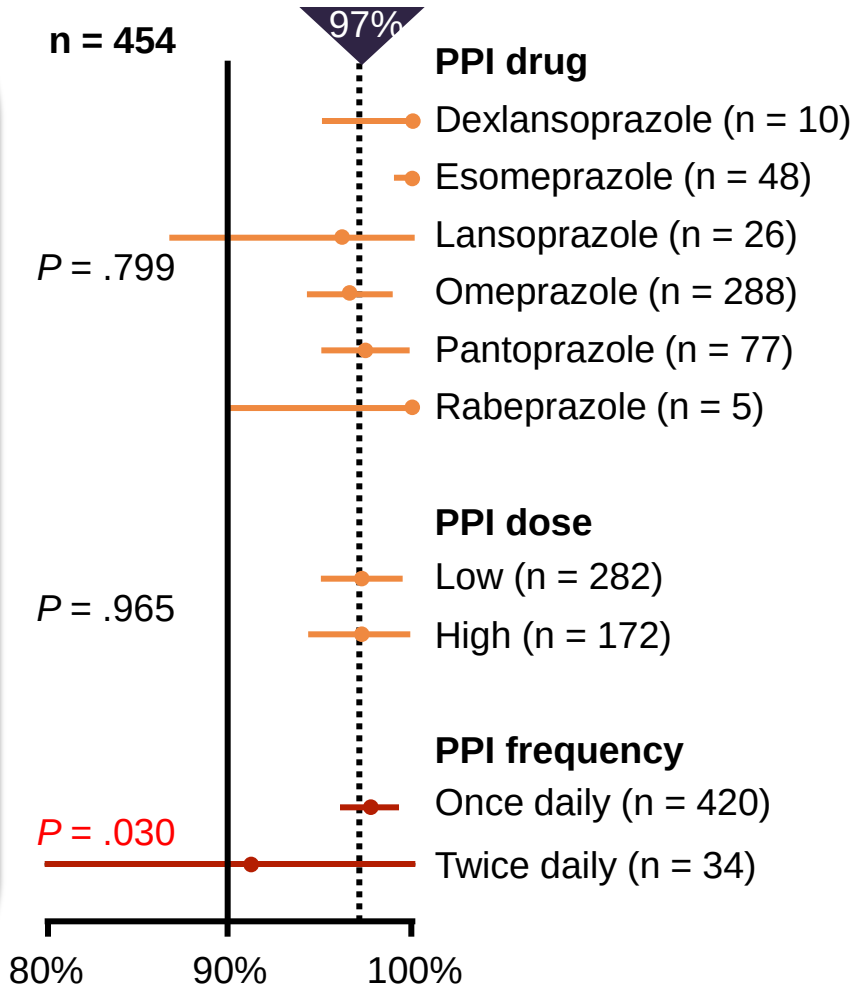

[1]Afdhal EASL Abstract LBP519

Slide credit: clinicaloptions.com

Do PPI's diminish the effectiveness of LDV/SOF?

Results[1]:

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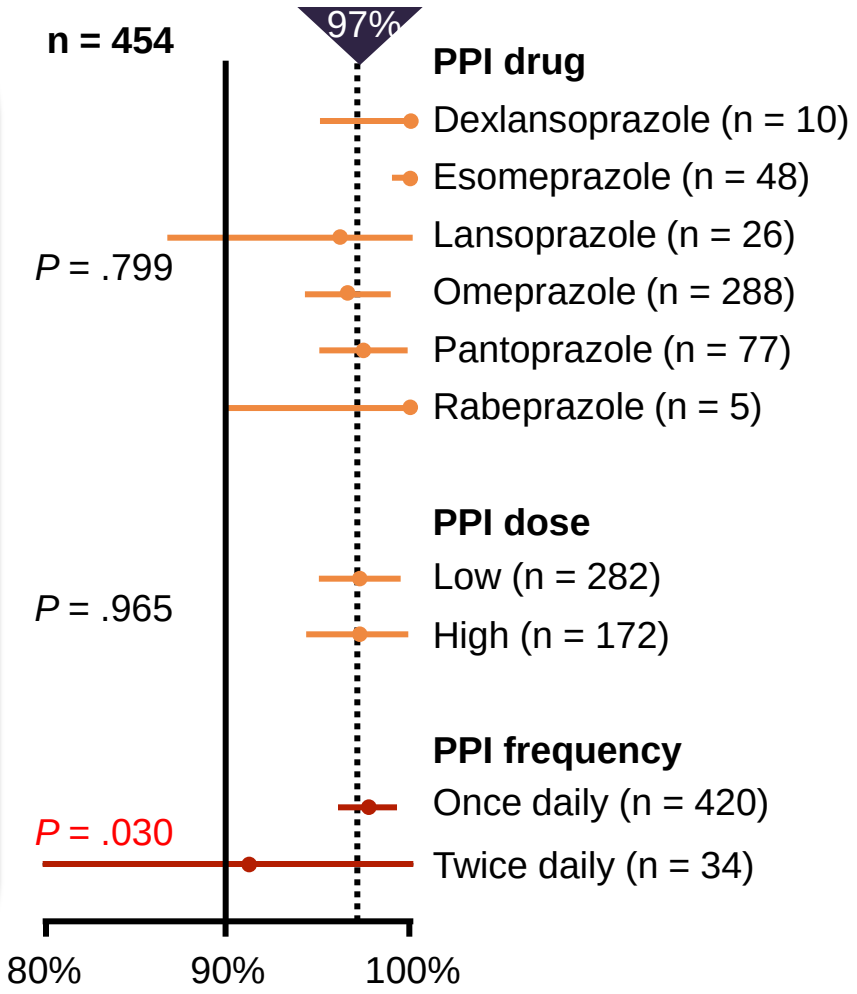
- Lo… (91.7%) on univariate analysis

Clinical Implications:

- Exercise caution using PPIs with LDV/SOF
- If strong indication for PPI or unable to stop the PPI and need to use LDV/SOF:
  - Ensure appropriate dose
  - Ensure appropriate timing (fasting, simultaneous with LDV/SOF)



[1]Afdhal EASL Abstract LBP519

Slide credit: clinicaloptions.com

What is the risk of HCC after HCV cure with DAAs?

Background:

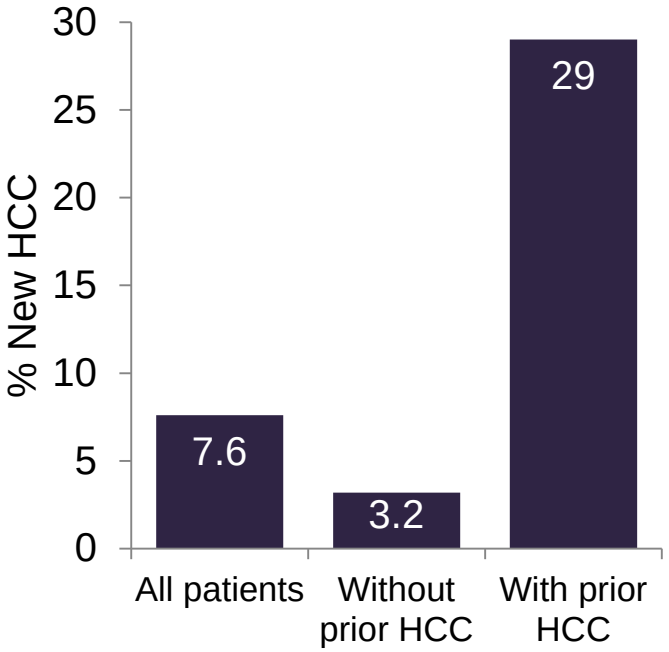
- SVR with IFN-based tx reduces HCC risk in pts with advanced fibrosis[1]
- Unexpectedly high HCC recurrence seen in 103 pts treated with DAAs[2]

Aim[3]: To evaluate the effect of DAA tx on HCC in pts with cirrhosis

Methods:

- Retrospective study of 344 HCV+ pts with cirrhosis (CPT A/B): 17% h/o HCC
- Baseline and 12-24 week post-treatment U/S (+CT or MRI if indeterminate)

Results:



- Factors a/w HCC:
  - Prior HCC
  - CPT class B
  - Liver stiffness >21.3
  - Treatment experience

[1]van der Meer AJ et al. JAMA 2012, [2]Reig M et al. J Hepatol 2016, [3]Buonfigliol EASL Abstract LBP506

What is the risk of HCC after HCV cure with DAAs?

Background:

- SVR with IFN-based tx reduces HCC risk in pts with advanced fibrosis[1]
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with cirrhosis (CPT A/B): 17% n/a HCC

- Baseline and 12-24 week post-treatment U/S (+CT or MRI if indeterminate)

Results:

- Prior HCC
- CPT class B
- Liver stiffness >21.3
- Treatment experience

Clinical Implications:

❖No clear short-term benefit of DAAs on HCC risk

- Impact on HCC recurrence in pts with HCC history warrants further investigation

❖HCC risk persists after DAA therapy in patients with HCV cirrhosis: monitoring for HCC after SVR should continue

[1]van der Meer AJ et al. JAMA 2012, [2]Reig M et al. J Hepatol 2016, [3]Buonfigliol EASL Abstract LBP506

Will my patient with decompensated cirrhosis get better with treatment?

Background:

- Good safety and efficacy for DAAs in compensated cirrhosis
- Clinical trials in decompensated cirrhotics demonstrate stabilization/ improvement of MELD and CPT scores in majority[1,2]
- Improvement in portal hypertensive complications seen with SVR[3]

[1]Manns M et al Lancet ID 2016, [2]Curry MP et al. NEJM 2015,
[3]Saxena AASLD 2015 Abstract 1825

Will my patient with decompensated cirrhosis get better with treatment?

Aim: To evaluate virologic and functional outcomes up to 12 months after end of DAA therapy in advanced HCV cirrhosis compared to untreated pts

Methods:

- HCV Research UK Database
  - Subset treated through Expanded Access Program (EAP) (SOF + LDV or DCV +/-RBV)
- Enrolled 6 months before EAP start
  - n=261; subsequently treated n=177
- Enrolled at/after EAP start and treated
  - n=409; SVR in 80% (329/409)

Results:

- First 6 months (includes 3 months tx)- treated pts benefit

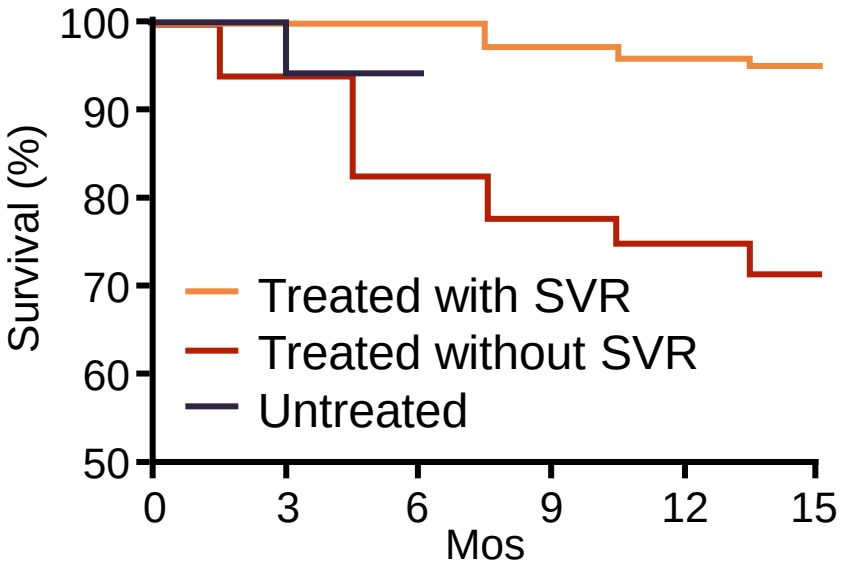
Event	Treated (n = 409)	Untreated (n = 261)
Death	3.2	5.7
Decompensation	**17.6**	**28.0***
New HCC	4.6	8.0
Sepsis	6.6	5.7
New OLT	6.6	3.8
Hospital admission	32.5	31.8
MELD worsening > 2	**23.0**	**37.9***
Total adverse outcomes	**52.1**	**63.6***

*p<0.05

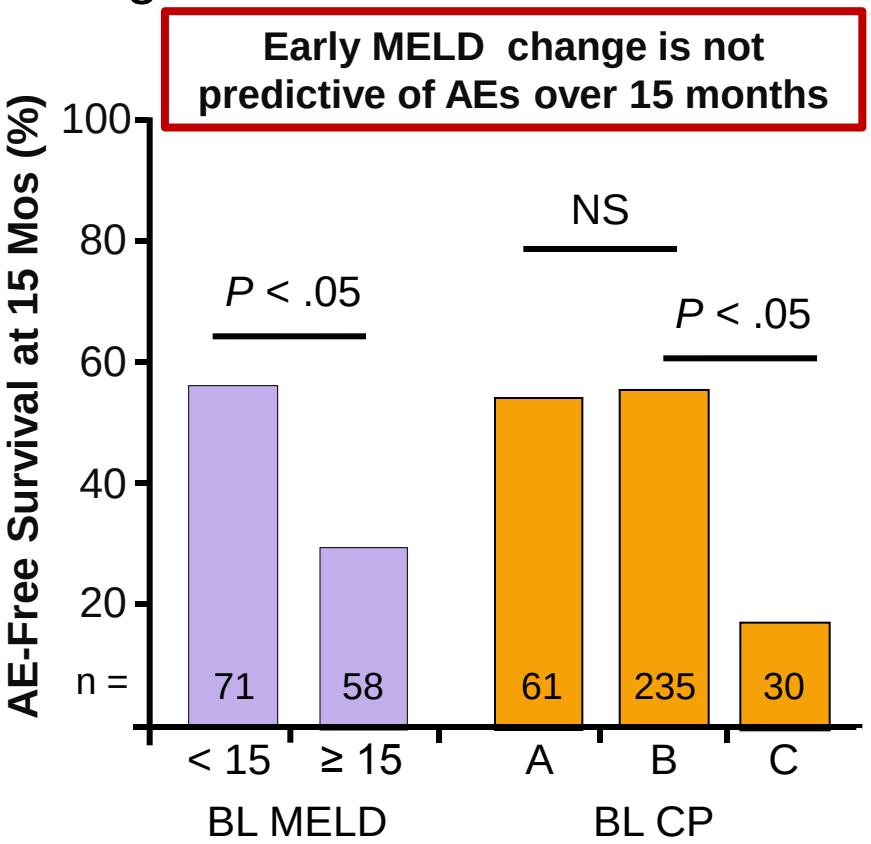
Cheung EASL Abstract PS097

Will my patient with decompensated cirrhosis get better with treatment?

- HCV treatment benefit limited to pts with SVR



- AE-free survival significantly greater for CP B vs CP C



Cheung EASL Abstract PS097

Slide credit: clinicaloptions.com

Will my patient with decompensated cirrhosis get better with treatment?

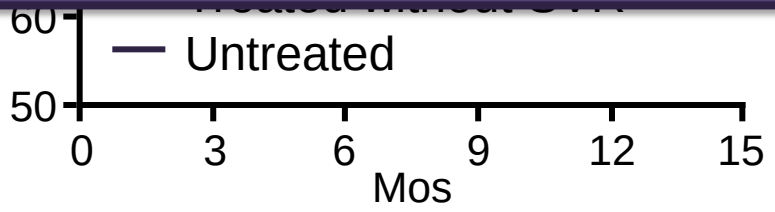
- HCV treatment benefit limited to pts with SVR
- AE-free survival significantly greater for CP B vs CP C

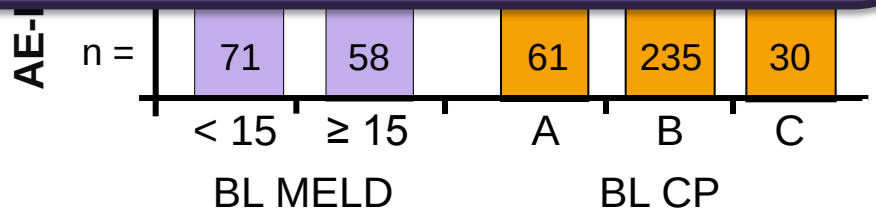
Clinical Implications:

❖Viral clearance leads to prolonged improvement in most CP-B pts

❖The most advanced pts (CP-C, MELD ≥18) have more SAEs, high short-term mortality and are less likely to derive long-term benefit

❖Refer decompensated cirrhotics to experienced HCV provider, ideally liver transplant center





Cheung EASL Abstract PS097

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RESISTANCE

RELAPSE

RETREATMENT

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

Background:

- Baseline NS5A RAVs impact treatment course with EBR/GRZ in patients with GT1a[1]
- Baseline RAV testing is not routinely performed before using other DAA regimens

[1]Zepatier package insert

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

Background:

- Baseline NS5A RAVs impact treatment course with EBR/GRZ in patients with GT1a[1]
- Baseline RAV testing is not routinely performed before using other DAA regimens

Aim[2]:

- Describe the prevalence of NS3, NS5A, and NS4B RAVS in real-world cohort of GT1 patients
- Evaluate the impact of baseline RAVs on effectiveness of therapy with LDV/SOF and SMV/SOF +/- RBV

Methods:

- HCV-TARGET (US)
  - Multicenter, prospective, observational cohort
  - 492 in RAV prevalence and 472 in efficacy analyses
  - Monogram biosciences assay used (pop sequence, 10% variant reporting threshold)

Results:

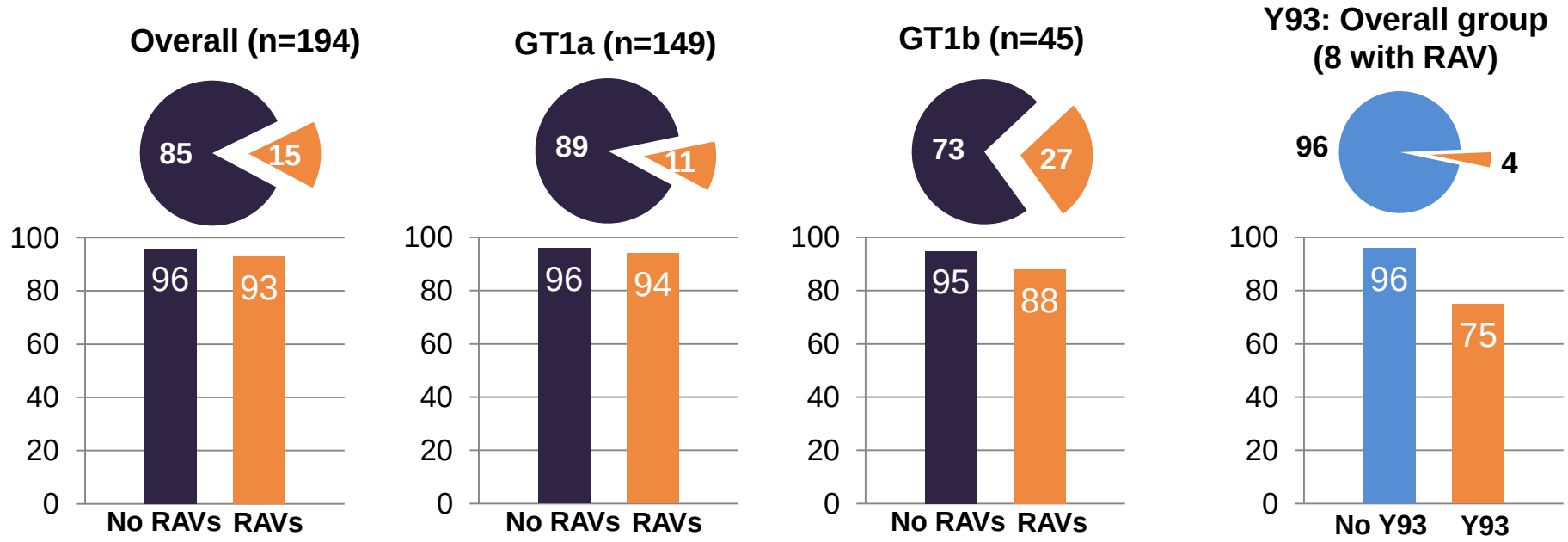
- Baseline RAV prevalence
  - NS3: 45% **GT1a>GT1b**
  - NS5A: 13% } **GT1b>GT1a**
  - NS5B: 8%

[1]Zepatier package insert, [2]Wang EASL Abstract PS0102

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

Results: LDV/SOF

- Baseline LDV RAVs at 28, 30, 31, 58, or 93
  - Non-significant 1% to 7% lower SVR12 depending on subgroup
- Baseline Y93 RAV
  - Infrequent (4%)
  - Significantly lower SVR12 (96% vs 75%)



Wang EASL Abstract PS0102

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

Results: LDV/SOF

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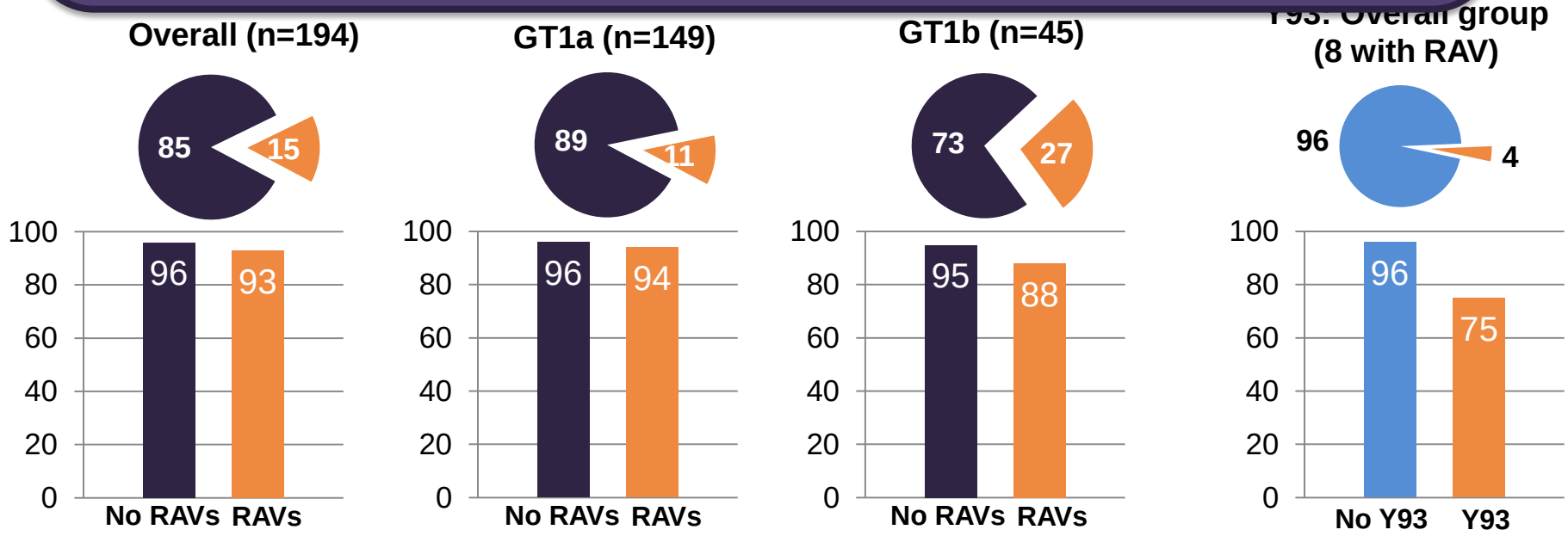
-

Clinical Implications: LDV/SOF:

- ❖Does not support routine baseline NS5A testing in DAA-naïve pts
- ❖Consider testing in “difficult to treat” patient populations
- ❖Consider adding RBV if baseline RAV present, especially if Y93



Wang EASL Abstract PS0102

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Background:

- Baseline NS5A RAVs impact treatment course with EBR/GRZ in patients with GT1a[1]
- Baseline RAV testing is not routinely performed before using other DAA regimens

Aim[2]:

Describe the prevalence of baseline RAVs and their impact on SVR in pts from phase 3 trials treated with OPrD +/- RBV

Methods:

- Analysis of data from 5 phase III trials using OPrD on label
  - Next generation sequencing at 1% and 15% detection thresholds

Results:

- GT1b: 100% SVR regardless of baseline RAVs
- GT1a:
  - non-significant 4% lower SVR with baseline NS5A RAVs
  - similar SVR rates with and without other RAVs

[1]Zepatier package insert, [2]Sarrazin EASL Abstract LBP503

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

Background:

- Baseline NS5A RAVs impact treatmen
  patients
- Baseline
  performe
  regimens

Methods:

- Analysis of data from 5
  g OPrD
  quencing at
  tion

Clinical Implications: OPrD:

- ❖Does not support routine baseline NS5A testing
- ❖Does not change current management

Aim[2]:

Describe the prevalence of baseline RAVs and their impact on SVR in pts from phase 3 trials treated with OPrD +/- RBV

Results:

- GT1b: 100% SVR regardless of baseline RAVs
- GT1a:
  - —non-significant 4% lower SVR with baseline NS5A RAVs
  - —similar SVR rates with and without other RAVs

[1]Zepatier package insert, [2]Sarrazin EASL Abstract LBP503

Does 12 week SVR really mean cure?

Aim: To determine long-term virologic and clinical outcomes in pts treated with DAAs using registry study data

Methods: Ongoing 3-yr registry of HCV pts treated in a Gilead-sponsored studies

Results:

- SVR: maintained in 99.7% (5414/5433)
  - 6 pts (0.1%) with late relapse
  - 12 pts (0.2%) with reinfection
  - 1 pt unable to determine relapse vs reinfection

Results:

- 6 pts with late relapse
  - Time to relapse from EOT 218-429 days
  - 3 GT1a, 3 GT3a
- 12 with reinfection
  - Time to reinfection 253-1086 days post-treatment

Lawitz EASL Abstract FRI-166

Does 12 week SVR really mean cure?

Aim: To determine long-term virologic a

Results:

Clinical Implications:

- ❖SVR12 is durable: SVR=Cure
  - Low rate of late relapse (0.1%)
- ❖Reinfection is not common in clinical trial population
- ❖Reinfection rates may be different in real world populations
  - High reinfection rates in HIV+ MSM in W. Europe (Martin EASL Abstract PS006) and HIV+ IDU (Martinello EASL Abstract FRI-184)
- ❖Counsel patients on reinfection prevention

86

- 1 pt unable to determine relapse vs reinfection

Lawitz EASL Abstract FRI-166

Can I retreat a patient who relapses after DAA therapy?

Background:

- Treatment failure is linked to selection of RAVs
- Selected NS3 RAVs do not persist long-term[1]
- Selected NS5A RAVs persist >2 years post-treatment[2]
  - Broad cross-resistance impacts retreatment strategies

Methods[3]:

- Open-label, Phase 2 study using OPrD + SOF + RBV for 12 or 24 wks in GT1 pts who failed DAA treatment
  - 16/22 failed OPr(D) regimen

Results:

- All 22 had RAVs prior to treatment
- Most common positions:

NS3: Q80(n=15), D168(n=5)

NS5A: Q30(n=12), M28(n=10), Y93(n=4)

NS5B: S556(n=7)

- Overall SVR 95% (21/22)
  - 1 relapse: GT1a, non-cirrhotic, prior telaprevir experience, NS3 Q80K and no other RAVs (at baseline and failure)

[1]Lenz EASL 2014, [2]Wyles EASL 2015, [3]Poordad DDW Abstract 604

Can I retreat a patient who relapses after DAA therapy?

Background:

- Treatment failure is linked to selection of RAVs
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Clinical Implications:

❖OPrD + SOF + RBV is effective in retreatment after DAA failure

❖Not applicable for patients with decompensation, GFR<30, or RBV-ineligible

❖May be cost-prohibitive

Meth

- Open-label, Phase 2 study using OPrD + SOF + RBV for 12 or 24 wks in GT1 pts who failed DAA treatment
  - –16/22 failed OPr(D) regimen

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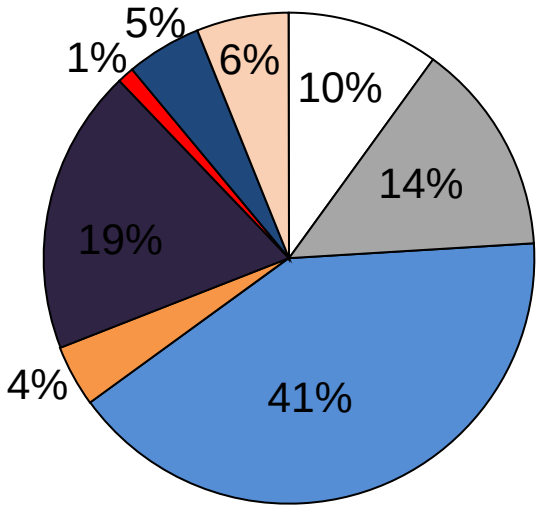
[1]Lenz EASL 2014, [2]Wyles EASL 2015, [3]Poordad DDW Abstract 604

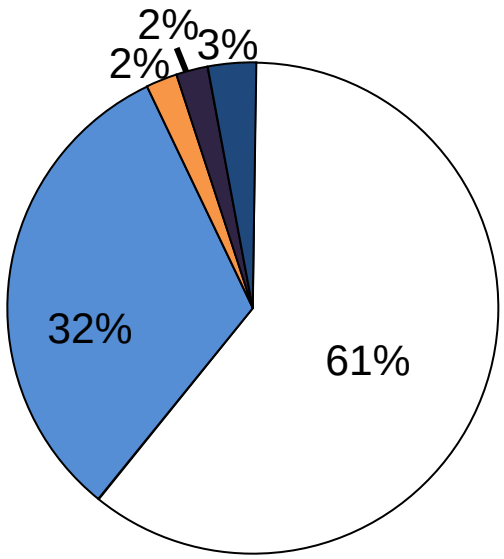
Can I retreat a patient who relapses after DAA therapy?

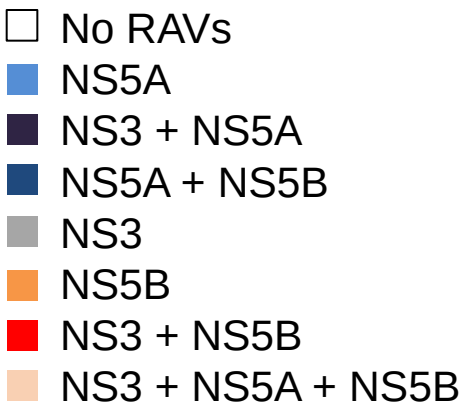
- Data from large German resistance database: N = 3549
  - 9% of pts with IFN-free DAA regimen failure (n = 310; excludes pts with GT1 HCV treated with SOF + RBV)
- Resistance analysis for drug class-specific RAVs with > 2-fold EC_{50} increase in 195 GT1 and 69 GT3 pts

GT1 (n = 195): 90% With RAVs



GT3 (n = 69)*: 39% With RAVs





*Previous GT3 tx: SOF + RBV (n = 33); DCV + SOF ± RBV (n = 20); LDV/SOF ± RBV (n = 15); SMV + SOF ± RBV (n = 1).

Vermehren EASL Abstract PS0103.

Slide credit: clinicaloptions.com

Can I retreat a patient who relapses after DAA therapy?

Previous DAA Regimen Failure	Retreatment Regimen	SVR12
GT1: SMV + SOF ± RBV	**NS5A inhibitor–containing regimen**	**91%**
	▪ LDV/SOF ± RBV 12 wks	8/8
	▪ LDV/SOF ± RBV 24 wks	9/10
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/3
	▪ OBV/PTV/RTV + DSV + RBV 24 wks	0/1
GT1: DCV or LDV + SOF ± RBV	**PI-containing regimen**	**86%**
	▪ SMV + SOF ± RBV 12 wks	2/2
	▪ SMV + SOF ± RBV 24 wks	1/1
	▪ OBV/PTV/RTV + DSV ± RBV 12 wks	3/4
GT3: SOF + RBV	**NS5A inhibitor–containing regimen**	**100%**
	▪ DCV + SOF + RBV 12 wks	2/2
	▪ DCV + SOF ± RBV 24 wks	4/4
	▪ LDV/SOF + RBV 24 wks	1/1

Vermehren EASL Abstract PS0103.

Slide credit: clinicaloptions.com

Can I retreat a patient who relapses after DAA therapy?

Previous DAA Regimen Failure	Retreatment Regimen	SVR12
GT1: SMV + SOF ± RBV	NS5A inhibitor–containing regimen	91%
	▪ LDV/SOF + RBV 24 wks	1/1

Clinical Implications:

- ❖RAV testing in DAA failures should be performed before considering retreatment
- ❖High SVR rates using individualized treatment approach based on RAV analysis:
  - Switching to different DAA class when available
  - Adding ribavirin
  - Extending treatment duration

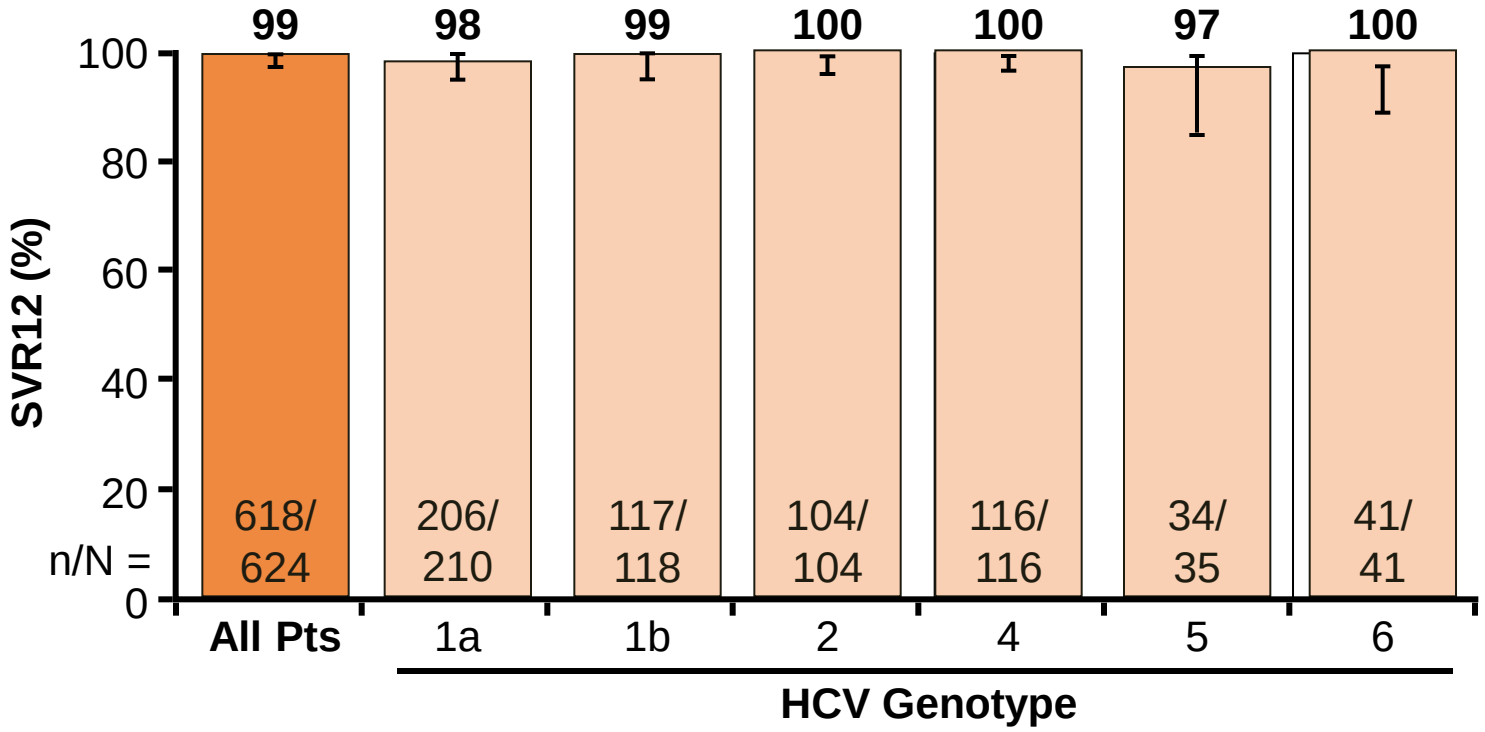
Vermehren EASL Abstract PS0103.

Slide credit: clinicaloptions.com

NEXT GENERATION ANTIVIRALS

ASTRAL-1: Sofosbuvir/Velpatasvir for GT1, 2, 4, 5, 6 HCV

- Double-blind, placebo-controlled trial (N = 740), tx naive or experienced
  - Pts randomized 5:1 to sofosbuvir/velpatasvir or placebo for 12 wks
  - Key baseline characteristics: cirrhosis 19%, tx exp'd 32%, BL NS5A RAVs 42%
- No impact of cirrhosis, tx experience, BL NS5A RAVs on SVR12 rates



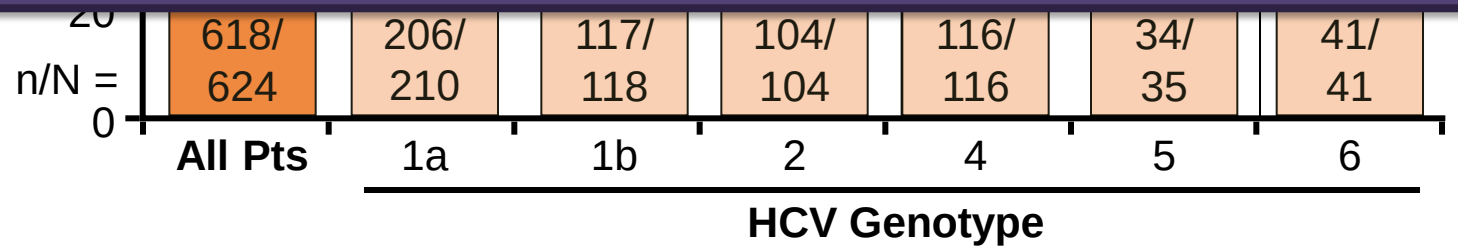
Feld JJ, et al. N Engl J Med. 2015.

Slide credit: clinicaloptions.com

ASTRAL-1: Sofosbuvir/Velpatasvir for GT1, 2, 4, 5, 6 HCV

New Data from EASL and DDW:

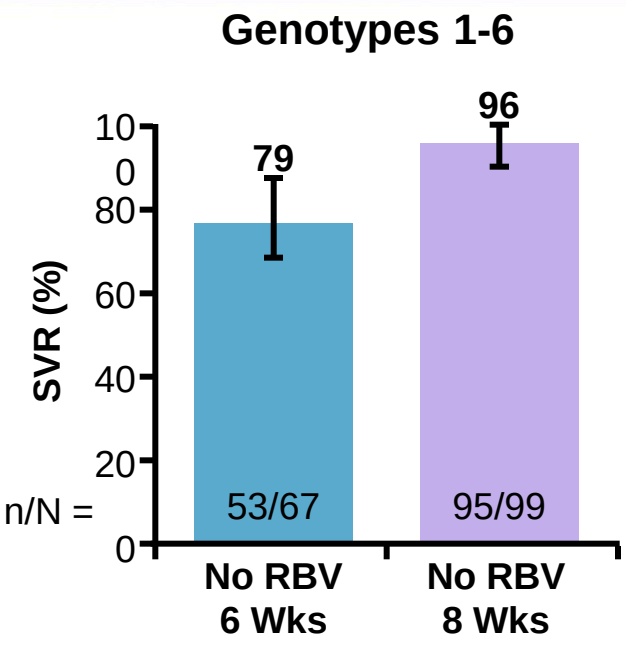
- ASTRAL-5: Safe and efficacious in HIV/HCV (Wyles EASL Abstract PS0104)
- ASTRAL-4: High SVR rates in decompensated cirrhotics (GT3 required RBV to achieve high rates) (Brown DDW Abstract 754)
- VEL/SOF + RBV x 24wks after VEL/SOF failure (Asselah EASL Abstract PS024)
  - GT1 (n=34): 97% SVR: RAVs had no effect on SVR
  - GT2 (n=14): 91% SVR: RAVs had no effect on SVR
  - GT3 (n=17): 76% SVR: 9/11 (82%) SVR among pts with GT3 and Y93H

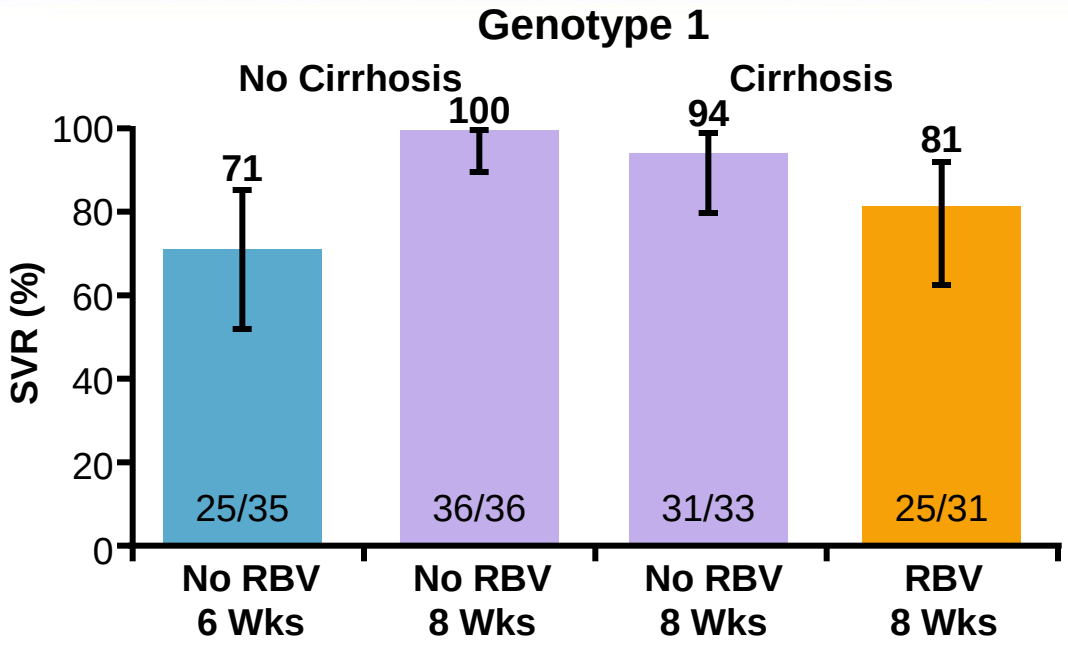


Feld JJ, et al. N Engl J Med. 2015.

Slide credit: clinicaloptions.com

VEL/SOF + GS-9857 for 6 or 8 Wks in Treatment-Naive Pts With GT1-6 HCV



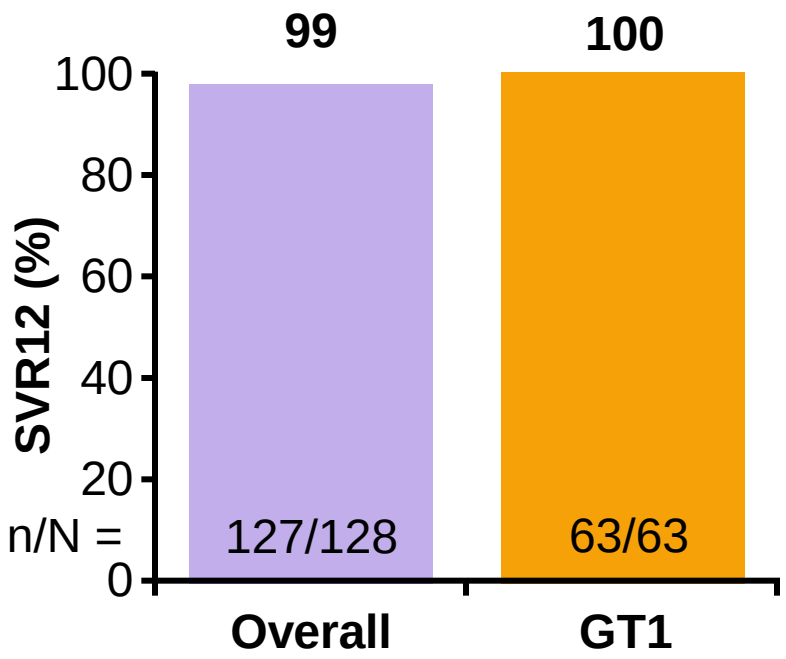


- 8 wks of VEL/SOF+GS9857 highly effective **including pts with RAVs and cirrhosis**
- No benefit of RBV with 8 wks
- Will the triplet be used as primary first-line treatment or as salvage treatment for persons who fail current DAAs?

Gane EASL 2016 Abstract SAT-138

VEL/SOF + GS-9857 for 12 Wks in Treatment-Experienced GT1-6 HCV

BL Characteristics (N = 128)	VEL/SOF + GS-9857
Cirrhosis, n (%)	61 (48)
Mean HCV RNA, log_{10} IU/mL (range)	6.3 (3.8-8.1)
HCV genotype, n (%)	
▪ 1	63 (49)
▪ 2	21 (16)
▪ 3	35 (27)
▪ 4/6	9 (7)
DAA experience, n (%)	
▪ None (GT2-6 only)	27 (21)
▪ 1 DAA class	36 (28)
▪ ≥ 2 DAA classes	65 (51)



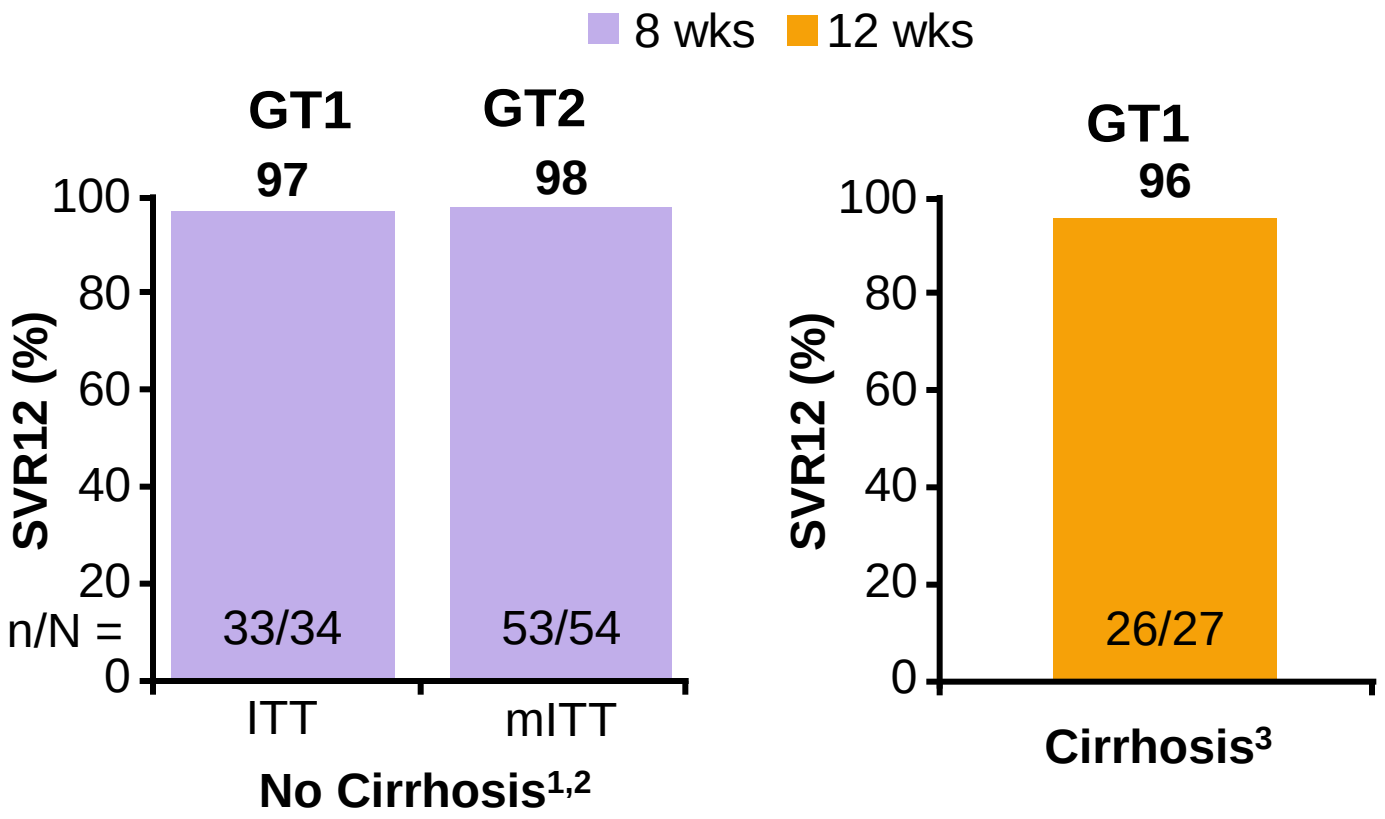
1 pt relapsed at post-treatment Wk 8: GT3, cirrhosis, prior SOF-failure, baseline Y93H

Lawitz EASL Abstract PS008.

Slide credit: clinicaloptions.com

SURVEYOR-I/II: ABT-493 + ABT-530 in Genotype 1 and 2

- ABT-493 + ABT-530: pan-genotypic 2nd-generation DAA combination
- Open-label, treatment naive or pegIFN/RBV experienced

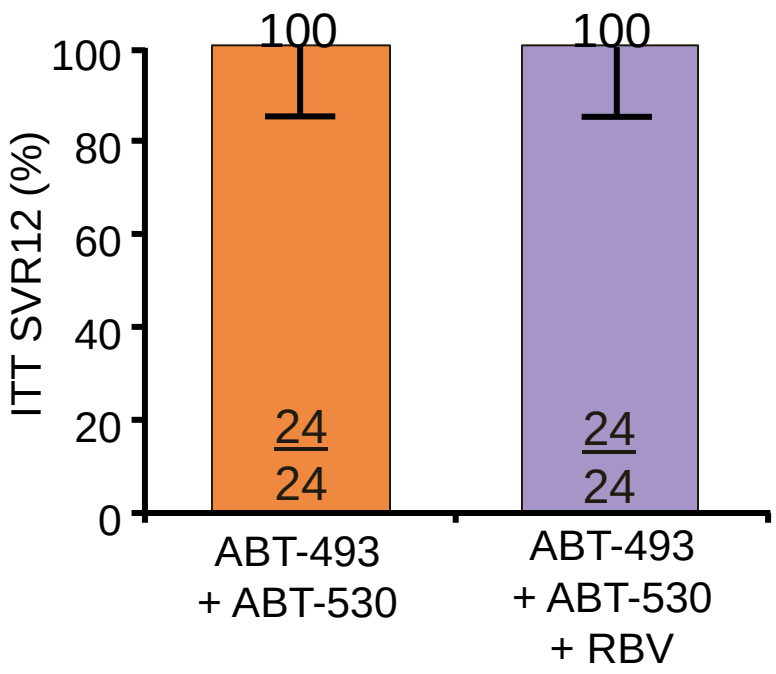


Poordad EASL Abstract SAT-157, Poordad DDW Abstract 752, Gane EASL Abstract SAT-135

ABT-493 + ABT-530 ± RBV x 12 Weeks

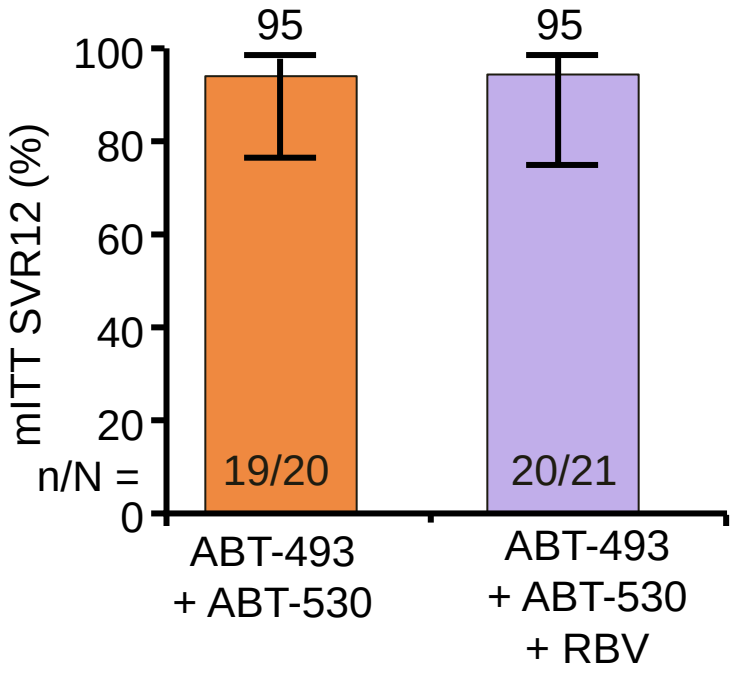
Genotype 3, Compensated Cirrhosis[1]

18/48 pts had NS3 and/or NS5A RAVs at BL



Genotype 1, Non-Cirrhotic, DAA Failures[2]

92% with NS3 and/or NS5A RAVs at BL



[1]Kwo PY EASL Abstract LBO1, [2]Poordad EASL Abstract GS11

What about HBV?

Tenofovir Alafenamide Compared with Tenofovir Disoproxil in Chronic HBV

Background:

- Tenofovir alafenamide (TAF)
  - Tenofovir (TFV) prodrug with greater plasma stability than TDF
  - Enhances delivery of active drug to hepatocytes
  - Lower circulating TFV relatively to TDF
  - Improved bone and renal safety in HIV+ pts

Methods:

- Double-blind, active-controlled, Phase 3 study
- 2:1 randomization to TAF 25 mg daily or TDF 300 mg daily
- Primary endpoint measures at 48 weeks

Results:

- HBeAg positive[1] and HBeAg negative[2], compared to TDF:
  - Higher rates of ALT normalization
  - Similar proportion w/undetected HBV DNA at 48 wks
  - Similar HBeAg loss and seroconversion
  - Significantly less declines in hip and spine BMD
  - Significantly smaller Cr increases

[1]Chan EASL Abstract GS12, [2]Buti EASL Abstract GS06

Tenofovir Alafenamide Compared with Tenofovir Disoproxil in Chronic HBV

Background:

- Te
- Pr

Clinical Implications:

- ❖TAF is as efficacious as TDF with more favorable side effect profile
- ❖TAF not clinically approved for treatment of chronic HBV
  - New drug application submitted to FDA January 2016
- ❖TAF-based regimens are clinically available for treatment of HIV
  - Elvitegravir/Cobicistat/Emtricitabine/TAF (Approved Nov 2015)
  - Emtricitabine/Rilpivirine/TAF (Approved March 2016)
  - Emtricitabine/TAF (Approved April 2016)

[1]Chan EASL Abstract GS12, [2]Buti EASL Abstract GS06

Take Home Points: HCV Cohort Data

- ✓ Excellent SVR rates achieved in routine clinical practice
  - ✓ Consult and adhere to clinical treatment guidelines
- ✓ 8-week LDV/SOF regimen is highly efficacious and underutilized in eligible GT1 patients
- ✓ Caution using PPIs with LDV/SOF
- ✓ HCC risk persists in patients with advanced fibrosis after cure- continue monitoring after SVR
- ✓ Decompensated patients should be referred to an experienced HCV provider, ideally at a LT center

Take Home Points: Resistance, Relapse, Retreatment

- ✓ DAA Naïve pts: Consider baseline RAV testing in “difficult to cure” populations before LDV/SOF treatment
- ✓ SVR12 is durable and = HCV cure (0.1% late relapse)
- ✓ DAA Failures: RAV testing should be performed before considering retreatment
  - ✓ If don’t want to wait to treat, individualized approach with available DAAs yields high SVR
  - ✓ If acceptable to wait, high SVRs can be achieved with next generation antivirals

Take Home Points: Next Generation Antivirals

- ✓ VEL/SOF: pan-genotypic, high SVR with 12 weeks
- ✓ VEL/SOF + GS-9857 and ABT-493 + ABT-530
  - ✓ DAA naïve: highly effective, short duration (8 weeks)
  - ✓ DAA failures: excellent SVR rates with 12 weeks
- ✓ Tenofovir Alafenamide (TAF) for chronic HBV
  - ✓ As efficacious as TDF (and higher rate of ALT normalization)
  - ✓ More favorable side effect profile
  - ✓ Currently available in combination regimens for HIV

Thank you!

Do baseline NS5A RAVs impact LDV/SOF or OPrD efficacy?

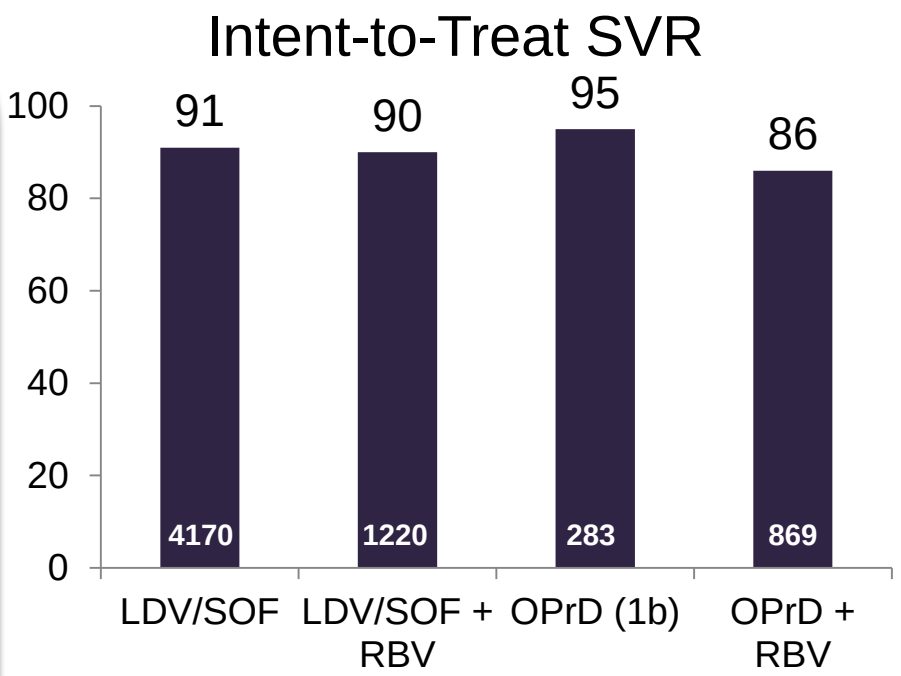
Fold-change in EC50	1a				1b	
Position	**M28T**	**Q30R**	**L31M/V**	**Y93H/N**	**L31V**	**Y93H/N**
Ledipasvir	20x	>100x	>100x/ >100x	>1,000x/ >10,000	20X	>100x/?
Ombitasvir	>1000x	>100x	<3x / >100x	>10,000x/ >10,000x	<10x	20x/50x
Daclatasvir	>100x	>1000x	>100x/ >1000x	>1,000x/ >10,000x	<10x	20x/50x
Elbasvir	20x	>100x	>10x / >100x	>1,000x/ >1,000x	<10x	>100x/--
Velpatasvir	<10x	<3x	20x/50x	100x/ >1000x	<3x/--	<3x/--

Wang C. AAC 2012. Cheng G. #1172. EASL 2012. Zhao Y. #A845 EASL 2012. Yang G. EASL 2013. Ng T. #639 CROI 2014.

What is the REAL WORLD effectiveness of current DAA regimens?

VA Clinical Case Registry:

- GT1 pts at 126 VA facilities
  - Ledipasvir/sofosbuvir (LDV/SOF) +/- RBV
  - Ombitasvir/paritaprevir/ritonavir + dasabuvir (OPrD) +/- RBV
- Limited to pts treated ≤12 wks
- Baseline characteristics
  - 29-47% African American
  - 26-45% BMI ≥ 30 kg/m^2
  - 2-5% HIV-coinfected
  - 11-52% FIB-4 >3.25
  - 16-53% Treatment experienced



Predictors of SVR*:

- BMI ≥ 30 kg/m^2
  - OR 0.66 (95% CI 0.49-0.88)
- FIB-4>3.25
  - OR 0.46 (95% CI 0.35-0.60)

Backus DDW Abstract 501

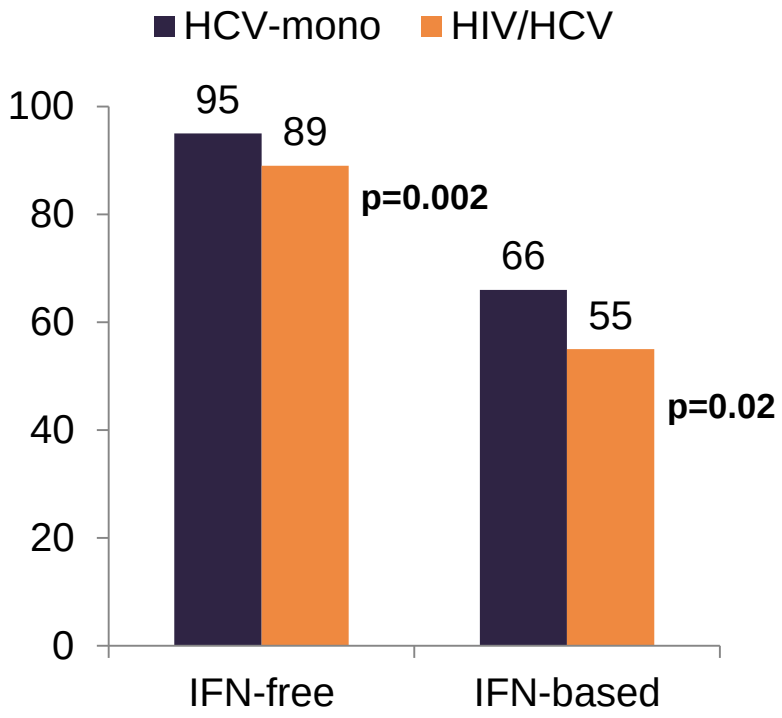
*Among pts who completed 12 weeks (N=4720)

What is the impact of HIV on the effectiveness of current DAAs?

HEPAVIR-DAA, GEHEP-MONO (Spain)

	IFN-free		IFN-based	
	HIV- n=404	HIV+ n=423	HIV- n=276	HIV+ n=173
Age	54	51*	51	49*
Male	67%	82%*	75%	84%**
GT 1	83%	67%*	91%	93%*
Cirrhosis	52%	64%*	50%	67%*

*p<0.001, **p=0.02

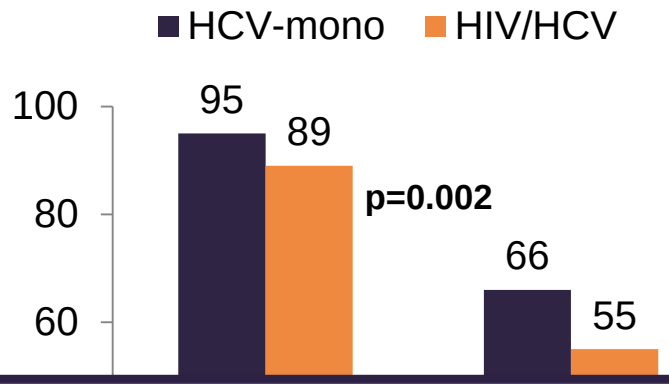


Neukam EASL Abstract LBP513

What is the impact of HIV on the effectiveness of current DAAs?

HEPAVIR-DAA, GEHEP-MONO (Spain)

	IFN-free		IFN-based	
	HIV- n=404	HIV+ n=423	HIV- n=276	HIV+ n=173
Age	54	51*	51	49*



Clinical Implications:

- ❖High SVR rates are achieved in HIV+ patients in routine practice
- ❖Consult and adhere to clinical treatment guidelines especially for drug-drug interactions with ART

Neukam EASL Abstract LBP513

HCV/HIV DDIs With Components of Selected ART Regimens

	SOF + SIM	SOF/LDV	SOF + DCV	PTV/RTV/OBV + DSV	GZR/EBV
Atazanavir + RTV	X	≈	≈	√	X
Darunavir + RTV	X	≈	√	X	X
Raltegravir	√	√	√	√	√
Dolutegravir	√	√	√	√	√
Elvitegravir + COBI	X	≈	≈	≈	X
Elvitegravir/COBI/ TAF/emtricitabine	X	√*	≈	X*	X
Efavirenz	X	≈	≈	X	X
Rilpivirine	√	√	√	X	√
Abacavir/lamivudine	√	√	√†	√	√
Tenofovir DF/ emtricitabine	√	≈ nephrotoxicity	√	√	√

No clinically significant interaction expected

Potential interaction may require adjustment to dosage, timing of administration, or monitoring

Do not coadminister

*EVG/COBI/TAF/FTC [package insert]. †Liverpool Drug Interactions Group.

Adapted from AASLD/IDSA Guidelines. February 2016.

What is the risk of HCC after HCV cure with DAAs?

Aim: To determine long-term virologic and clinical outcomes in pts treated with DAAs using registry study data

Results:

- SVR: HCC in 0.3% (16/5433)

Clinical Implications:

- ❖No clear short-term benefit of DAAs on HCC risk
  - Impact on HCC recurrence in pts with HCC history warrants further investigation
- ❖HCC risk persists after DAA therapy in patients with HCV cirrhosis: monitoring for HCC after SVR should continue

Cirrhotic	SVR	n=1086	n=900	n=602	n=319	n=150	n=60	n=4
	HCC	5 (<1)	5 (<1)	6 (1)	3 (<1)	0	0	0
	Non-SVR	n=117	n=90	n=83	n=50	n=41	n=7	n=0

Lawitz EASL Abstract FRI-166

Will my patient with decompensated cirrhosis get better with treatment?

Background:

- Good safety and efficacy for DAAs in compensated cirrhosis
- Clinical trials in decompensated cirrhotics demonstrate stabilization/ improvement of MELD and CPT scores in majority[1,2]
- Improvement in portal hypertensive complications seen with SVR[3]

Aim[4]: To evaluate factors that may identify patients with advanced cirrhosis most likely to benefit from treatment

Methods:

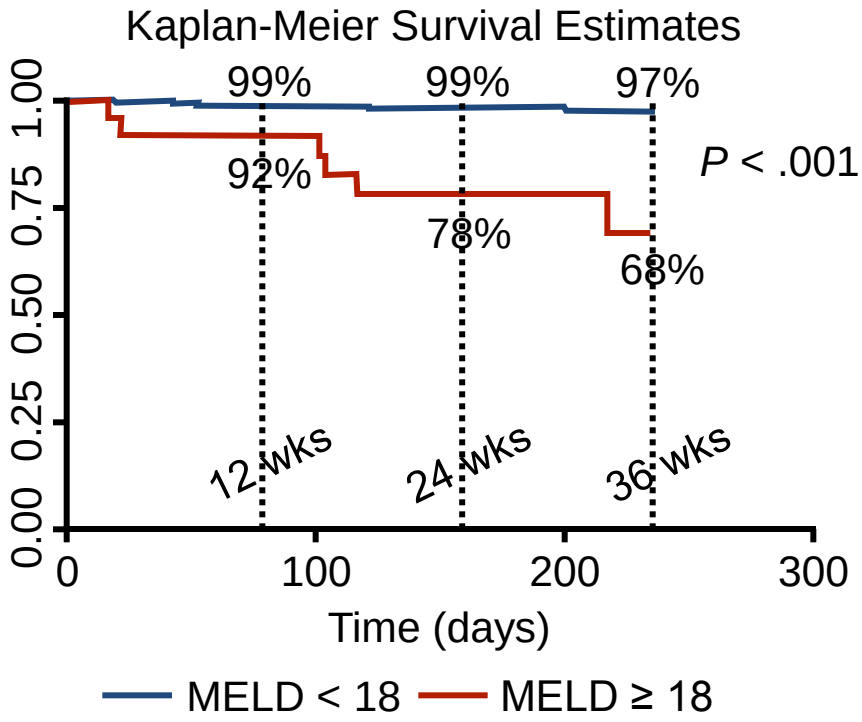
- HEPA-C registry (Spain)
- Retrospective study of non-LT candidates or pts listed for LT but did not receive LT during/within 12 wks after tx
  - CPT A: 564 (70%), 7% w/HCC
  - CPT B/C: 175 (30%), 10% w/HCC
- Received 12-24 wks tx with various regimens +/- RBV
  - SIM+SOF: 45%
  - SOF: 3%
  - DCV+SOF: 22%
  - DCV+SIM: 2%
  - LDV/SOF: 16%
  - PrD: 2%
  - OPrD: 10%

[1]Manns M et al Lancet ID 2016, [2]Curry MP et al. NEJM 2015, [3]Saxena AASLD 2015 Abstract 1825, [4]Fernandez-Carrillo EASL Abstract GS01

Will my patient with decompensated cirrhosis get better with treatment?

- SVR12 rate lower for CP B/C vs CP A (78% vs 94%; *P* < .001)
- SAE incidence higher for CP B/C vs CP A (50% vs 11.7%; *P* < .001)
- Death rate higher for CP B/C vs CP A (6.4 % vs 0.9%; *P* < .001)

Predictor	SAE		Death (On Study)	
	OR (95% CI)	Multiv. *P* Value	OR (95% CI)	Multiv. *P* Value
CP B/C vs A	**2.16 (1.29-3.64)**	**.004**	**1.73 (0.39-7.64)**	**.034**
MELD	**1.31 (1.2-1.43)**	**< .001**	**1.34 (1.16-1.53)**	**< .001**
MELD ≥ 18	NR	.171	NR	**< .001**
Platelets	0.99 (0.98-0.99)	.008	1.002 (0.99-1.02)	.151
Platelets < 100,000	2.94 (1.8-4.8)	< .001	NR	.711



Fernandez-Carrillo EASL Abstract GS01

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