A new era of HCV clinical management

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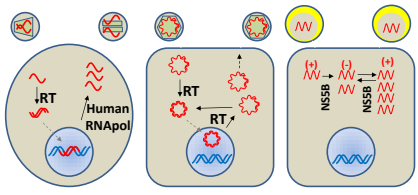
Goal of HCV treatment is <u>viral cure</u>

HCV life Cycle favors resistance development not persistence



	HIV	HBV	HCV
Stable genome	Provirus	cccDNA	(none)
Virion NA polymerase	Host RNApol	HBV RT	HCV NS5B
Error-prone replications per cell	One	Multiple	Multiple
Plasticity of genome	High	Constrained	Very high
Recombination	Common	Common	Rare

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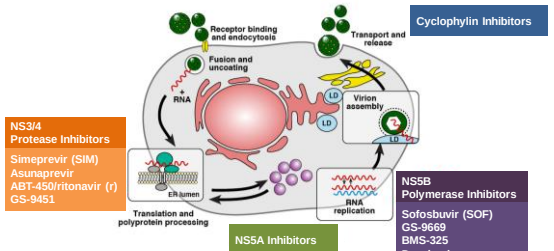
Direct-Acting Antivirals for Hepatitis C



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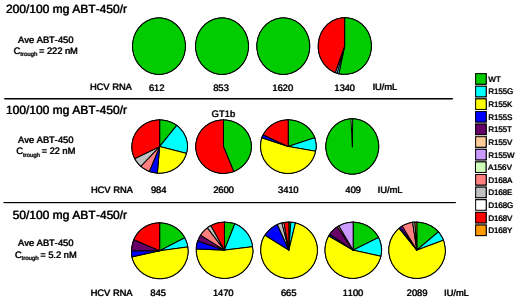
Inhibitors of NS3/4A Protease

Mechanism	Prevent the proteolytic cleavage of the HCV polyprotein at four junctions: NS3-4A, 4A-4B, 4B-5A, 5A-5B Block inactivation of cellular proteins required for innate immunity?
Antiviral activity	Potent
	HCV genotype, most are not effective against GT 3
Resistance barrier	Low; 1a < 1b Baseline resistance ~ 5 – 7% (population sequencing)
Pharmacokinetics	Variable, daily to thrice daily
Drug interaction potential	High
Approved agents	Simeprevir, boceprevir and telaprevir

Rapid selection of resistant variants with HCV PI monotherapy

Clonal sequence analysis with ABT-450/r for 3 days

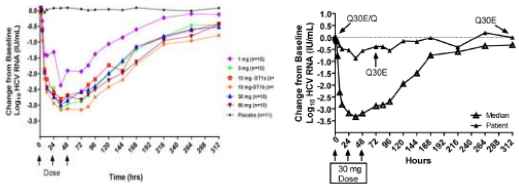


Pilot-Matias TM *et al, 46th EASL*, Berlin, 2011, Abs#1107

Inhibitors of NS5A

Mechanism	No enzymatic activity for NS5A Agents bind to NS5A to directly to inhibit replication and viral assembly/release
Antiviral activity	Potent
	Multiple genotypes
Resistance barrier	Low; 1a < 1b Baseline resistance ~ 15 – 20% (population sequencing)
Pharmacokinetics	Once daily
Drug interaction potential	Low to moderate
Approved agents	Soon --- ledipasvir, daclatasvir, ombitasvir *Included in most oral DAA combinations*

Antiviral activity of ledipasvir monotherapy over 3 days



Lawitz EJ et al. J Hepatol 2012

Non-nucleoside Inhibitors of NS5B polymerase

Mechanism	Inhibition of polymerase function by targeting one of at least four allosteric sites (thumb 1, 2; palm 1,2) Heterogeneous group of agents
Antiviral activity	Variable
	Variable, HCV genotype and subtype
Resistance barrier	Low; 1a < 1b Baseline resistance ~ 20% (population sequencing)
Pharmacokinetics	Variable, daily to thrice daily
Drug interaction potential	Variable
Approved agents	Soon – dasabuvir; BMS-791325

Nucleos(t)ide Inhibitors of NS5B polymersase

Mechanism	Inhibition of polymerase synthesis of positive and negative strand RNA by targeting active site with incorporation in the elongating RNA leading to chain termination
Antiviral activity	Potent
	Consistent, HCV genotypes
Resistance barrier	High; 1a > 1b No baseline resistance (clonal sequencing)
Pharmacokinetics	Once daily
Drug interaction potential	Low
Approved agents	Sofosbuvir

Sofosbuvir resistant variants are rarely observed prior to or following exposure

- S282T: unfit mutant-replication 2-5% of WT
- Not detected in any patient at baseline
- Not detected by deep sequencing in any of the non-SVR patients in phase 3 studies
  - 225 nonSVR (221 deep sequenced): No S282T
  - None in ION studies
- S282T was detected in 1 patient in LONESTAR study (SOF/LDV) and 1 patient in SPARE study

No shift in EC50 versus Reference after non-SVR

Svarovskaia E. AASLD 2013.

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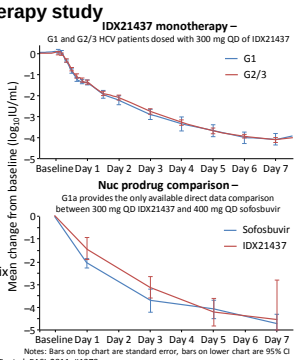
IDX21437: Profile and 7 day virologic data from proof-of-concept monotherapy study

- IDX21437 - Uridine nucleotide analog prodrug
- Favourable preclinical profile
  - Potent and pan-genotypic activity *in vitro*
  - Toxicology profile provides good safety margins
  - Clean cardiac safety Favorable DDI profile
- 39 HCV patients dosed with IDX21437 for 7 days
  - No SAEs or discontinuations to AEs and no safety signals
- Jun 9, 2014 - Merck agreed to buy Idenix for about $3.85 billion



Notes: Bars on top chart are standard error, bars on lower chart are 95% CI

Source of sofosbuvir data is the NUCLEAR Study Cohort 3: Lawitz E, et al. EASL 2011, #1370

Genotype 1

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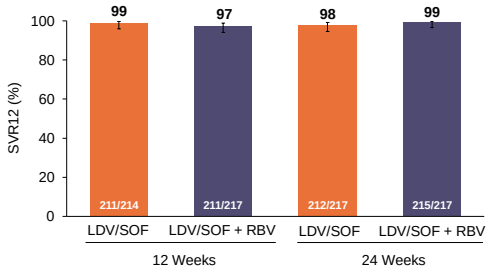
ION-1: Co-formulated Sofosbuvir/Ledipasvir QD daily ± Ribavirin BID for 12 or 24 weeks

- 865 patients - Genotype 1, treatment naïve, ± cirrhosis



Error bars represent 95% confidence intervals.
Mangia A, et al.EASL 2014. Abst. O164.

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ION-1 Results: Reasons For Not Achieving SVR

GT 1 Treatment Naive

	12 Weeks		24 Weeks	
Patients, n (%)	**LDV/SOF n=214**	**LDV/SOF + RBV n=217**	**LDV/SOF n=217**	**LDV/SOF + RBV n=217**
SVR12	211 (99)	211 (97)	212 (98)	215 (99)
Breakthrough	0	0	1 (<1)	0
Relapse	1 (<1)	0	1 (<1)	0
Lost to follow-up	2 (<1)	6 (3)	3 (1)	2 (1)

- Single on-treatment breakthrough was due to non-compliance
  - Patient had no detectable levels of LDV or SOF at the time of virologic failure

Mangia A, et al. 49th EASL; London, England; April 9-13, 2014. Abst. O164.

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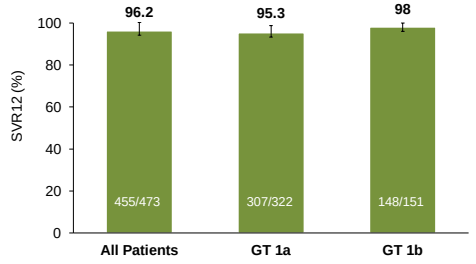
SAPPHIRE-I: Co-formulated ABT450/r/Ombitasvir QD + Dasabuvir BID + Ribavirin BID for 12 weeks

- 473 patients - Genotype 1, Treatment naïve, No cirrhosis



Feld J, et al. 49th EASL; London, England; April 9-13, 2014. Abst. O60.

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SAPPHIRE-I: Breakthrough and Relapse Rates in Patients Receiving 3D + RBV

Event, n/N (%)	3D + RBV N=473
SVR12	455/473 (96)
Virologic failure	
Breakthrough	1/473 (<1)
Relapse	7/463 (2)
Prematurely discontinued study drug*	7/473 (2)
Lost to follow-up after completing treatment	3/473 (<1)

*Patients (n=7) who prematurely discontinued without breakthrough; 2 due to AEs, 5 withdrew consent/lost to follow-up.

Feld J, et al. 49th EASL; London, England; April 9-13, 2014. Abst. O60.

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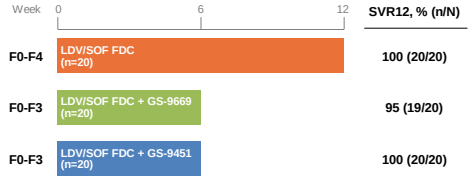
SYNERGY: Sofosbuvir/Ledipasvir FDC ± GS-9669 QD (non-nucleoside NS5B polymerase inhibitor) or GS-9451 QD (NS3 protease inhibitor)

- 60 patients - Genotype 1, Treatment naïve
- No patients with cirrhosis in the six week arms



Ledipasvir/sofosbuvir 90/400 mg QD; GS-9669 500 mg QD; GS-9451 80 mg QD.
Kohli A, et al. CROI 2014. Abstract 27LB.

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Genotype 2
Genotype 3

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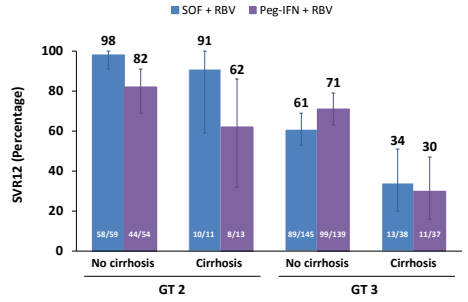
FISSION: 12 weeks of Sofosbuvir + RBV ± PegIFN
SVR12 by Genotype and Cirrhosis



Error bars represent 95% confidence intervals.

Gane E, et al. 48th EASL; Amsterdam, Netherlands; April 24-28, 2013. Abst. 5.

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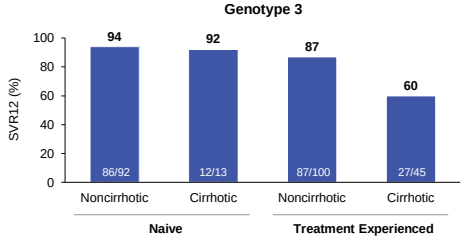
VALENCE: 24 weeks of Sofosbuvir + RBV
GT 3 IFN Naive, Ineligible or Treatment Failures

- Phase 3 study in Europe
- Genotype 2/3, naive/experienced



Zeuzem S et al, AASLD 2013. Abstract 1085.

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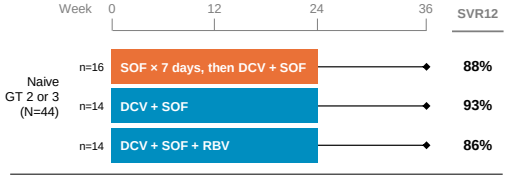
Daclatasvir + Sofosbuvir ± RBV
GT 2, GT 3 Treatment Naive



Phase 3 Trial (NCT02032901) currently enrolling

Naive or Experienced GT 3 N=150 — DCV + SOF

Drug dosing: daclatasvir (DCV): 60 mg QD, sofosbuvir (SOF): 400 mg QD.
Sulkowski MS, et al. N Engl J Med. 2014;370:211-221; Clinical Trials.gov.

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Genotype 4

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SOF + RBV in the treatment of G4-infected patients of Egyptian ancestry

- Treatment-naive (n=28) and -experienced patients (n=32)

	SOF + RBV 12 wks		SOF + RBV 24 wks	
	Naive (n=14)	Experienced (n=17)	Naive (n=14)	Experienced (n=15)
EOT	31/31 (100%)		29/29 (100%)	
SVR4	11/14 (79%)	10/17 (59%)	14/14 (100%)	14/15 (93%)
SVR12	**11/14 (79%)**	**10/17 (59%)**	**14/14 (100%)**	**13/15 (87%)**

Ruane PJ, et al. EASL 2014, London, P1243

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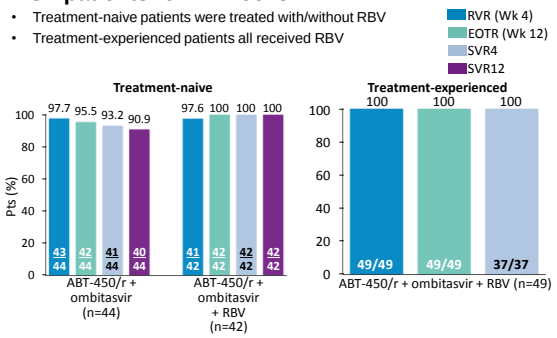
PEARL-I study: ABT-450/r/Ombitasvir ± RBV in G4 patients for 12 weeks

- Treatment-naive patients were treated with/without RBV
- Treatment-experienced patients all received RBV



Hezode C, et al. EASL 2014, London, OS8

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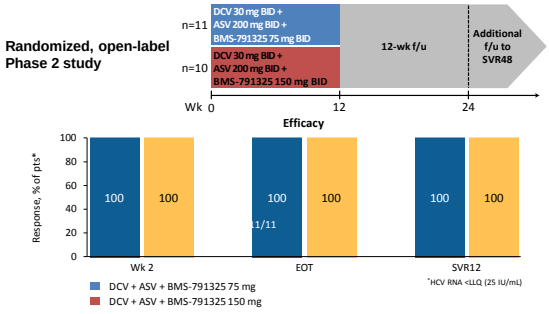
DCV + ASV + BMS-791325 for treatment-naive patients with chronic HCV G4 infection



Hassanein T, et al. EASL 2014, London, P1163

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Genotype 1, 2, 3, 4, 5 and 6: Pan-genotypic

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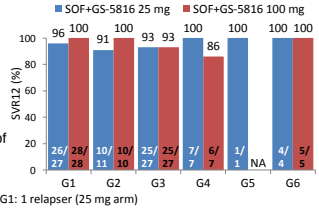
SOF + GS-5816 for 12 weeks in treatment-naïve patients with genotype 1,2,3,4,5, or 6 infection

- GS-5816: Pan-genotypic NS5A inhibitor
  - Two doses, 25 or 100 mg
- 154 patient enrolled
  - SOF 400 mg QD + GS-5816 QD
  - No Ribavirin
- Rapid virologic response in 153 of 154
- Most frequent AEs: Fatigue, headache, nausea
- No DC due to AEs
- No treatment related SAEs



- G1: 1 relapser (25 mg arm)
- G2: 1 death after EOT (25 mg arm)
- G3: 1 pt stopped for non-response Wk 8 (25 mg arm); 1 reinfection (100 mg arm); 2 relapsers (1 in in each arm)
- G4: 1 pt lost to f/u (100 mg arm)

- 3 of 4 virologic failures -- 25 mg dose
- Phase 3 trials are underway with the fixed-dose combination of SOF 400 mg/5816 100 mg

Everson GT, et al. EASL 2014, London, O111

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HIV/HCV Coinfection

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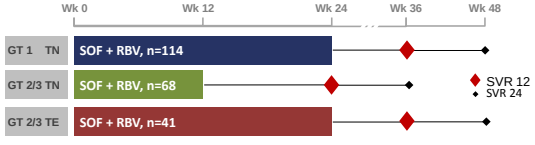
Sofosbuvir + Ribavirin for chronic HCV infection in HIV-infected persons



- Broad inclusion criteria
  - Cirrhosis permitted with no platelet cutoff
  - Hemoglobin: ≥12 mg/dL (males); ≥11 mg/dL (females)
- Wide range of ART regimens allowed
  - Undetectable HIV RNA for >8 weeks on stable ART regimen
- Baseline CD4 count
  - ART treated: CD4 T-cell count >200 cells/mm^3 and HIV RNA < 50 c/mL
  - ART untreated: CD4 T-cell count >500 cells/mm^3

Sulkowski et al JAMA 2014 in press

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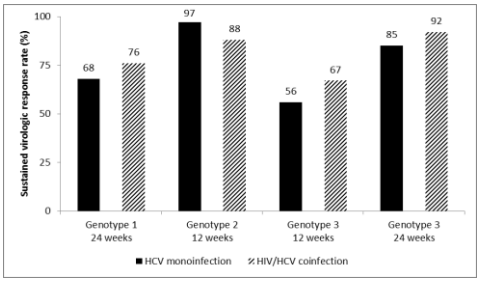
Sofosbuvir + Ribavirin for HCV infection in persons with and without HIV coinfection



Sulkowski MS. J Hepatology 2014 in press

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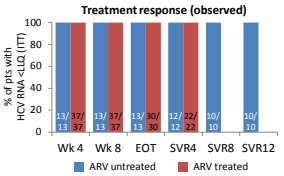
SOF/LDV for 12 wks in HIV/HCV-coinfected patients

BL characteristics	ARV untreated n=13	ARV treated n=37
Median age (range)	59 (48–63)	58 (34–75)
Male, n (%)	7 (54)	30 (81)
African American, n (%)	10 (77)	32 (86)
G1a, n (%)	9 (75)	30 (81)
HAI fibrosis stage 3, n (%)	5 (38)	8 (22)
Median CD4 T-cell count (range)	687 (319–1287)	576 (113–1612)
ARVs, (%)		
TDF/FTC + EFV		15 (41)
TDF/FTC + RAL		10 (27)
TDF/FTC + RPV		8 (21)
RPV/RAL		3 (8)
EFV/RAL		1 (3)



- SOF/LDV safely administered in combination with several ARV regimens
  - No significant CD4 or HIV RNA changes
  - No renal toxicity observed
  - Well tolerated with no discontinuations

Osinusi A, et al. EASL 2014, London, O14

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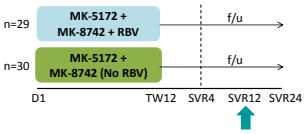
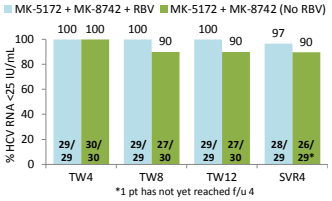
MK-5172/MK-8742 ± RBV for 12 wks in patients with HCV genotype 1/HIV coinfection: C-WORTHY study



- Virologic failures:
  - 1 relapse in +RBV arm
  - 2 breakthroughs and 1 lost to f/u in no RBV arm
- No HIV breakthrough
- AE profile consistent with RBV



*1 pt has not yet reached f/u 4

- Treatment with MK-5172 + MK-8742 ± RBV for 12 weeks demonstrated high efficacy (90–97% 4 weeks after EOT + SVR4)

Sulkowski M, et al. EASL 2014, London, O63

MK-5172 (100 mg QD) + MK-8742 (50 mg QD); 12 wks

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Biologic challenges to HCV cure in persons with HCV mono-infection HCV/HIV co-infection

- Persistence of HCV infection following treatment in some patients, particularly in those with cirrhotic livers
  - Biologic mechanisms?
  - Reservoirs?
- Resistance to HCV DAA
  - Baseline and selected variants
  - Strategies for HCV cure in the patients with resistant virus?
- Drug interactions with concurrent medications such as antiretroviral or tuberculosis drugs (rifampin)

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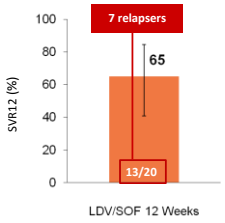
ELECTRON-2 – Sofosbuvir/ledipasvir for patients With CPT B Cirrhosis

	GT 1 CPT Class B
Median total bilirubin, mg/dL (range)	1.5 (0.7-3.7)
Median serum albumin, g/dL (range)	3.1 (2.3-3.8)
Median INR (range)	1.2 (1.0-3.0)
Ascites, n (%)	4 (20)
Hepatic encephalopathy, n (%)	6 (30)
Median platelet count, $10^3/\mu L$ (range)	84 (44-162)



Gane EJ, et al. EASL 2014. Abstract O6.

Error bar represents the 95% confidence interval.

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Patients with virologic failure in ION-2 Genotype 1 treatment experienced

12 Week Treatment Group	Age	Race	Sex	GT	IL28B	Cirrhotic	Prior Rx (Peg-IFN+RBV)	Prior Treatment Response	NS5A RAVs at BL	NS5A RAVs at Relapse
SOF/LDV+RBV	63	B	M	1a	CT	Yes	+PI	Non-Responder	None	Q30K(>99%)
SOF/LDV+RBV	60	W	M	1a	CT	Yes		Relapse/ Breakthrough	Y93H(1.20%)	Q30L(76.43%) Q30R(22.94%) Y93H(>99%)
SOF/LDV+RBV	60	W	M	1a	TT	Yes	+PI	Non-Responder	L31M(>99%)	Q30H(>99%) L31M(>99%)
SOF/LDV+RBV	65	W	M	1a	CT	Yes		Relapse/ Breakthrough	None	M28T(>99%) Q30R(>99%)
SOF/LDV	62	W	M	1b	CT	Yes		Null Responder	None	L31V(>99%)
SOF/LDV	64	W	M	1b	CT	Yes	+PI	Relapse/ Breakthrough	None	L31M(96.81%) Y93H(>99%)
SOF/LDV	64	W	M	1a	CT	Yes	+PI	Relapse/ Breakthrough	None	Q30H(9.80%) Y93H(93.93%)
SOF/LDV	61	W	M	1b	CT	No		Null Responder	Y93H(59.82%)	Y93H(>99%)
SOF/LDV	58	W	F	1a	CT	No	+PI	Non-Responder	Q30R(1.43%) Y93N(97.60%)	Y93N(>99%)
SOF/LDV	57	W	F	1a	CT	No	+PI	Relapse/ Breakthrough	M28T(1.03%) Q30R(>99%) L31M(>99%)	Q30R(>99%) L31M(>99%)
SOF/LDV	54	W	M	1a	CT	No		Partial Responder	Q30H(98.76%) Y93H(98.07%)	Q30H(98.92%) Y93H(>99%)

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Patients with virologic failure in SAPHHIRE 1 (No cirrhosis) following 3D + RBV

- Virologic failure occurred in 8/473 (1.7%) patients. Each of these patients had at least 1 resistance-associated variant at the time of virologic failure.

Patient	GT	Type of Virologic Failure	NS3	NS5A	NS5B
1	1a	Breakthrough at Week 12	R155K, D168V	Q30R	S556G, D559N
2	1a	Relapse at PT Week 2	D168V	M28T	S556G
3	1a	Relapse at PT Week 2	V36A, D168V	M28T	none
4	1a	Relapse at PT Week 8	none	M28V*, H58P*	none
5	1a	Relapse at PT Week 8	D168V	Q30R	Y561H
6	1a	Relapse at PT Week 8	D168V	Q30R	none
7	1a	Relapse at PT Week 12	D168V	Y93N*	S556G
8	1b	Relapse at PT Week 2	Y56H, D168V	L31M*, Y93H*	S556G*

*Variant also present at baseline.

Persistence of NS5A resistant variants

- **Following 3-day monotherapy with samatasvir, treatment emergent RAVs at position 31 persisted for > 1.5 years in patients with 1a infection and ~ 1 year in patients with 1b infection**

Table 4: Persistence of RAVs at NS5A positions 28, 30, 31 and 93 over time in GTs 1-4

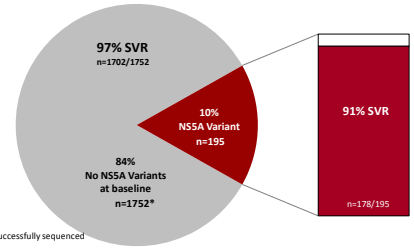
Genotype	Subject	RAVs present at EOT	Time Point 1		Time Point 2		Time Point 3		Time Point 4		Time Point 5	
			Variants	Months	Variants	Months	Variants	Months	Variants	Months	Variants	Months
1a	1	M28T/M, L31I/L	–	6.2	L31I/L	9.2	L31I	12.2	L31I/L	15.2	L31I/L	18.2
	2	M28T/M, L31M/L	L31M/L	7.0	L31I/L/M/V	10.0	L31I/L/M/V	13.0	Q30R, L31M/L	16.0	L31M/L	19.0
	3	Q30G/E, L31M/L, Y93Y/H	–	6.9	L31M	9.9	L31M/L	12.9	L31M/L	15.9	L31M/L	18.9
	4	M28T/M, Y93Y/H	–	8.0	L31M/L	11.0	L31M/L	14.0	L31M/L	17.0	L31M/L	20.0
	5	< low	L31M	6.9	L31M	9.9	L31M/L	12.9	–	15.9	–	18.9

Heinrich et al International Workshop on Antiviral Drug Resistance, June 3-7, 2014; Berlin, Germany

Baseline NS5A Variant Analysis (10% cut-off)

ION Phase 3 Program (ION-1, ION-2, ION-3)

- HCV failure associated with NS5A resistant variants
- No S282T (SOF) resistance detected



*5 Subjects not successfully sequenced

Dvory-Sobel H et al. HepDART 2013
www.informedhorizons.com/resistance2014/presentations.html

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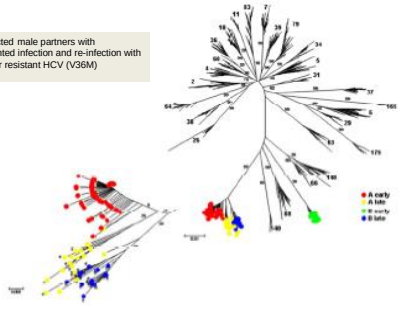
Infection and/or reinfection with DAA resistant hepatitis C

HIV-infected male partners with documented infection and re-infection with telaprevir resistant HCV (V36M)



Franco et al. Gastroenterology 2014

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Conclusions

- A short course of highly active, oral combination DAA regimens will offer *the potential* for HCV cure to most infected persons
  - Few side effects
  - Daily or twice daily dosing
  - Pre-treatment work-up required will be minimal (HCV RNA level, HCV genotype and hemoglobin (if RBV)
  - Minimal on-treatment monitoring will be needed
- Barriers to HCV cure will not be related to the characteristics of the drugs, the virus or the patients
  - *No Access ≈ No cure*
  - *Poor Adherence ≈ HCV drug resistance*