Treatment of HCV in 2015: A Case-based approach

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Disclosure Statement

- In the past 2 years, Dr Shafran has received research funding or honoraria related to HCV from:

  - AbbVie Laboratories
  - Boehringer Ingelheim
  - Bristol Myers Squibb
  - Gilead Sciences
  - Merck
  - Roche
  - Vertex

Objectives

By the end of this program, participants will have a better understand of:

- The 2015 Canadian Hepatitis C guidelines;
- The clinical use of IFN-Free treatment of HCV infection in a variety of patient types

Hepatitis C Epidemiology

- ~170 million cases worldwide (c/w ~35M with HIV)
- ~250,000 cases in Canada (~ 0.8% of population)
- HCV is the leading cause of chronic liver disease, cirrhosis, liver failure and liver cancer in western countries
- HCV is the leading indication for liver transplantation worldwide (~40% of cases)
- Unlike HAV & HBV, no vaccine is available (or imminent)
- HCV is ***curable*** with a finite course of antiviral therapy

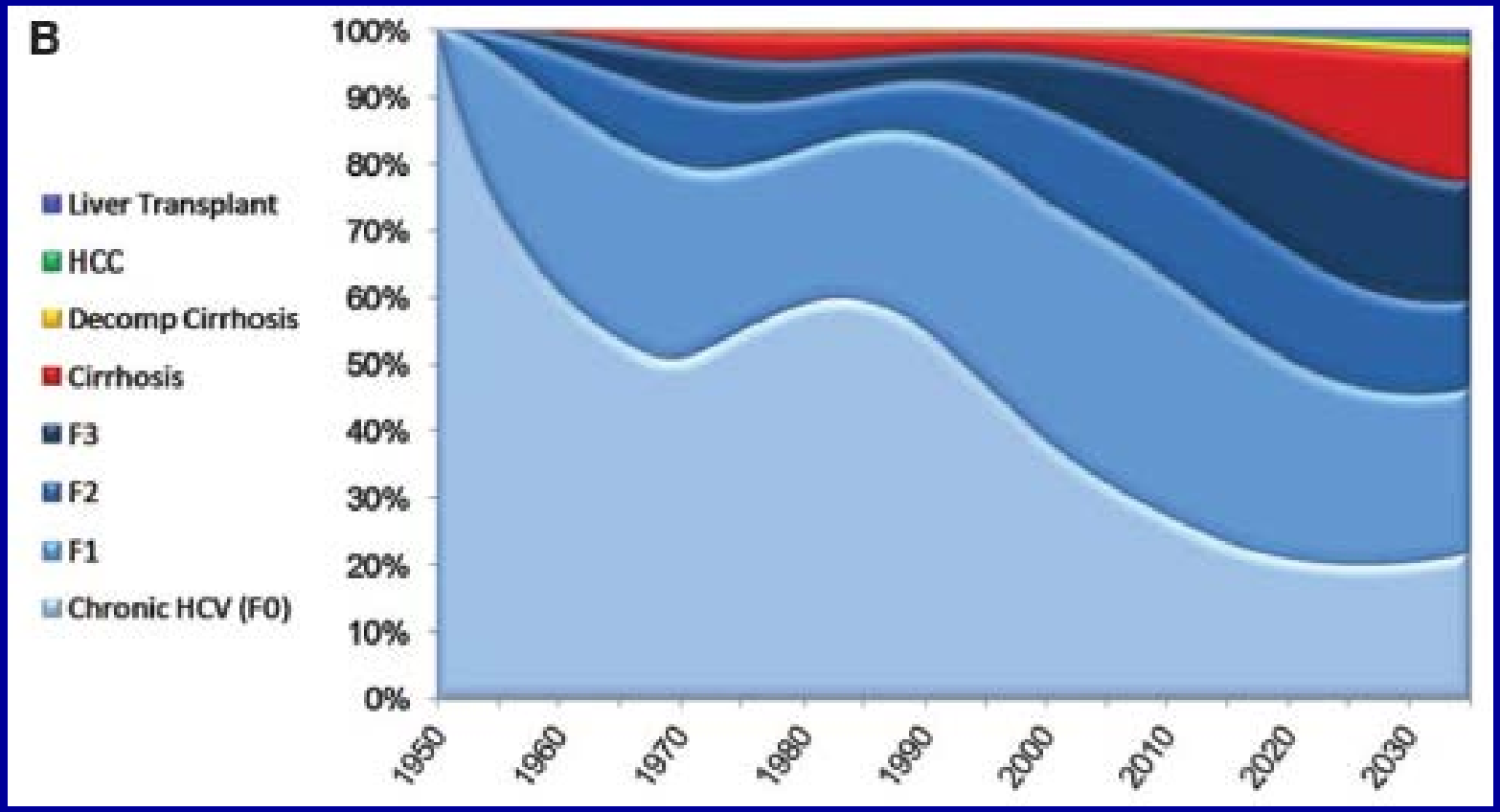
Canadian HCV Epidemiology

- **Incident disease is falling**
  - Blood products screened since 1990
  - Needle exchange programs
  - Shift from IV to inhaled (crack) cocaine
  - Better infection control practices in health care
- **Prevalent disease is steadily progressing**
  - “Boomers” are aging and fibrosis is progressing
  - It is predicted that the peak incidence of cirrhosis and HCC is yet to come

Burden of disease and cost of chronic hepatitis C virus infection in Canada

Robert P Myers MD MSc[1], Mel Krajden MD[2], Marc Bilodeau MD[3], Kelly Kaita MD[4], Paul Marotta MD[5], Kevork Peltekian MD[6], Alnoor Ramji MD[7], Chris Estes MPH[8], Homie Razavi PhD[8], Morris Sherman MD[9]

- Burden of advanced disease continues to increase

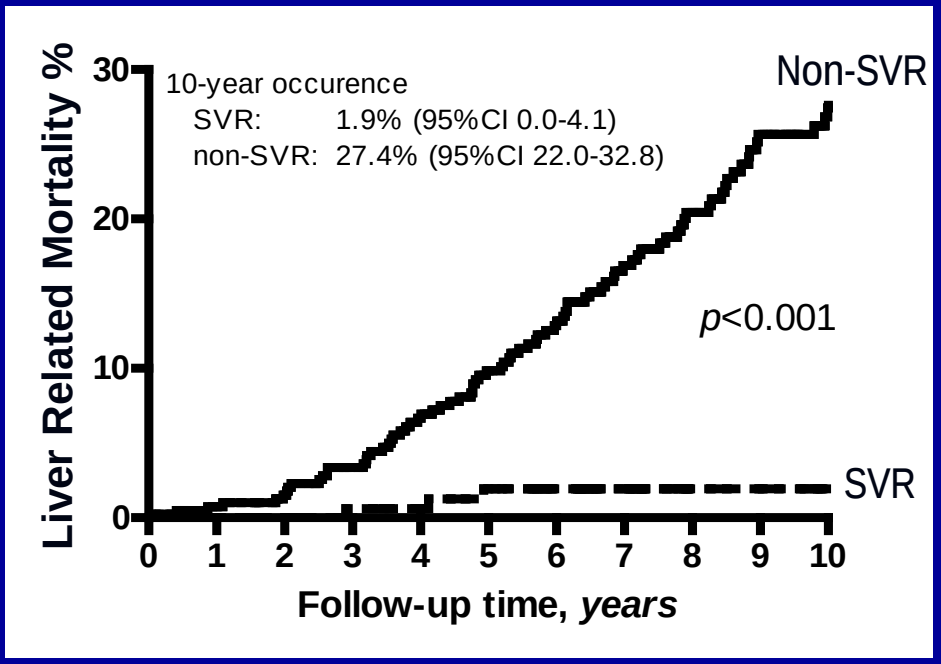


Can J Gastroenterol Hepatol 2014;28:243-50.

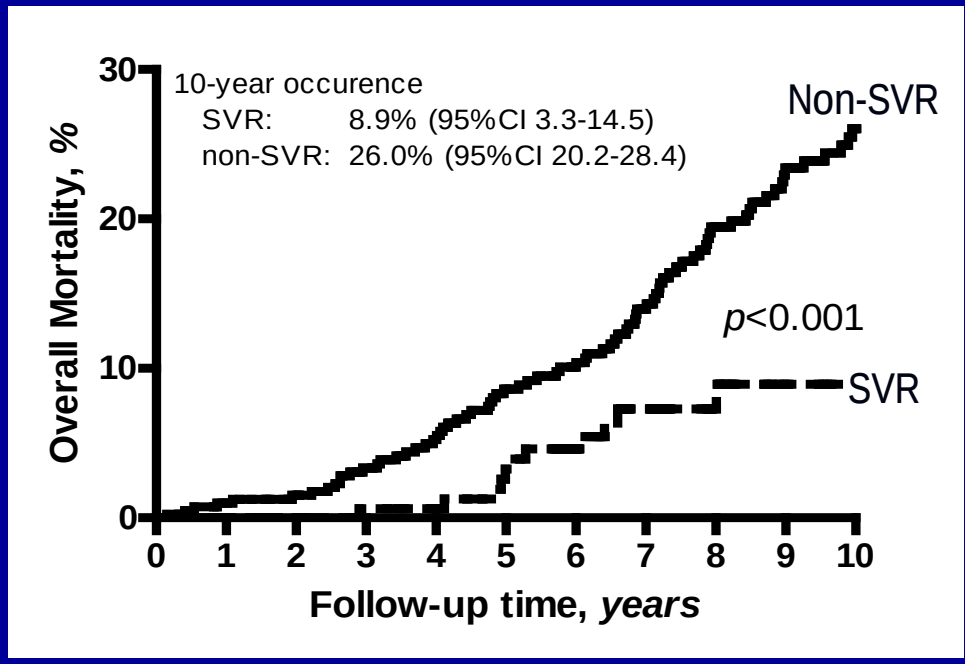
Curing HCV Saves Lives

Long-term follow-up of patients treated for HCV with F3/F4 at baseline

Liver Related Mortality

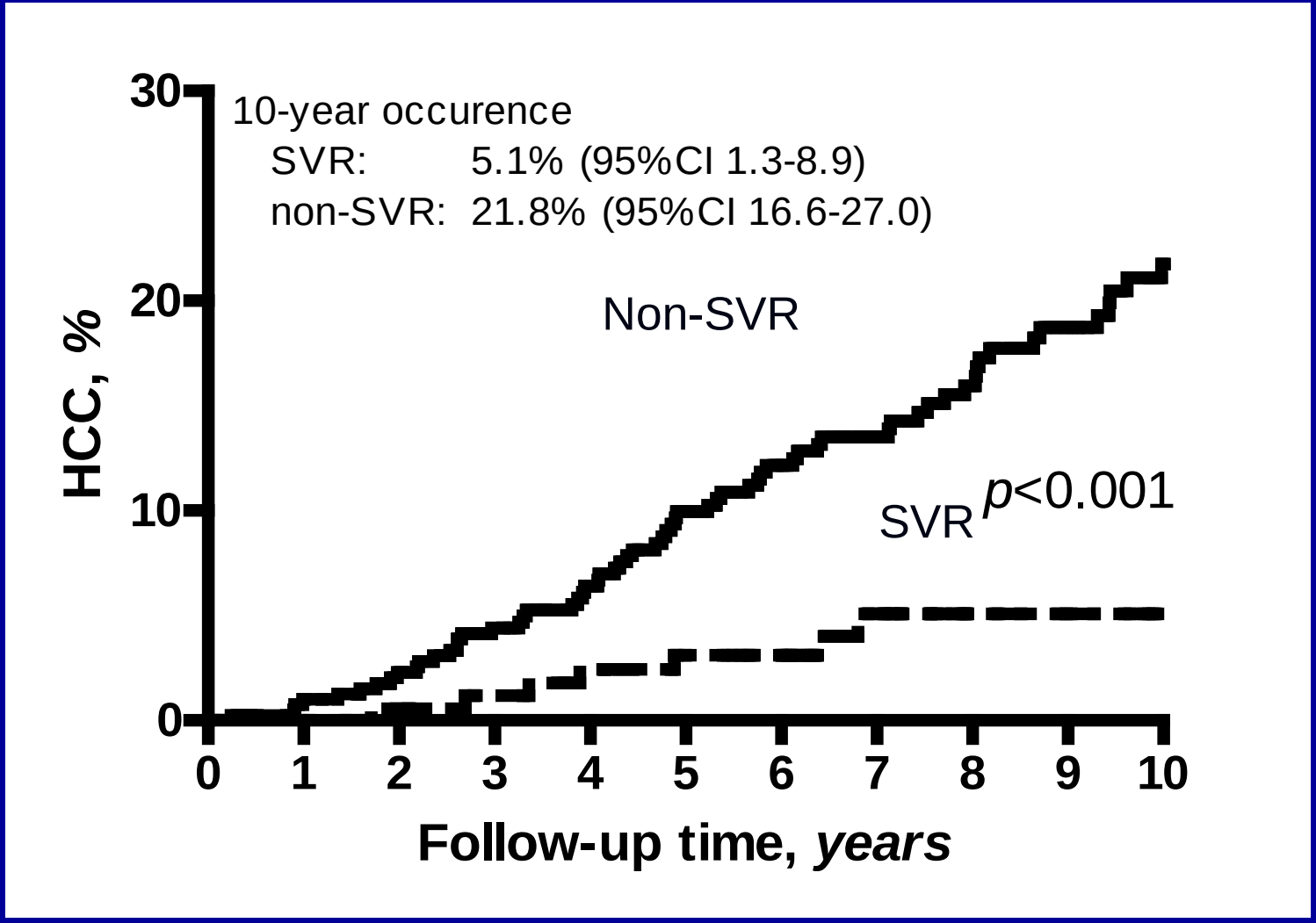


All Cause Mortality



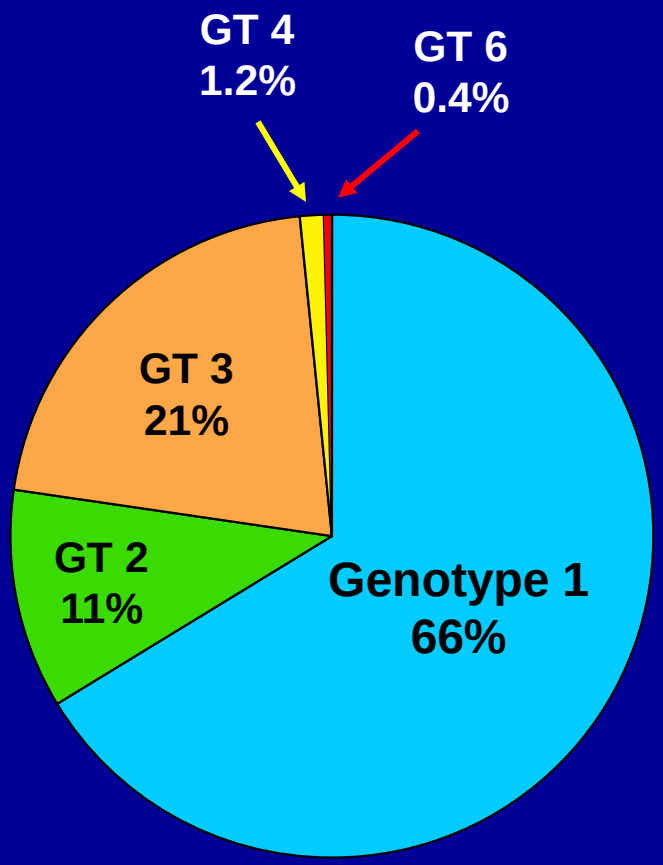
Van der Meer AJ, et al. *JAMA* 2012;308:2584-93.

Curing HCV Markedly Reduces the Incidence of Hepatocellular Carcinoma (HCC)



Van der Meer AJ, et al. *JAMA* 2012;308:2584-93.

Distribution of HCV Genotypes in Alberta 2000-2012 (n= 14,192)



G1a:1b ratio ~ 3:1

Tang J. Alberta Provincial Laboratory of Public Health

An update on the management of chronic hepatitis C: 2015 Consensus guidelines from the Canadian Association for the Study of the Liver

Robert P Myers MD MSc[1]*, Hemant Shah MD MScCH HPTE[2]*, Kelly W Burak MD MSc[1], Curtis Cooper MD[3], Jordan J Feld MD MPH[2]*

Can J Gastroenterol Hepatol 2015; 29:19-34.

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American Association for the Study of Liver Diseases

AASLD

Recommendations for Testing, Managing, and Treating Hepatitis C

IDSA

Infectious Diseases Society of America

www.hcvguidelines.org

Case 1: Robert J

- 57 yo M welder
- PH IDU age 20-25
- 2002 tested anti-HCV+ when trying to purchase life insurance
- Nov 2002: Liver Bx: METAVIR A2F2, genotype 1a
- 2003: treated with PegIFN + RBV: null responder
- Mar 2012: FS 10.3 kPa, METAVIR F3 equivalent
- Apr 2012: started PegIFN + RBV + telaprevir
- Met week 4 futility: HCV RNA > 1000 IU/mL; antiviral therapy stopped

Case 1: Robert J

- Apr 2015: FS 11.4 kPa (METAVIR F3), ALT 93, AST 68. CBC-D, creatinine, albumin, T bilirubin, prothrombin time normal; anti-HIV-, HBsAg-. HCV RNA 1.7M IU/mL
- P/E normal
- He is motivated to be treated for HCV

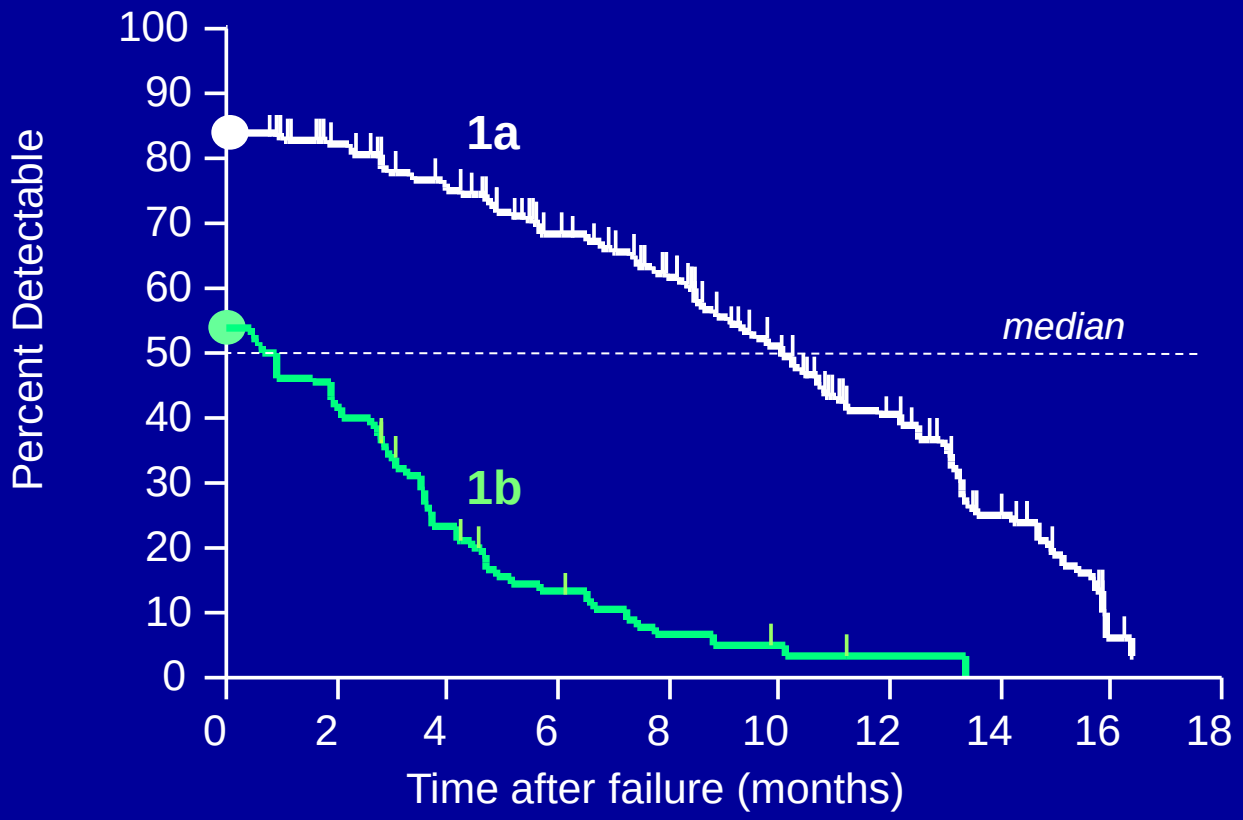
Q1: Which IFN-free regimens for HCV G1 are approved in Canada?

1. Sofosbuvir/ledipasvir
2. Paritaprevir/ombitasvir/ritonavir + dasabuvir ± ribavirin
3. Sofosbuvir + simeprevir
4. Daclatasvir + asunaprevir
5. Daclatasvir/asunaprevir/baclabuvir
6. Grazoprevir/elbasvir
7. 1, 2 and 3
8. 1, 2, 3, and 4
9. 1 through 6

Q2: Which IFN-free regimen is appropriate for a patient who failed treatment with PegIFN + RBV + a HCV NS3 protease inhibitor?

1. Sofosbuvir/ledipasvir
2. Paritaprevir/ombitasvir/ritonavir + dasabuvir ± ribavirin
3. Sofosbuvir + simeprevir
4. Daclatasvir + asunaprevir
5. Daclatasvir/asunaprevir/baclabuvir
6. Grazoprevir/elbasvir

Probability of TVR Resistant Variant Over Time by Subtype in Patients Failing PR + TVR



- Significant difference ($p<0.0001$) between subtypes for the time to become WT by population sequencing (median, 95% CI)
  - 1a: 10 months (9,11)
  - 1b: 0.8 months (0,2)

Sullivan J, et al. *Clin Infect Dis* 2013; 57:221-9.

Effect of Prior NS3 PI Treatment on Response to SOF + SMV

Prior Exposure to BOC or TVR	SVR 12
No	118/127 (93%)
Yes	35/46 (76%)

Bichoupan K, et al. CROI 2015. Abstract 149.

There is expected to be overlap between RAVs due to PI-based therapies. Because the PTV_R/OBV/DSV regimen contains a PI and other regimens with documented activity in these patients are available (ie, SOF/LDV) (9), this regimen should not be used in patients who have failed another PI (eg, TVR, BOC or SIM).

Canadian HCV Treatment Guidelines. *Can J Gastroenterol Hepatol* 2015; 29:19-34.

Recommended regimen for patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Daily fixed-dose combination ledipasvir (90 mg)/sofosbuvir (400 mg) for 12 weeks is recommended for retreatment of patients without cirrhosis who have HCV genotype 1 infection, regardless of subtype, in whom a prior PEG-IFN, RBV, and HCV protease inhibitor regimen has failed.

Rating: Class I, Level A

AASLD/IDSA HCV Treatment Guidelines

Case 1: Robert J

- He commences treatment with sofosbuvir/ledipasvir 400/90 mg once daily

- After 4 weeks of therapy, serum HCV RNA is 46 IU/mL by Abbott RealTime PCR

Q3: Which course of action do you recommend?

1. Stop treatment due to futility
2. Extend treatment to 12 weeks
3. Extend treatment to 24 weeks
4. Stop treatment after 8 weeks, as originally planned

Utility of Hepatitis C Viral Load Monitoring with Ledipasvir and Sofosbuvir Therapy (Poster 689)

Sreetha Sidharthan[1,2], Anita Kohli[1,3], Anu Osinusi[1,2,4], Amy Nelson[2,5], Zayani Sims[1], Kerry Townsend[2,5], Lydia Tang[2], Michael Polis[5], Henry Masur[1], Shyam Kottilil[2,5]

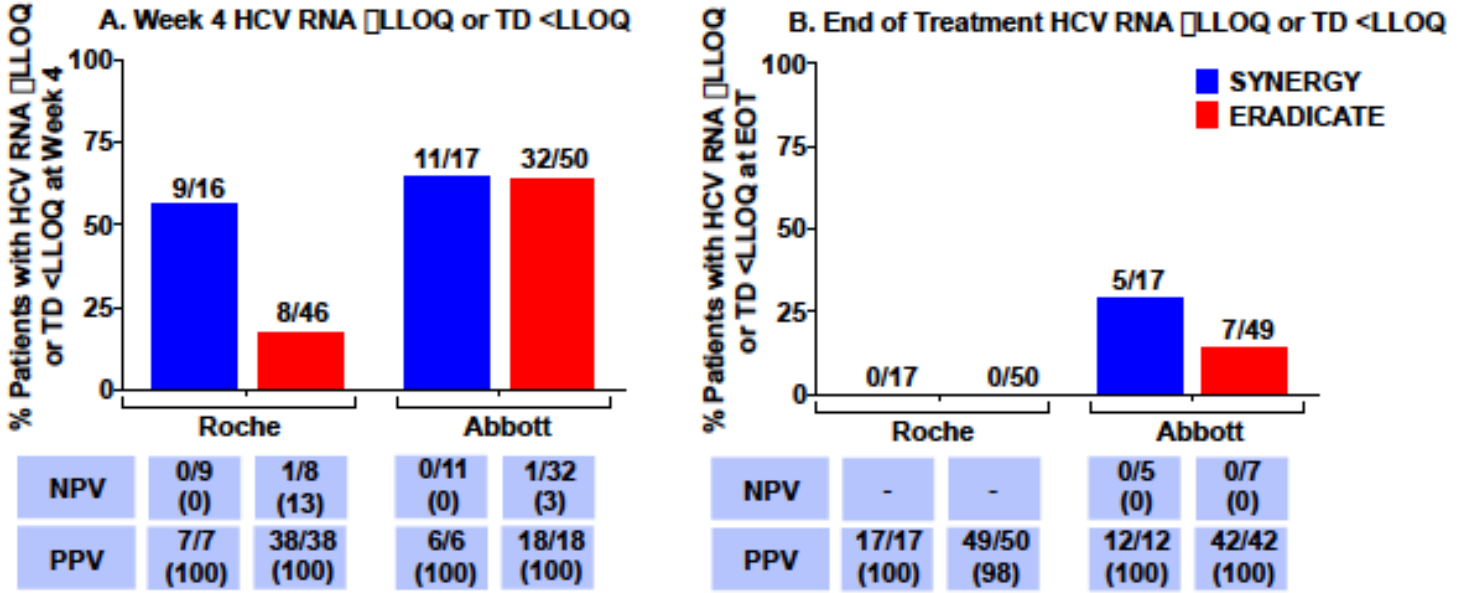
[1]Critical Care Medicine Department, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD, USA [2]Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, USA [3]Clinical Research Directorate/Clinical Monitoring Research Program, Leidos Biomedical 18 Research, Inc. (formerly SAIC-Frederick, Inc), Frederick National Laboratory for Cancer Research, Frederick, MD, USA, [4]Gilead Sciences Inc, Foster City, CA, USA, [5]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.

METHODS

Study Design

- 67 HCV genotype 1 patients without cirrhosis or prior treatment experience were enrolled in two NIAID phase 2 trials and treated with a single pill regimen of LDV/SOF (90 mg/400 mg) once daily for 12 weeks:
  - SYNERGY[1]: HCV mono-infected participants without cirrhosis (n=17) SVR in 17/17
  - ERADICATE[2]: HIV/HCV co-infected participants without cirrhosis – on combination antiretroviral (ARV) therapy (n=37) or ARV naïve (n=13)
- Primary outcome measurement was sustained virologic response (SVR12), defined as HCV RNA below lower limit of quantification (LLOQ) 12 weeks post-treatment. SVR in 49/50

Figure 2: Patients with HCV RNA ≥LLOQ or TD <LLOQ at W4 and EOT



	A. Week 4 HCV RNA ≥LLOQ or TD <LLOQ				B. End of Treatment HCV RNA ≥LLOQ or TD <LLOQ			
	Roche		Abbott		Roche		Abbott	
	SYNERGY	ERADICATE	SYNERGY	ERADICATE	SYNERGY	ERADICATE	SYNERGY	ERADICATE
NPV	0/9 (0)	1/8 (13)	0/11 (0)	1/32 (3)	-	-	0/5 (0)	0/7 (0)
PPV	7/7 (100)	38/38 (100)	6/6 (100)	18/18 (100)	17/17 (100)	49/50 (98)	12/12 (100)	42/42 (100)

One patient on SYNERGY and four patients on ERADICATE did not have a Roche assay completed at week 4. The patient who experienced viral relapse on ERADICATE did not have an Abbott assay completed at end of treatment.

- The majority of patients with HCV RNA ≥LLOQ or HCV RNA TD <LLOQ at week 4 achieved SVR12 (NPV <13%).
- 5 patients on SYNERGY and 7 patients on ERADICATE had HCV RNA TD <LLOQ at EOT by the Abbott assay. All 12 patients achieved SVR12. By the Roche assay, all patients had HCV RNA TND <LLOQ at EOT.

Utility of Hepatitis C Viral Load Monitoring with Ledipasvir and Sofosbuvir Therapy (Poster 689)

Sreetha Sidharthan[1,2], Anita Kohli[1,3], Anu Osinusi[1,2,4], Amy Nelson[2,5], Zayani Sims[1], Kerry Townsend[2,5], Lydia Tang[2], Michael Polis[5], Henry Masur[1], Shyam Kottilil[2,5]

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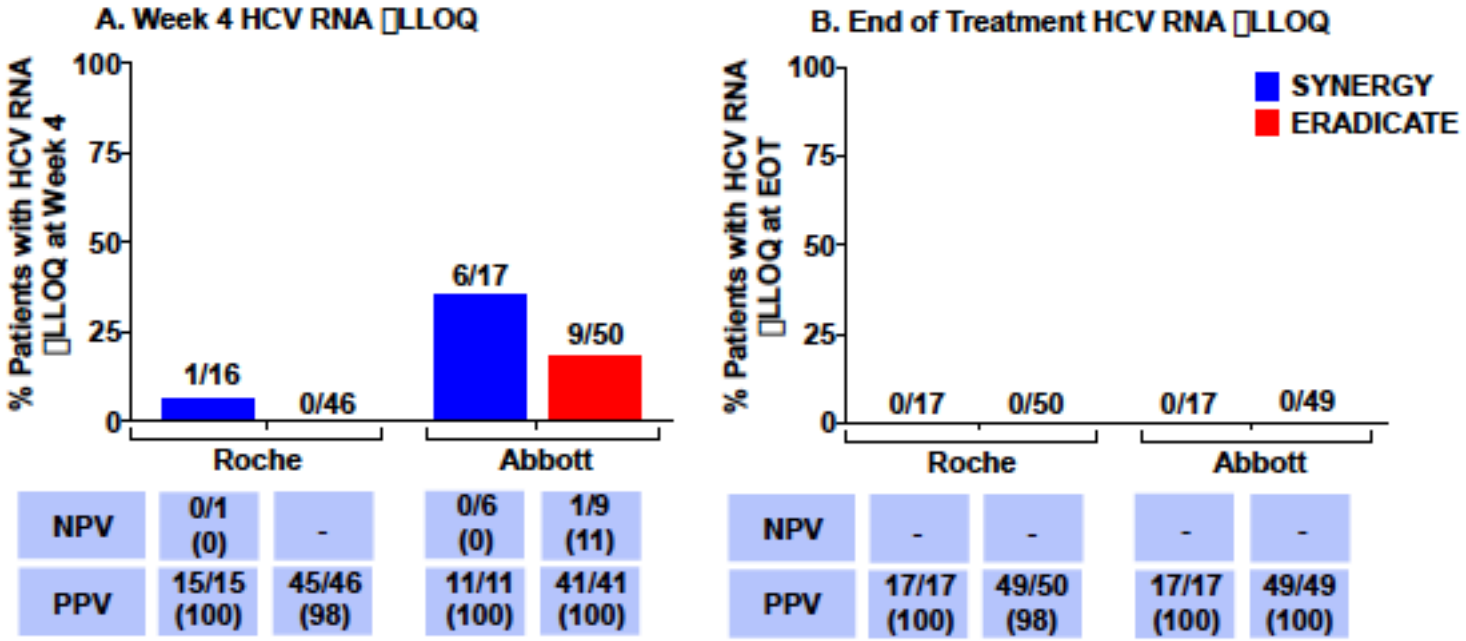
Figure 3: Patients with HCV RNA ≥LLOQ at W4 and EOT



	Roche		Abbott	
NPV	0/1 (0)	-	0/6 (0)	1/9 (11)
PPV	15/15 (100)	45/46 (98)	11/11 (100)	41/41 (100)

	Roche		Abbott	
NPV	-	-	-	-
PPV	17/17 (100)	49/50 (98)	17/17 (100)	49/49 (100)

- The majority of patients with HCV RNA ≥LLOQ achieved SVR12 (NPV <11%).
- All patients had HCV RNA <LLOQ at EOT.

Case 2: Sandra K

- 48 yo F realtor attended FP for annual physical
- P/E normal except trace pedal edema; wt 78 kg
- U/A revealed 4+ proteinuria and 10-15 RBC/hpf
- CBC-D, glucose, HbA1c, C3, C4, IgA normal
- ANA-, anti-GBM-, ANCA-, HBsAg-, anti-HIV-, MSU-
- Creatinine 105 µmol/L, albumin 35 g/L, urine protein/creatinine 240, urine albumin/creatinine 202
- Patient referred to nephrologist

Case 2: Sandra K

- Nephrologist orders U/S and anti-HCV
- U/S shows normal kidneys, liver and spleen
- Anti-HCV+; HCV RNA and GT then ordered
- HCV RNA 1.6M IU/mL, genotype 2
- ALT 38, AST 33, PT 1.0, bilirubin 11 µmol/L
- Nephrologist opinion: high probability that patient has MPGN secondary to HCV; favors treatment of HCV as first step in management rather than renal biopsy or immune therapy

Influence of Antiviral Therapy in Hepatitis C Virus–Associated Cryoglobulinemic MPGN

Laurent Alric, MD, PhD, Emmanuelle Plaisier, MD, Sophie Thébault, MD, Jean-Marie Péron, MD, PhD, Lionel Rostaing, MD, PhD, Jacques Pourrat, MD, Pierre Ronco, MD, Jean-Charles Piette, MD, and Patrice Cacoub, MD

- In those with SVR, cryoglobulin levels at the end of treatment (0.29 ± 0.4 g/L) and end of follow-up (0.25 ± 0.4 g/L) were decreased ($P < 0.05$) compared with pretreatment values (1.38 ± 2.2 g/L).
- Conversely, no changes in serum cryoglobulinemia levels were observed in nonresponders or controls.

Am J Kidney Dis 2004;43:617-23.

CASL 2015

6. Patients with extrahepatic manifestations of HCV should be considered for antiviral therapy (Class 1, Level A).

AASLD/IDSA HCV Treatment Guidelines

When and in Whom to Initiate HCV Therapy Table 1. Settings of Liver-Related Complications and Extrahepatic Disease in Which HCV Treatment is Most Likely to Provide the Most Immediate and Impactful Benefits

Highest Priority for Treatment Owing to Highest Risk for Severe Complications

Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)

Rating: Class I, Level A

Organ transplant

Rating: Class I, Level B

Type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations (eg, vasculitis)

Rating: Class I, Level B

Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Rating: Class IIa, Level B

Case 2: Sandra K

- You arrange a FS which reveals a liver stiffness of 5.8 kPa (METAVIR F0-1 equivalent)

Q4: Which course of action do you recommend?

1. Renal biopsy before making a treatment decision
2. Liver biopsy before making a treatment decision
3. High dose corticosteroids for presumed MPGN
4. Dual PegIFN + RBV for HCV
5. Dual sofosbuvir + RBV for HCV

35. In treatment-naive patients with HCV genotype 2, SOF (400 mg daily) should be given with weight-based RBV for 12 weeks (Class 1, Level A).

Recommended regimen for treatment-naive patients with HCV genotype 2 infection.

Daily sofosbuvir (400 mg) and weight-based RBV (1000 mg [<75 kg] to 1200 mg [≥75 kg]) for 12 weeks is recommended for treatment-naive patients with HCV genotype 2 infection.

Rating: Class I, Level A

Extending treatment to 16 weeks is recommended in patients with cirrhosis.

Rating: Class IIb, Level C

Case 2: Sandra K

- She commences treatment with sofosbuvir 400 mg plus ribavirin 1200 mg daily x 12 weeks

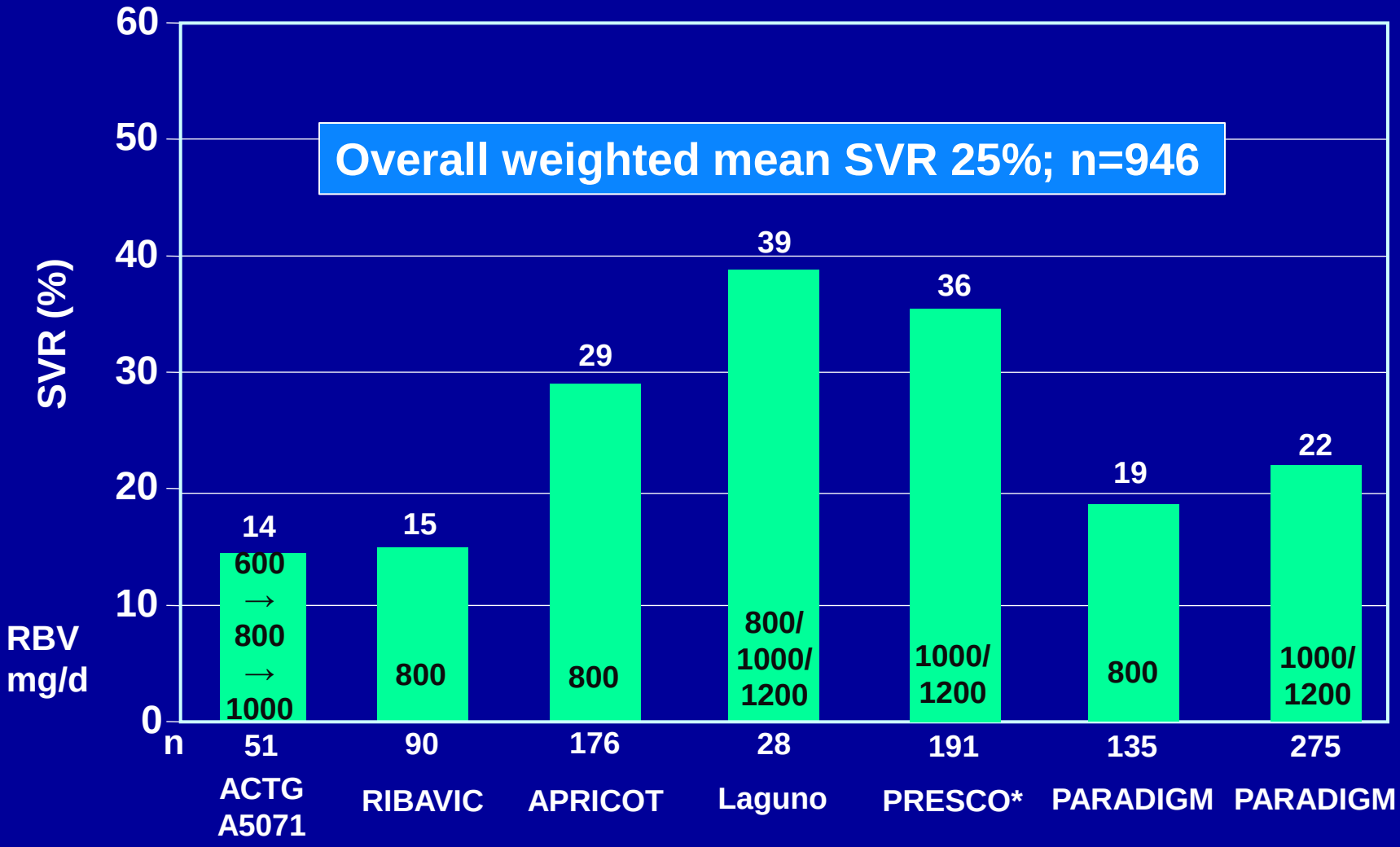
Case 3: Kevin R

- 38 yo M laborer
- PH: IDU 1998-2008
- 2004: tested anti-HCV+, anti-HIV-
- 2008: incarcerated in a federal prison;
  - tested anti-HIV+; CD4 310 (20%), HIV RNA 72,000, GART: no resistance
  - HCV RNA+, ALT 96, HBsAg-, anti-HBs+, anti-HBc+
  - CBC-D, creatinine, albumin, bilirubin, PT, alk phos N.
  - started on ART with Atripla; HIV RNA becomes undetectable

Case 3: Kevin R

- 2009:
  - Still incarcerated
  - HIV RNA undetectable on Atripla
  - CD4 460 (26%)
  - HCV RNA 4.2M IU/mL, genotype 1a
  - Patient offered dual therapy with PR and told that expected SVR is ~25%
  - Patient declined offer for HCV Rx

SVR in HCV Genotype 1 in the HIV Co-infected Treated with PegIFNα + RBV x 48 weeks



* a few patients were treated for 72 weeks

Chung R, et al. *NEJM* 2004;351:451-9.
Torriani FJ, et al. *NEJM* 2004;351:438-50.
Carrat F, et al. *JAMA* 2004;292:2839-48.
Laguno M, et al. *AIDS* 2004;18:F27-F36.
Núñez M, et al. *AIDS Res Hum Retrovirus* 2007;23:972-82.
Rodriguez-Torres M, et al. *HIV Clin Trials* 2012;13:142-52.

Case 3: Kevin R

November 2012:

- Still incarcerated
- HIV RNA remains undetectable on Atripla
- BOC and TVR approved by HC but not funded by CSC
- Patient is released from custody on parole

Case 3: Kevin R

March 2013:

- HIV RNA remains undetectable on Atripla
- CD4 530 (29%)
- PLT 127, ALT 88, AST 107, AFP 14
- Hb, WBC, albumin, bilirubin N
- FS 16.0 kPa (F4 equivalent)
- Gastroscopy: no varices
- Abdo U/S: slightly coarse liver, no focal liver lesions, spleen 13.6 cm

Case 3: Kevin R

March 2013:

- Patient offered anti-HCV Rx with PR + BOC or TVR, but advised that:
  1. He would need to change ART to avoid drug-drug interactions
  2. Duration of PR backbone would be 48 weeks, given presence of cirrhosis
  3. Expected SVR rate would be 50-60%, given presence of cirrhosis
  4. IFN-free therapy is expected in 2-3 years

Case 3: Kevin R

March 2013:

- Patient declined current HCV Rx and opted to await future HCV Rx options
- He continued on Atripla and stopped all EtOH intake
- Screening abdo U/S continue every 6 months
- He has only public prescription drug coverage

Case 3: Kevin R

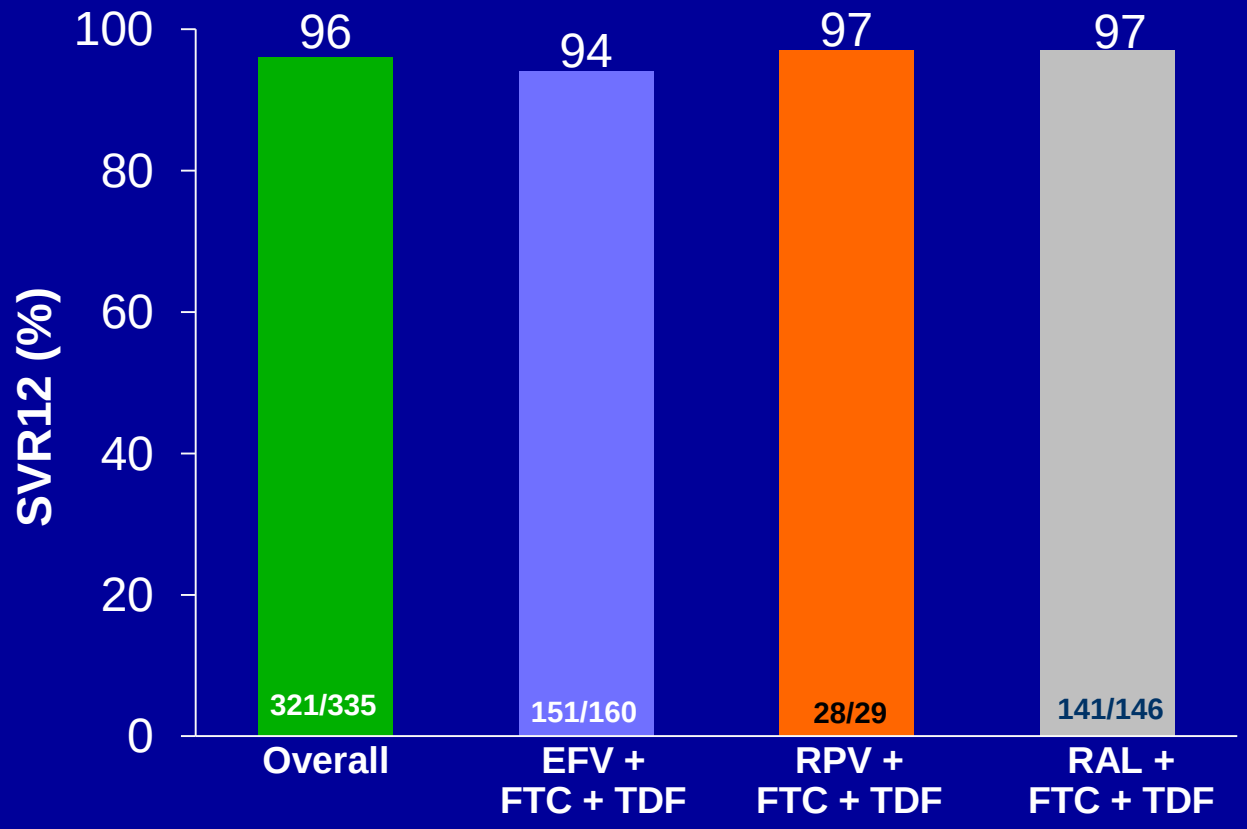
April 2015:

- Patient remains on Atripla with undetectable HIV RNA and CD4 is 680 (33%)
- Screening abdominal U/S continues to show no focal hepatic lesion, spleen 14.4 cm
- PLT 98, albumin 36, PT 1.2, T bilirubin 17, ALT 102, AST 123, AFP 17, Cr 84
- FS 18.4 kPa
- Gastroscopy: mild PHG, small grade 1 esophageal varix, not requiring intervention

Q5: What do you recommend?

1. No HCV Rx yet
2. Must change ART from Atripla in order to safely treat HCV
2. Continue Atripla and treat HCV with PR + sofosbuvir
3. Continue Atripla and treat with sofosbuvir/ledipasvir
4. Change ART to Complera and treat with paritaprevir/ombitasvir/r + dasabuvir + RBV
5. None of the above

ION-4: SOF/LDV x 12 weeks in the HCV-HIV Co-infected (98% GT1): SVR12 by HIV ARV Regimen



Naggie S, et al. CROI 2015, Oral #LB-152.

DDIs of Note in the HIV-HCV Co-infected-1

HCV Regimen	Problem Drug	Interaction
PR	ZDV	↑ anemia
SOF + RBV	none	
SOF/LDV	Rosuvastatin	Up to 7-fold ↑ rosuvastatin AUC
	EFV	34% ↓ LDV AUC*
	Atazanavir/r	96% ↑ LDV AUC
	TDF/FTC/EFV	98% ↑ TFV AUC*
	TDF/FTC/RPV	40% ↑ TFV AUC*
	TDF/FTC + DRV/r	50% ↑ TFV AUC
	TDF/FTC + ATZ/r	35% ↑ TFV AUC

* Not likely clinically significant based on ION-4 (160 received EFV, 29 received RPV)

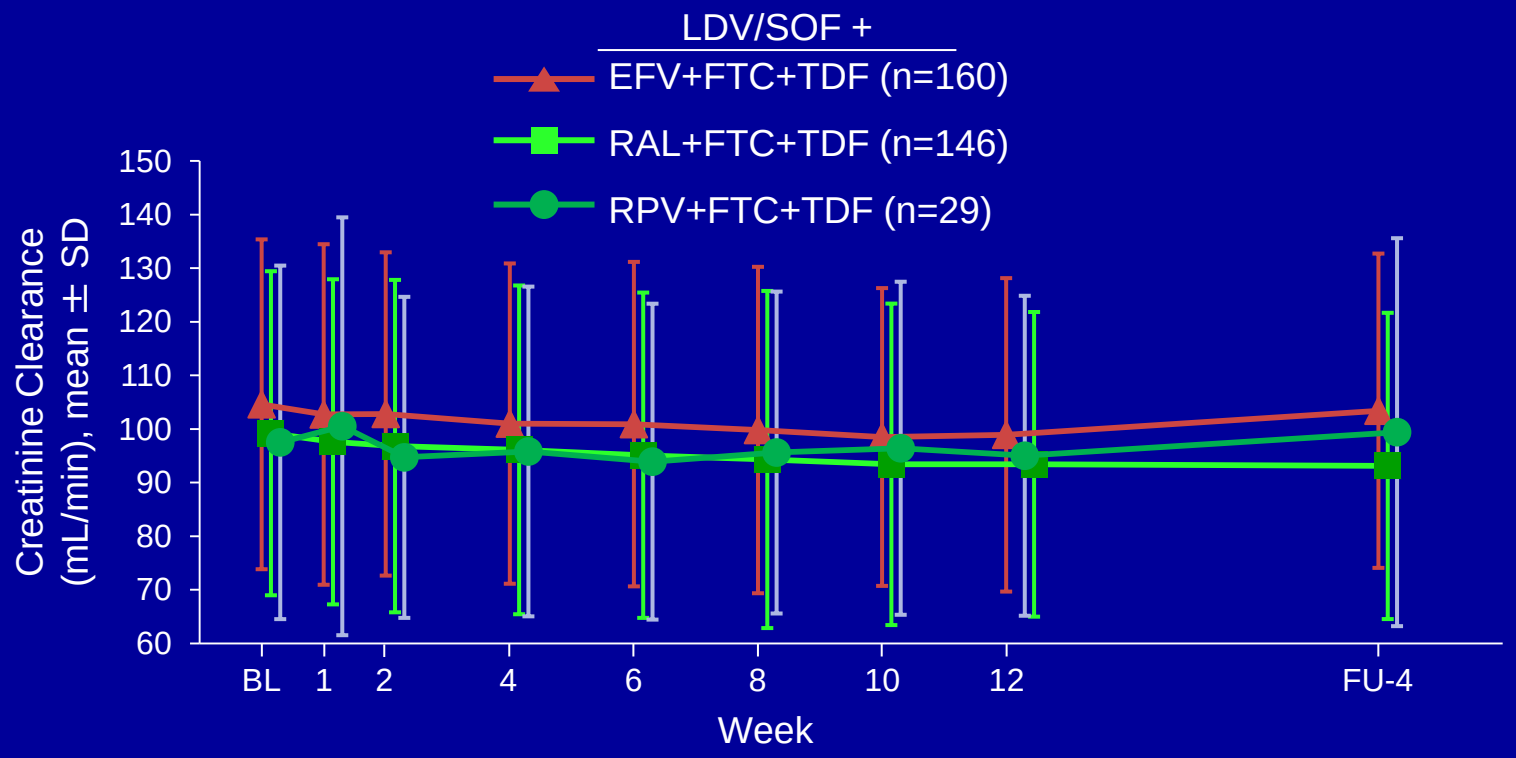
- **Because ledipasvir increases tenofovir levels, concomitant use mandates consideration of creatinine clearance (CrCl) rate and should be avoided in those with CrCl below 60 mL/min. Because potentiation of this effect is expected when tenofovir is used with ritonavir-boosted HIV protease inhibitors, ledipasvir should be avoided with this combination (pending further data) unless antiretroviral regimen cannot be changed and the urgency of treatment is high.**

Rating: Class IIa, Level C

For combinations expected to increase tenofovir levels, baseline and ongoing assessment for tenofovir nephrotoxicity is recommended.

Rating: Class IIa, Level C

ION-4: eGFR and Renal Safety



- No grade 3 or 4 creatinine abnormalities nor any grade 3 or 4 AEs in the renal or urinary disorder occurred in study
- 4 patients had change in creatinine ≥ 0.4 mg/dL (35.4 µmol/L); all achieved SVR
  - 2 completed treatment with no ART change
  - 1 discontinued TDF, 1 had dose reduction of TDF

Naggie S, et al. CROI 2015, Oral #LB-152

DDIs of Note in the HIV-HCV Co-infected-2

HCV Regimen	Problem Drug	Interaction
PTV/OMB/r + DSV + RBV	EFV	Poorly tolerated, ↑ALT
	RPV	Up to 273% ↑RPV exposure
	ETR	↓ DAA exposures
	LPV/r	Cannot unbundle RTV, 2.2 fold ↑PTV exposure
	DRV	52% ↓DRV trough, no clinical data
	RAL	Up to 134% ↑ RAL exposure*
	OCs	Contraindicated due to ↑ALT
	Rosuvastatin	7.1 fold ↑Cmax, 2.6 fold ↑AUC

* Not likely clinically significant based on 35 patients in TURQUOISE-1

- **Paritaprevir/ritonavir/ombitasvir plus dasabuvir should be used with antiretroviral drugs with which it does not have substantial interactions: raltegravir (and probably dolutegravir), enfuvirtide, tenofovir, emtricitabine, lamivudine, and atazanavir.**
- **The dose of ritonavir used for boosting of HIV protease inhibitors may need to be adjusted (or held) when administered with paritaprevir/ritonavir/ombitasvir plus dasabuvir and then restored when HCV treatment is completed. The HIV protease inhibitor should be administered at the same time as the fixed-dose HCV combination.**

Rating: Class IIa, Level C

Case 3: Kevin R

April 2015:

- Patient is continued on Atripla
- Sofosbuvir/ledipasvir is started for a 12-week course