# HCV therapy in HIV

Mark Sulkowski, MD
Professor of Medicine
Johns Hopkins University School of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Baltimore, Maryland

JOHNS HOPKINS
MEDICINE

# Disclosures

PI for research grants related to HCV

- Funds paid to Johns Hopkins University
- AbbVie, BMS, Gilead, Janssen, Merck

DSMB related to HBV

- Funds paid to Johns Hopkins University
- Gilead

Scientific advisor/Consultant related to HCV

- AbbVie, Achillion, BMS, Gilead, Janssen, Merck

The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies

# Case

51 year-old black man referred for evaluation

- HIV/AIDS – Presented to the ED with untreated HIV (CD4 = 35 cells/mm$^{3)}$ and cryptococcal meningitis – treated successfully and started on ARVs
  - 9 months later -- taking EFV/TDF/FTC with HIV RNA < 20 copies/mL; CD4 = 202 cells/mm$^3$
- HCV seropositive; no prior treatment
- Injection heroin use ~ 8 x per month
  - Enrolled in buprenorphine/naloxone program

# Case - continued

- He has elevated serum ALT level = 98 U/L and AST 157 U/L; platelet count 98,000
- HCV RNA = 740,000 IU/mL
- HCV genotype 1a
- After missing his first referral for evaluation, he presents in January 2015 to the hepatitis clinic

# http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

## Fibrosis-4 (FIB-4) Calculator

The Fibrosis-4 score helps to estimate the amount of scarring in the liver. Enter the required values to calculate the FIB-4 value. It will appear in the oval on the far right (highlighted in yellow).

$$\text{FIB-4} = \frac{\text{Age } (\textit{years}) \times \text{AST Level } (\textit{U/L})}{\text{Platelet Count } (10^9/L) \times \sqrt{\text{ALT } (\textit{U/L})}} = 8.25$$

Age (*years*): 51

AST Level (*U/L*): 157

Platelet Count ($10^9/L$): 98

ALT (*U/L*): 98

**Interpretation:**
Using a lower cutoff value of 1.45, a FIB-4 score <1.45 had a negative predictive value of 90% for advanced fibrosis (Ishak fibrosis score 4-6 which includes early bridging fibrosis to cirrhosis). In contrast, a FIB-4 >3.25 would have a 97% specificity and a positive predictive value of 65% for advanced fibrosis. In the patient cohort in which this formula was first validated, at least 70% patients had values <1.45 or >3.25. Authors argued that these individuals could potentially have avoided liver biopsy with an overall accuracy of 86%.

Source: Sterling RK, Lissen E, Clumeck N, et. al. Development of a simple noninvasive index to predict significant fibrosis patients with HIV/HCV co-infection. Hepatology 2006;43:1317-1325.

# Case - continued

- He underwent liver CT scan that reveal a nodular appearing liver with mild splenomegaly
- His HIV RNA is detected at 40 copies/mL but on repeat is < 20 copies/mL
- He has continued in the on-site buprenorphine/naloxone program
  - Reports ongoing use of injection heroin “a couple of times a month”
  - Denies sharing needles and/or equipment

# HCV treatment considerations

- Treatment readiness – adherence to visits, medications and prevention of reinfection
- Drug interactions between ART and HCV DAAs
  - Continue Efavirenz + Tenofovir/FTC?
  - Switch to another ART regimen?
- Which HCV regimen?
- How long?

# Multiple, highly effective, oral antiviral regimens are the result of successful translational research

| | Antiviral | | | | |
|---|---|---|---|---|---|
| | NS3 | NS5A | Non-Nuc NS5B | Nuc NS5B | RBV |
| **Paritaprevir/ritonavir/Ombitasvir + Dasabuvir**<br>**Asunaprevir/Daclatasvir/Beclabuvir FDC** | ● | ● | ● | | 1a only ● |
| **Grazoprevir/Elbasvir FDC** | ● | ● | | | |
| **Sofosbuvir/Ledipasvir FDC**<br>**Sofosbuvir + Daclatasvir** | | ● | | ● | |
| **Sofosbuvir + Simeprevir** | ● | | | ● | |
| **MK3682/Elbasvir/Grazoprevir FDC**<br>**Sofosbuvir/Ledipasvir/GS9857 FDC** | ● | ● | | ● | |

# AASLD/IDSA Guidance for Genotype 1 HCV Patients With Compensated Liver Disease

| Population | LDV/SOF | OMV/PTV/RTV + DSV | SMV + SOF |
|---|---|---|---|
| GT 1a, no cirrhosis | 12 wks | 12 wks + RBV | 12 wks ± RBV |
| GT 1a, cirrhosis | 12 wks | 24 wks + RBV | 24 wks ± RBV |
| GT 1b, no cirrhosis | 12 wks | 12 wks | 12 wks |
| GT 1b, cirrhosis | 12 wks | 12 wks + RBV | 24 wks |
| GT 1 P/R failure, no cirrhosis | 12 wks | 12 wks + RBV (1a)<br>12 wks (1b) | 12 wks ± RBV |
| GT 1 P/R failure, cirrhosis | 24 wks or<br>12 wks + RBV | 24 wks + RBV (1a)<br>12 wks + RBV (1b) | 24 wks ± RBV |
| GT 1 PI failure, no cirrhosis | 12 wks | Not recommended | Not recommended |
| GT 1 PI failure, cirrhosis | 24 wks or<br>12 wks + RBV | Not recommended | Not recommended |
| GT1, renal failure (eGFR < 30 mL/min | Not recommended | 12 weeks + RBV 200 mg/day (1a) and no RBV (1b) | Not recommended |

AASLD/IDSA/IAS–USA. Recommendations for testing, managing, and treating hepatitis C.

# AASLD/IDSA/IAS-USA Guidance: Treatment of HCV in persons with HIV coinfection

***Recommended regimens for HIV/HCV-coinfected individuals.***

**HIV/HCV-coinfected persons should be treated and retreated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications (see Initial Treatment of HCV Infection and Retreatment of Persons in Whom Prior Therapy Has Failed sections).**

**Rating:** Class I, Level B

- Treatment should be prioritized in patients at high risk for liver-related complications
  - Includes patients with HCV/HIV coinfection, regardless of fibrosis stage
- Treating patients at high risk for transmitting HCV to others may decrease transmission and HCV disease prevalence
  - Includes MSM with high-risk sexual practices and active injection drug users

AASLD and IDSA. HCV Management Guidance. 2015

# ARV Interaction Score Card

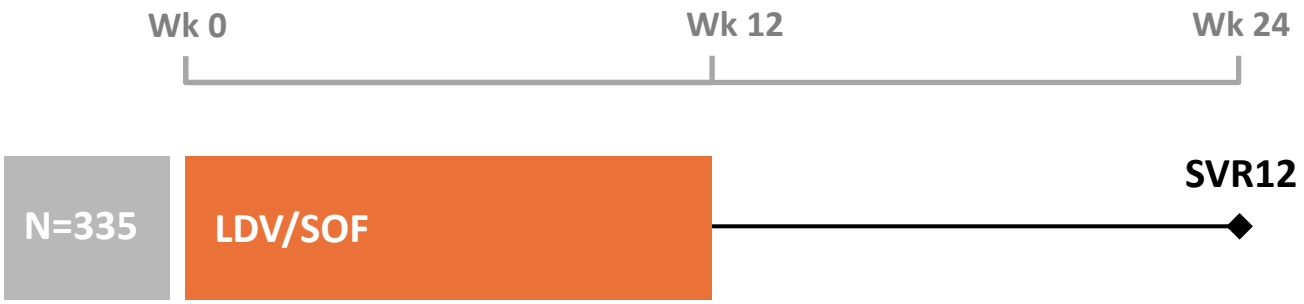
| | Simeprevir | Sofosbuvir | Ledipasvir | Daclatasvir | AbbVie 3D |
|---|---|---|---|---|---|
| ATV/r | No data | ATV ↔ SOF ↔ | No data | DCV ↑* | ATV ↔; ABT450 ↑ |
| DRV/r | SIM ↑; DRV ↔ | SOF ↑; DRV ↔ | No data | DCV (↑) | DRV ↓; 3D ↓ |
| LPV/r | No data | No data | No data | DCV↔ | LPV ↔; ABT450 ↑ |
| TPV/r | No data | No data | No data | No data | No data |
| EFV | SIM ↓; EFV ↔ | SOF ↔; EFV ↔ | LDV ↓; EFV ↓ | DCV ↓* | No PK data** |
| RPV | SIM ↔; RPV ↔ | SOF ↔; RPV ↔ | LDV ↔; RPV ↔ | No data | ABT450 ↑; RPV ↑ |
| ETV | No data | No data | No data | No data | No data |
| RAL | SIM ↔; RAL ↔ | SOF ↔; RAL ↔ | LDV ↔; RAL ↔ | No data | 3D ↔; ↑ RAL |
| ELV/cobi | No data | No data | No data | No data | No data |
| DLG | No data | No data | No data | No data | No data |
| MVC | No data | No data | No data | No data | No data |
| TDF | SIM ↔; TDF ↔ | SOF ↔; TDF ↔ | LDV ↔; ↑TDF | DCV ↔; TDF ↔ | 3D ↔; TDF ↔ |

* Decrease DCV dose to 30mg QD, Increase DCV dose to 90mg QD, ** 3D + EFV led to premature study discontinuation due to toxicities

Adapted from Dr. Jennifer Kiser and DHHS ARV guidelines

# NUCLEOS(T)IDE ANALOGUE NS5B POLYMERASE INHIBITOR + OTHER AGENTS

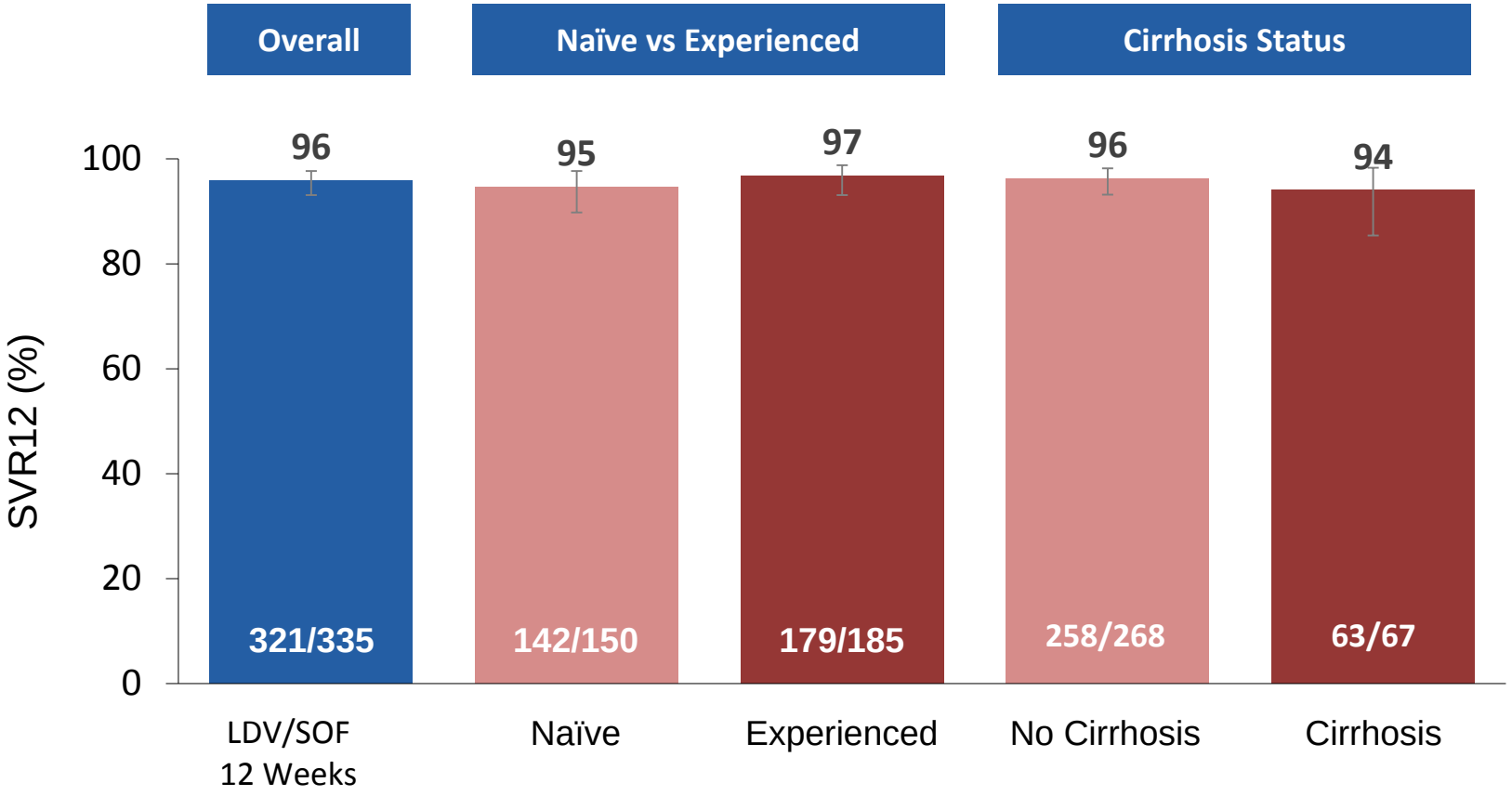
# ION-4: Ledipasvir/Sofosbuvir for persons with HIV and HCV genotype 1 and 4 infection




- Phase 3, multicenter, open-label study (NCT02073656)
- HCV GT 1 or 4 patients in US, Canada, and New Zealand
- Broad inclusion criteria
  - HCV treatment-naïve or treatment-experienced
  - 20% with compensated cirrhosis
  - Platelets ≥50,000/$mm^3$; hemoglobin ≥10 mg/dL, CrCl ≥60 mL/min
  - HIV-1 positive, HIV RNA <50 copies/mL; CD4 cell count >100 cells/$mm^3$
- ART regimens included emtricitabine and tenofovir disoproxil fumarate plus efavirenz, raltegravir, or rilpivirine

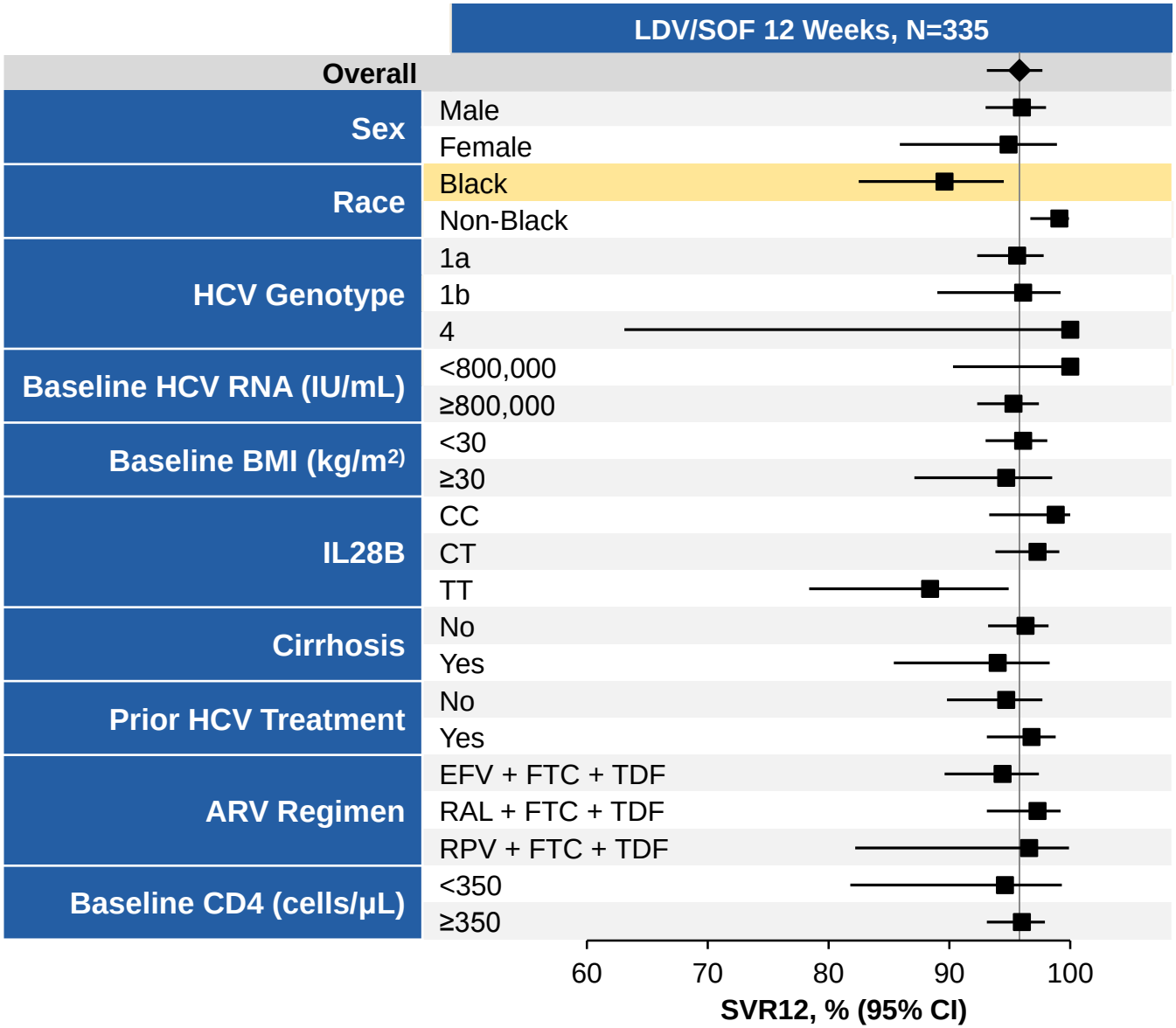
# ION4: SVR12 by Prior Treatment Experience and Cirrhosis Status

HIV-HCV (ION-4)



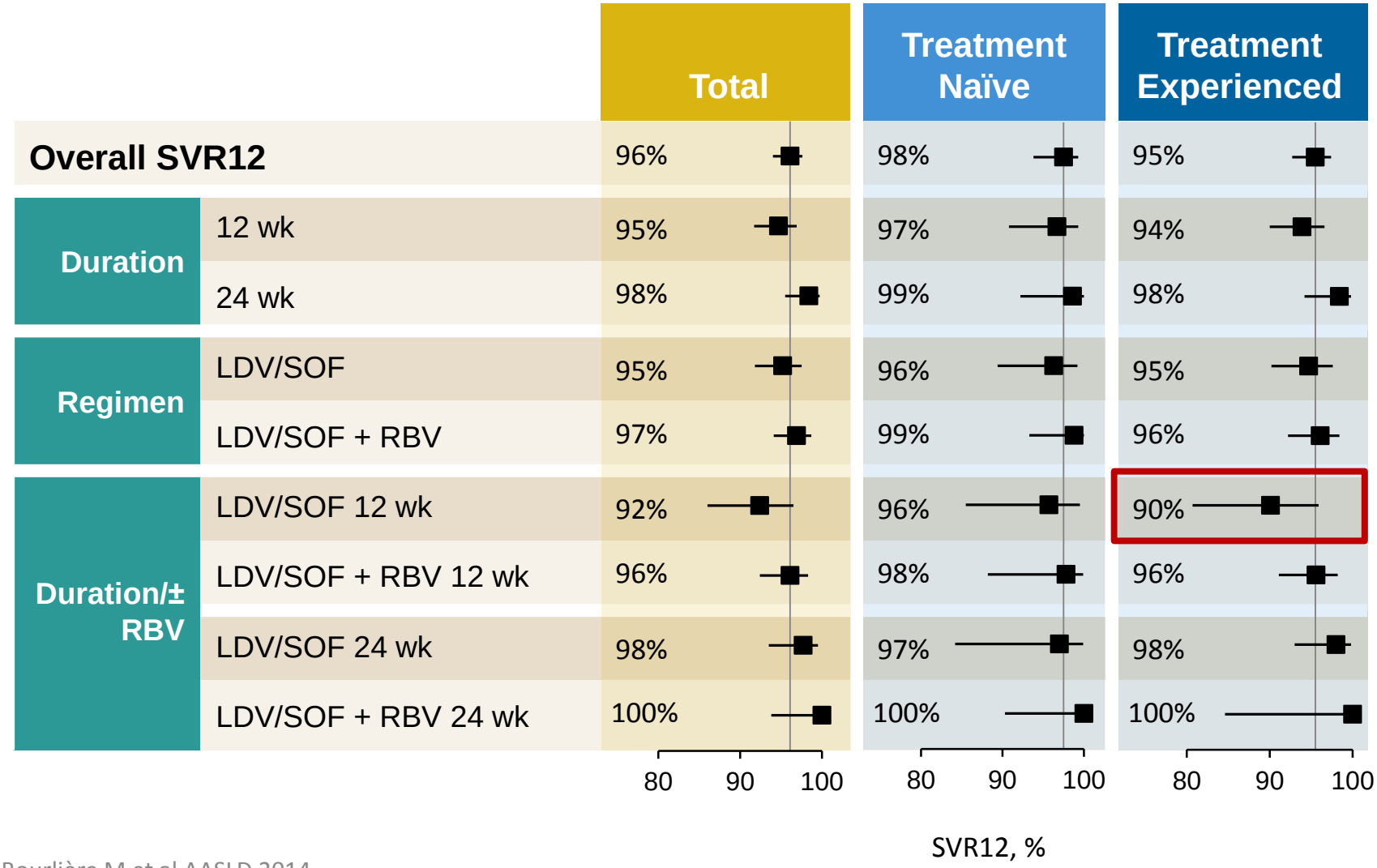
# ION4: SVR12 in Subgroups

HIV-HCV (ION-4)




Statistically significant in multivariate analysis

# LDV/SOF in HCV monoinfected patients
## *SVR12 by Treatment Regimen*




Bourlière M et al AASLD 2014

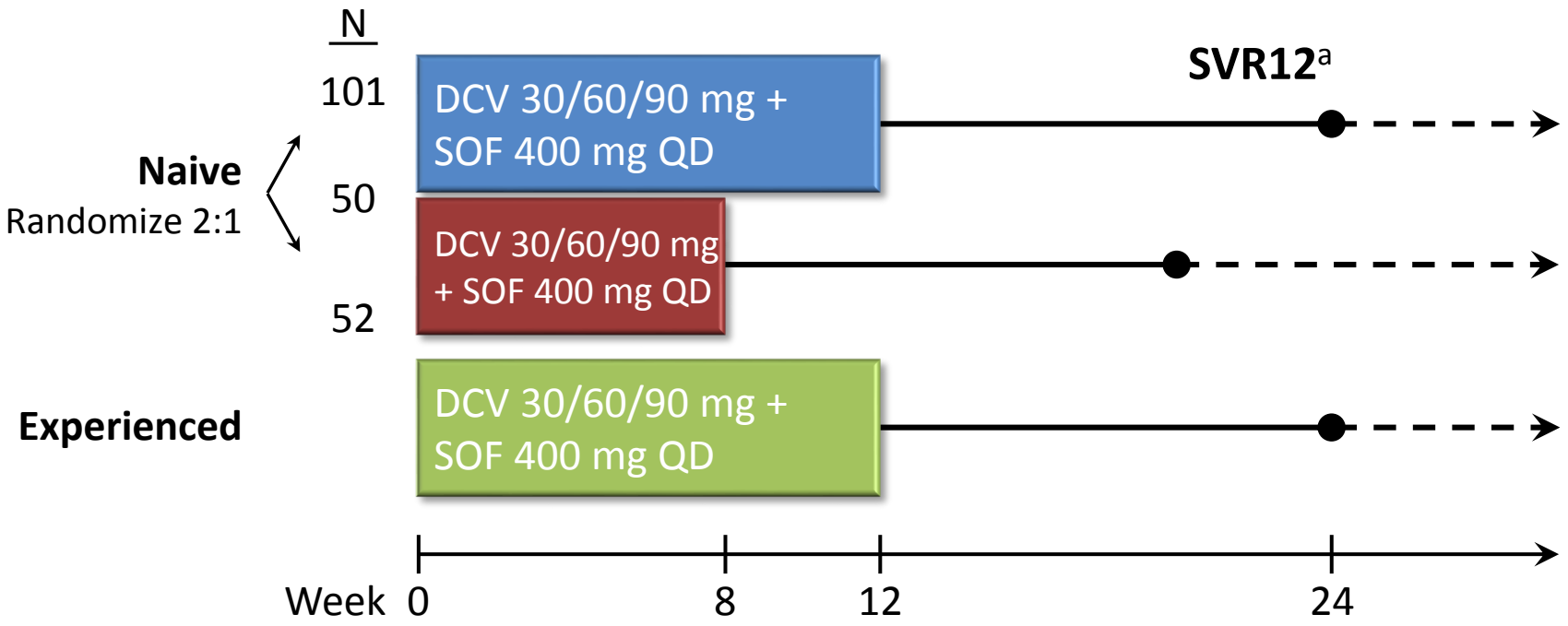
# ION4: Safety Summary

| | Patients, n (%) | LDV/SOF 12 Weeks N=335 |
|---|---|---|
| Overall safety | AEs | 257 (77) |
| | Grade 3–4 AE | 14 (4) |
| | Serious AE | 8 (2)* |
| | Treatment D/C due to AE | 0 |
| | Death | 1 (<1)† |
| | Grade 3–4 laboratory abnormality | 36 (11) |

- Stable CD4 counts through treatment and follow-up phase
- No patient had confirmed HIV virologic rebound

- Serious AEs in >1 patient were hepatocellular carcinoma (n=2) and portal vein thrombosis (n=2) in patients with cirrhosis.
- †Confirmed IV drug user developed *Staphylococcus aureus* sepsis, endocarditis with associated embolic brain abscesses, and multi-organ system failure.

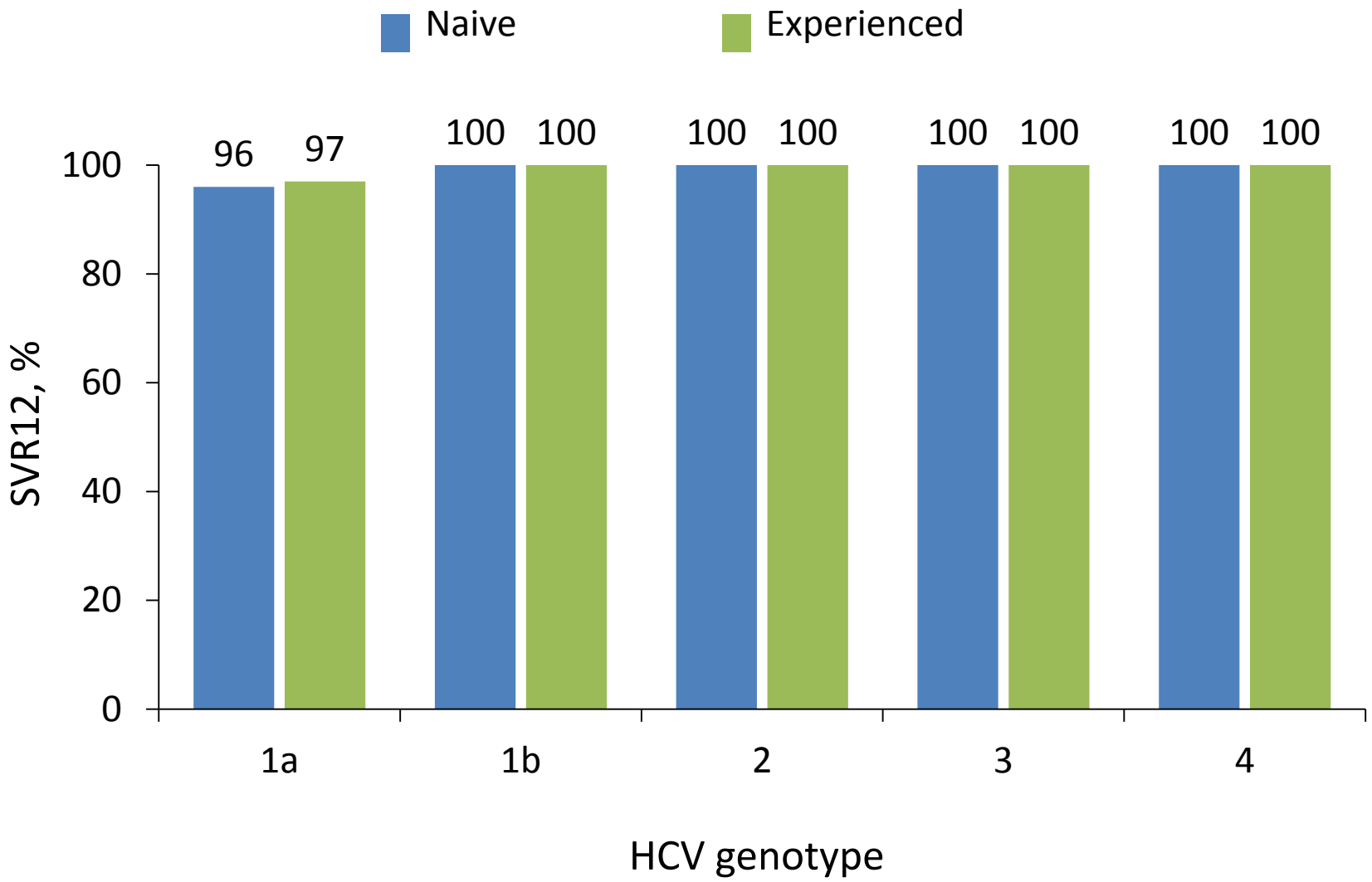
# ALLY-2: SOF/Daclatsvir



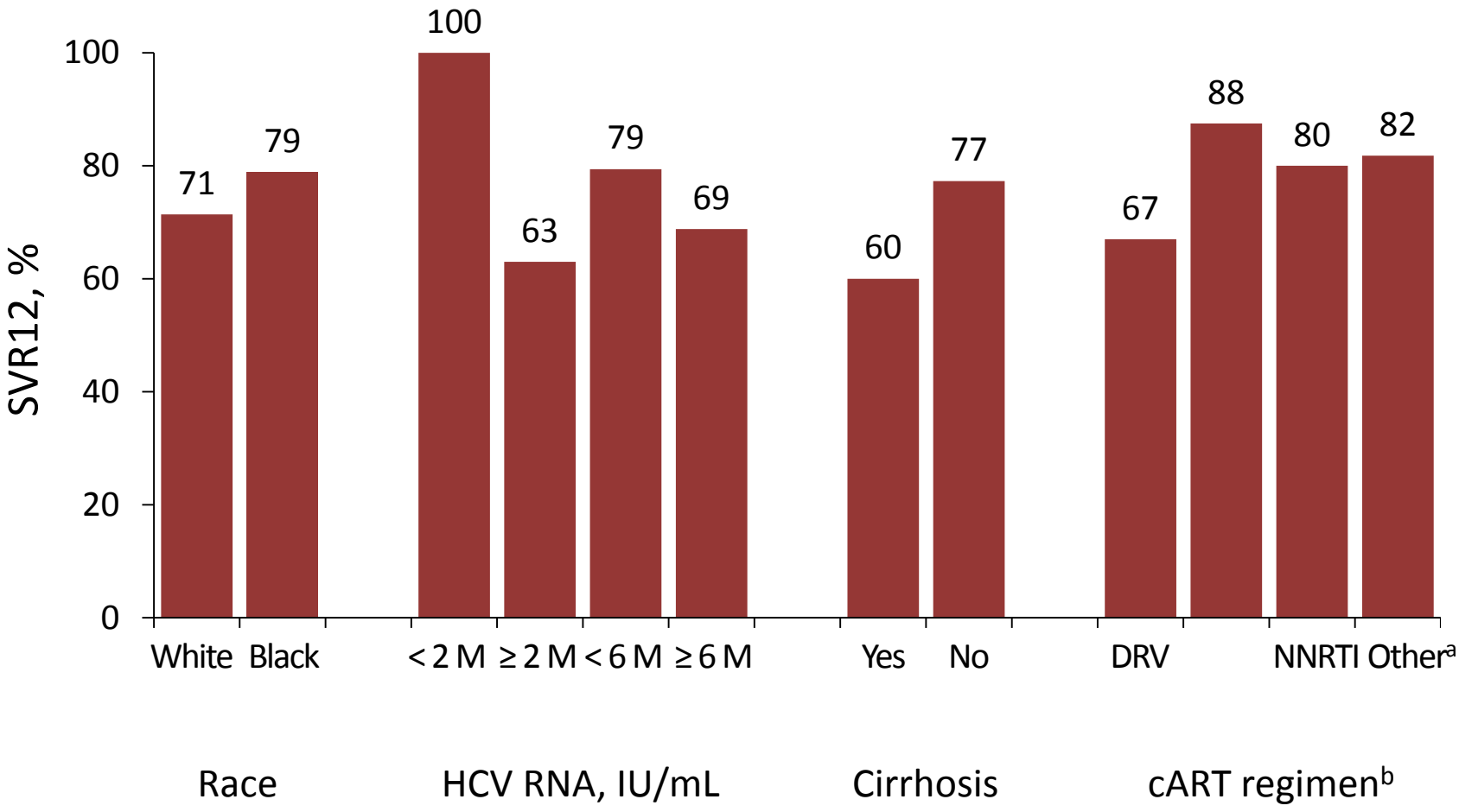

- Primary endpoint: SVR12 in treatment-naive patients with GT 1 treated for 12 weeks
- Standard DCV dose is 60 mg
  - Dose-adjusted for concomitant ARV therapy: 30 mg with ritonavir-boosted PIs,[b] 90 mg with NNRTIs except RPV

[a] HCV RNA <LLOQ (TD or TND) at posttreatment Week 12, assessed using the Roche HCV COBAS TaqMan Test v2.0 (LLOQ 25 IU/mL).
[b] New data suggest that DCV 60mg/day is recommended when used with DRV/r or LPV/r regimens [Eley et al. HIVDART 2014; Poster 63]

# ALLY-2: SVR12 by HCV Genotype: 12-Week Groups

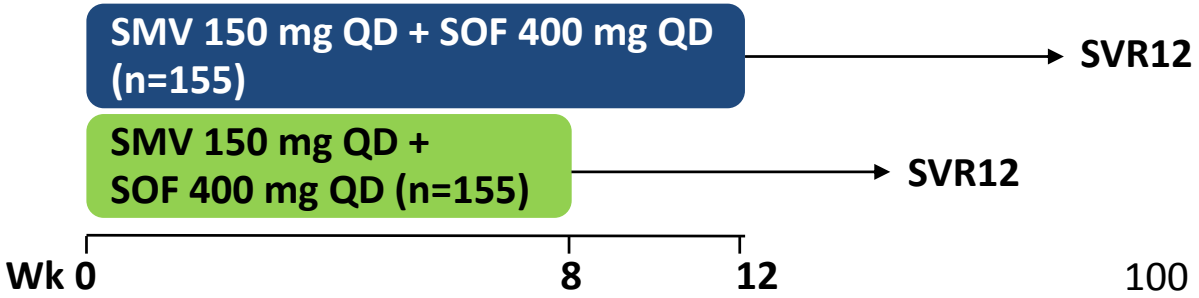


# ALLY-2: Low SVR rate with 8 weeks of SOF/Daclatasvir

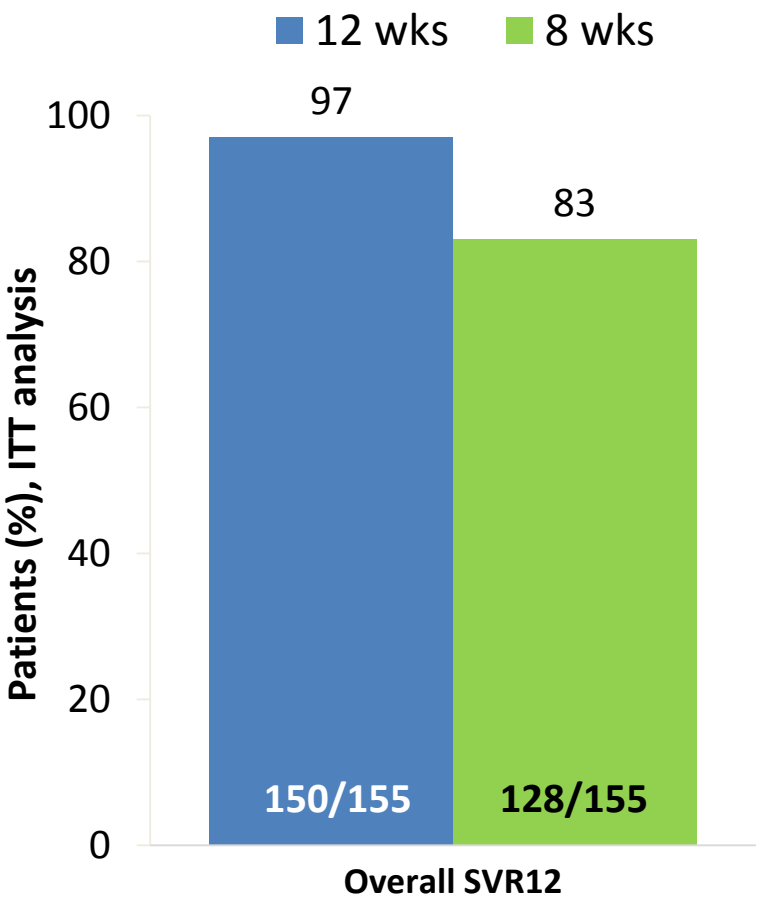



[a]RAL, n=8; DTG, n=1; no cART, n=2. [b]DCV dose was reduced to 30 mg/day with ritonavir-boosed PI regimens in ALLY-2; new data suggest that DCV 60mg/day is recommended when used with DRV/r or LPV/r regimens [Eley et al. HIVDART 2014; Poster 63]

# 8- or 12-week regimen of simeprevir (SIM) + sofosbuvir (SOF) in G1 patients without cirrhosis: OPTIMIST-1

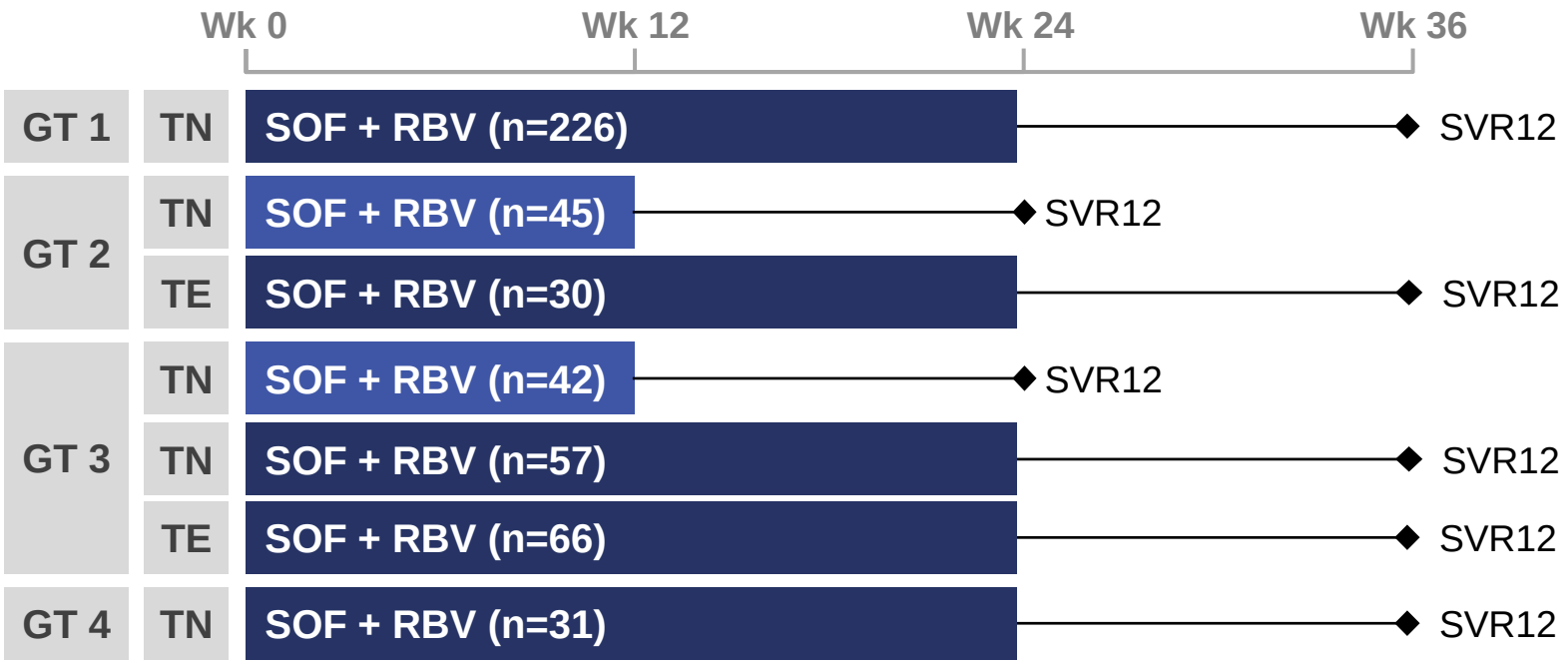



| Baseline characteristics | SMV + SOF, 12 wks n=155 | SMV + SOF, 8 wks n=155 |
|---|---|---|
| Age, median yrs | 56 | 56 |
| Male, n (%) | 82 (53) | 87 (56) |
| BMI, median kg/m$^2$ | 28.0 | 26.9 |
| White, n (%) | 120 (77) | 125 (81) |
| Hispanic or Latino, n (%) | 24 (15) | 24 (15) |
| HCV geno/subtype, n (%) | | |
| 1a | 116 (75) | 116 (75) |
| With Q80K | 46 (40) | 49 (42) |
| Without Q80K | 70 (60) | 67 (58) |
| 1b | 39 (25) | 39 (25) |
| BL HCV RNA ($log_{10}$ IU/mL) | 6.83 | 6.85 |
| IL28B CC/CT/TT, % | 28/55/17 | 26/55/18 |
| Treatment history, n (%) | | |
| Naive | 115 (74) | 103 (66) |
| Experienced | 40 (26) | 52 (34) |




Kwo P, et al. EASL 2015, Vienna. #LP14

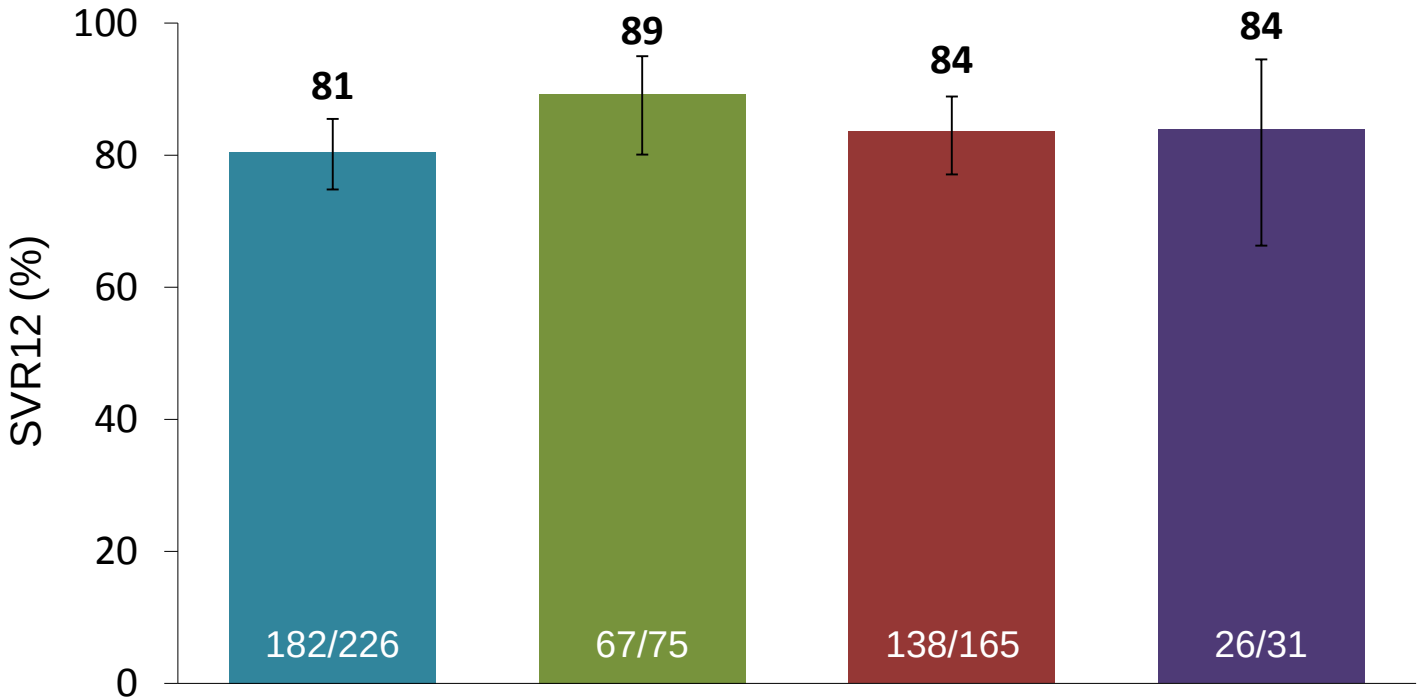
# Sofosbuvir plus Ribavirin for HCV genotype 1, 2, 3 and 4 in persons with HIV/HCV coinfection




- Broad inclusion criteria
  - Targeted 20% enrollment of patients with compensated cirrhosis; no platelet cutoff
  - Hemoglobin: ≥12 mg/dL (males); ≥11 mg/dL (females)
  - Undetectable HIV RNA for ≥8 weeks, on stable ART regimen
- Baseline CD4 count
  - ART treated: >200 cells/µL; untreated: >500 cells/µL
- The aim of these studies was to evaluate the safety and efficacy of interferon-free regimens of SOF + RBV in HIV-HCV co-infected patients

# SOF/RBV: SVR by HCV genotype

## GT 1-4 HIV-HCV (PHOTON-1 and 2)



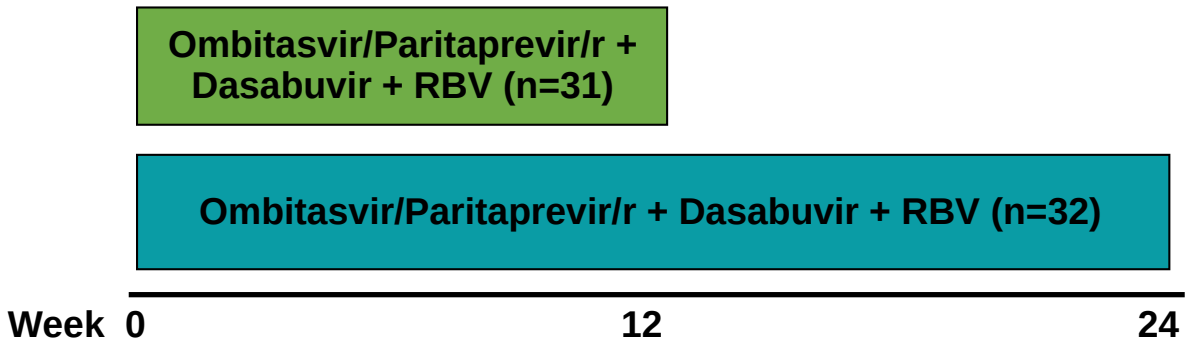

| | TN GT 1 | TN + TE GT 2 | TN + TE GT 3 | TN GT 4 |
|---|---|---|---|---|
| Relapse, n (%) | 39 (17) | 3 (4) | 23 (14) | 5 (16) |
| Breakthrough, n (%) | 1 (0.4) | 1 (1) | 1 (0. 6) | 0 |
| Lost to follow-up, n (%) | 2 | 1 | 2 | 0 |
| Withdrew consent, n (%) | 2 | 3 | 1 | 0 |

# PROTEASE + NS5A + OTHER AGENTS (NO NUCLEOSIDE)

# TURQUOISE-I: Ombitasvir/Paritaprevir/r + Dasabuvir + RBV in HCV Genotype 1 With HIV Co-Infection

## Phase 3

**Open-label**
**HCV genotype 1**
**HCV RNA >10,000 IU/mL**
**HCV treatment-naïve or**
**PR experienced**
**Child-Pugh A cirrhosis**
**Stable HIV disease**
**ART restricted to regimens based on:**
**Atazanavir (44%)**
**Raltegravir (56%)**

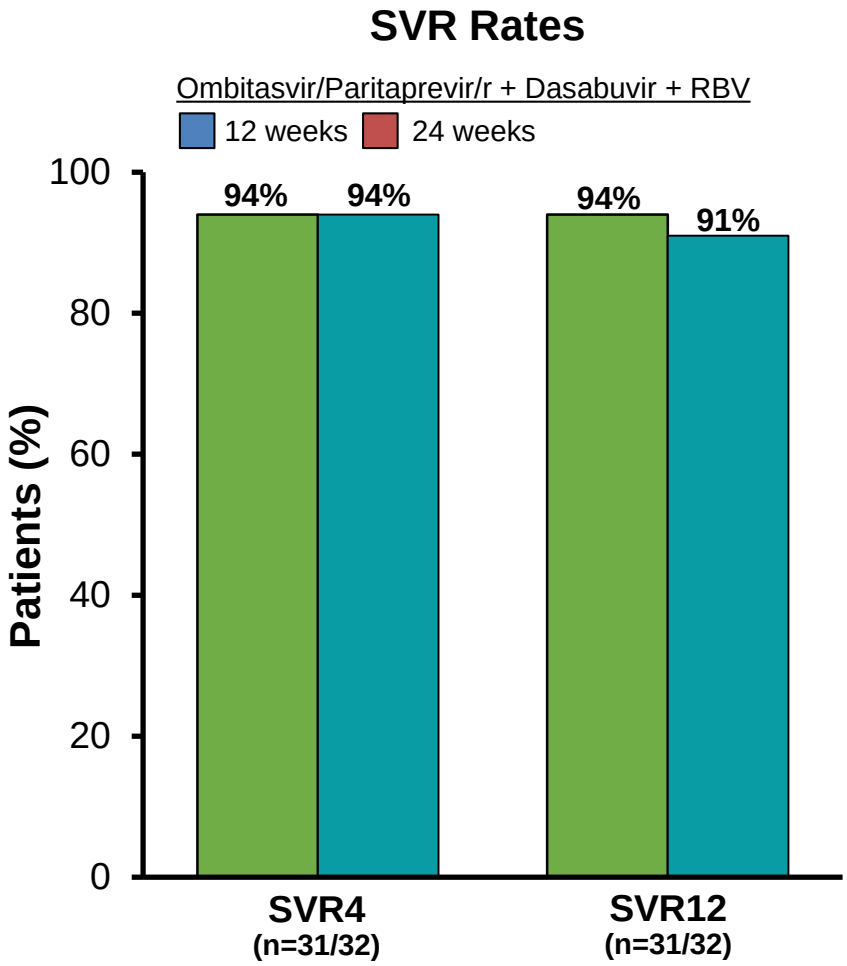



Ombitasvir/paritaprevir/r 25/150/100 mg qd; dasabuvir 250 mg bid. RBV (1000-1200 mg).
Primary endpoint: SVR12.
Baseline demographics and disease characteristics:
- Male: 92%; age: 51 years; black: 24%.
- Genotype 1a: 89%.
- IL28B non-CC: 81%.
- Treatment naïve: 67%.
- Prior PR response:
  - Relapse: 6%.
  - Partial response: 11%.
  - Null response: 16%.
- Cirrhosis: 19%.

Sulkowski JAMA 2014 .

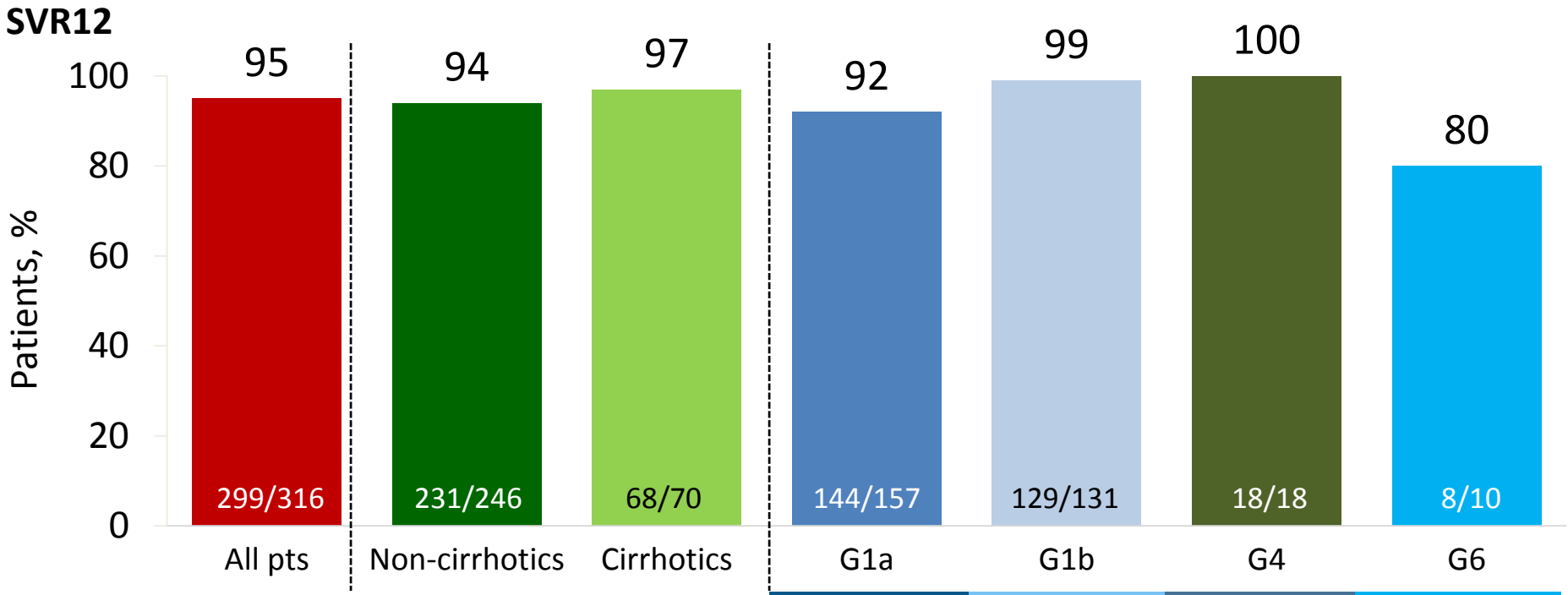
# TURQUOISE-I: Ombitasvir/Paritaprevir/r + Dasabuvir + RBV in HCV Genotype 1 With HIV Co-Infection

- Virologic failure (n=2)
  - Both were genotype 1a, prior PR null responders, and cirrhotic
  - Relapse (12-week regimen) and breakthrough (24-week regimen)
- Reinfection (n=2)
  - Between post-treatment weeks 4 and 12
- Safety
  - No treatment-emergent serious adverse events or discontinuations due to adverse events
  - RBV dose reduction (n=6, all achieved SVR)
  - Most common adverse events
    - Fatigue, insomnia, nausea, headache
  - Indirect hyperbilirubinemia most common laboratory abnormality (17/63 overall; 15 of 17 were receiving atazanavir-based ART)




Sulkowski JAMA 2014

# C-EDGE treatment-naive study: 12-week regimen of grazoprevir/elbasvir (GZR/EBR) in G1/4/6 patients



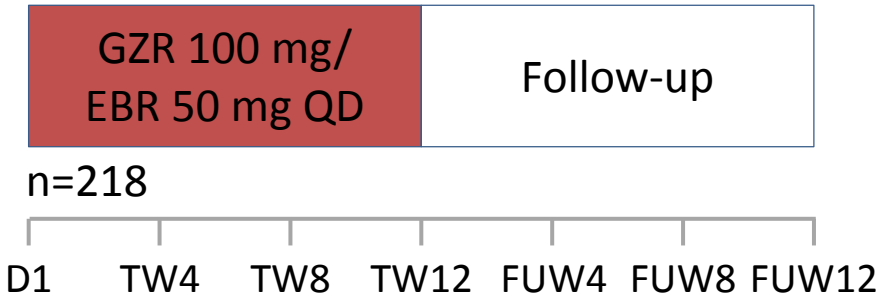

| | G1a | G1b | G4 | G6 |
|---|---|---|---|---|
| Non-VF | 3 | 1 | 0 | 0 |
| Breakthrough | 1 | 0 | 0 | 0 |
| Relapse | 9 | 1 | 0 | 2 |

- Good safety and tolerability profile: No drug-related SAE; 2 deaths unrelated to drugs
- Lab: No concurrent ALT/Bili increase, no anemia

VF = virologic failure

Zeuzem S, et al. Annals of Internal Medicine 2015

# C-EDGE co-infection: Phase 3 study of GZR/EBR in patients with HCV/HIV




**Patient demographics**

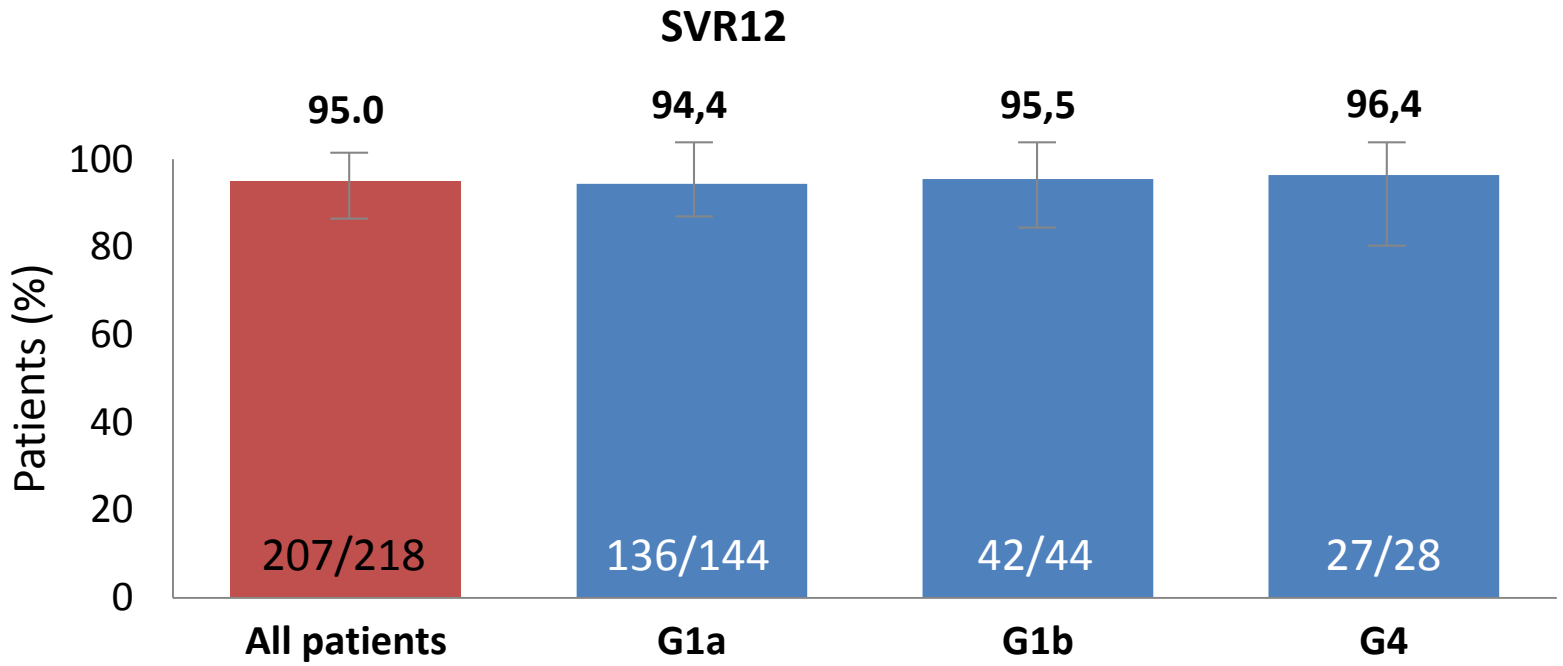
| | All patients N=218 |
|---|---|
| Age, years, mean (SD) | 48.7 (8.9) |
| Male gender, n (%) | 183 (83.9) |
| Race, n (%) | |
| White | 167 (76.6) |
| Black or African-American | 38 (17.4) |
| Asian | 6 (2.8) |
| Other | 7 (3.2) |
| Ethnicity, n (%) | |
| Hispanic/Latino | 14 (6.4) |
| Not Hispanic/Latino | 194 (89.0) |
| Not reported | 10 (4.6) |

| | All patients N=218 |
|---|---|
| HCV genotype, n (%) | |
| 1a | 144 (66.1) |
| 1b | 44 (20.2) |
| 1 other | 1 (0.5) |
| 4 | 28 (12.8) |
| 6 | 1 (0.5) |
| Baseline HCV RNA >800,000 IU/mL, n (%) | 130 (59.6) |
| Cirrhosis, n (%) | 35 (16.1) |
| IL28B CC, n (%) | 77 (35.3) |
| ART, n (%) | |
| Receiving ART with undetectable HIV RNA | 211 (96.8) |
| Naive to ART | 7 (3.2) |
| Baseline CD4 count (cells/mm$^3$) | |
| Mean (SD) | 613 (0.57) |
| Median (1st–3rd quartile) | 568 (424–766) |
| ART, n (%) | |
| ABC-containing regimen | 47 (21.6) |
| TDF-containing regimen | 164 (75.2) |
| RAL | 113 (51.8) |
| DTG | 59 (27.1) |
| RPV | 38 (17.4) |

Rockstroh JK, et al. EASL 2015, Vienna. #P0887

ABC: Abacavir; TDF: Tenofovir; RAL: Raltegravir; DTG: Dolutegravir; RPV: Rilpivirine

# C-EDGE co-infection: Phase 3 study of GZR/EBR in patients with HCV/HIV




| | | | | |
|---|---|---|---|---|
| Lost to f/u or d/c unrelated to VF | **4** | 3 | 1 | 0 |
| Breakthrough | **0** | 0 | 0 | 0 |
| Relapse | **6** | 4 | 1 | 1 |
| Reinfection | **1** | 1 | 0 | 0 |

Rockstroh JK, et al. EASL 2015, Vienna. #P0887

# C-EDGE co-infection: Phase 3 study of GZR/EBR in patients with HCV/HIV

**SVR12 subgroup analysis (full analysis set)**

| Patients with: | All patients N=218 |
|---|---|
| SAE, n (%) | 6 (2.8) |
| Serious drug-related AE, n (%) | 0 (0) |
| d/c due to AE, n (%) | 0 (0) |
| Deaths, n (%) | 0 (0) |
| Any AE, n (%) | 167 (76.6) |
| Fatigue | 29 (13.3) |
| Headache | 27 (12.4) |
| Nausea | 20 (9.2) |
| Late ALT or AST >5.0x ULN, n (%) | 2 (0.9) |
| Lowest Hb level on Tx, n (%) | |
| ≥8.5 to <10 g/dL | 1 (0.5) |
| Elevation of total bilirubin, n (%) | |
| >2.5–5.0x baseline | 8 (3.7) |
| >5.0x baseline | 1 (0.5) |
| Creatinine >2.5x baseline, n (%) | 0 (0) |

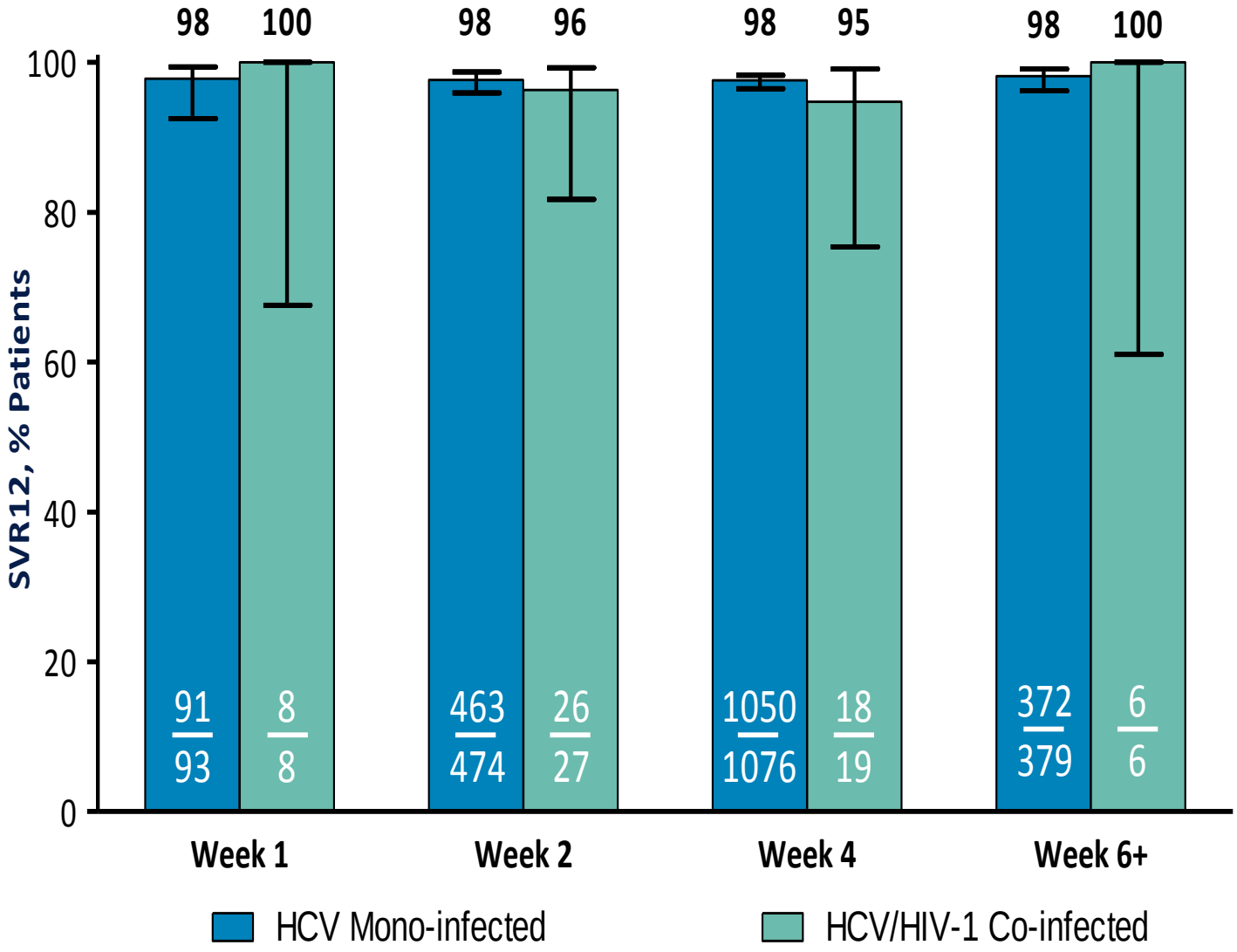
- GZR/EBR QD was safe and well tolerated with high SVR
- Due to DDI – limited ART

Rockstroh JK, et al. EASL 2015, Vienna. #P0887

# Case 1 - continued

- He continues on EFV/TDF/FTC per recommendation of his primary HIV clinician and his preference (no side effects)
- He continues buprenorphine/naloxone
- Initiates treatment with LDV/SOF single tablet daily for a planned 12 weeks (no RBV based on ION-4)
  - After 1 week HCV RNA is < 29 IU/mL/Detected

# SVR12 by Time to HCV RNA Suppression <15 IU/mL




Wyles CROI 2015

# Case - continued

- He completes 12 weeks of treatment with EFV/TDF/FTC  plus LDV/SOF single tablet daily
  - Changes to his antiviral regimens were not possible in the limited available timeframe
- At post-treatment week 4, his ALT = 15 and HCV RNA = not detected
  - He reports that he his rarely using injection heroin
  - He is no longer followed in the buprenorphine/naloxone program (reasons not entirely clear)

# Reinfection following sofosbuvir-based regimens and SVR12 (N=3004): Phylogenetic Analyses

| Patient | Study | Genotype | | Phylogenetic Distance |
|---|---|---|---|---|
| | | Baseline | Post-Treatment | |
| 1 | PHOTON-2 | 4d | 1a | Not related |
| 2 | PHOTON-1 | 1a | 1a | Not related |
| 3 | PHOTON-2 | 1a | 1a | Not related |
| 4 | GS-US-334-0119 | 1b | 1b | Not related |
| 5 | FUSION | 3a | 3a | Not related |
| 6 | PHOTON-2 | 1a | 1a | Distantly related |
| 7 | FUSION | 3a | 3a | Distantly related |
| 8 | PHOTON-1 | 3a | 3a | Closely related |
| 9 | VALENCE | 3a | 3a | Closely related |
| 10 | VALENCE | 3a | 3a | Closely related |
| 11 | FISSION | 3a | 3a | Closely related |
| 12 | PHOTON-2 | 3a | 3a | Closely related |

Sarrazin C, et al. 50th EASL; Vienna, Austria; April 22-26, 2015. Abst. O063.

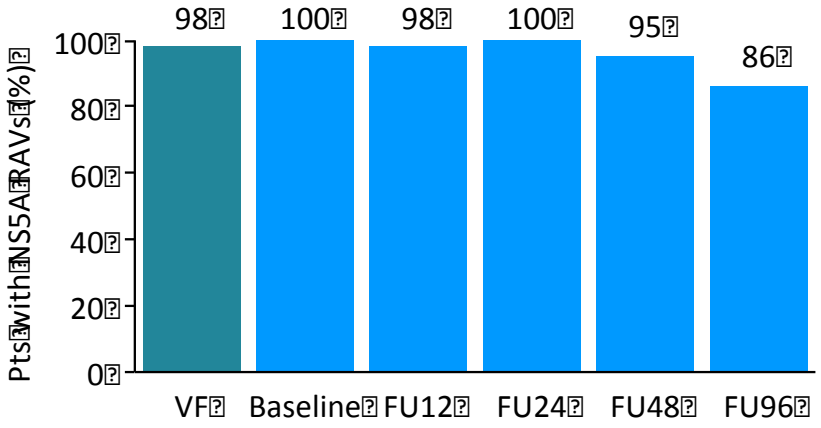
# Long-term persistence of HCV NS5A resistance-associated variants after treatment

## Persistence of PTV (PI), OBV (NS5A) and DSV (NNI NS5B) RAVs

| Target | RAV | G1a n (%) | G1b n (%) | FU24 n/N (%) | FU48 n/N (%) |
|---|---|---|---|---|---|
| NS3 | R155K | 9 (13) | 0 | 10/13 (77) | 2/7 (29) |
| NS3 | **D168V** | 35 (52) | 3 (43) | 21/55 (38) | 2/53 (4) |
| NS5A | M28V/T | 20 (30) | 0 | 32/33 **(97)** | 21/21 **(100)** |
| NS5A | **Q30E/K/R** | 29 (43) | 0 | 38/41 **(93)** | 25/28 **(89)** |
| NS5B | **S556G** | 23 (35) | 1 (14) | 27/30 (90) | 17/22 (77) |

Krishnan P, et al. EASL 2015, Vienna. #O057

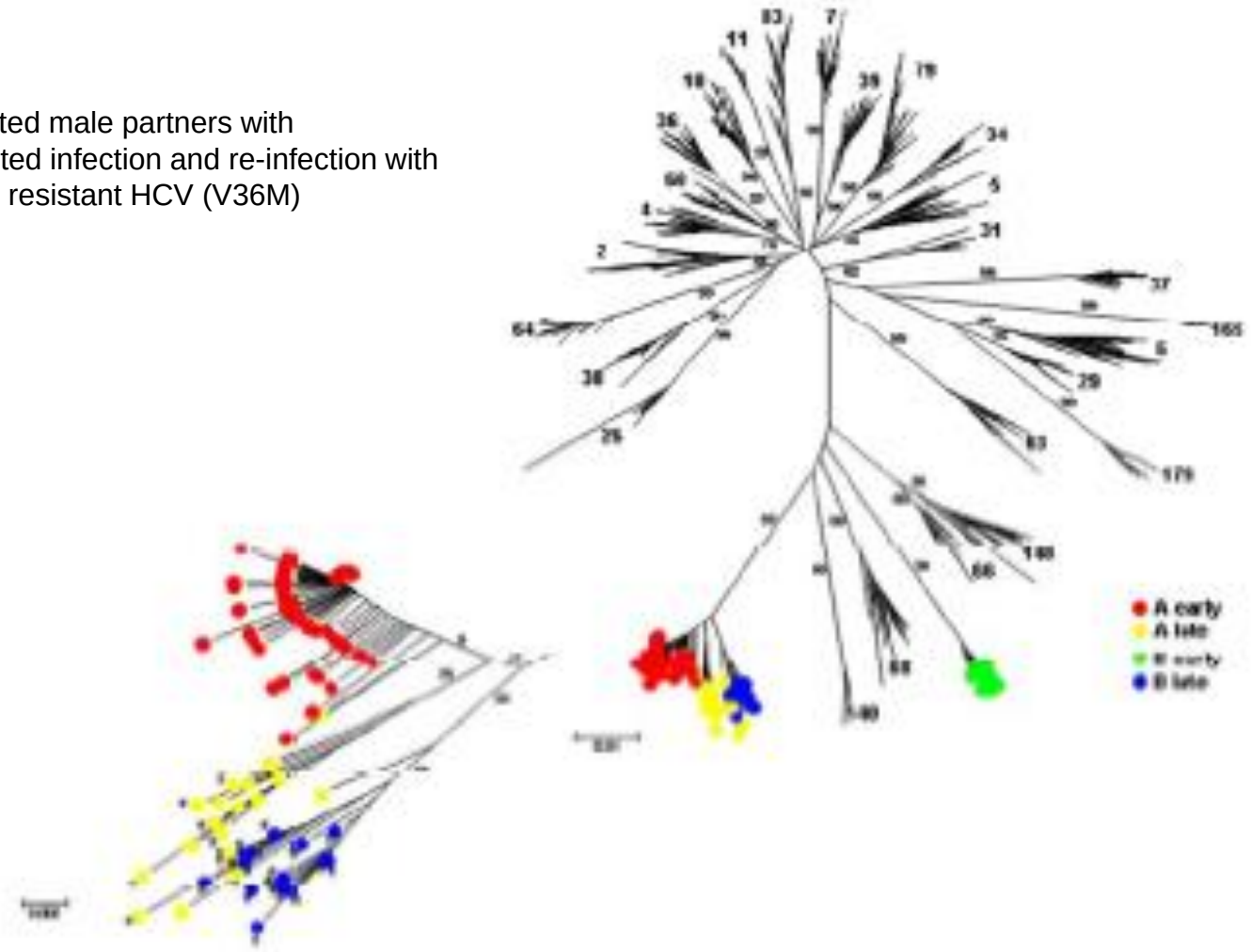
## Persistence of LDV (NS5A) RAVs




Wyles D, et al. EASL 2015, Vienna. #O059

# Reinfection with DAA resistant HCV

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




Franco et al. Gastroenterology 2014

# HCV therapy in HIV

- Treatment of HCV in persons with HIV coinfection is “high priority” independent of liver disease stage
- Treatment readiness – adherence to visits/meds and prevention of reinfection
- Potential drug interactions between HIV and HCV drugs must be carefully considered
- HCV treatment regimens do not differ from HCV mono-infection with respect to efficacy, safety and tolerability
- Reinfection rates after HCV cure may be higher in persons with HIV infection (prospective studies needed)