# Treatment of HCV : 100 % cure ?

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Tarik Asselah (MD, PhD)

Professor of Medicine
Hepatology, Chief INSERM UMR 1149,
Hôpital Beaujon, Clichy, France.

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anRS French National Agency for Research on AIDS and Viral Hepatitis | An autonomous agency at Inserm |

# Disclosures

- Employee of Paris Public University Hospitals (AP-HP, Beaujon's Hospital) and University of Paris

- Principal investigator for research grants : Funds paid to Hospital (AP-HP)

  - Consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, Roche.

  - Grants from : ANR, CNRS , INSERM , University of Paris, ANRS

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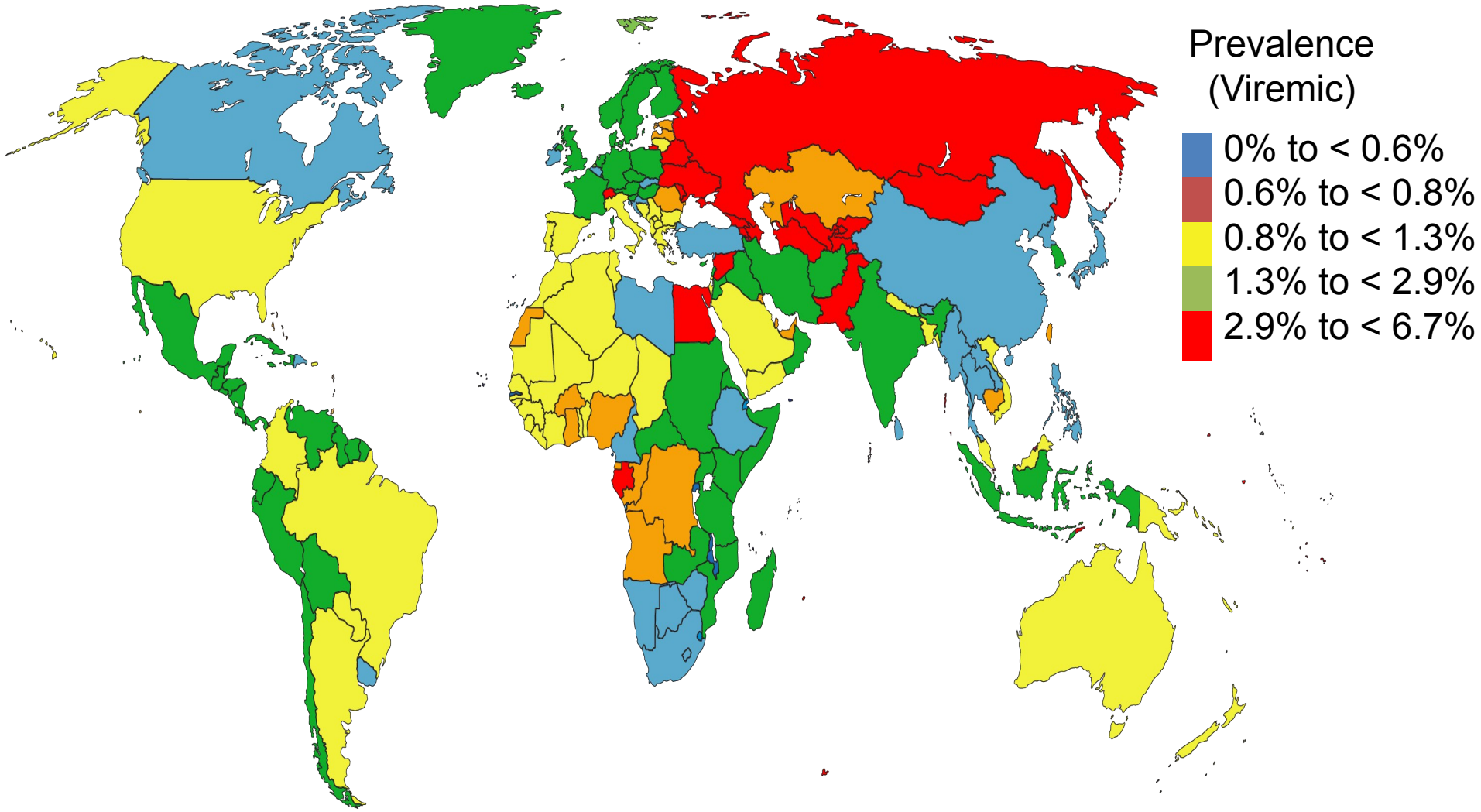
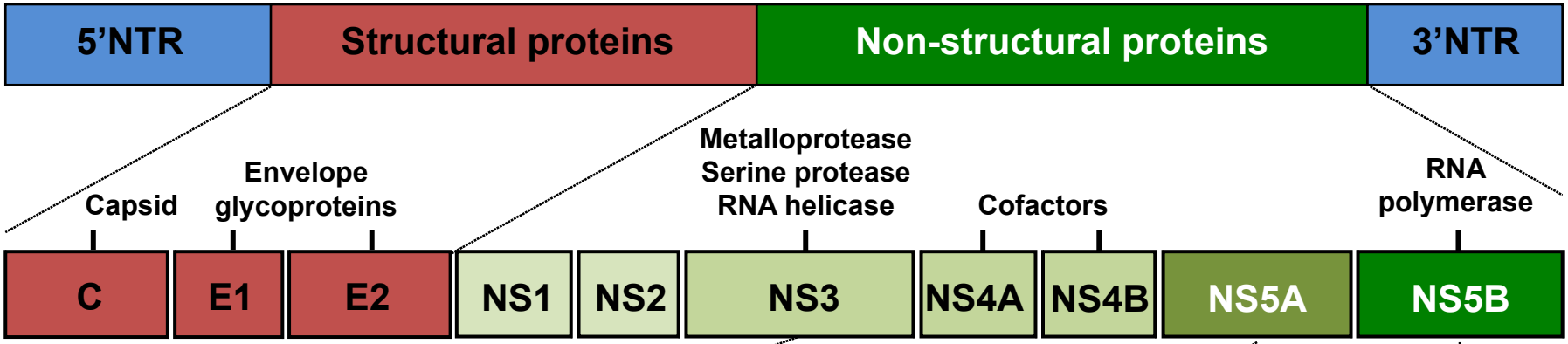
1. **Introduction**
2. Sofosbuvir/Velpatasvir (Epclusa®)
3. Glecaprevir/Pibrentasvir (Maviret®)
4. Grazoprevir/Elbasvir (Zepatier®)
5. Challenges to achieve HCV elimination

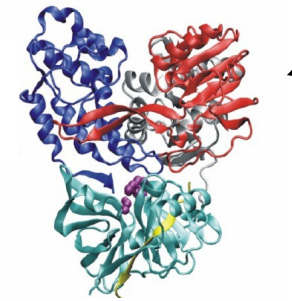
# Estimated 70 Million Persons Living With HCV

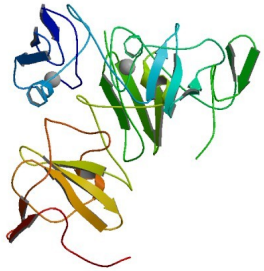


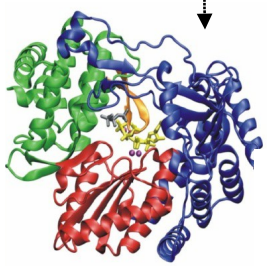

Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2:161-176.

# Direct-acting antivirals : a Revolution







**Protease inhibitors**
**« …previr »**

- Paritaprevir
- Glecaprevir
- Grazoprevir
- Voxilaprevir

**NS5A inhibitors**
**« ….asvir »**

- Ledipasvir
- Velpatasvir
- Pibrentasvir
- Ombitasvir
- Elbasvir
- Daclatasvir

**Polymerase inhibitors**
**« …..buvir »**

| Nucs | Non-Nucs |
|---|---|
| Sofosbuvir | Dasabuvir |

*Asselah et al. Liver Int* 2018, in press.

SOF

LDV

VEL

VOX

SOF + RBV
12–24 weeks

SOF/LDV
± RBV
8†–24
weeks

SOF/VEL
± RBV
12 weeks

SOF/VEL/VOX
12 weeks

Jan 2014 | May 2014 | Sept 2014 | Nov 2014 | Jan 2015 | July 2016 | July 2017

SOF + SMV
± RBV
12–24
weeks

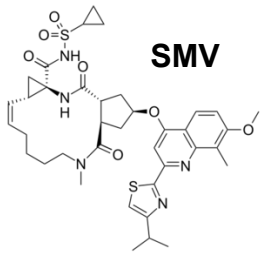
SOF + DCV
± RBV
12–24
weeks

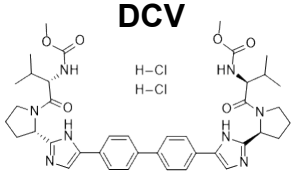
OMV/PTV/RTV

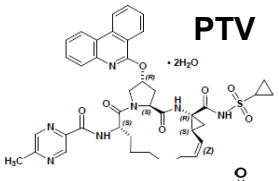
± DSV ± RBV
12–24 weeks

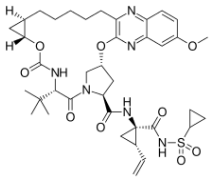
GRZ/EBV
± RBV
12–16
weeks

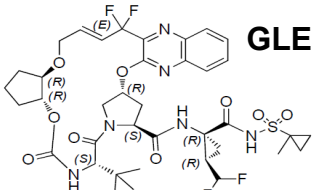
GLE/PIB
8–12 weeks

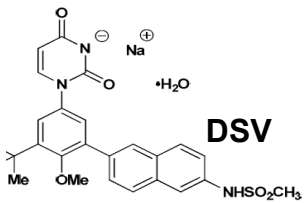

SMV

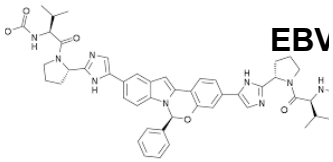

DCV

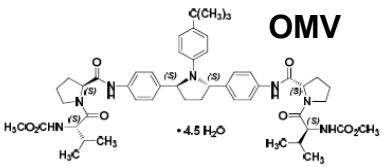

PTV

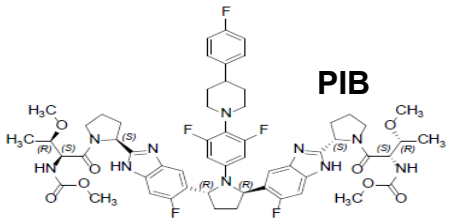

GRZ


GLE


DSV

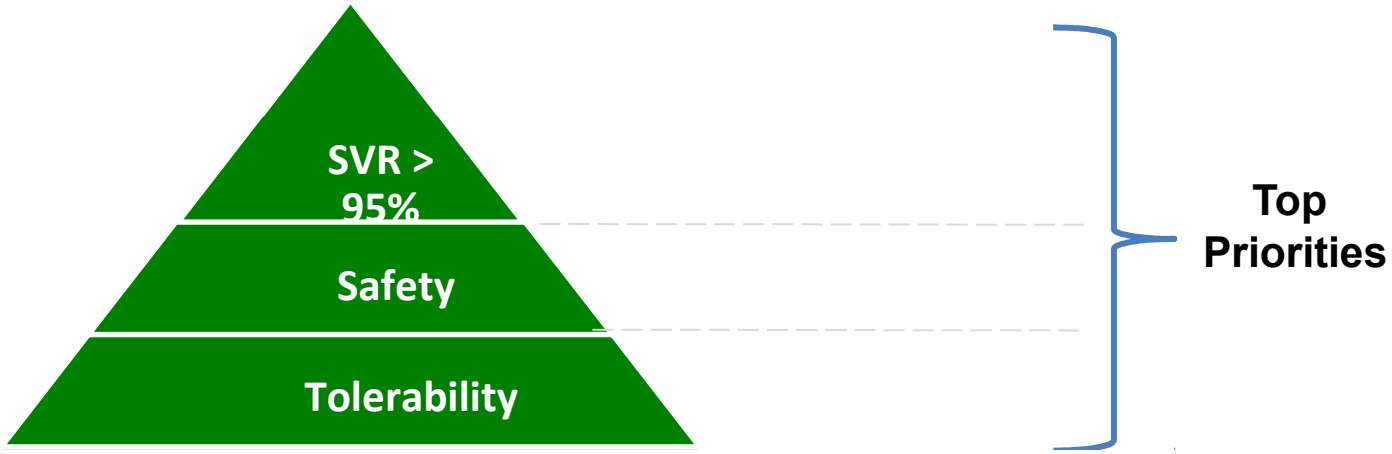

EBV


OMV

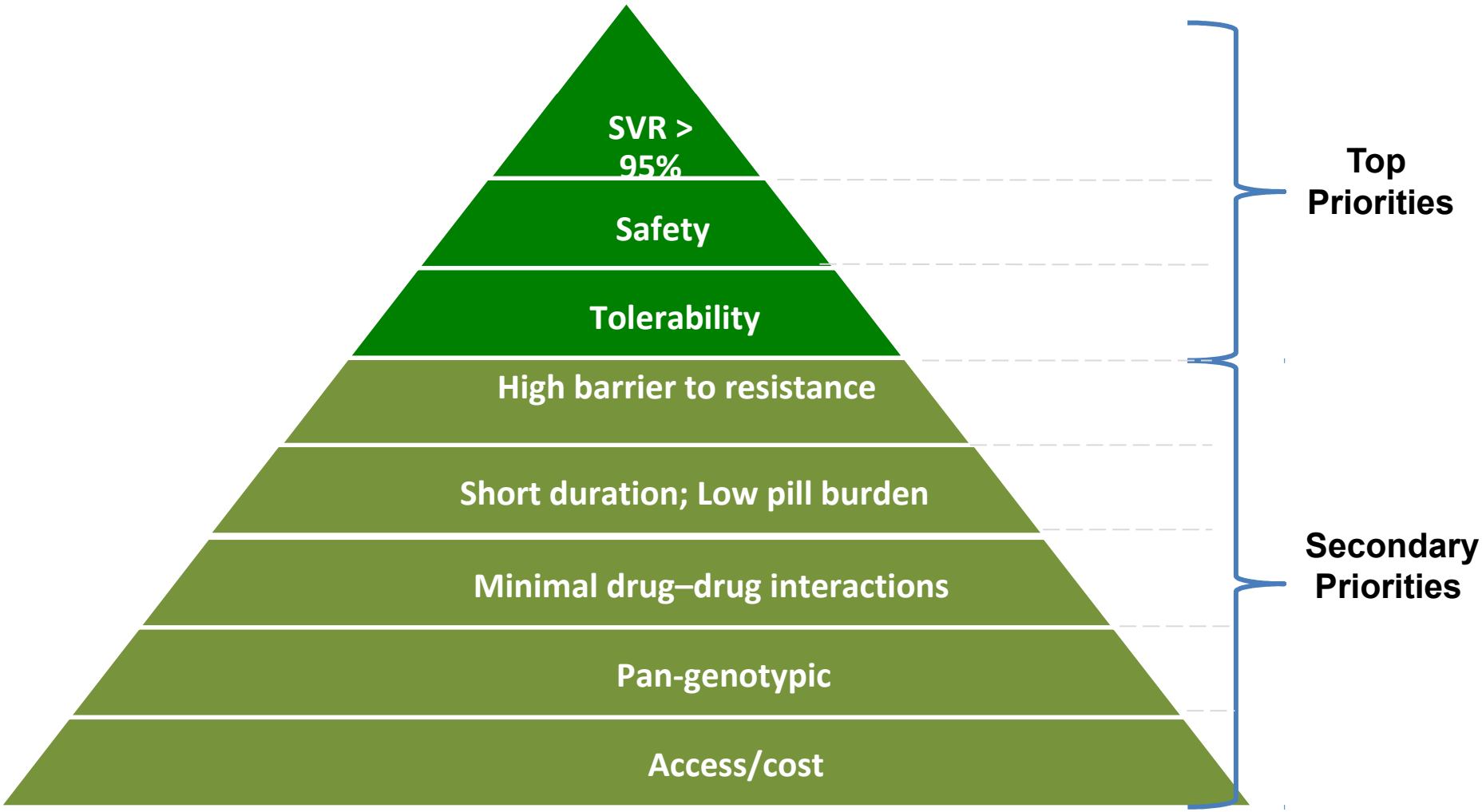

PIB

*Asselah et al. Liver Int* 2018, in press.

# Priorities for Direct-acting antivirals



# Priorities for Direct-acting antivirals



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# Velpatasvir/Sofosbuvir: A Single Tablet Regimen (STR)

**SOF**
**Nucleotide NS5B polymerase inhibitor**

- **Sofosbuvir (SOF)1,2**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet

**VEL**
**NS5A inhibitor**

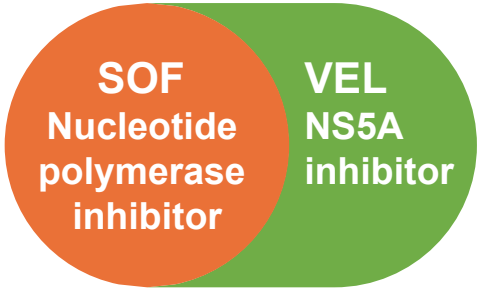
- **Velpatasvir (VEL; GS-5816)3-5**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

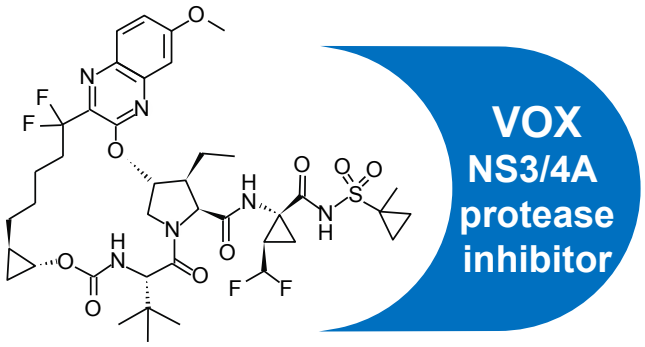
**SOF** + **VEL**

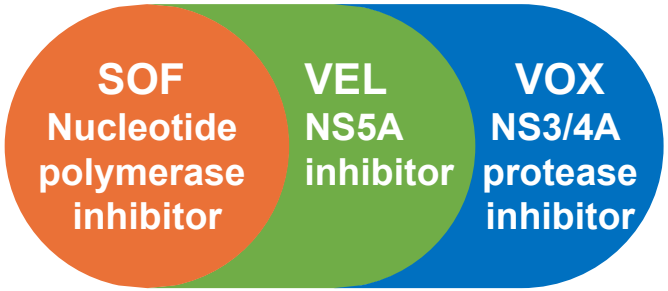
- **SOF/VEL Single Tablet Regimen (STR)**
  - Once daily, oral, STR (400/100 mg)

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191;
4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. EASL 2013, poster 1082.

# Voxilaprevir/Velpatasvir/Sofosbuvir: STR




## Sofosbuvir (SOF)/Velpatasvir (VEL)

**SOF**: Nucleotide polymerase inhibitor with activity against HCV GT 1–6

**VEL**: Potent pangenotypic NS5A inhibitor

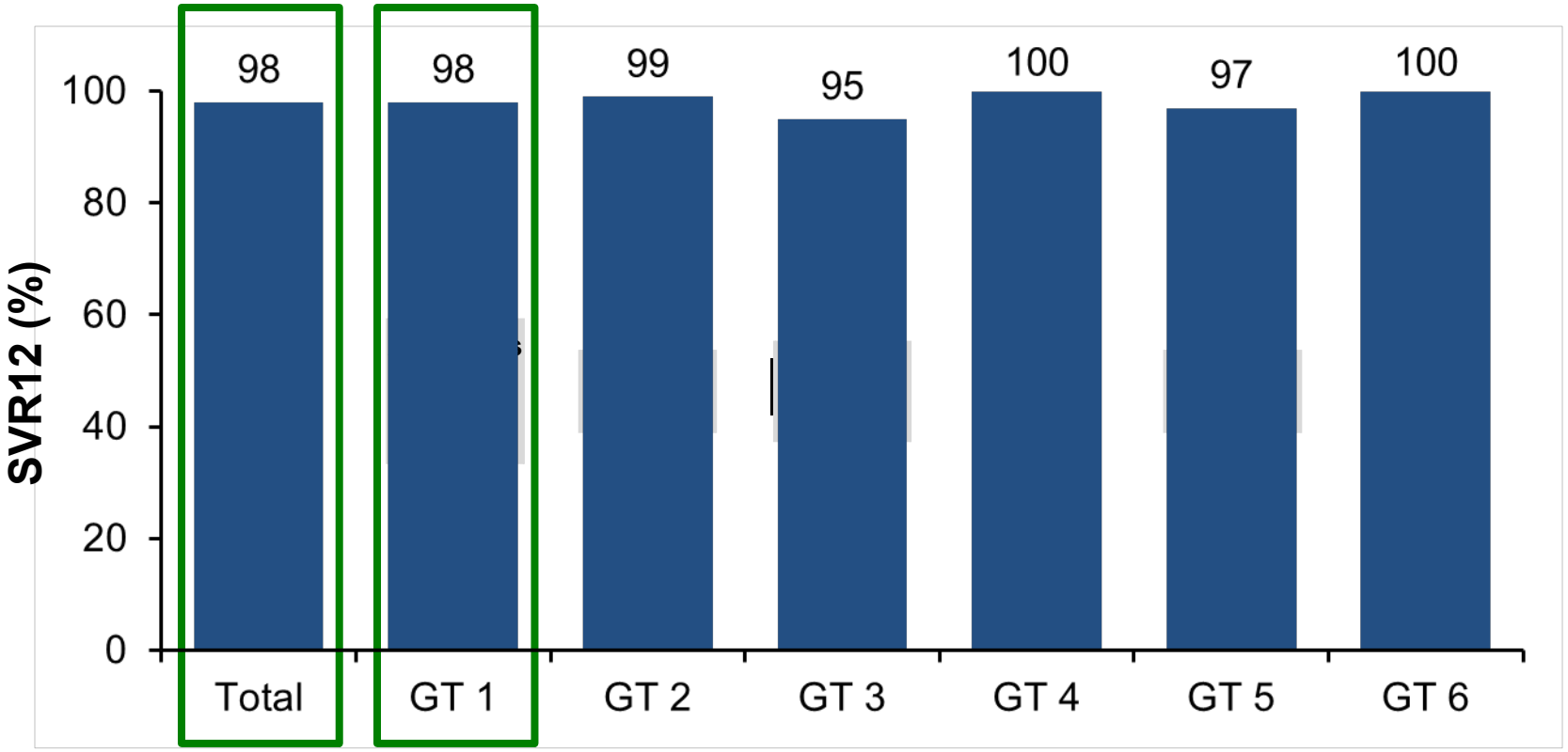
## Voxilaprevir (VOX)

HCV NS3/4A PI with potent antiviral activity against GT 1–6, including most RASs

## SOF/VEL/VOX

Once daily, oral, fixed-dose combination (400/100/100 mg) for GT 1–6

# Velpatasvir/Sofosbuvir (Epclusa®) for 12 weeks across all genotypes (ASTRAL-1, ASTRAL-2 and ASTRAL-3)

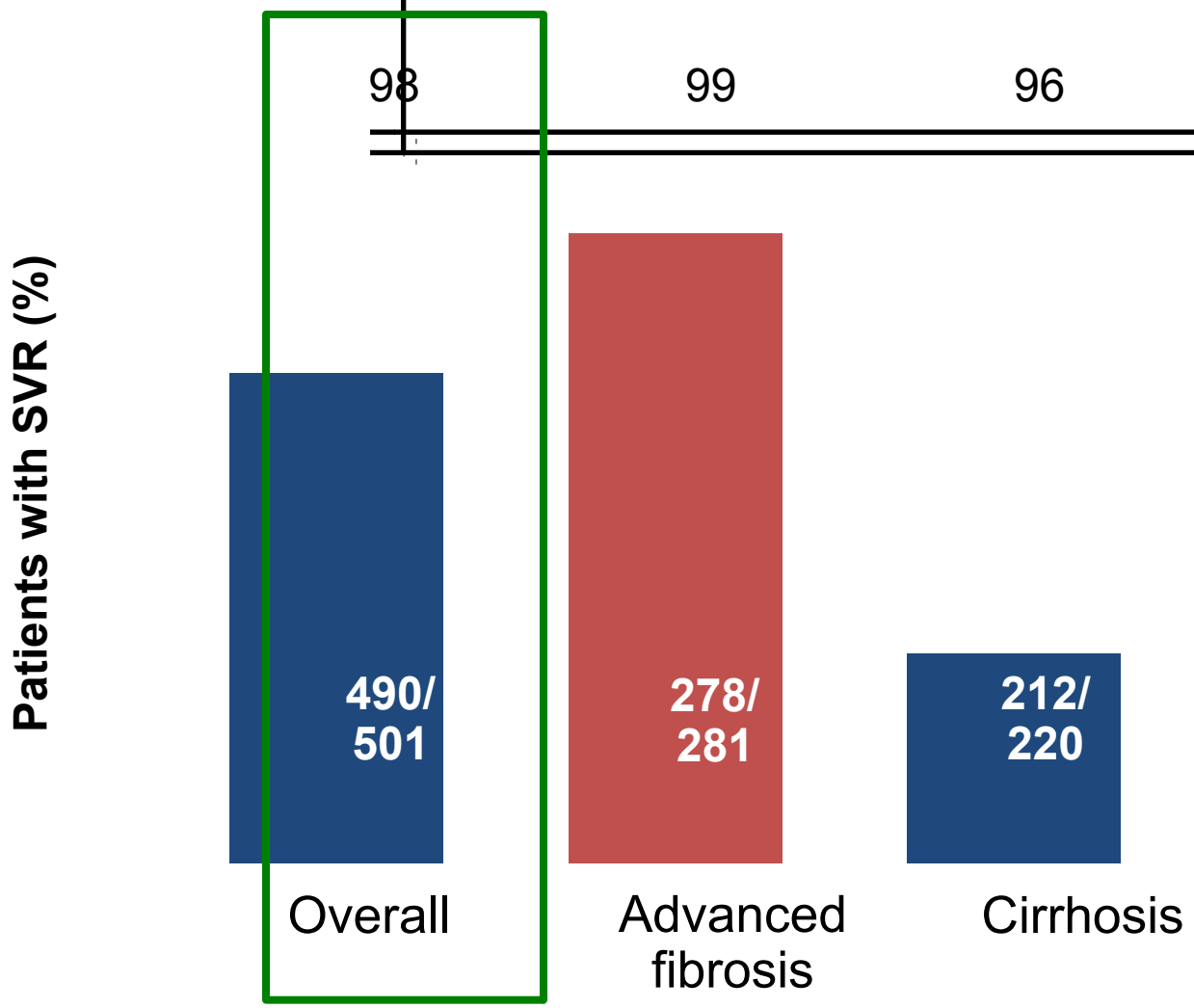



- 2% of patients experienced one or more SAE; no SAEs were considered study drug related
- 2 patients discontinued treatment due to AEs

AE: adverse event; D/C: discontinuation; LTFU: lost to follow-up; SAE: serious adverse event

Agarwal K, et al. EASL 2016; Poster #SAT-195;
Jacobson I, et al. EASL 2016; Poster #SAT-168

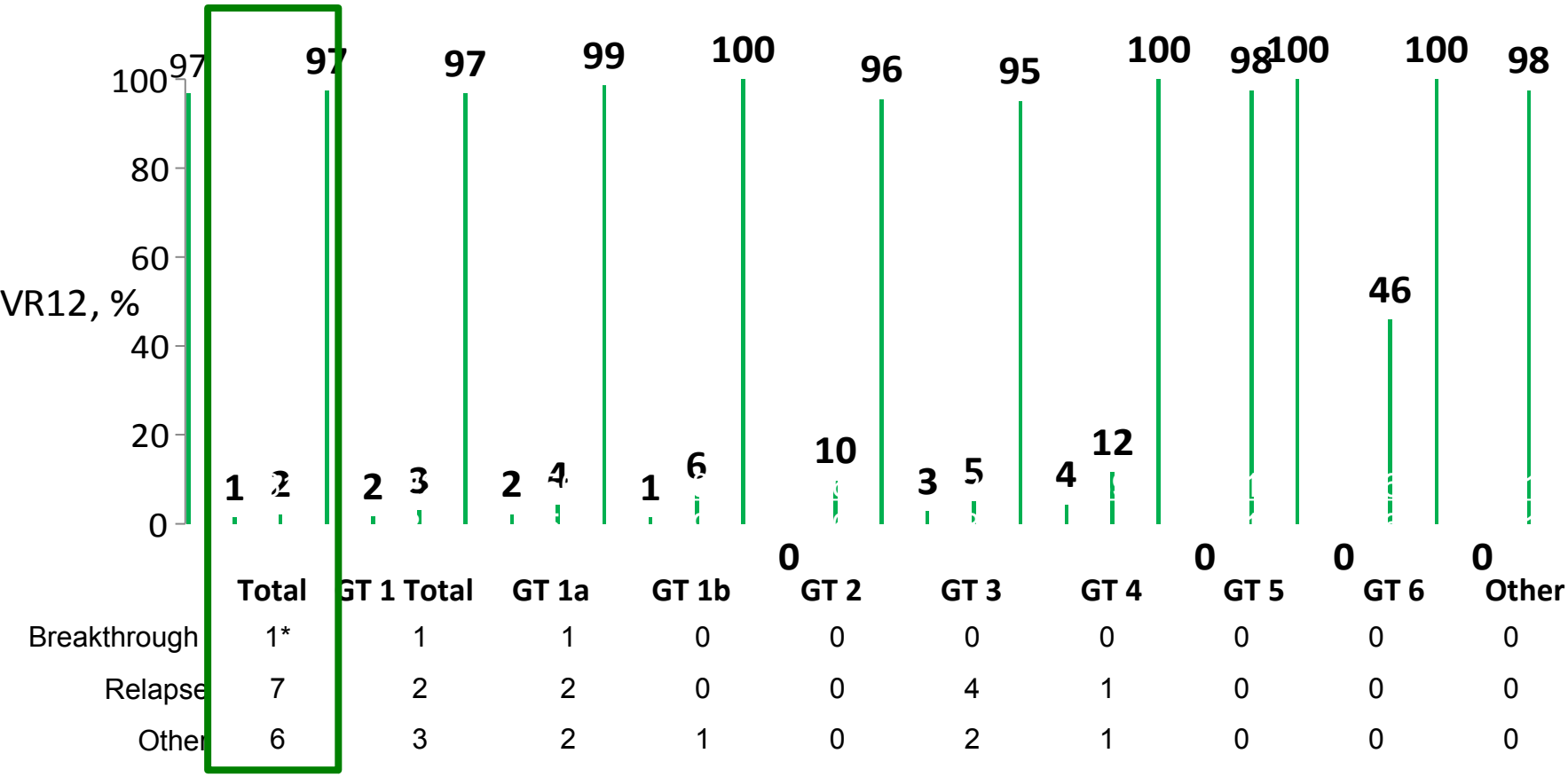
# SOF/VEL (Epclusa®) is effective in patients with advanced fibrosis and cirrhosis (ASTRAL 1, 2 & 3)




*Asselah T, et al. Liver Int 2018, in press*

# SOF/VEL/VOX for 12 Weeks in DAA-Experienced Patients

Integrated Efficacy Analysis of POLARIS-1 and -4




**The SVR12 rate was 97% (431/445) in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks; Rates were similar regardless of genotype**

*Patient had drug levels consistent with nonadherence.

Roberts, EASL 2017, SAT-280

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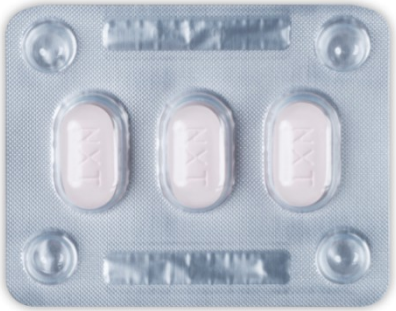
# Glecaprevir/Pibrentasvir (Maviret®)

**Glecaprevir**
**(ABT-493)**
pangenotypic
NS3/4A protease inhibitor

2nd generation3



**Pibrentasvir**
**(ABT-530)**
pangenotypic
NS5A inhibitor

2nd generation3

Collectively: G/P

In vitro:1,2

- High barrier to resistance
- Potent against common NS3 polymorphisms (eg., positions 80, 155, and 168) and NS5A polymorphisms (eg., positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

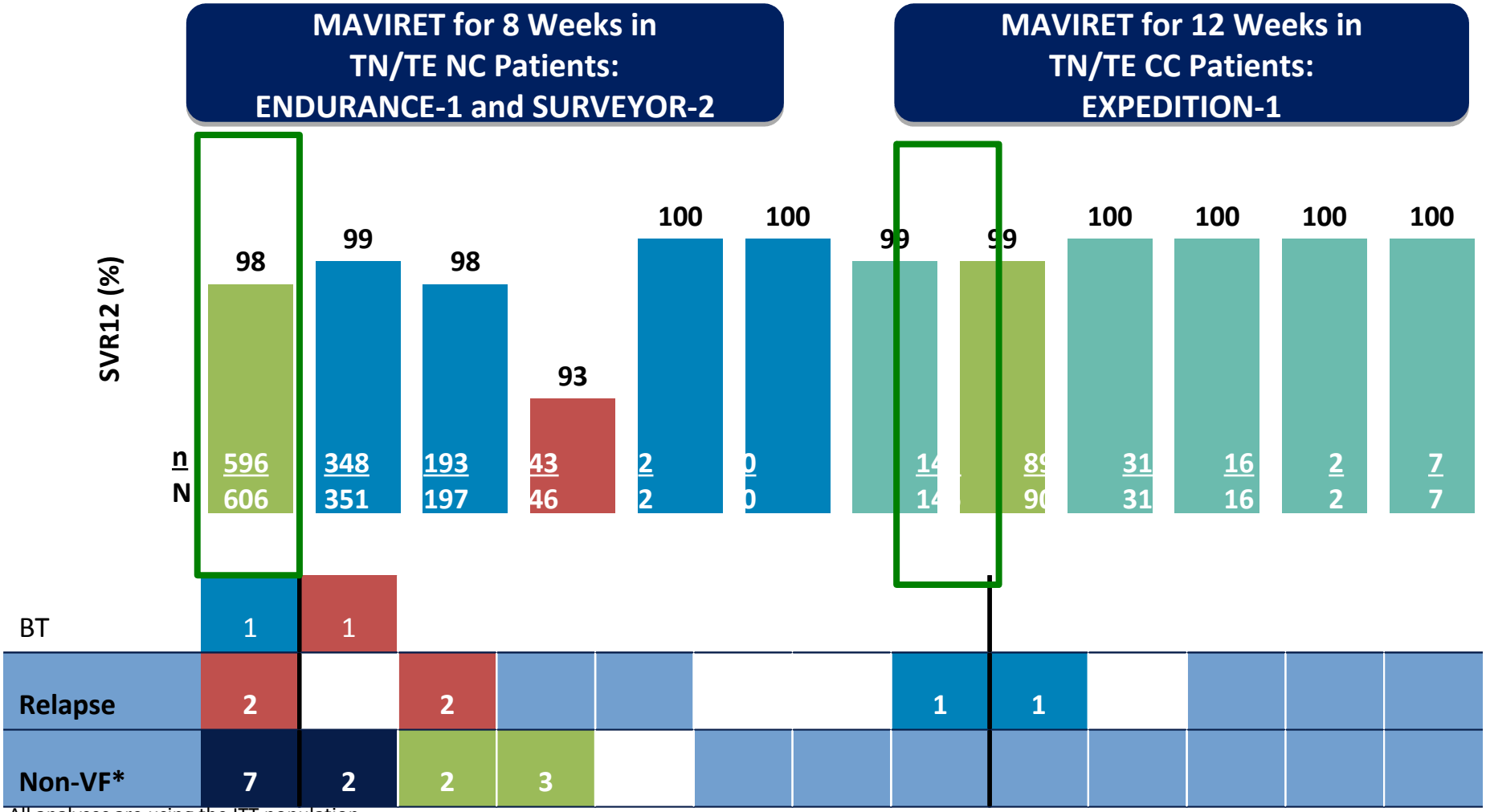
**Clinical PK & metabolism:**

- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is co-formulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg.
Glecaprevir was identified by AbbVie and Enanta.

1. Ng TI, et al. Abstract 636. CROI, 2014.
2. Ng TI, et al. Abstract 639. CROI, 2014.
3. Pawlotsky, Gastroenterology 2016

# Glecaprevir/Pibrentasvir (Maviret) in Patients with HCV GT1, 2, 4-6 Infection with or without Compensated Cirrhosis




All analyses are using the ITT population.

TN, treatment-naïve; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± pegIFN; NC, non-cirrhotic; CC, compensated cirrhotic; ITT, intent-to-treat; BT, breakthrough; VF, virologic failure.

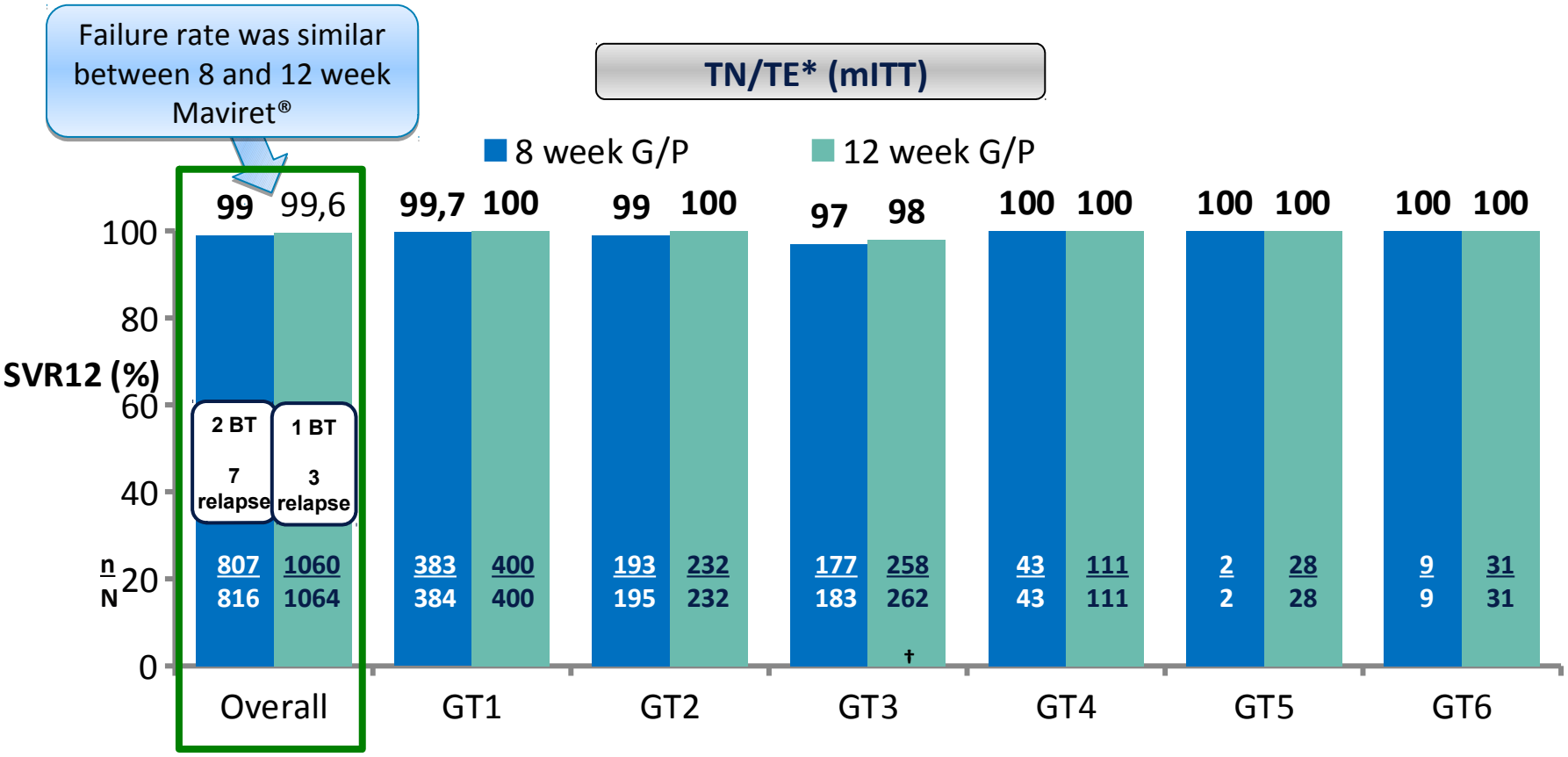
*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.


MAVIRET Summary of Product Characteristics; Accessed August 2017.

. Asselah T, et al. Clin Gastroenterol Hepatol. 2017

# Integrated Efficacy Analysis: High SVR Rates with 8 and 12 Weeks of Glecaprevir/Pibrentasvir in GT1–6 Patients without Cirrhosis

Integrated efficacy analysis of 8- or 12-weeks Maviret treatment in non-cirrhotic patients with GT1–6 infection across seven phase 2 or 3 clinical trials

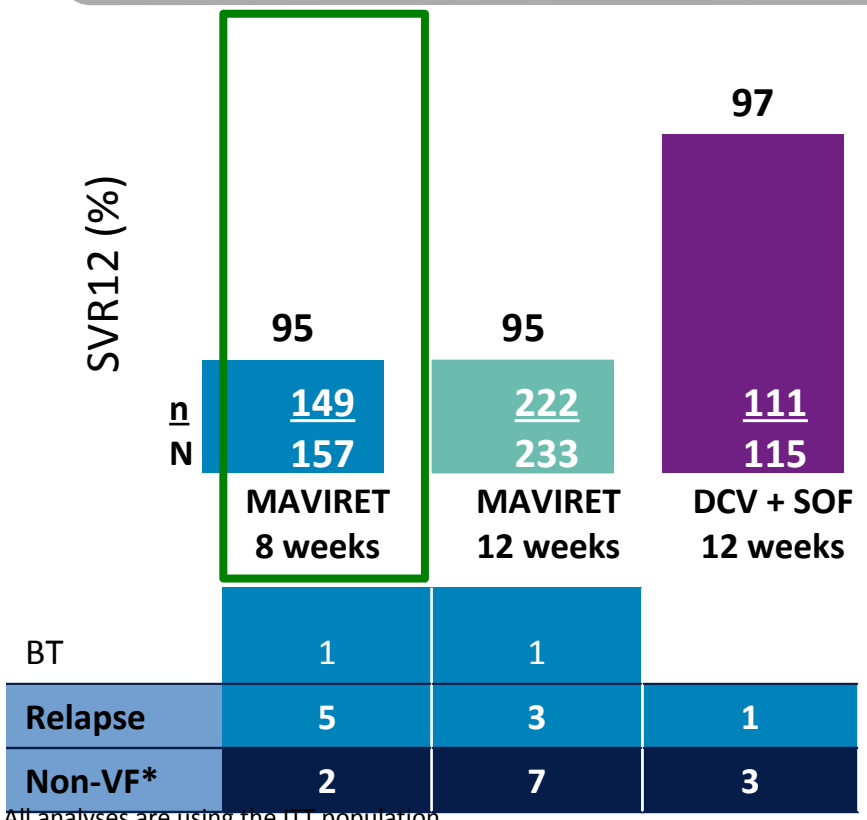



BT, breakthrough; mITT, modified intent-to-treat, (excludes non-virologic failures);
*TE, treatment-experienced (includes patients with prior SOF use); TN, treatment-naive
Includes patients with prior SOF use (8-week Maviret [n = 7] and 12-week Maviret [n = 9]);
† All GT3 patients were treatment-naïve

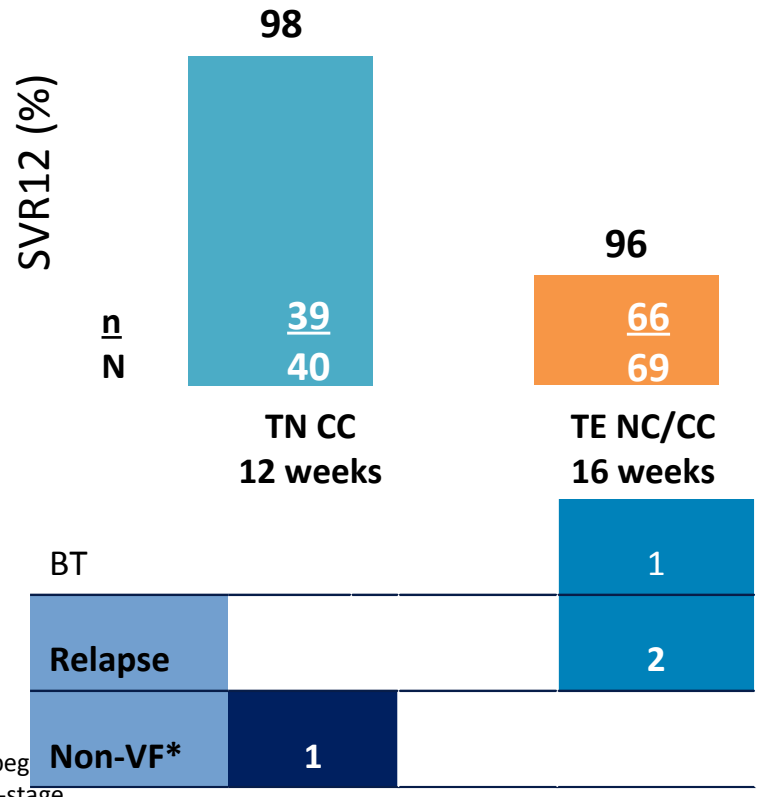
Puoti M, *et al. J Hepatol* 2017; **66**(Suppl):S721 (poster presentation SAT-233).

# Glecaprevir/Pibrentasvir (Maviret) in Patients with HCV GT3 Infection with or without Compensated Cirrhosis

## MAVIRET for 8 or 12 Weeks in TN NC Patients: ENDURANCE-3




## MAVIRET for 12 Weeks in TN CC Patients, or 16 Weeks in TE NC/CC Patients: SURVEYOR-2 Part 3




All analyses are using the ITT population.
TN, treatment-naïve; TE, treatment-experienced with IFN or pegIFN ± RBV, or SOF + RBV ± peg
BT, breakthrough; CC, compensated cirrhosis; NC, noncirrhotic; DCV, daclatasvir; ESRD, end-stage renal disease; SOF, sofosbuvir; TE, treatment experienced; TN, treatment naive; VF, virologic failure.
*Includes patients who discontinued due to adverse events, lost to follow-up, or withdrew.

MAVIRET Summary of Product Characteristics; Accessed August 2017.

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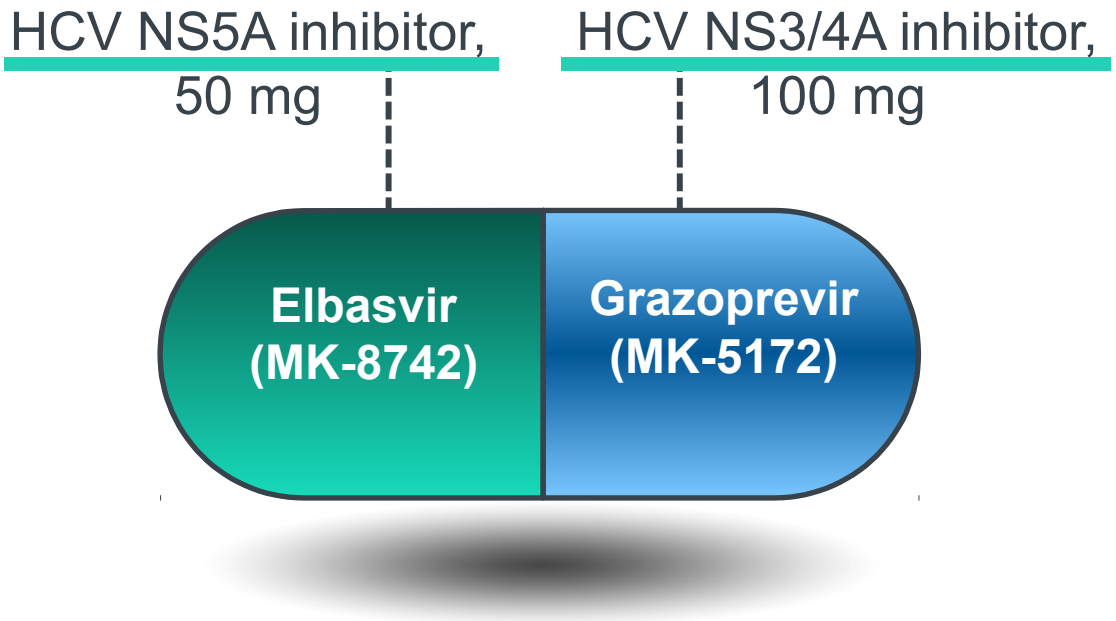
# Elbasvir/Grazoprevir (Zepatier®)



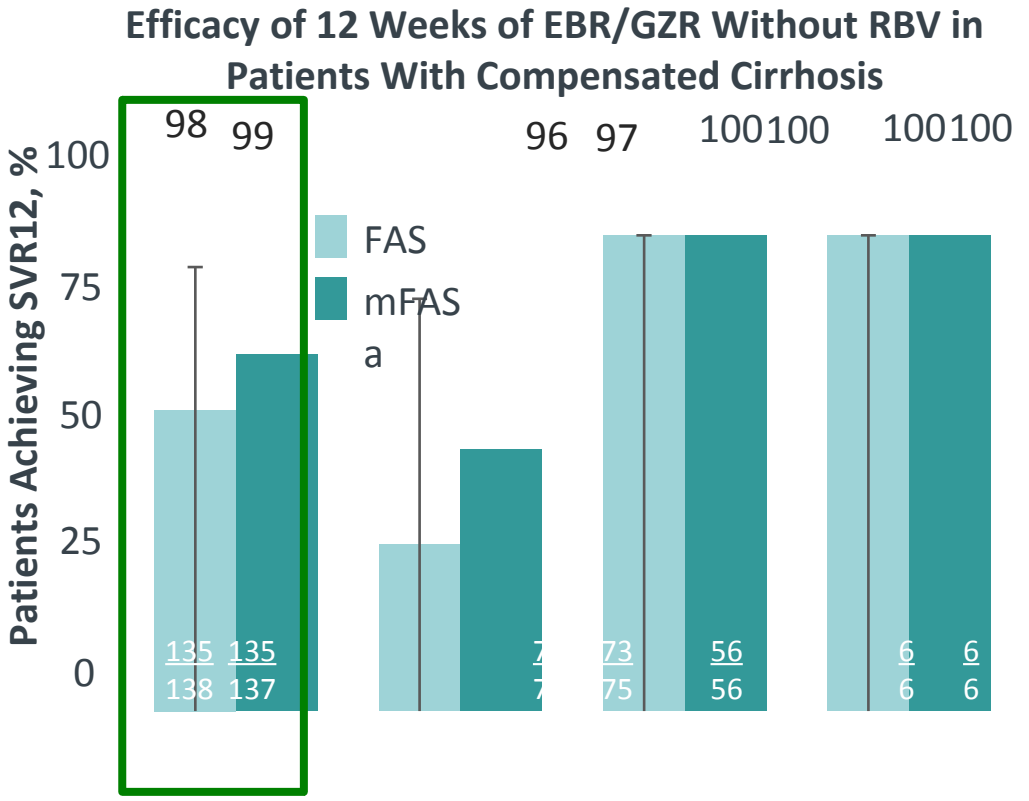

- High activity in vitro1–3
- Efficacious in GT1 & GT4 treatment-naive and treatment-experienced cirrhotic and noncirrhotic patients with HCV, and in HIV/HCV coinfected patients4–6
- All-oral, once-daily regimen

HCV = hepatitis C virus; HIV = human immunodeficiency virus.

**1.** Summa V et al. *Antimicrob Agents Chemother*. 2012:56;4161–4167. **2.** Coburn CA et al. *ChemMedChem*. 2013;8:1930–1940. **3.** Harper S et al. *ACS Med Chem Lett*. 2012;3:332–336. **4.** Zeuzem S et al. *Ann Intern Med*. 2015;163:1–13. **5.** Lawitz E et al. *Lancet*. 2015;385:1075–1086. **6.** Rockstroh JK et al. *Lancet HIV*. 2015;2:e319–e327.

# EBR/GZR in Treatment-Naive Patients With Cirrhosis

- Integrated analysis of patients with cirrhosis from 6 clinical trials in the Phase 2/3 clinical program
- Patient population
  - Treatment-naive
  - With or without HIV-1 coinfection



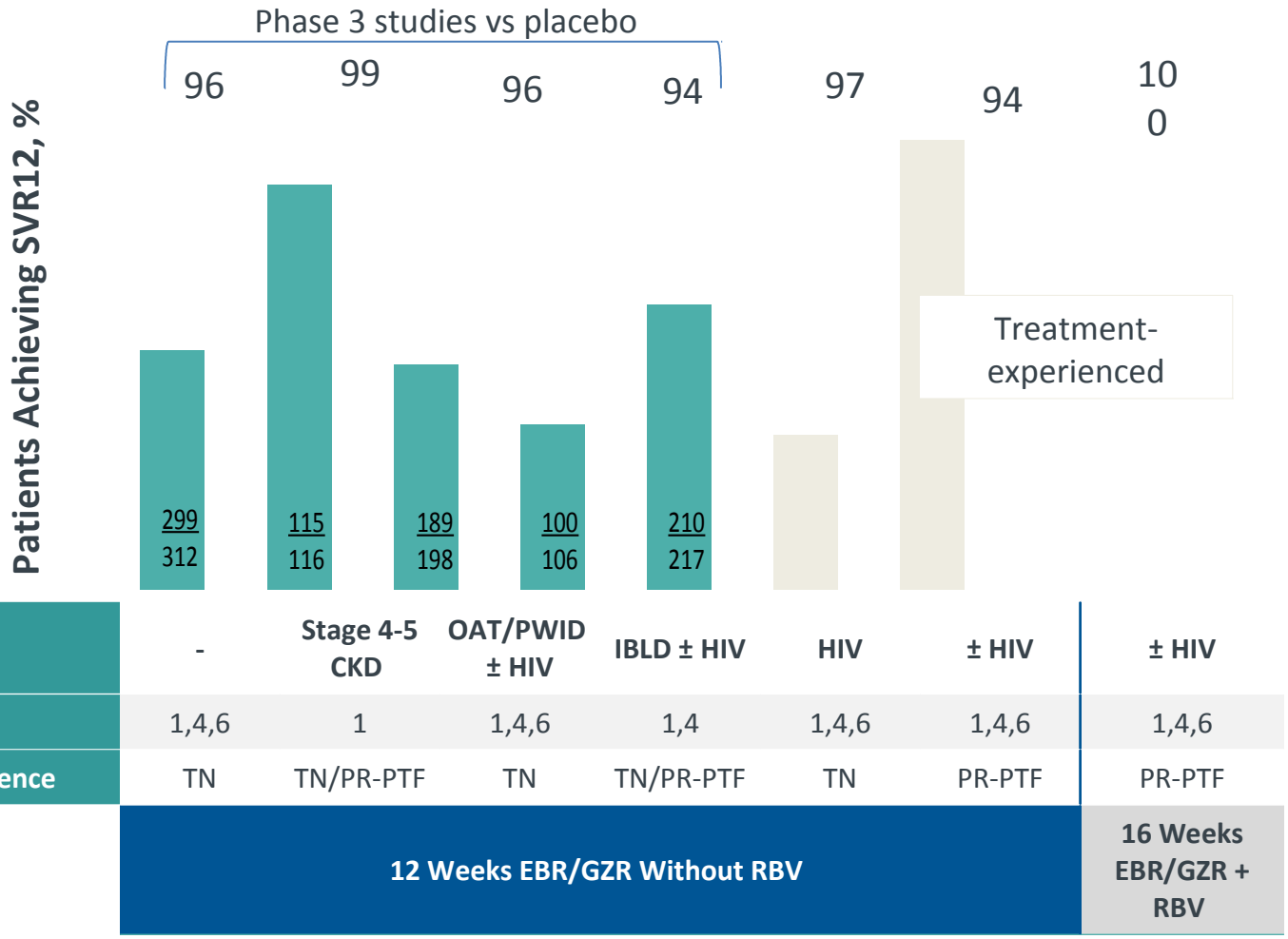

| | | | | |
|---|---|---|---|---|
| LTFU/early discontinuation | 1b | 1b | 0 | 0 |
| Breakthrough | 1 | 1 | 0 | 0 |
| Relapse | 1 | 1 | 0 | 0 |

a mFAS excludes patients who discontinued treatment for reasons unrelated to study medication.
bDeath (coronary artery disease).
EBR/GZR = elbasvir/grazoprevir; RBV = ribavirin; FAS = full analysis set; SVR12 = sustained virologic response 12 weeks after the cessation of treatment; GT = genotype; LTFU = lost to follow up; mFAS = modified full analysis set.

**1.** Jacobson I et al. AASLD 2015, Abstract 42.

# Elbasvir/Grazoprevir (Zepatier): Efficacy in Different Patient Populations

*Overall mFASa SVR12 rates from the Phase 3 clinical trial program*




| Comorbidity | - | Stage 4-5 CKD | OAT/PWID ± HIV | IBLD ± HIV | HIV | ± HIV | ± HIV |
|---|---|---|---|---|---|---|---|
| Genotypes | 1,4,6 | 1 | 1,4,6 | 1,4 | 1,4,6 | 1,4,6 | 1,4,6 |
| Treatment Experience | TN | TN/PR-PTF | TN | TN/PR-PTF | TN | PR-PTF | PR-PTF |
| | 12 Weeks EBR/GZR Without RBV | | | | | | 16 Weeks EBR/GZR + RBV |

amFAS excludes patients who failed for reasons unrelated to study medication.

EBR/GZR = elbasvir/grazoprevir; SVR12 = sustained virologic response 12 weeks after the cessation of treatment; CKD = chronic kidney disease; OAT = opioid agonist therapy; PWID = people who inject drugs; IBLD = inherited blood disorders; TN = treatment naive; HIV = human immunodeficiency virus; TE = treatment experienced; RBV = ribavirin; PR = peginterferon + ribavirin; PTF = prior-treatment failure; mFAS= modified full analysis set.

**1.** Roth D et al. *Lancet*. 2015;386:1537–1545. **2.** Dore GJ et al. EASL 2016, SAT-163. **3.** Hezode C et al. EASL 2016, SAT-128. **4.** Zeuzem S et al. *Ann intern Med*. 2015;163:1–13. **5.** Rockstroh JK et al. *Lancet HIV*. 2015;2:e319–e327. **6.** Kwo P et al. *Gastroenterology*. 2017;152:164–175.

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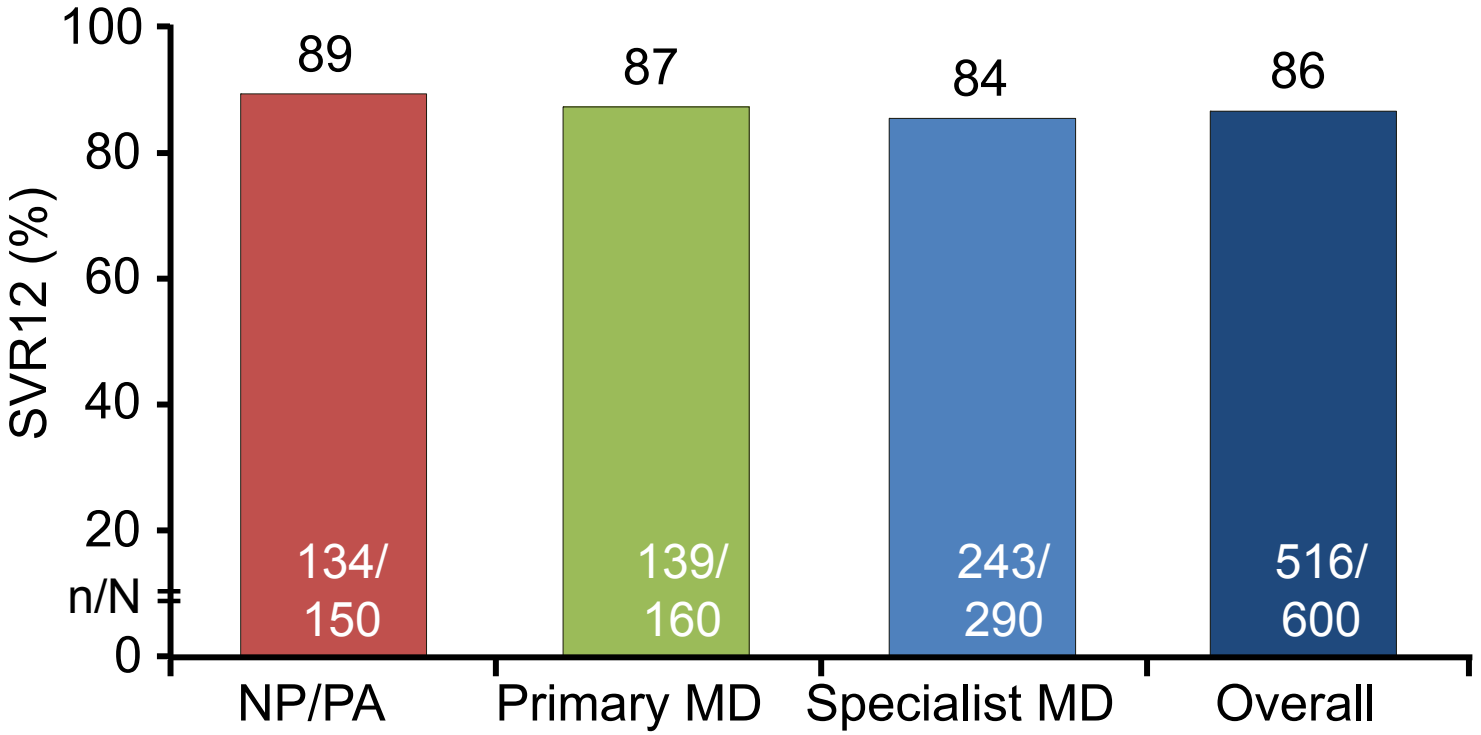
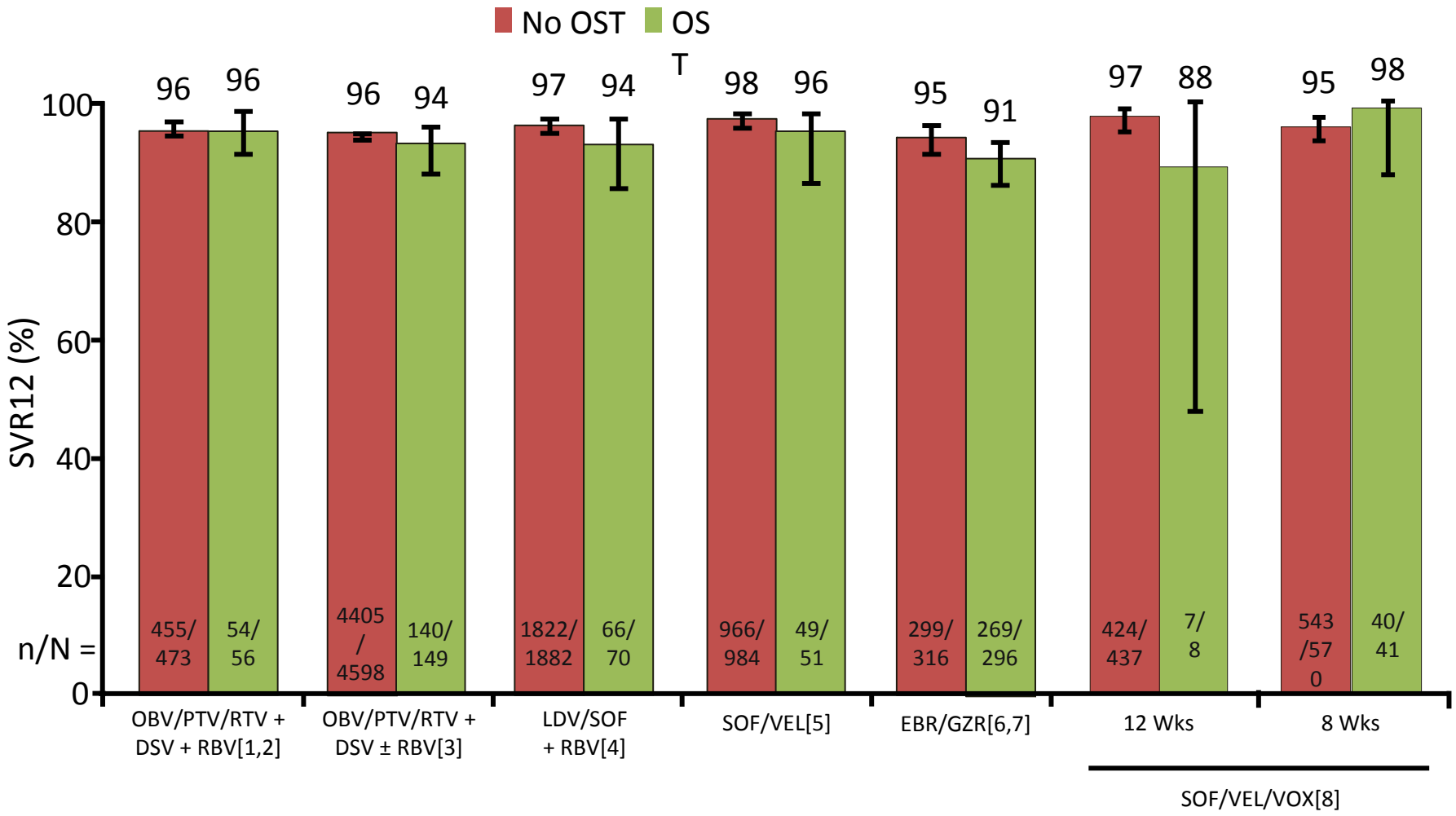
# ASCEND: Nonrandomized Phase IV Trial of HCV Treatment Outcomes by DAA Prescriber Type

- Pts (N = 600) from 13 urban, FQHCs in DC, all treated with LDV/SOF per FDA prescribing info; all providers given 3-hr **training** in AASLD/IDSA HCV guidance




Kattakuzhy S, et al. Ann Intern Med. 2017;167:311-318.

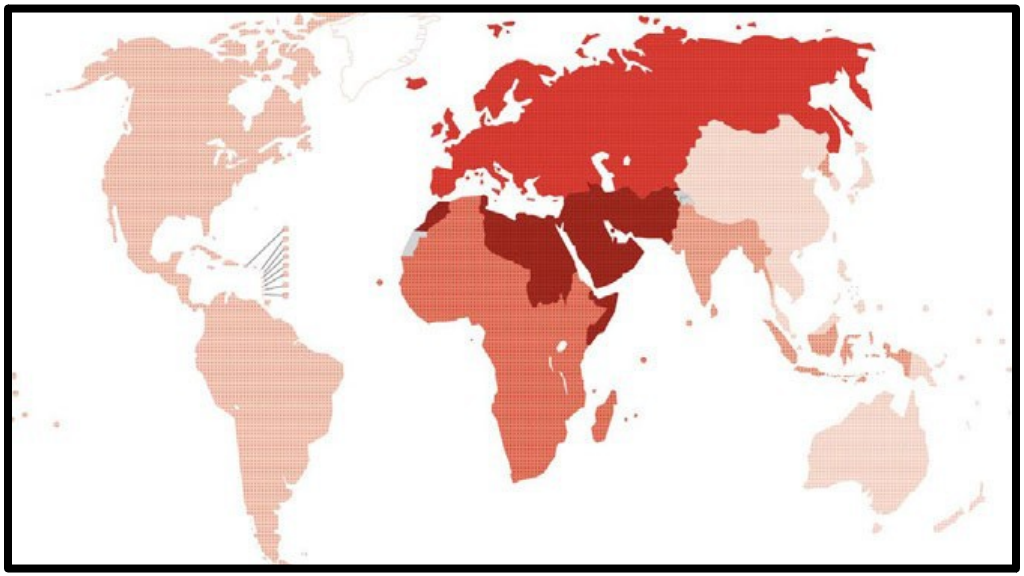
# IFN-Free DAA Therapy: Opioid Substitution Therapy vs No Opioid Substitution Therapy

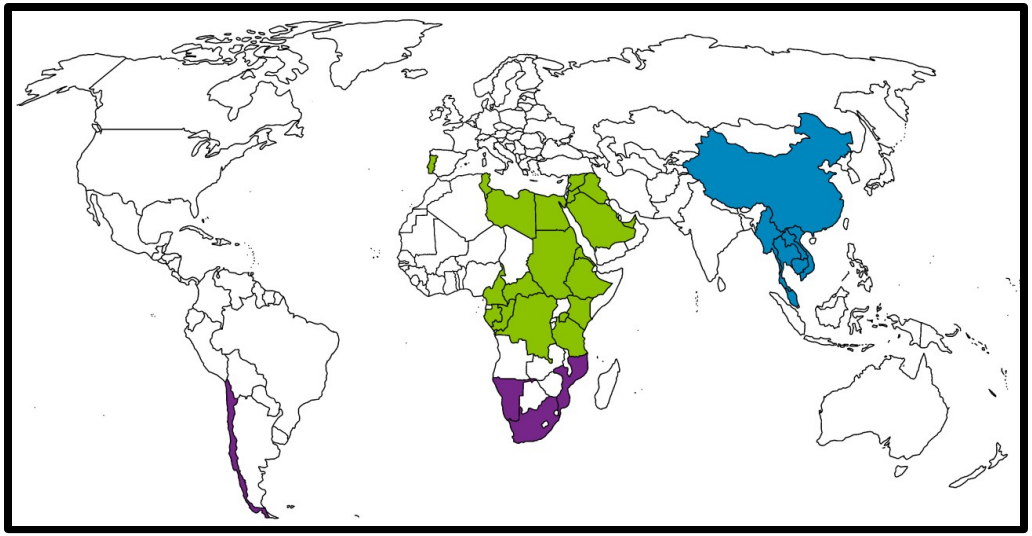




1. Feld JJ, et al. N Engl J Med. 2014;370:1594-1603.; 2. Puoti M, et al. AASLD 2014. Abstract 1938.
3. Grebely J, et al. EASL 2017. Abstract FRI-236.; 4. Grebely J, et al. Clin Infect Dis. 2016;63:1405-1411.
5. Grebely J, et al. Clin Infect Dis. 2016;63:1479-1481.; 6. Zeuzem S, et al. Ann Intern Med. 2015;163:1-13.
7. Dore GJ, et al. Ann Intern Med. 2016;165:625-634.; 8. Grebely J, et al. EASL 2017. Abstract FRI-235.

# The need to cure of all HCV infected Patients, No patient left behind





**Incidence rate (per 100 000)**

| WHO region | Map key | Best estimate |
|---|---|---|
| Africa | | 31,0 |
| America | | 6,4 |
| Middle East | | 62,5 |
| Europa | | 61,8 |
| South Est Asia | | 14,8 |
| West Pacific | | 6,0 |
| Total | | 23,7 |

*Hutin J-F, Suisse, WHO, EASL 2017*

GT4

GT5

GT6

Asselah et al. Eliminating Hepatitis C within Low Income Countries – the need to cure Genotypes 4, 5, 6. Journalof Hepatology, 2018 in press

# How to achieve HCV elimination

**PREVENTION**

- Harm reduction
- Infection control
- Blood safety

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*Asselah et al. Liver Int* 2018, in press.