HCV therapy : Clinical case

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Disclosures

- Professor Asselah is an employee of AP-HP (Beaujon's Hospital) and University of Paris

- Principal investigator for research grants

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  - Professor Asselah is a consultant, expert and speaker for: Abbvie, Bristol-Myers Squibb, Gilead, Janssen, Merck Sharp Dohme, Roche.

  - Professor Asselah has received grants from : ANR, CNRS , APHP, INSERM , University of Paris, ANRS

First Clinical Case : Patient with HCV Genotype 4 infection

- French Male, 48 years old
- Adressed by GP in July 2015 for HCV genotype 4 infection

Past History

- Former drug user in the 80's (PWID), stopped in 1989
- Treatment with IFN declined by the patient (affraid of side effects)
- Lost to follow-up up

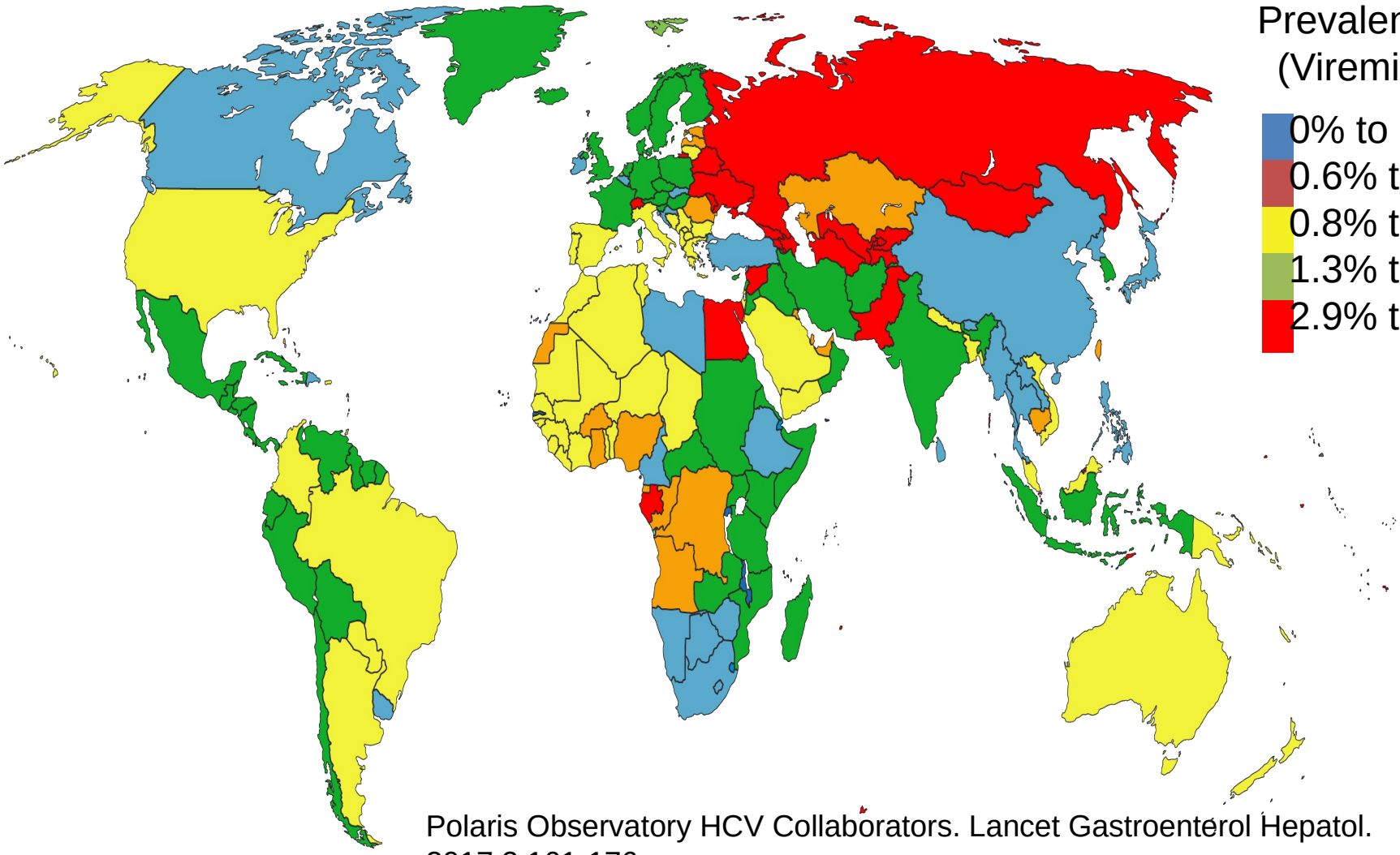
Habitus

- Moderate alcohol cunsomption (40 g/d)
- Tobacco cunsomption : 30 p/y
- Weight 85 Kg; height 178 cm

Physical examination no signs of liver disease

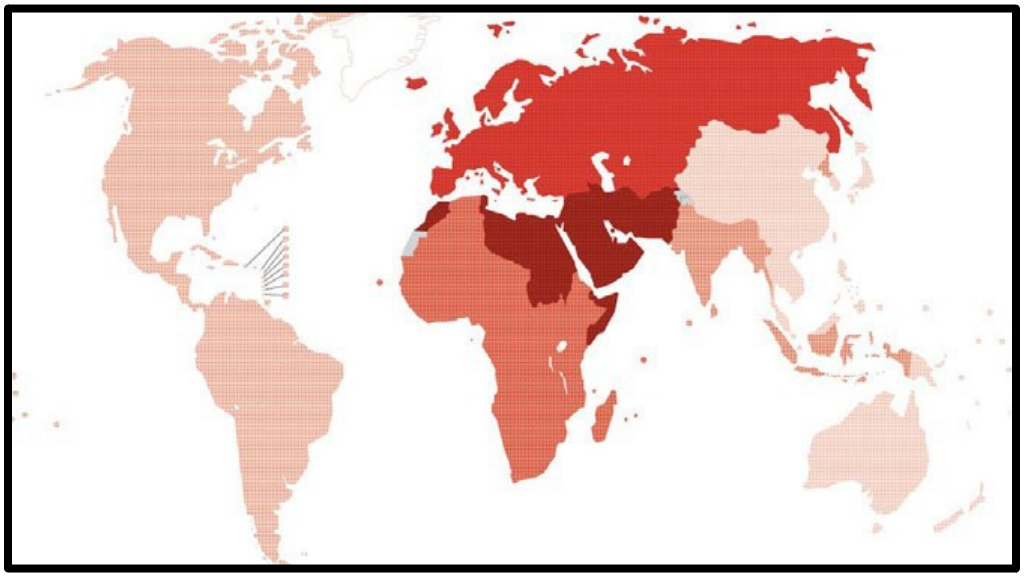
Q1 - What is the number of Persons Living With HCV worldwide (estimation) with genotype distribution ?

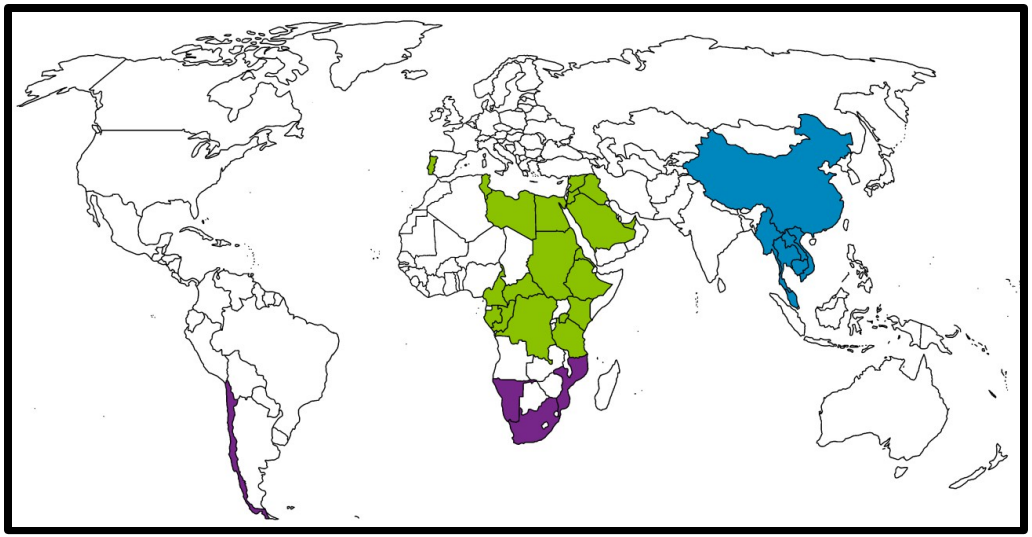
Estimated 70 Million Persons Living With HCV



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

Epidemiology





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

First Clinical Case : Patient with HCV Genotype 4 infection

Laboratory analysis

- AST: 60 (ULN 40 IU/L)
- ALT: 75 (ULN 40 IU/L)
- Gamma GT: 150 (ULN 50 IU/L)
- Alkaline phosphatase: 140 (ULN 130 IU/L)
- Total Bilirubin: 15 (<17 µmol/L)
- Prothrombin Time: 100 %
- Factor V 100 %
- Platelet count: 250 000 /mm3

Virology

- HCV Genotype 4
- HCV RNA 450 000 IU/ml
- HBS-Ag and HIV negative

First Clinical Case : Patient with HCV Genotype 4 infection

- FibroScan: 6.0 kPa
- APRI : 0.6

Q2 – How do you interpret these fibrosis tests?

Q3 - What do you recommend for this patient ?

Q3 - What do you recommend for this patient ?

A – Stop alcohol prior to start HCV therapy

B – Stop alcohol and start HCV therapy

C – Stop tobacco

D – Diet and exercise for overweight

E – Look for concomittant treatment for DDI

Q4 - What do you expect from HCV cure ?

Q4 - What do you expect from HCV cure ?

- Improving survival
- Decreasing the incidence of cirrhosis
- Decreasing hepatocellular carcinoma
- Improving overall quality of life

Treatment recommendations for GT 4 treatment-naïve and treatment-experienced patients without and with compensated cirrhosis

Treatment recommendations for GT 4 patients without cirrhosis							
		LDV/SOF	**SOF/VEL**	**OMV/PTV/ RTV**	**GRZ/EBV**	**SOF + DCV**	**SOF + SMV**
GT 4	**TN**	12 weeks	12 weeks	+ RBV 12 weeks	12 weeks	12 weeks	12 weeks
	TE	+ RBV 12 weeks 24 weeks	12 weeks	+ RBV 12 weeks	12 weeks, if HCV RNA ≤800,000 (5.9 log) IU/mL or + R BV 16 weeks, if HCV RNA >800,000 (5.9 log) IU/mL	+ RBV 12 weeks 24 weeks	+ RBV 12 weeks 24 weeks

SOF + DCV + RBV for 12 weeks and SOF + DCV for 24 weeks are not approved in the EU for non-cirrhotic GT 4 patients; SOF + DCV for 12 weeks is not approved in the EU for cirrhotic GT 4 patients. Regimens not included in the SmPC posology table (Table 1) are shown in grey.

DCV: daclatasvir; EBV: elbasvir; GRZ: grazoprevir; LDV: ledipasvir; OMV: ombitasvir; PTV: paritaprevir; RTV: ritonavir; SMV: simeprevir; SOF: sofosbuvir; TE: treatment-experienced; TN: treatment-naïve; VEL: velpatasvir

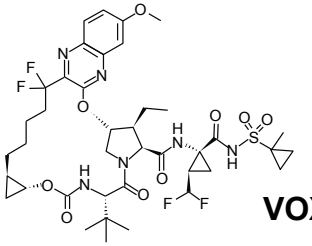
EASL. J Hepatol 2017; 66:153–194

Q5 - What are the data with the recently approved DAAs ?

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

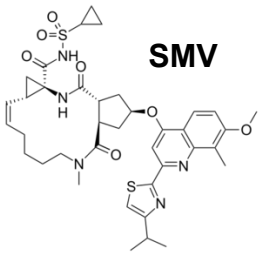
SOF + DCV
± RBV
12–24
weeks

OMV/PTV/RTV

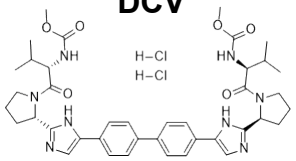
± DSV ± RBV
12–24 weeks

GRZ/EBV
± RBV
12–16
weeks

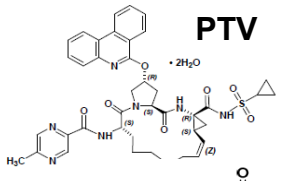
GLE/PIB
8–12 weeks



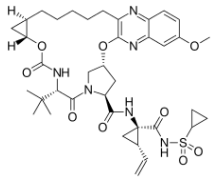
SMV



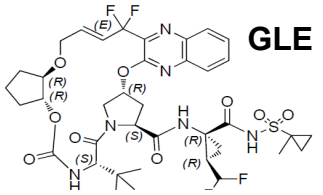
DCV



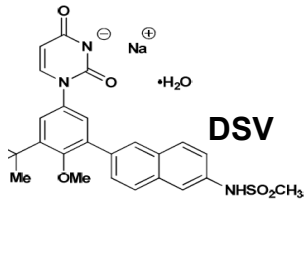
PTV



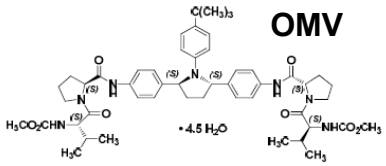
GRZ



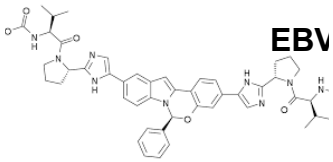
GLE



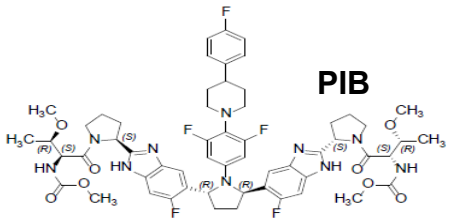
DSV



OMV



EBV



PIB

Asselah, Marcellin & Schinazi. Liver Int 2018, in

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

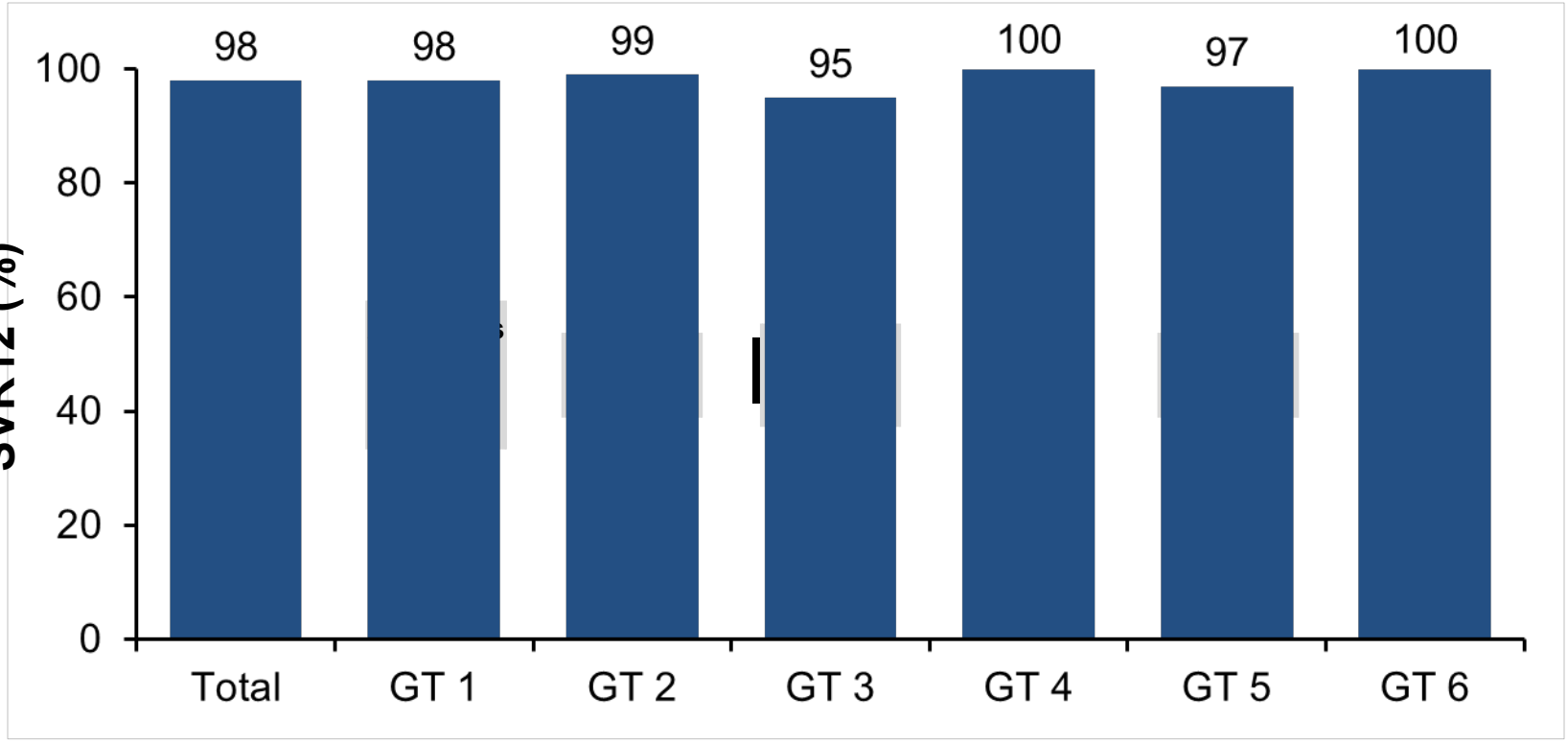
- **Velpatasvir (VEL; GS-5816)3-5**
  - Picomolar potency against GT 1–6
  - 2nd-generation inhibitor with improved resistance profile

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.

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

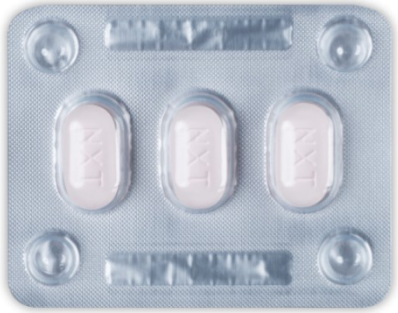
AE: adverse event; D/C: discontinuation; LTFU: lost to follow-up; SAE: serious adverse event

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

Glecaprevir/Pibrentasvir (Mavyret®)

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:

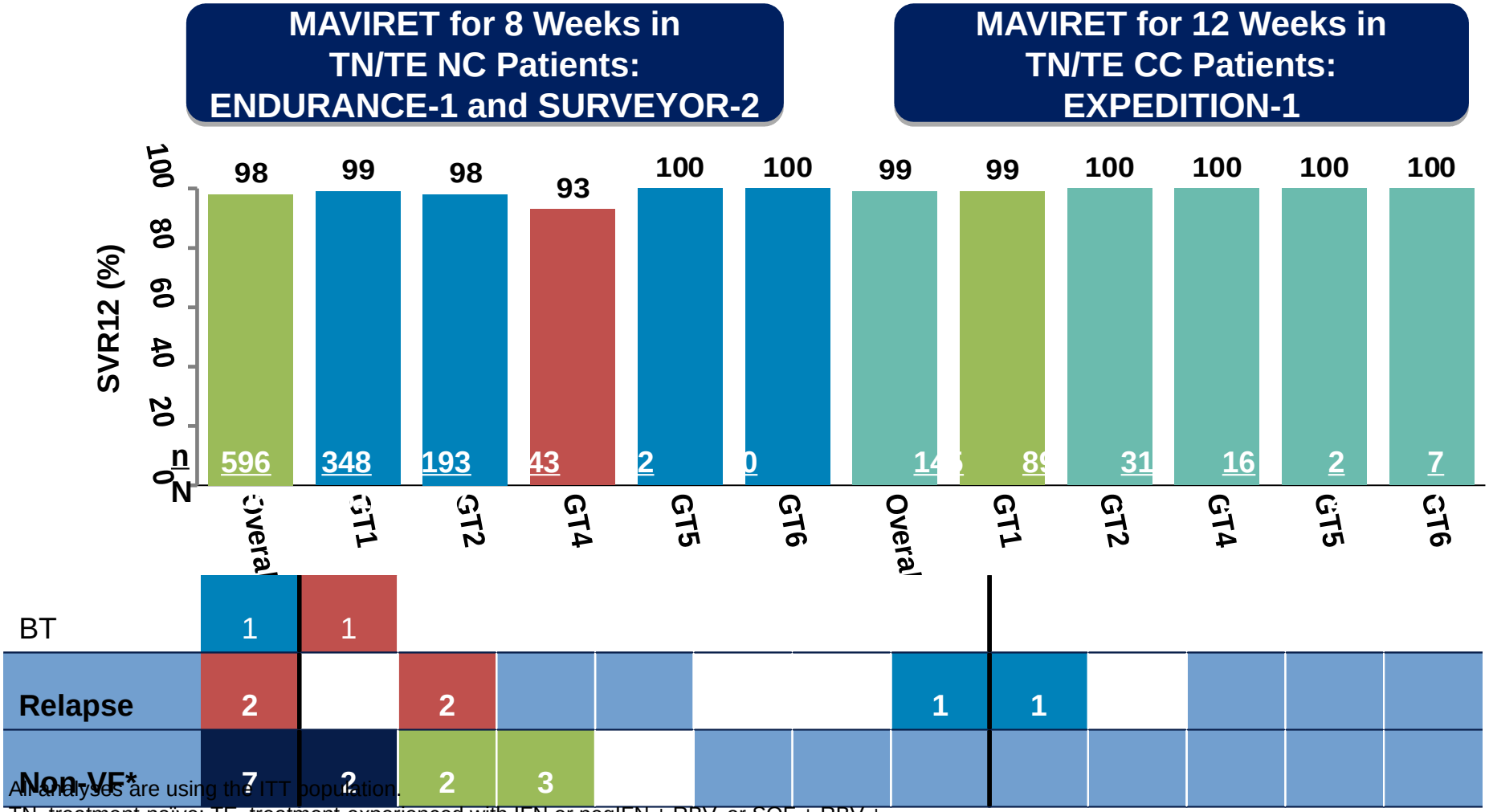
- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

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.

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



All analyses are using the ITT population.
TN, treatment-naive; 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

Where are we in 2017 ?

- Need to increase screening
  - Universal access (linkage to care)
  - Efforts for PWID population
  - Achieve HCV elimination