HCV treatment: the use of the new pangenotypic drugs in special populations

Stanislas Pol, MD, PhD

Liver Department, Hôpital Cochin
Inserm U-1223, Institut Pasteur
Université Paris Descartes, Paris, France

stanislas.pol@aphp.fr

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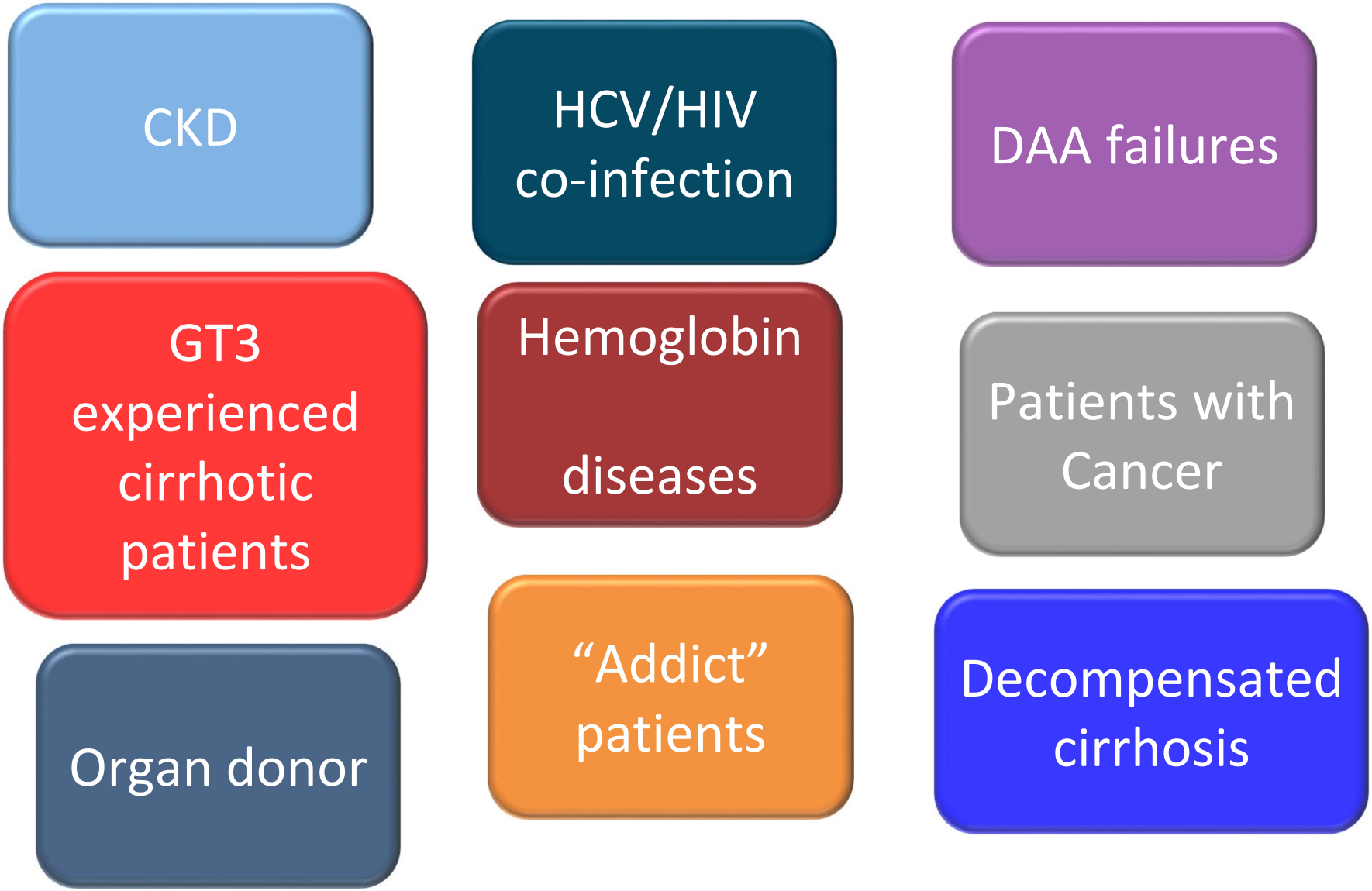
Disclosures

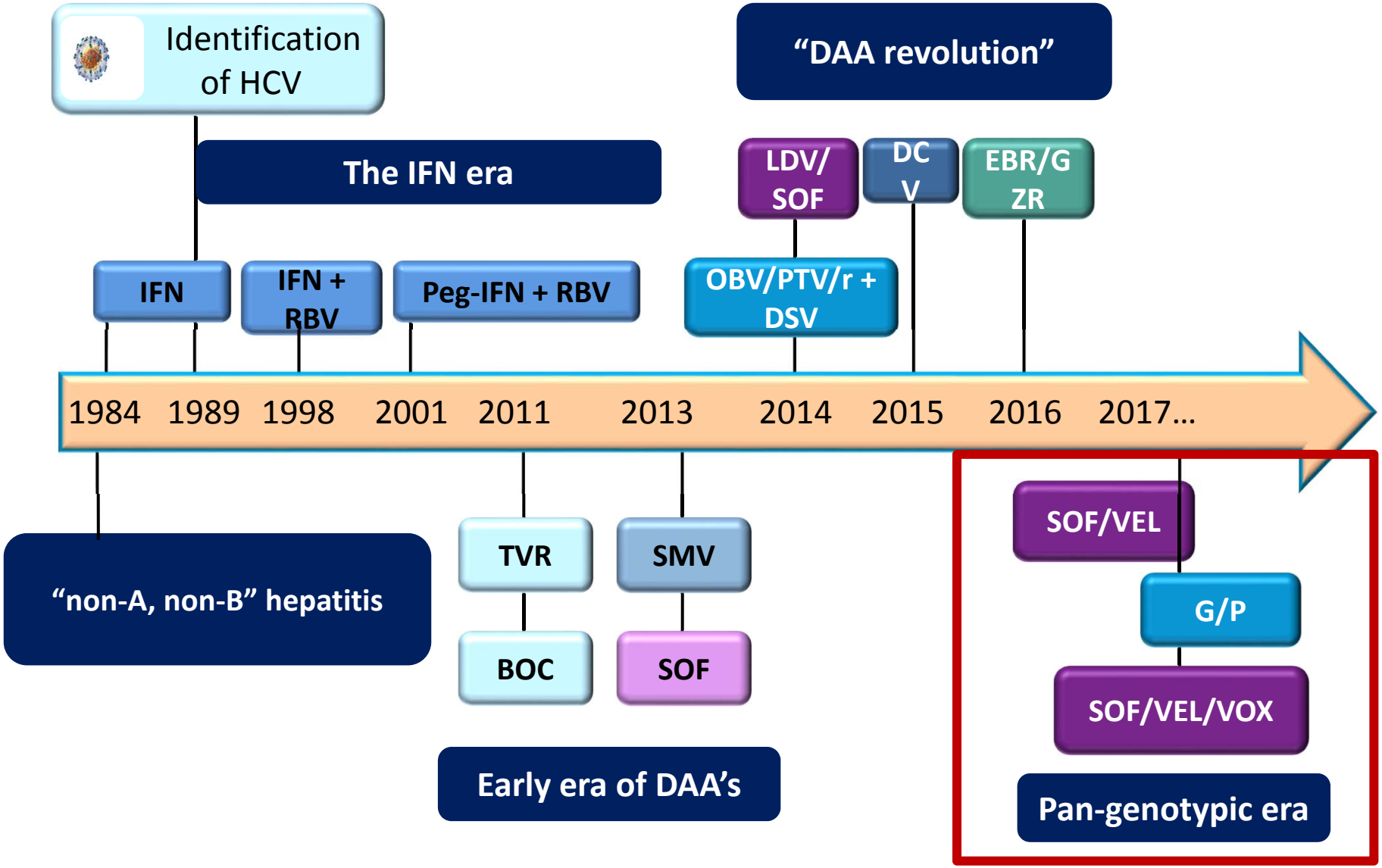
Speaker or **Board member** : BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Abbvie

Grants : BMS, Gilead, Roche, MSD

“Special Populations” in the Pan-genotypic Era

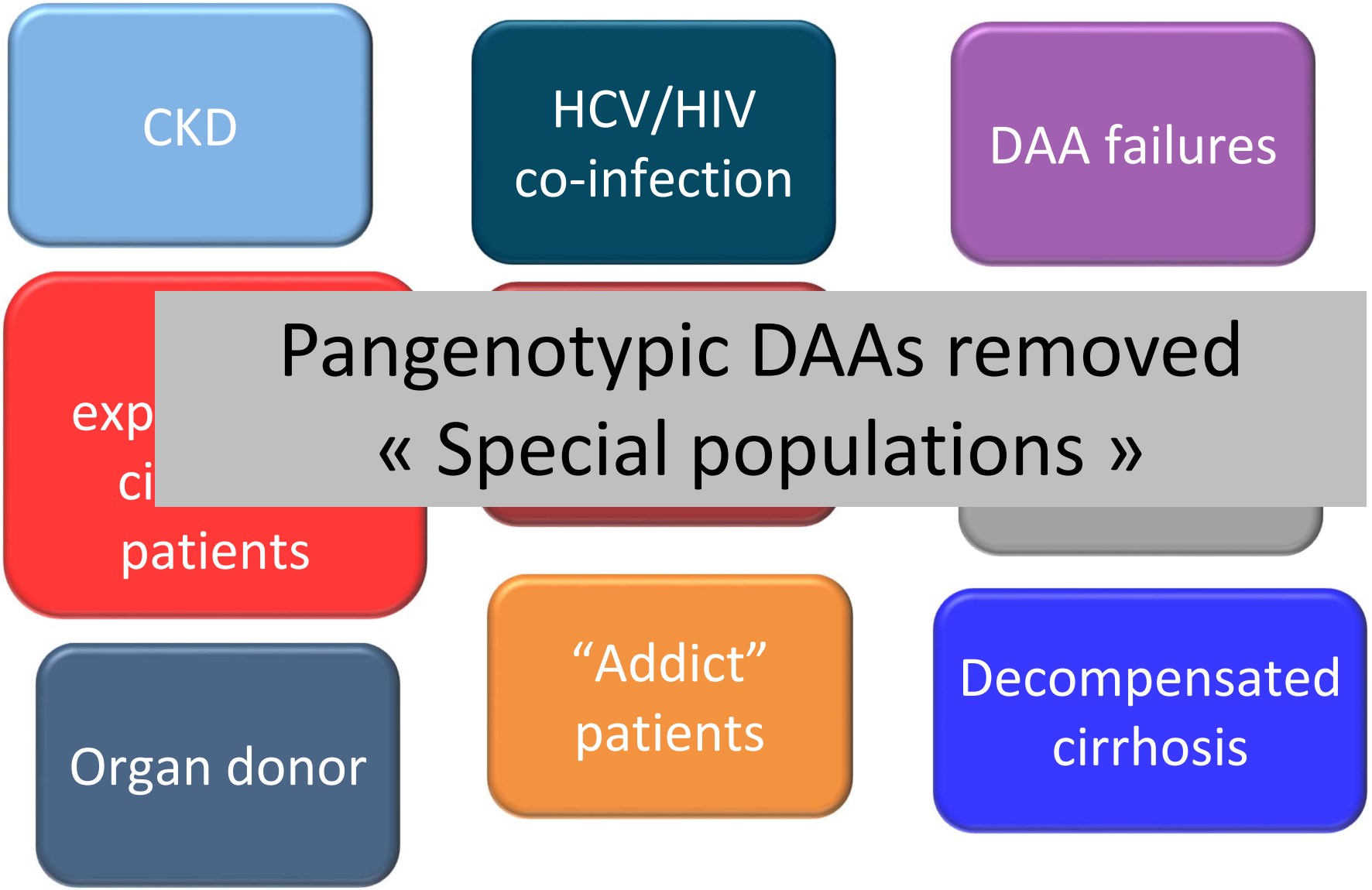


Progress in HCV treatments



Pawlotsky JM, et al. J Hepatol 2016; Pol S et al. Nat Rev Nephrology 2019

“Special Populations” in the Pan-genotypic Era



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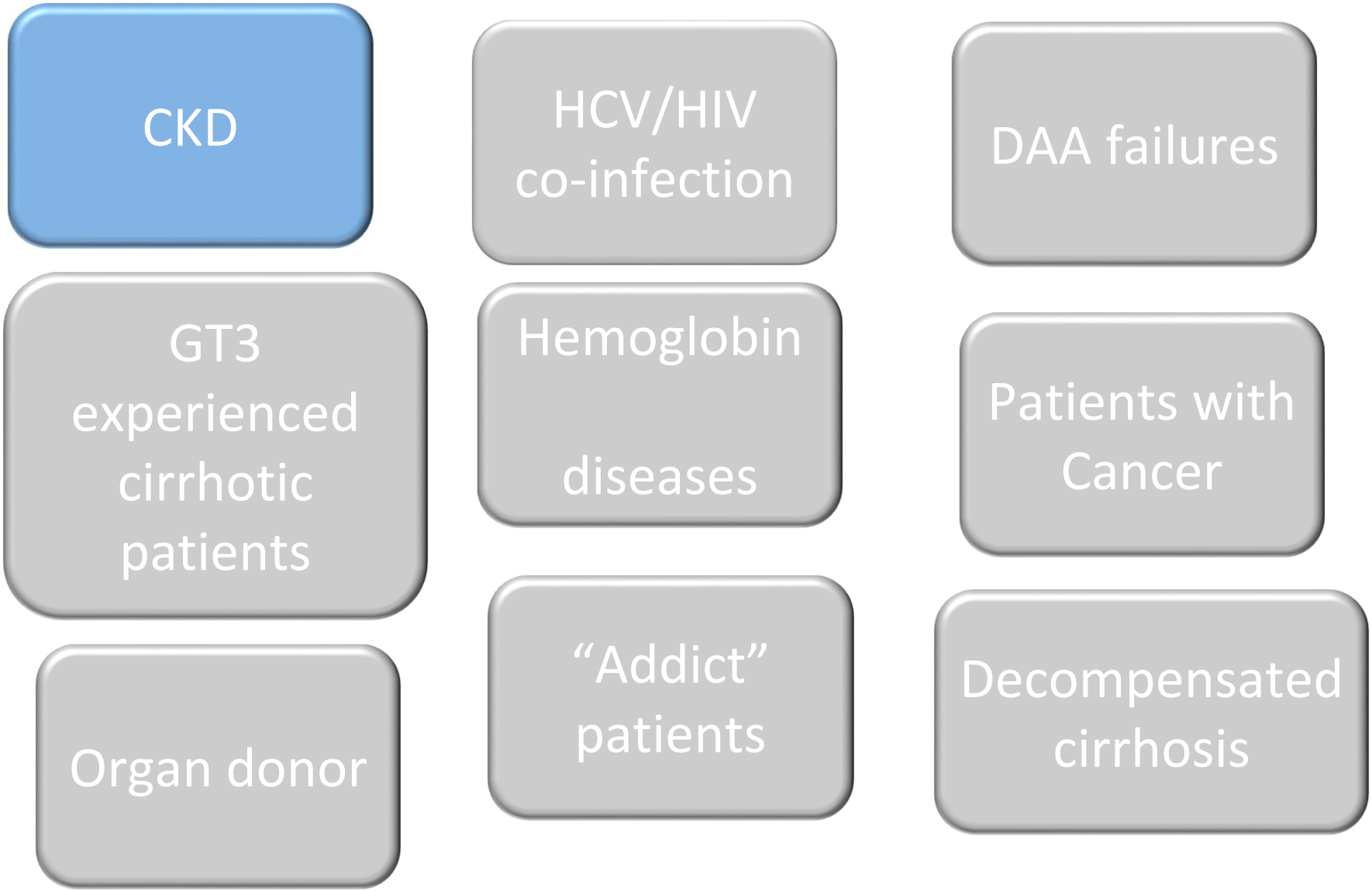
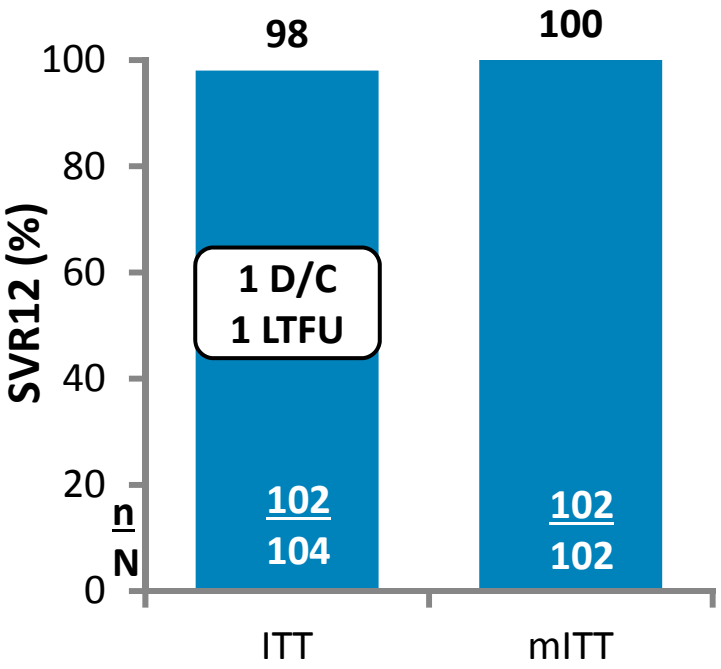


High SVR12 rates with 12 weeks G/P in GT1–6 patients with CKD4-5

Single-arm, open-label study to evaluate the efficacy and safety of G/P in patients with HCV GT1–6 infection and renal impairment

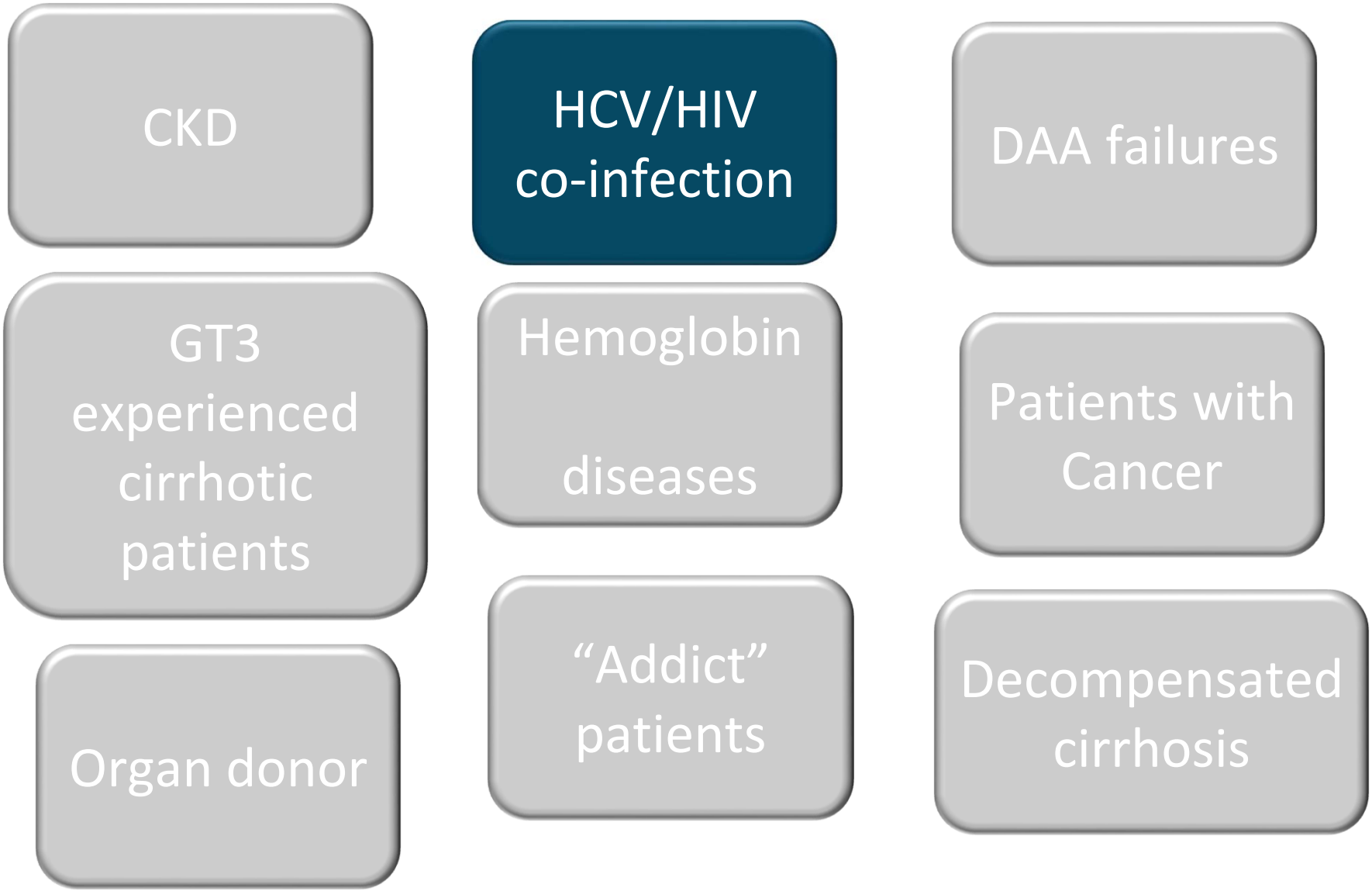
Characteristic, n (%)	G/P N = 104
HCV genotype	
1a / 1b / other	23 (22) / 29 (28) / 2 (2)
2	17 (16)
3	11 (11)
4 / 5 / 6	20 (19) / 1 (1) / 1 (1)
Prior treatment history	
Naive	60 (58)
IFN/pegIFN ± RBV	42 (40)
SOF + RBV ± pegIFN	2 (2)
Compensated cirrhosis	
Yes	20 (19)
No	84 (81)
CKD stage	
Stage 4	13 (12)
Stage 5	91 (88)
Hemodialysis	85 (82)



- CKD, chronic kidney disease; D/C, discontinued; LTFU, lost to follow up; ITT, intent-to-treat; mITT, modified ITT (excludes patients who did not achieve SVR12 for non-virologic reasons).

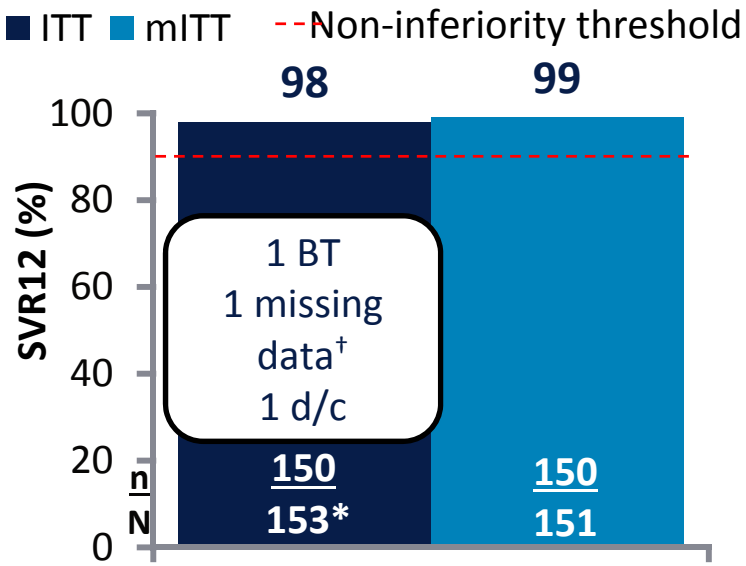
Gane EJ, et al. NEJM 2017

“Special Populations” in the Pan-genotypic Era



G/P in GT1–6 HIV/HCV co-infected patients: EXPEDITION-2

Phase 3, multicenter study evaluating G/P treatment in HCV/HIV-1 co-infected patients for 8 weeks (non-cirrhotic) or 12 weeks (cirrhotic)



ARV use at baseline:

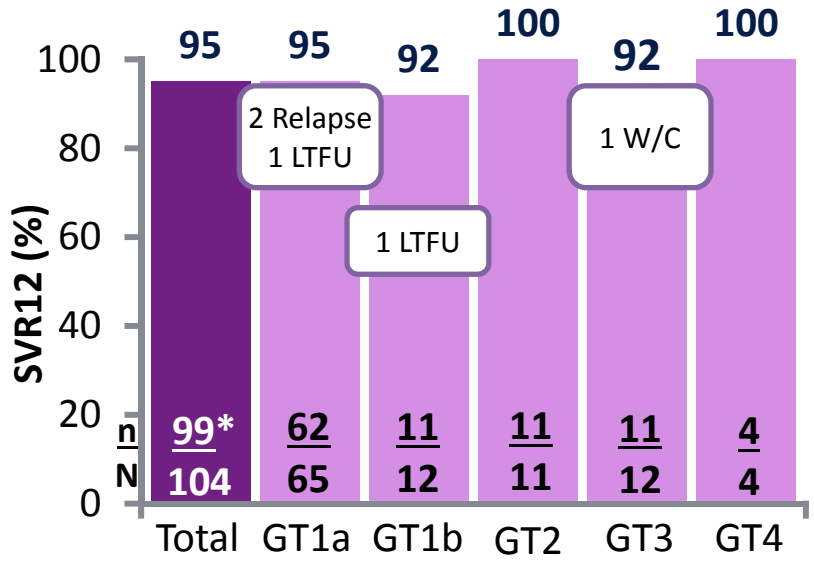
- PI (DRV, LPV/r) 0%
- NNRTI (RPV) 21%
- Integrase inhibitor (RAL, EVG/COBI or DTG) 74%
- NRTI (TDF/ TAF) 61%; (ABC) 39%

Safety, n (%)	Without Cirrhosis 8 Weeks N = 137	With Cirrhosis 12 Weeks N = 16
DAA-related SAE	0	0
AE leading to d/c	0	1 (6)‡
AEs occurring in ≥5% of patients Fatigue Nausea Headache Nasopharyngitis	18 (13) 12 (9) 12 (9) 12 (9)	0 1 (6) 0 0
ALT, grade ≥3 (>5 x ULN)	0	0
AST, grade ≥3 (>5 x ULN)	0	0
Total bilirubin, grade ≥3 (>3 x ULN)	1 (0.7)	0

Rockstroh J, et al. J Hepatol 2017; **66**(Suppl 1)**:** S102–103.

SOF/VEL for 12 Weeks in Patients Coinfected with HCV and HIV-1: The ASTRAL-5 Study

Phase 3, open-label, single-arm study in HCV/HIV co-infected patients with HCV GT1–4



ARV use at baseline:

- PI (DRV, LPV or ATV) 50%
- NNRTI (RPV) 13%
- Integrase inhibitor (RAL or EVG) 36%
- Other (>1 of the above classes) 7%

D/C, discontinuation; LTFU, lost to follow-up; W/C, withdrew consent.
* n = 2 patients pending SVR12 visit, both achieved SVR4;
† Acute radial nerve palsy and left toe infection/sepsis/UTI.

Wyles D, et al. J Hepatol 2016; **64**(Suppl 2)**:** S188–189 (PS104).

“Special Populations” in the Pan-genotypic Era

CKD

HCV/HIV co-infection

DAA failures

GT3 experienced cirrhotic patients

Hemoglobin diseases

Patients with Cancer

Organ donor

“Addict” patients

Decompensated cirrhosis

DAAs failures are rare

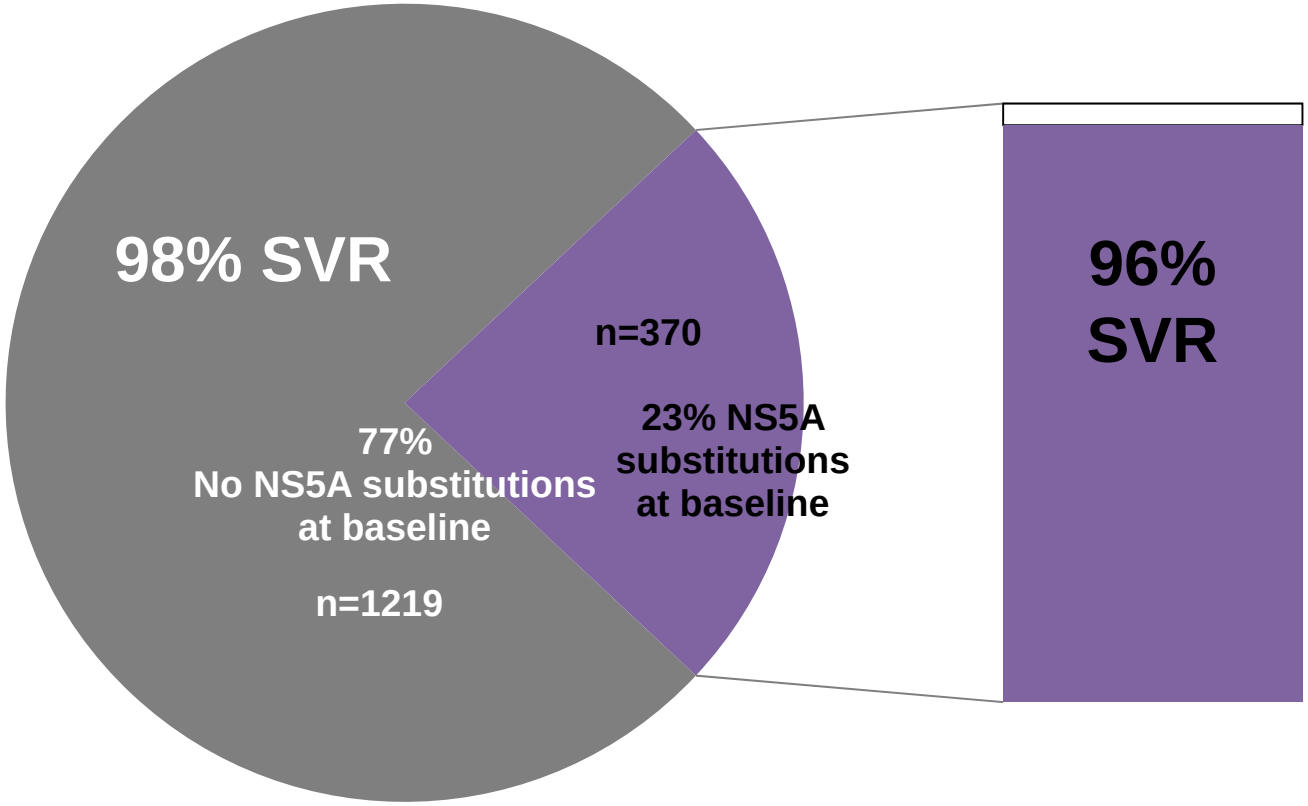
Summary of Phase 3 studies of IFN-free therapy in GT1 patients published in the New England Journal of Medicine in 2014*

Trial	Regimen
ION-1	LDV/SOF ± RBV
ION-2	LDV/SOF ± RBV
ION-3	LDV/SOF ± RBV
SAPPHIRE-I	OMV/PTV/RTV + DSV + RBV
SAPPHIRE-II	OMV/PTV/RTV + DSV + RBV
PEARL-III	OMV/PTV/RTV + DSV + RBV
PEARL-IV	OMV/PTV/RTV + DSV + RBV
TURQUOISE-II	OMV/PTV/RTV + DSV + RBV

*Included treatment-naïve and -experienced patients +/- cirrhosis;
LDV/SOF + RBV for 12 weeks is not approved for use in HCV by the EMA

Liang J, Ghany MG. N Engl J Med 2014;370:2043–7

Moderate impact of NS5A mutations on SVR (ION-1, ION-2, ION-3 studies)

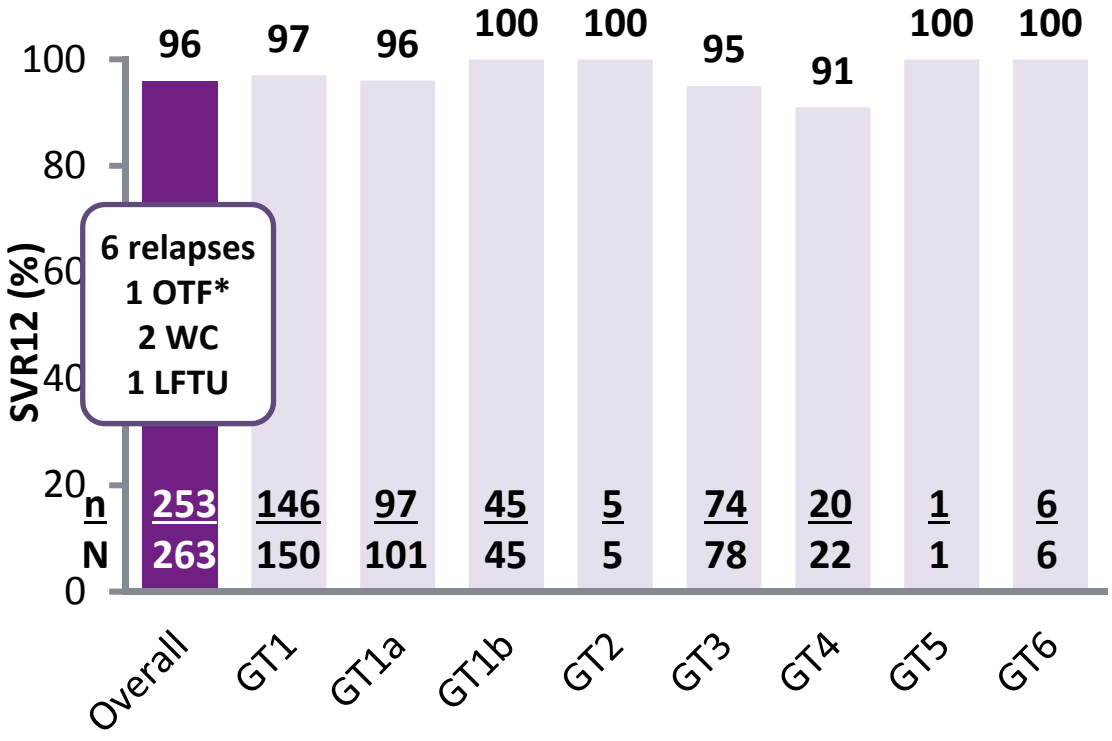


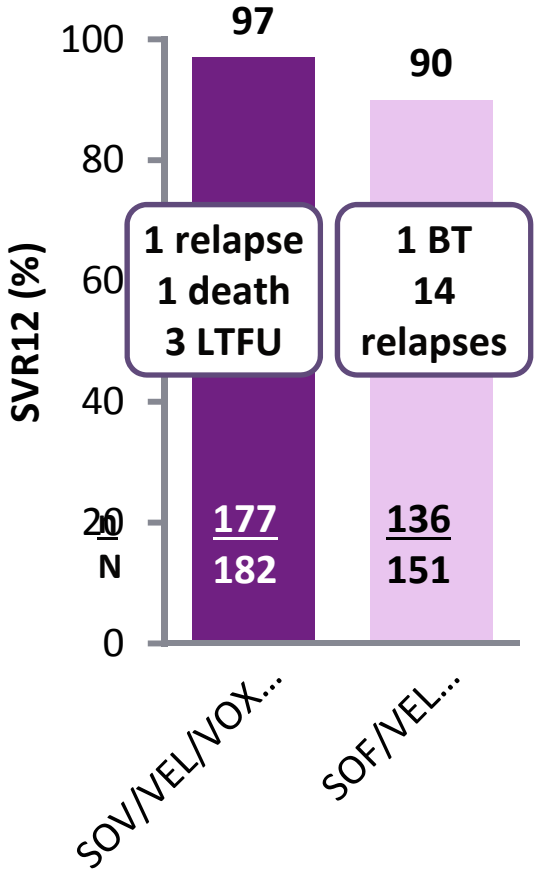
Gilead Sciences, Inc. Harvoni (ledipasvir/sofosbuvir), US PI, October 2014; Data on file.
Gilead Sciences, Inc; Gilead Sciences Europe Ltd; Harvoni (ledipasvir/sofosbuvir), SmPC, July 2015.

SOF/VEL/VOX or SOF/VEL in DAA-experienced patients with GT1–6 HCV infection: POLARIS1&4

POLARIS-1
SOF/VEL/VOX for 12 weeks in NS5A inhibitor-experienced
HCV GT1–6-infected patients

POLARIS-4
SOF/VEL/VOX or SOF/VEL for 12 weeks in DAA-experienced (non-NS5A) HCV GT1–6-infected patients



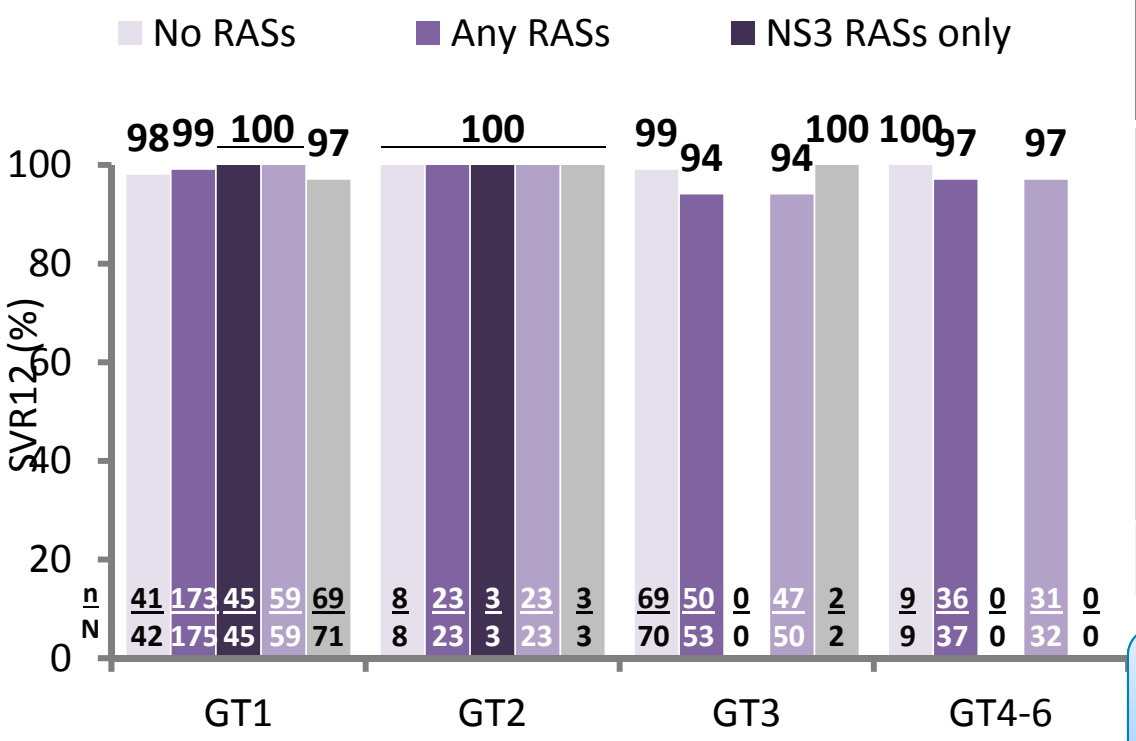


LTFU, lost to follow up; BT, Breakthrough; OTF, On-treatment failure; WC, Withdrew consent.
*Exposure was consistent with non-adherence.

Bourlière M, et al. NEJM 2017

Impact of RAS on the efficacy of SOF/VEL/VOX for 12 Weeks in DAA-experienced patients

Integrated resistance analysis of baseline* and treatment-emergent NS3, NS5A and NS5B RASs in DAA-experienced HCV GT1–6 patients treated with SOF/VEL/VOX for 12 weeks in the POLARIS-1 (NS5A inhibitor-experienced) and -4 (DAA-experienced) studies



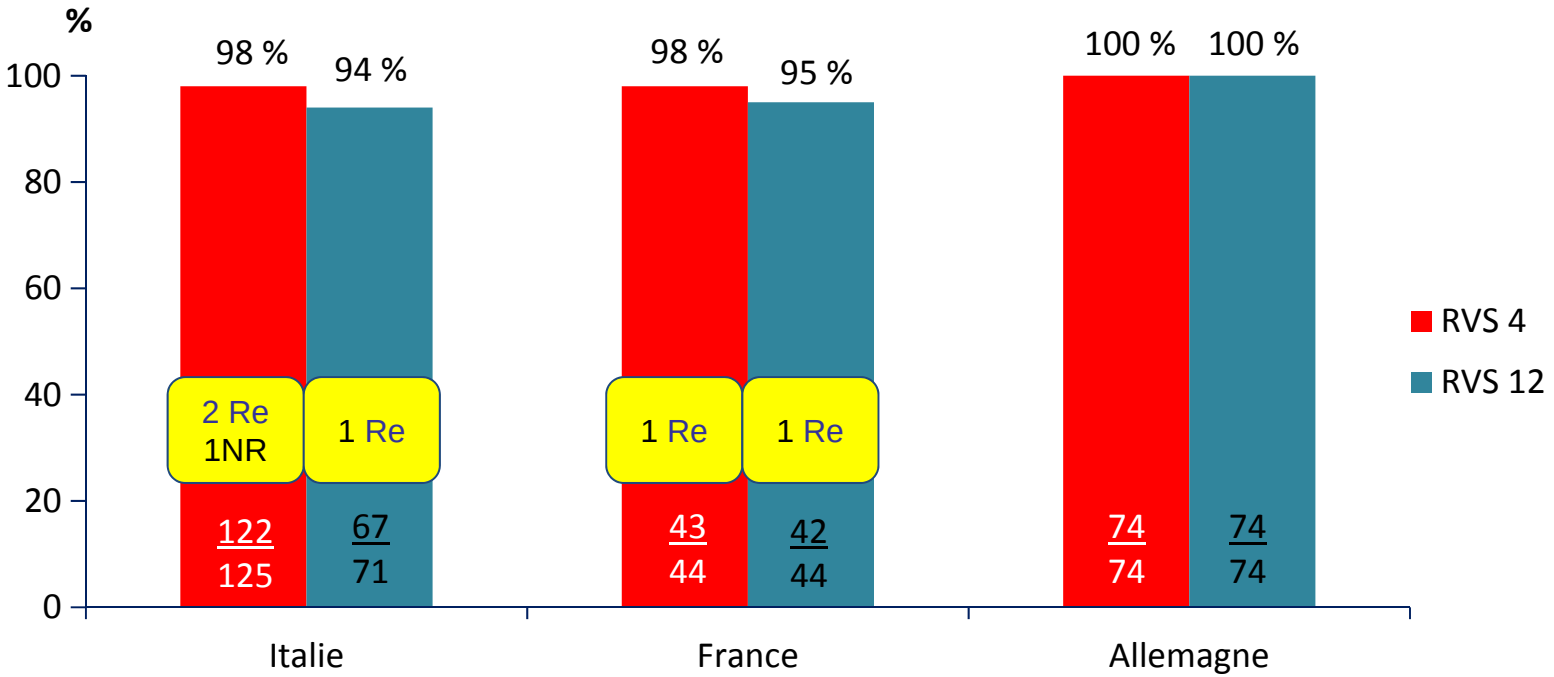
Study	HCV GT of patients who relapsed
POLARIS-1	1a 3a 3a 3a 3a 4d
POLARIS-4	1a

Of the 7 patients who relapsed, 1 (GT4d) had treatment-emergent NS5A Y93H RAS

RASs, resistance associated substitutions.
* 15% cut-off.

Sarrazin C, et al. J Hepatol 2017; **66** (Suppl 1):S299)

SOF/VEL/VOX in DAA-experienced patients with GT1–4 HCV infection: real world data



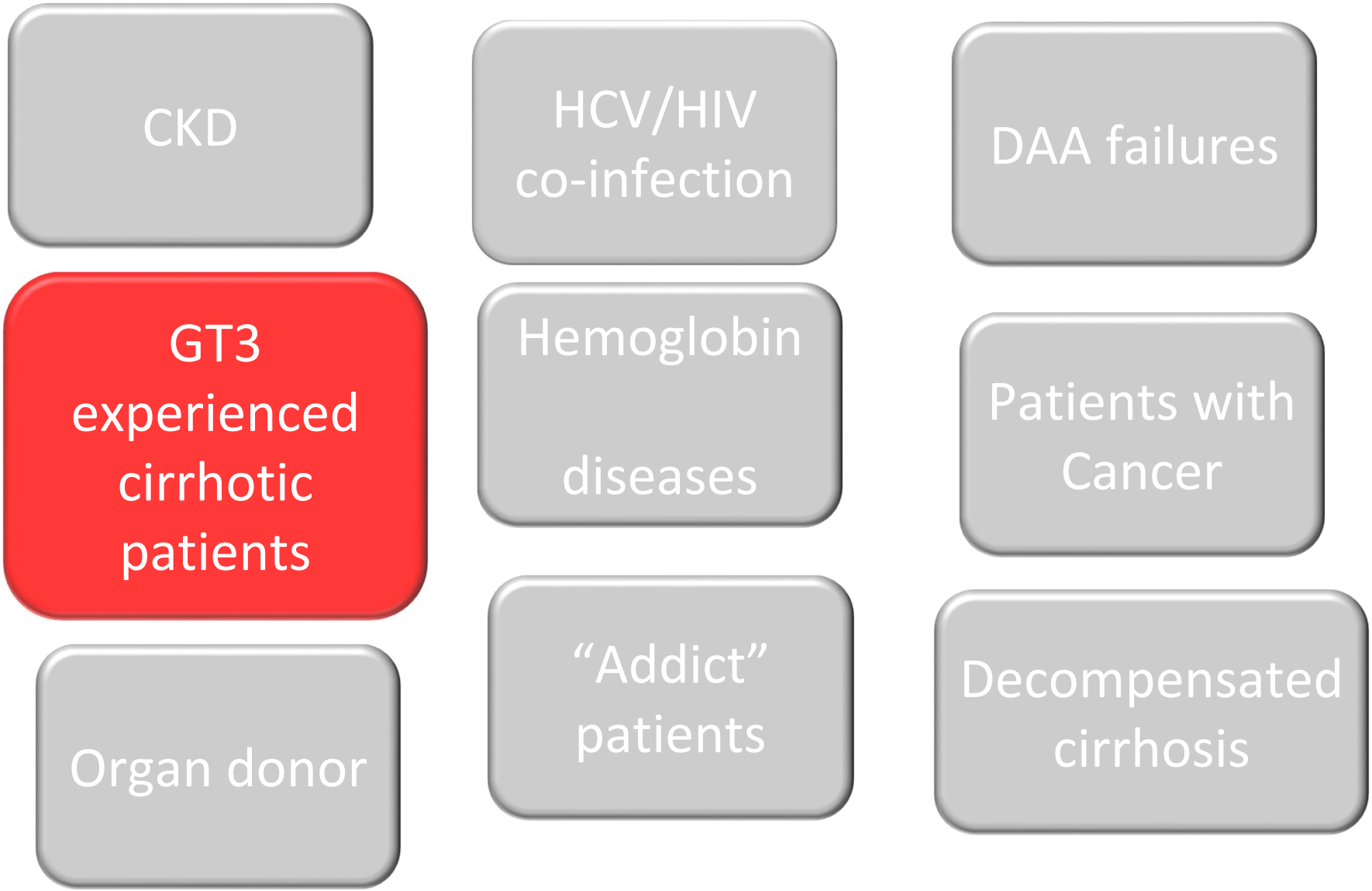
Re : relapse
NR : non response

SVR12 F0-F3 100 % vs 93 %F4
SVR12 if VR W4: 99 % vs 88 % if non VR W4

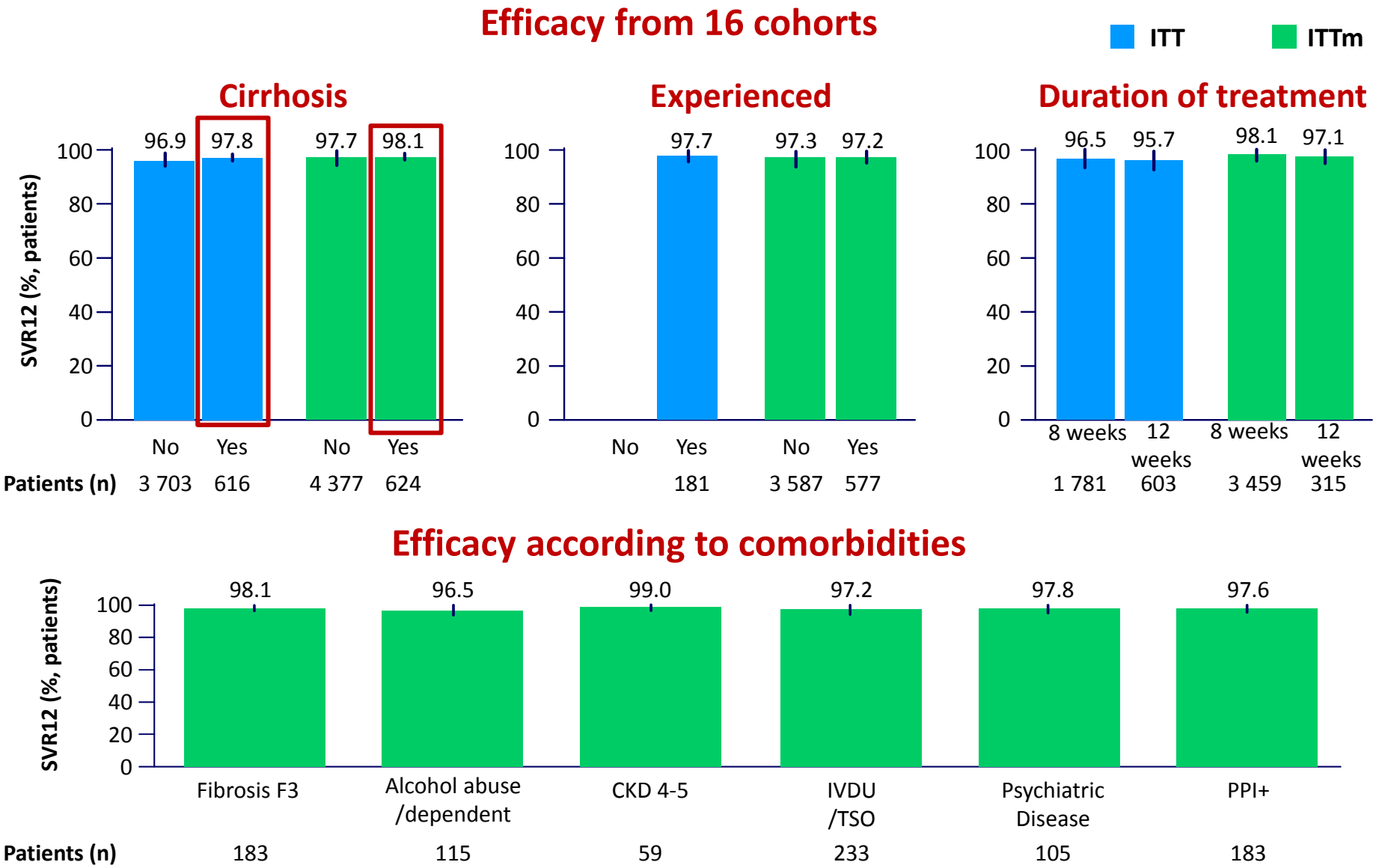
25 GT-3, 46 GT-1, 3 GT-4

Degasperi E, Italiy, EASL 2019, Abs. THU-131
Hezode C, France, EASL 2019, Abs. THU-142
Vermehren J, Germany, EASL 2019,Abs THU-188

“Special Populations” in the Pan-genotypic Era

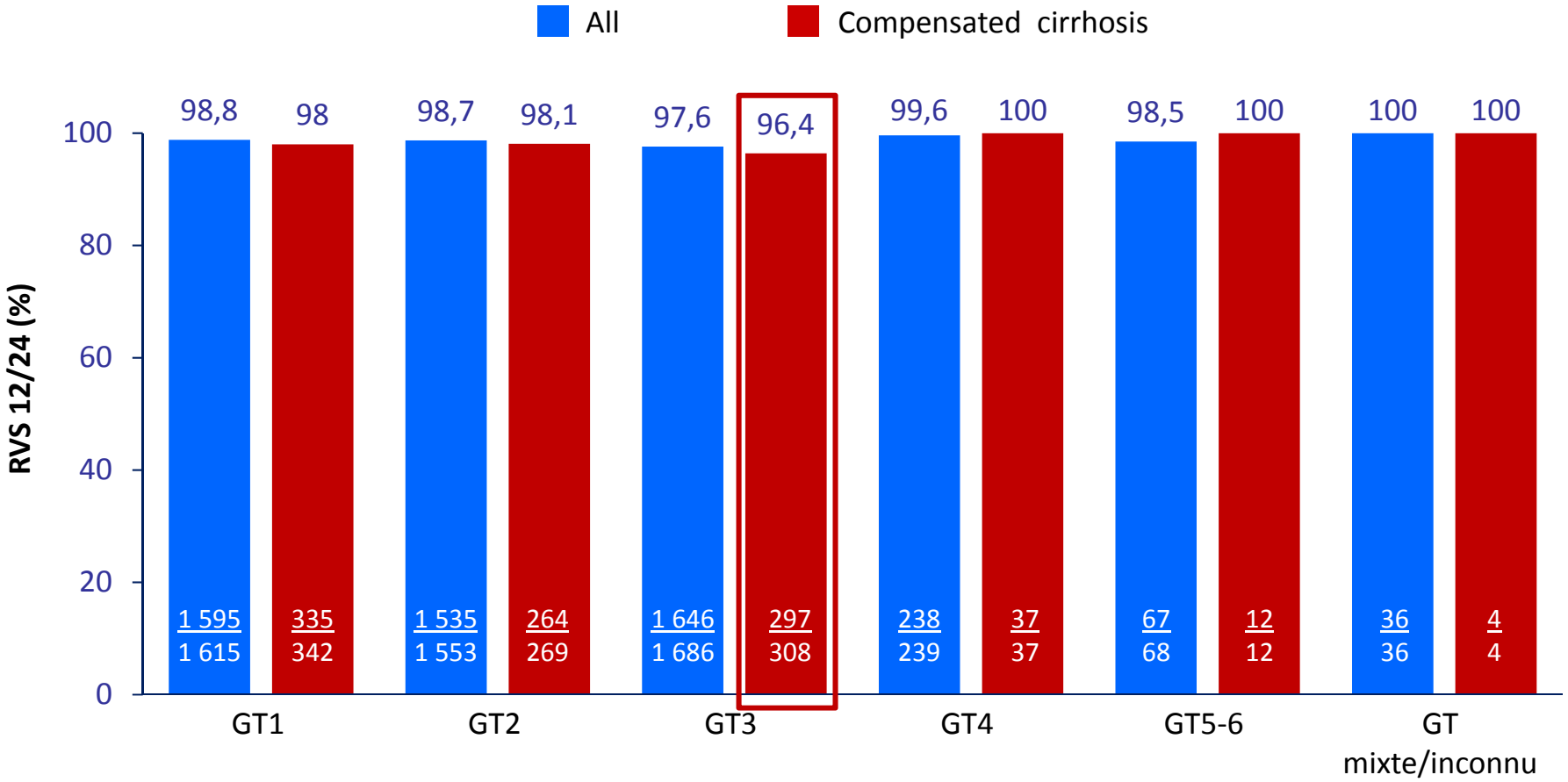


G/P: « real world » results from Germany



Cornberg M et al, Germany, EASL 2019, Abs. PS-184

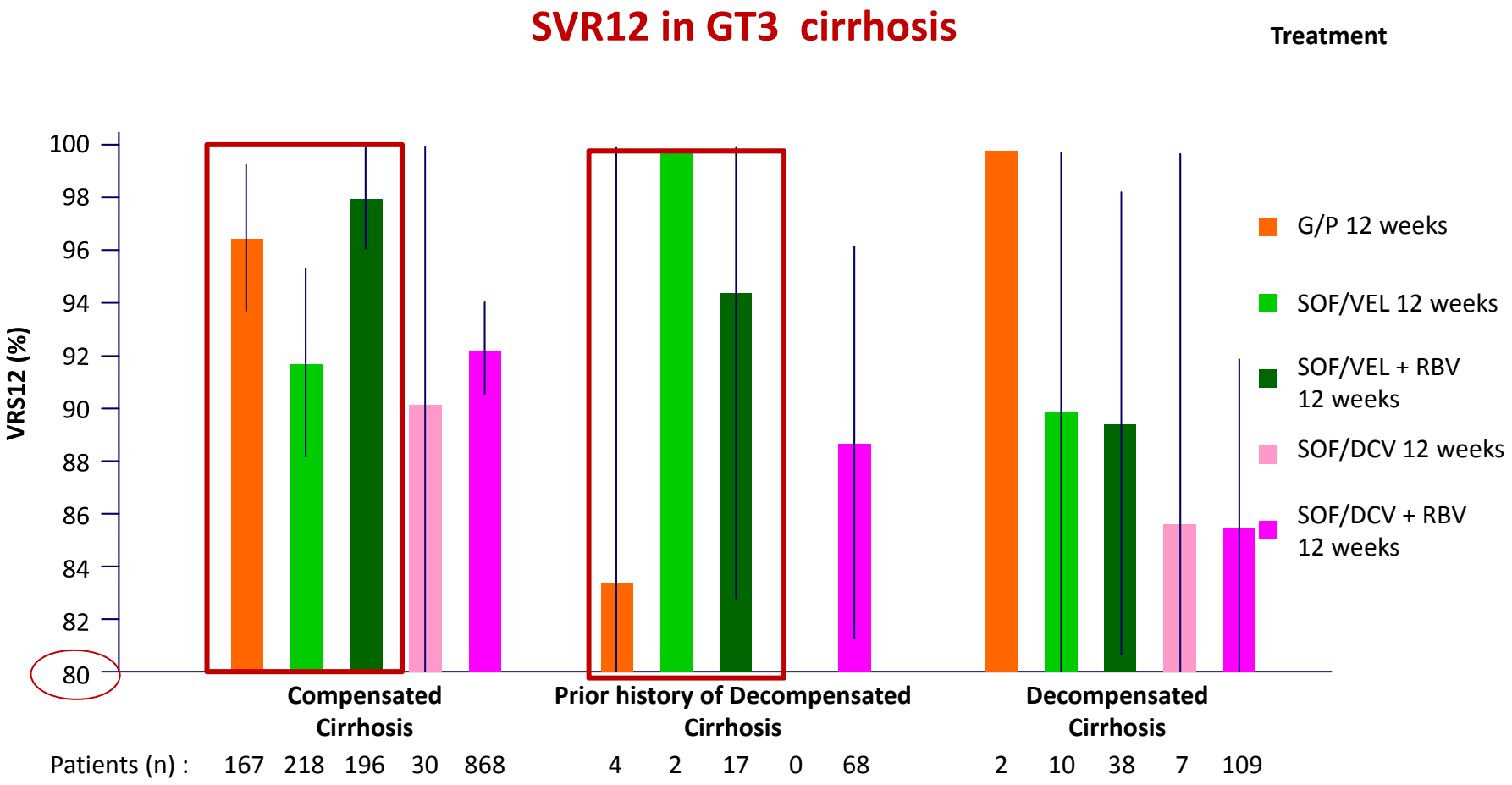
SOF/VEL: « real world » results from 12 observatory studies



Mangia A et al., Italy, EASL 2019, Abs. GS-03

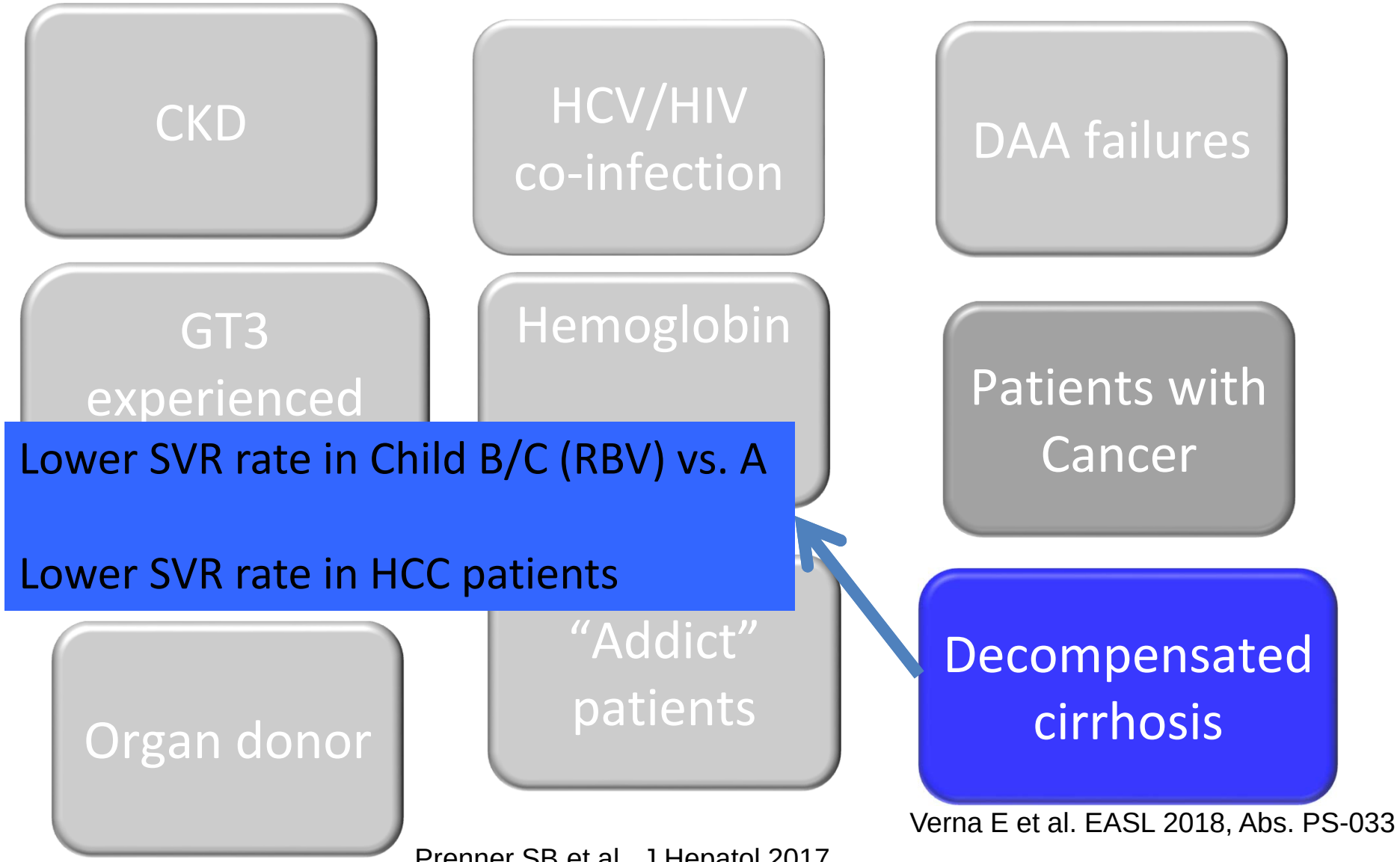
Genotype 3: « real world » results from UK

- 14 603 patients: SVR12 in the global population : 95.59 % ; SVR12 in GT3: 95.04 %



Drysdale K et al, UK, EASL 2019, Abs. LB-07

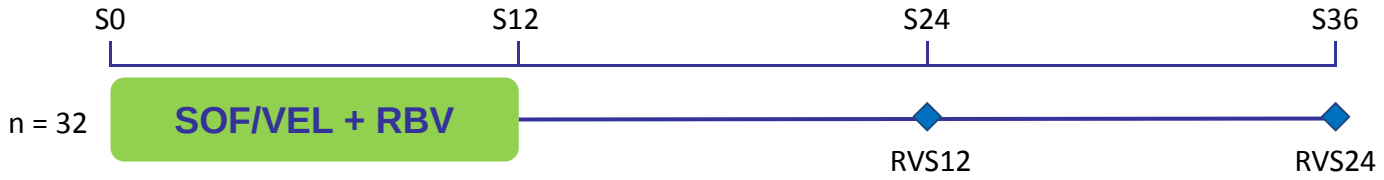
“Difficult-to-treat Populations” in the pan-genotypic era



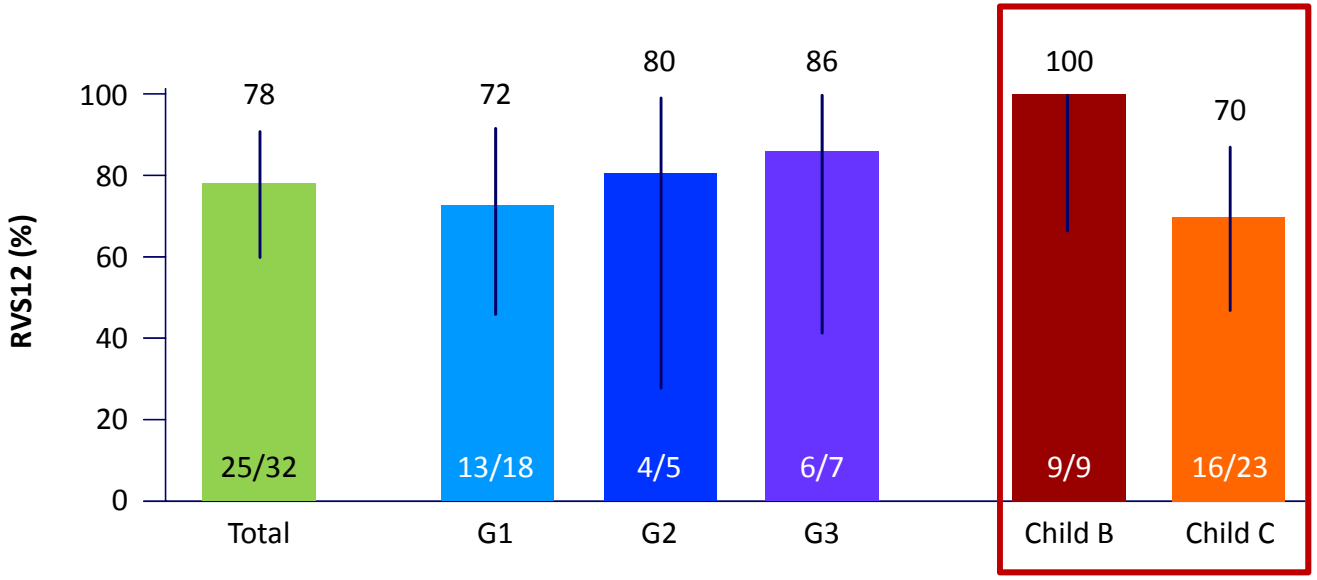
Prenner SB et al., J Hepatol 2017

Verna E et al. EASL 2018, Abs. PS-033

Sofosbuvir/velpatasvir/ribavirin 12 weeks in Child B/C cirrhosis

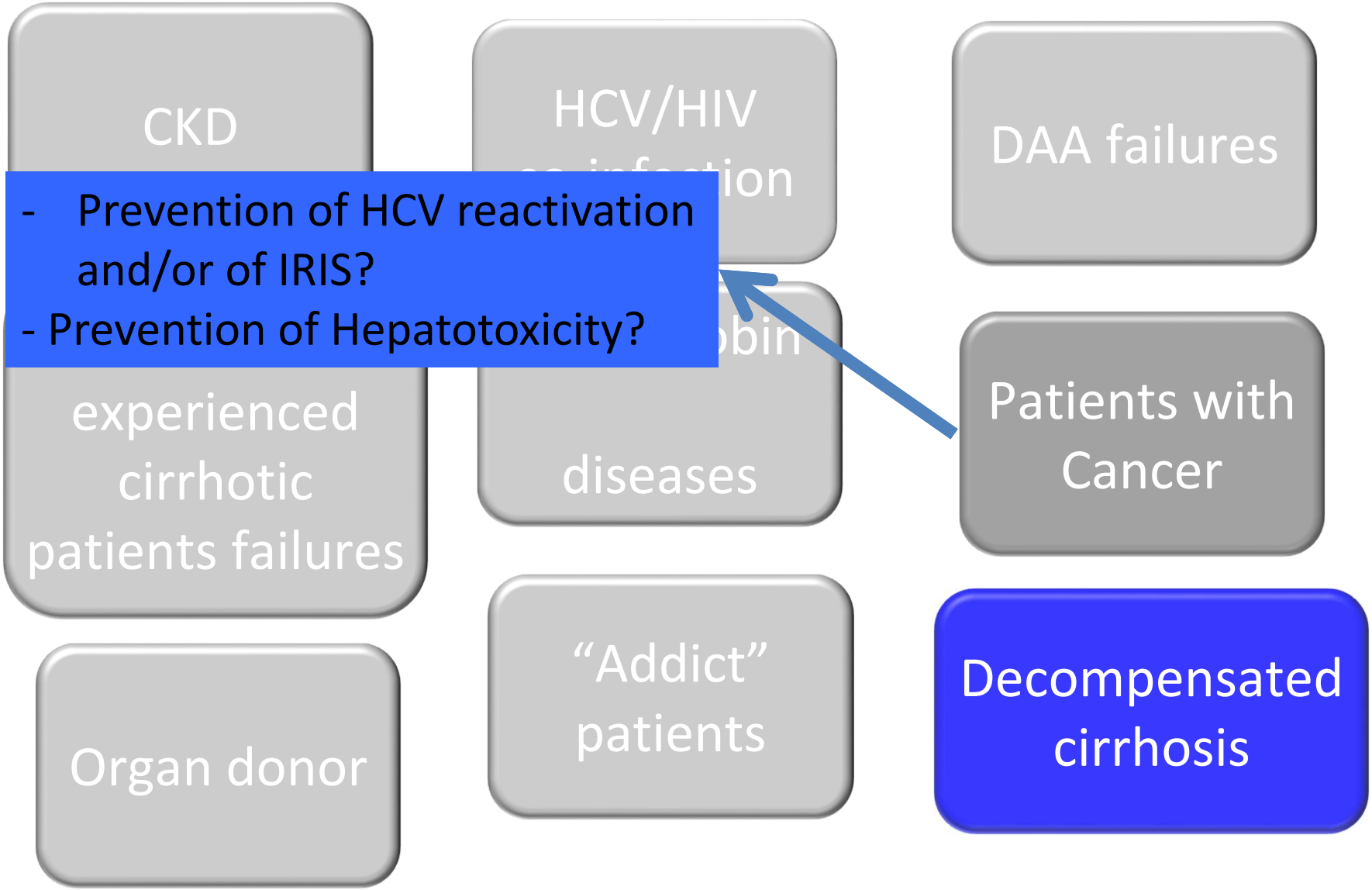


RBV 600 mg/j : titration to ≤ 1000-1200 mg/d



Flamm S et al, USA, EASL 2019, Abs. THU-138

“Difficult-to-treat Populations” in the pan-genotypic era



Remaining issues to achieve SVR and Elimination

- Drug-drug interaction
- Adherence
- Safety
- Follow-up of cured patients
- Prevention of re-infection

Drug-drug interaction

Sometimes easy…

Effect on antiretroviral drugs \ Effect on anti-HCV drugs		Sofosbuvir (SOF) / Velpatasvir(VEL)	Glecaprévir (GLE) / Pibrentasvir (PIB)
Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI)	Zidovudine (ZDV)	Not recommended if RBV associated	Not recommended if RBV associated
	Tenofovir disiproxil fumarate (TDF)	Possible TDM + renal monitoring	Possible
	Tenofovir alafénamide (TAF)	Possible	Possible
	Emtricitabine (FTC)	Possible	Possible
	Lamivudine (3TC)	Possible	Possible
	Abacavir (ABC)	Possible	Possible
Non Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	Efavirenz (EFV)	Not recommended	Contra-indicated
	Nevirapine (NVP)	Not recommended	Contra-indicated
	Etravirine (ETR)	Not recommended	Contra-indicated
	Doravirine (DOR)	Possible	Possible
	Rilpivirine (RPV)	Possible	Possible TDM RPV + ECG monitoring
Protease Inhibitors (PI)	Atazanavir/r (ATV/r)	Possible TDM ATV + bilirubin monitoring	Contra-indicated
	Darunavir/r (DRV/r)	Possible	Contra-indicated
	Lopinavir/r (LPV/r)	Possible	Contra-indicated
	Fosamprenavir/r (FPV/r)	Not recommended	Contra-indicated
	Tipranavir/r (TPV/r)	Not recommended	Contra-indicated
Integrase Inhibitors (INI)	Raltegravir (RAL)	Possible	Possible
	Dolutegravir (DTG)	Possible	Possible
	Elvitegravir/Cobicistat (EVG/c)	Possible	Contra-indicated
Entry/Fusion Inhibitors	Maraviroc (MVC)	Possible	Possible
	Enfuvirtide (T20)	Possible	Possible

Adjustment of comedications (statins)

or adjustment of the DAA choice to comedications

www.hep-druginteractions.org

Drug-drug interaction

… and sometimes almost impossible

- **Reduced choice:**

- **But:**

	Grazoprévir	Glécaprévir	Ledipasvir	Elbasvir	Velpatasvir	Pibrentasvir	Sofosbuvir
Metabolism	**CYP3A4**	**CYP3A4**	Weak (oxydative)	**CYP3A4**	**CYP2C8+ CYP2B6 CYP3A4**	-	- GS-331007 (uridine via hydrolysis)
Transporter	**Pgp OATP1B**	**Pgp, BCRP OATP1B1/3**	**Pgp BCRP**	**Pgp**	**Pgp, BCRP OATP**	**Pgp, BCRP**	**Pgp, BCRP**

➢ **Drug monitoring : dosage Cmin ledipasvir + SOF007 metabolite at D7 and follow-up**

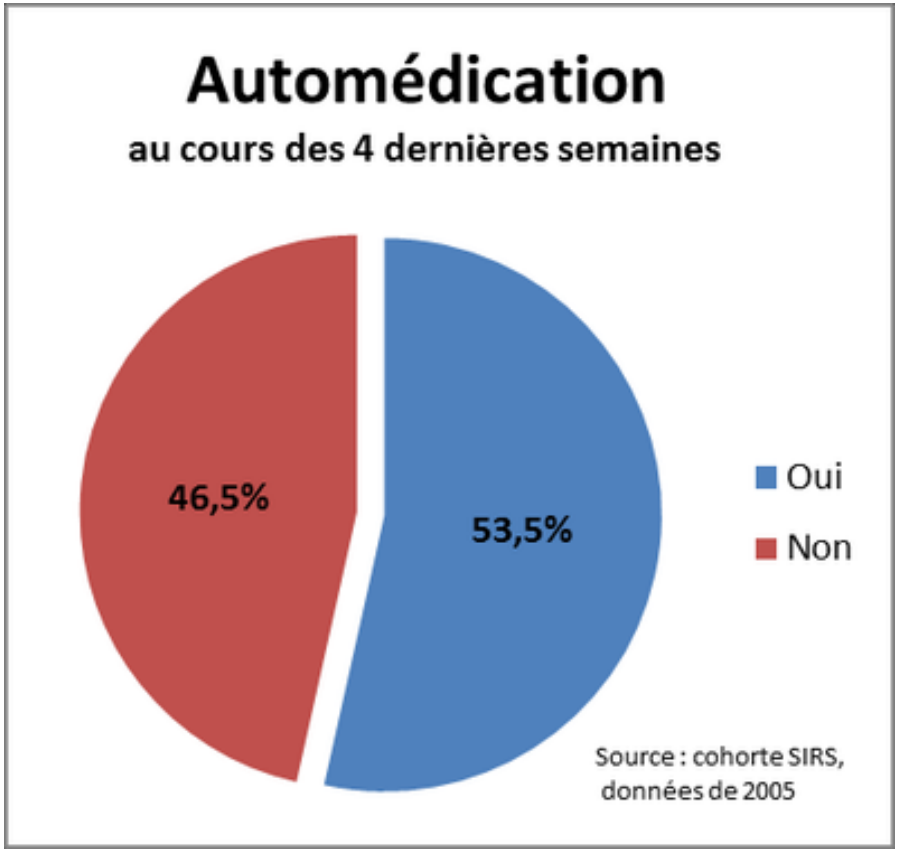
➢ **Dose-adjustment: limitation of the STR**

http://www.hep-druginteractions.org (accessed Nov 2017).

Drug-drug interaction

Auto-medication, herbs, plants…

« Drug intake the last 4 weeks without prescription »



1. Doliprane® / sanofi
2. Oscillococcinum®/Boiron
3. Humex® / Urgo
4. Strepsils® / Reckitt
5. Lysopaine® / Boehringer
6. Berroca® / Bayer santé familiale
7. Daflon® / Servier
8. Nurofen Flash® / Reckitt
9. Nicorette® / Johnson & Johnson
10. Fervex® / BMS/Upsa

And what about cocaine, metamphetamine, chemsex …?

Non-adherence and SVR

- Comparison of 101 SVR^{+} patients to 43 SVR^{-} patients
- Non-adherence (as defined by non intake of at least 7 pills of Sofosbuvir + Ledipasvir) was the key factor of treatment failure

Factors Associated With LDV/SOF Treatment Failures

Characteristics	Patients who achieved SVR 24 n=101	LDV/SOF Failures n=32	OR (95% CI)	p value
Age, mean (range) years	61 (28-80)	61 (34-80)	--	0.70
Black Race	23 (23%)	16 (57%)	3.84 (1.67-8.86)	0.001
*Male Sex	58 (57%)	22 (81%)	3.86 (1.37-10.85)	0.007
Cirrhosis	53 (52%)	15 (53%)	0.91 (0.41-2.01)	0.81
Platelets<100,000/mm^3	28 (28%)	9 (32%)	1.02 (0.42-2.47)	0.97
^BMI>25kg/m^2	64 (67%)	20 (71%)	1.28 (0.53-3.08)	0.59
*Albumin<3.5 g/dL	18 (18%)	7 (26%)	1.34 (0.50-3.60)	0.56
PPI Use	30 (30%)	7 (25%)	0.78 (0.31-1.93)	0.59
*Non-adherence	2 (1.98%)	8 (28.6%)	16.3 (3.26-81.92)	<0.0001
# of on treatment visits, mean (range)	2.55 (1-9)	2.86 (1-6)	--	0.09

* Data for 132 patients available

^ Data for 128 patients available

Sarpel D et al. AASLD 2016

CO22
HEPATHER

DAA and tolerance

Nb person-year	DAA+ N = 10271	DAA- N = 14233
SAE	1383 (13.5%)	1476 (10.4%)
Arythmia	35 (0.3%)	40 (0.3%)
Cardiac failure	29 (0.3%)	26 (0.2%)
Pulmonary hypertension	3 (0.03%)	2 (0.01%)
Death	151 (1.5%)	228 (1.6%)
SAE of fatal evolution		
Tumors	54	94
Hepato-biliary disease	21	25
Infections	17	33
Cardiac disease	12	17
Others	47	59

Diallo A et al. AASLD 2017

DAA and tolerance: brady-arrythmia

Example 2 : patient 4

D0 : ECG before treatment with sofosbuvir and daclatasvir

↓

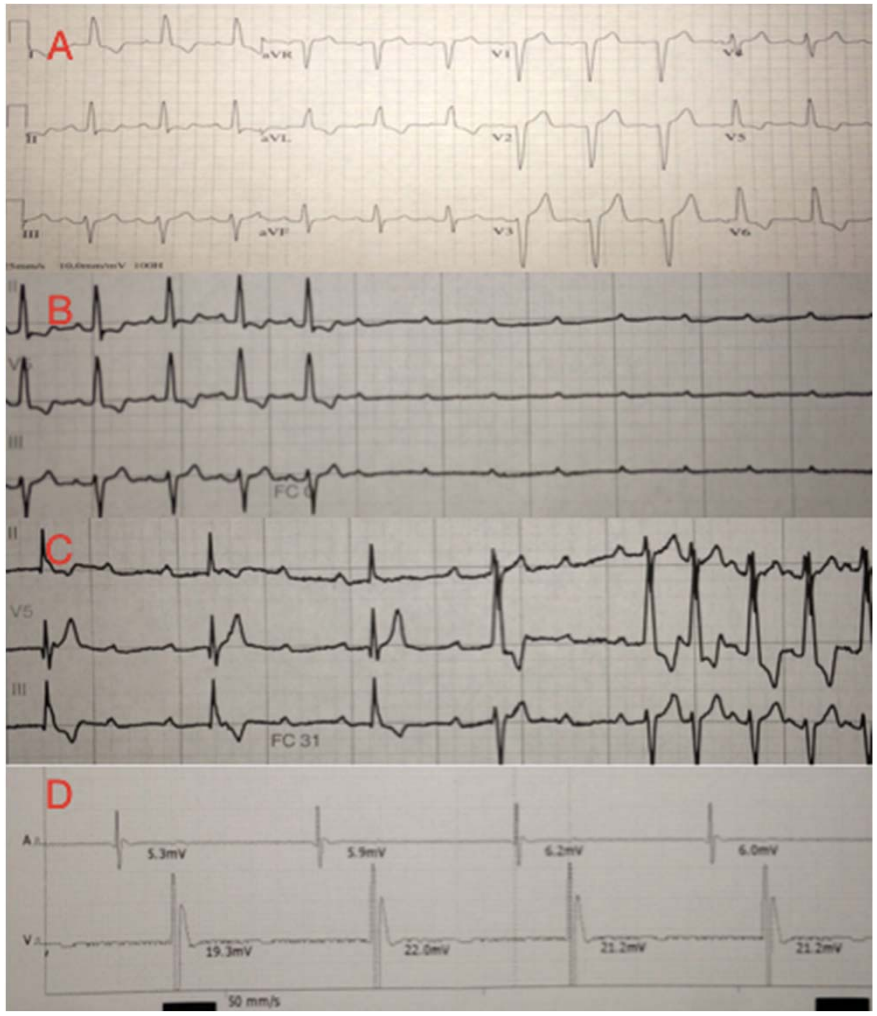
D6 : ECG before syncope, 1th degree atrioventricular block

↓

D6 : Intermittent 3rd degree atrioventricular block

↓

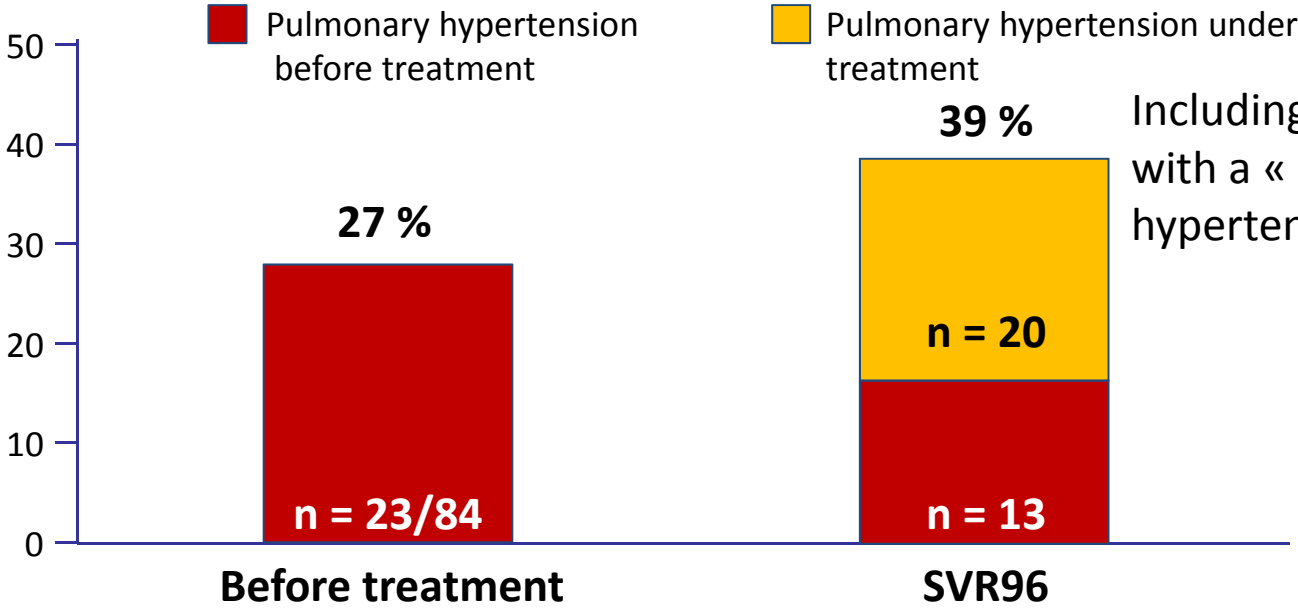
Recording of pacemaker: Complete spontaneous resolution of atrioventricular block after treatment discontinuation



Fontaine H et al. NEJM 2015

DAA and tolerance: pulmonary hypertension after SVR in cirrhotics

Effect of DAA on pulmonary hypertension (PAPm > 20 mmHg)



Including 3.5 % (3 patients) with a « true » pulmonary hypertension

➔ **Portal hypertension decreases over time with SVR but > 70 % of patients keep a significant portal hypertension at SVR96**

➔ **39 % of patients have an increase in the mean pulmonary arterial pressure , even if it remains post-capillary in more of 95 % of cases**

Lens S et al, Spain, EASL 2019, Abs. PS-017

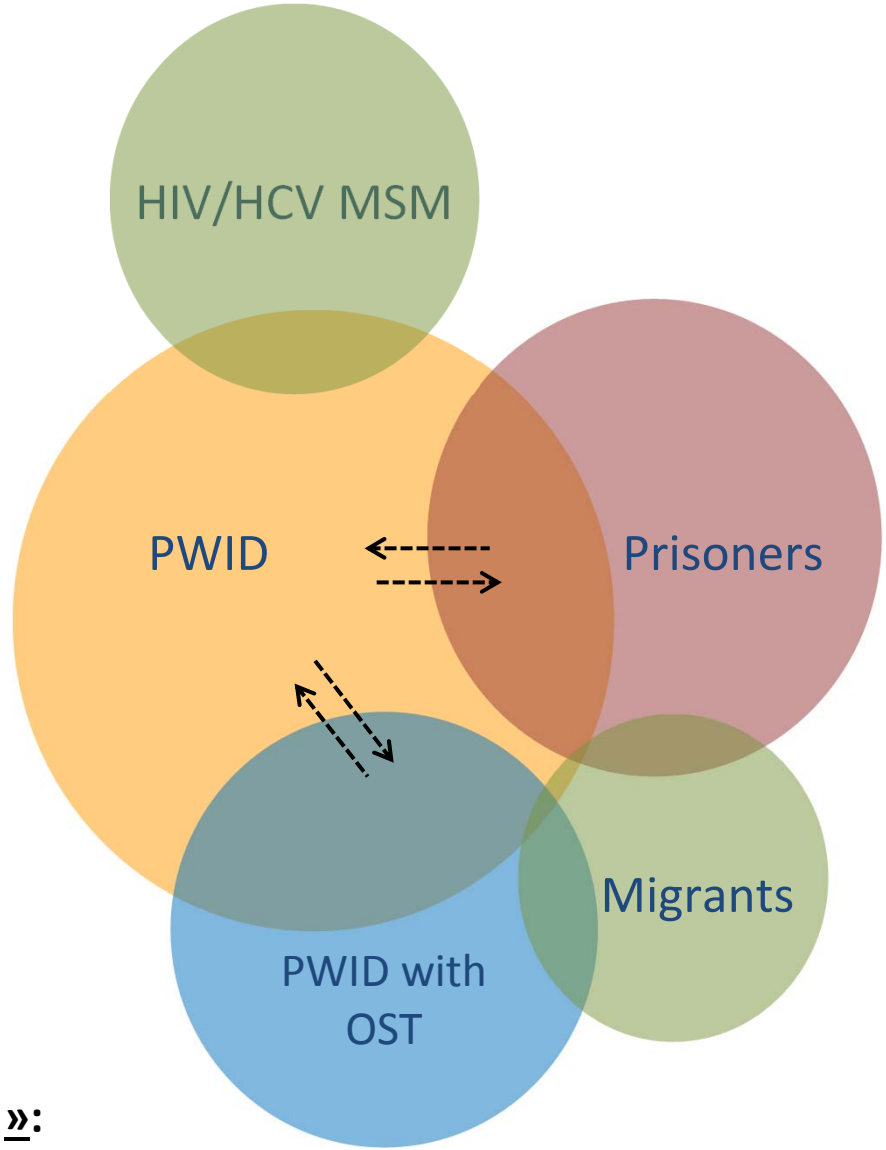
HCV treatment of special populations with pangenotypic drugs

- High & pangenotypic efficacy of the different regimens removed the « special » and almost the « difficult-to-treat » populations: SOF/VEL or SOF/VEL/VOX (12 weeks) and G/P (8/12 weeks) may be easily used according to the patient profile

- The main remaining limitations are drug-drug interaction (including phytotherapy) and adherence

- Safety of DAAs is fair which does not exclude very rare and potentially severe adverse events

Patients difficult-to-maintain in the care



« <u>Diagnosis</u> Burn-out <u>»</u>:

5- fold higher HCV infections virales C than diagnosis in 2016 in 10/91 countries

5- fold lower cure than new HCV infections in 23/91 countries Hill A et al. J Viral Erad 2017