HCV treatment of special populations with pangenotypic drugs

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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

CKD

HCV/HIV co-infection

DAA failures

GT3 experienced cirrhotic patients failures

Hemoglobin diseases

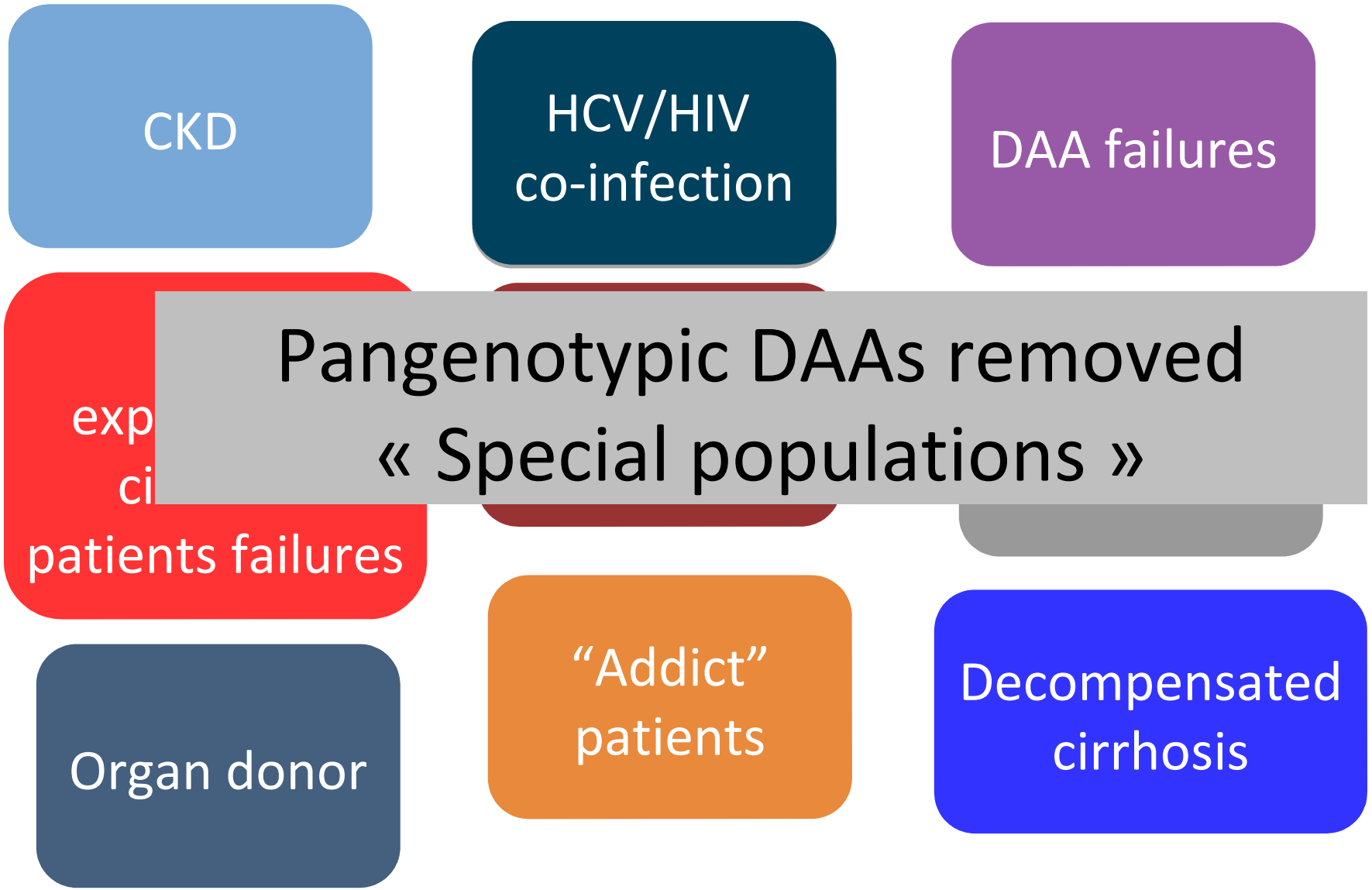
Patients with Cancer

Organ donor

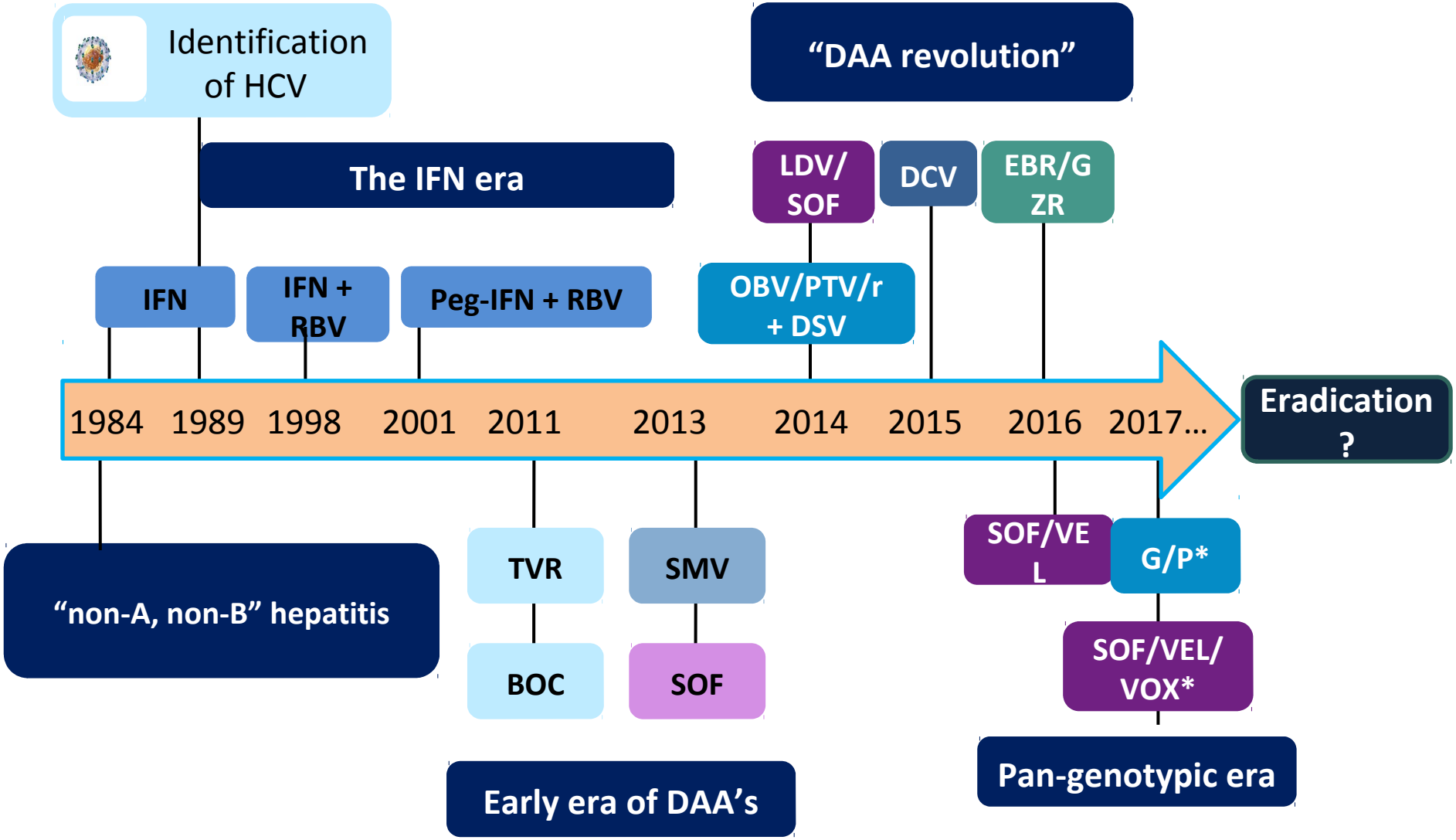
“Addict” patients

Decompensated cirrhosis

“Special Populations” in the Pan-genotypic Era



HCV Timeline



- * Regimen not currently approved

Pawlotsky JM, et al. J Hepatol 2016; 62: S87–99; Manns M, et al. Nat Rev Dis Primers 2017;3:1–19.

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CKD Patients : limited pangenotypic DAA treatment options

EASL Recommendations

GT1a: OBV/PTV/r + DSV or EBR/GZR for 12 weeks + RBV*

GT1b: OBV/PTV/r + DSV or EBR/GZR for 12 weeks

GT4: OBV/PTV/r + DSV for 12 weeks + RBV* or EBR/GZR for 12 weeks

SOF should be used with caution because no dose recommendation can be given

If treatment is urgently needed in†;
GT2: SOF/VEL or DCV + SOF for 12 weeks
GT3: SOF/VEL or DCV + SOF for 12 weeks , with RBV* or 24 weeks without RBV

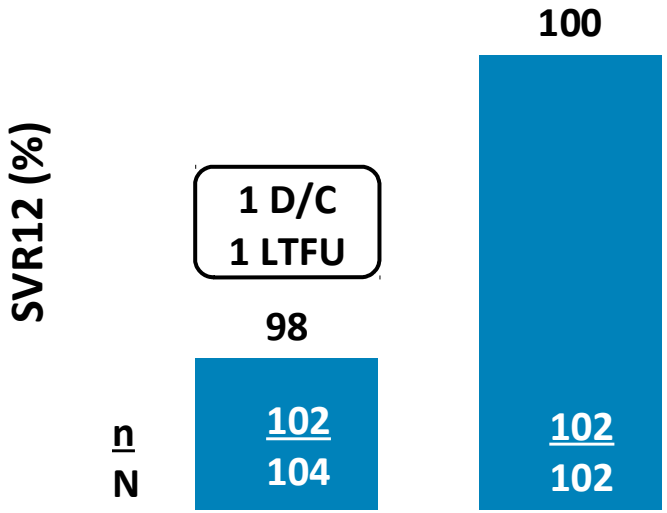
Severe renal impairment includes patients with eGFR < 30 mL/min/1.73 m2.
* 200 mg/day if haemoglobin level is >10 g/dl at baseline
†Renal function may worsen and should be carefully monitored and treatment should be interrupted immediately in case of deterioration.

EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol (2016), http://dx.doi.org/10.1016/j.jhep.2016.09.001

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)

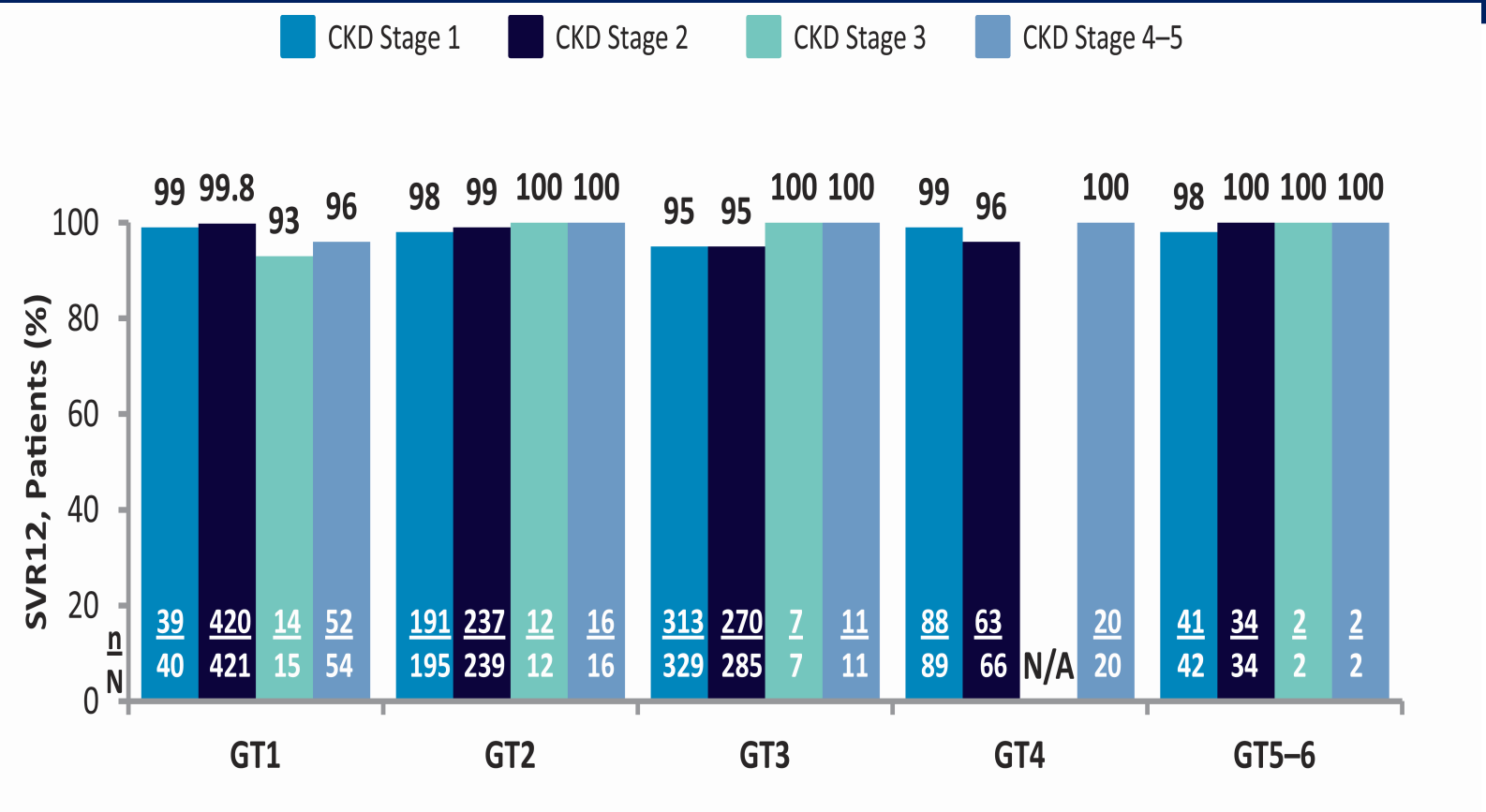


; D/C, discontinued; LTFU, lost to follow up;
ot achieve SVR12 for non-virologic reasons).

Gane EJ, et al. NEJM 2017

Efficacy of G/P is irrespective of degree of renal dysfunction in HCV GT1-6 infected patients with or without cirrhosis

An integrated efficacy, safety, and PK analysis of HCV GT1–6-infected patients treated with G/P for 8 (n = 822), 12 (n = 1347), or 16 (n = 69) weeks from eight phase 2 and 3 clinical trials, as a function of CKD stage



Pol S, et al. J Hepatol 2017; 66(Suppl 1):S738.

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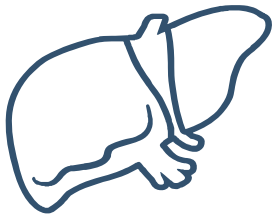
Clinical Relevance of the HIV/HCV Co-infection

~37 million individuals living with HIV worldwide,
~4 million of whom in Europe, North America, and Central Asia

~2.3 million
HIV/HCV co-infected individuals worldwide

The estimated prevalence of HCV in HIV-infected individuals ranges from **5% to 33%**

HIV co-infection leads to enhanced rates of HCV replication and decreased rates of HCV clearance after acute infection



HIV/HCV co-infected individuals have increased risk for liver fibrosis, hepatic decompensation, kidney disease, and death

HCV virologic cure significantly reduces incidence of **liver-related events, liver decompensation, HCC, and mortality8**

Guidelines for co-infected patients

- **EASL**: Should be treated as mono-infected patients9
- **AASLD**: Should be treated and retreated as mono-infected patients
- Treatment courses of LDV/SOF shorter than 12 weeks are not recommended

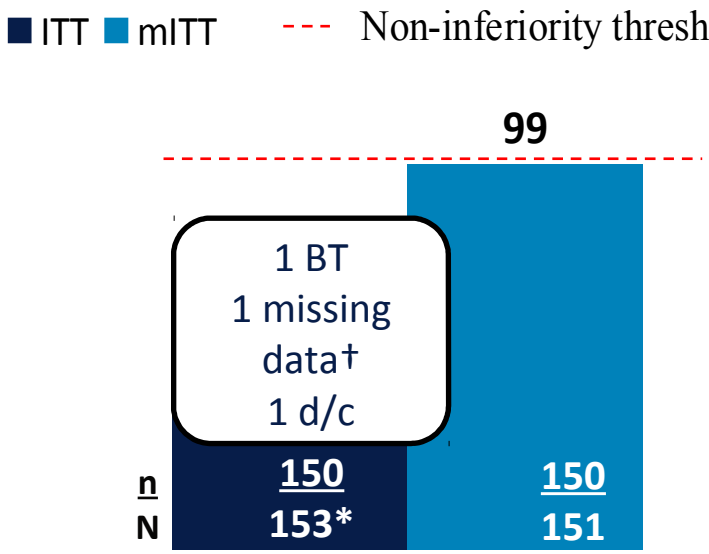
Co-infected patients should be monitored for DDIs

- **EASL**: A1
- **AASLD**: Class I, Level B

DDI, drug-drug interaction; HCC, hepatocellular carcinoma.

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:

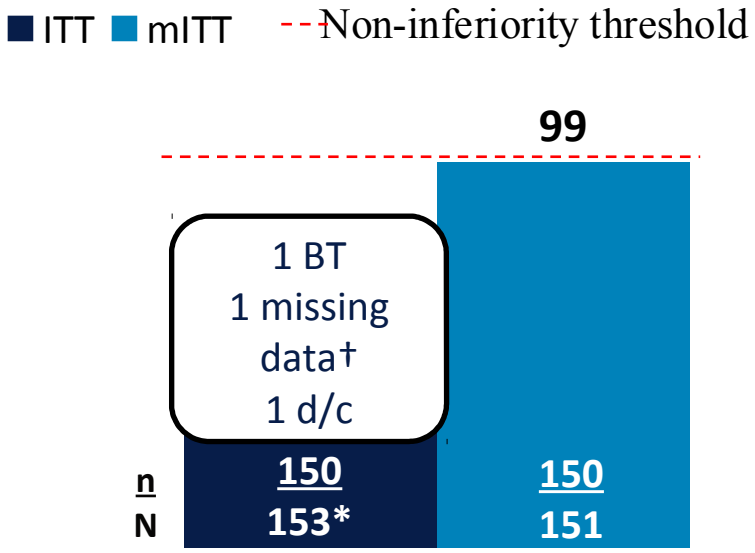
- PI (DRV, LPV/r) 0%
- NNRTI (RPV) 21%
- Integrase inhibitor (RAL, EVG/COBI or DTG) 74%
- NRTI (TDF/ TAF) 61%; (ABC) 39%

BT, breakthrough; d/c, discontinuation; mITT, excludes non-virologic failure.
* Including 3 SOF-experienced patients; † Patient achieved SVR4, but was lost to follow-up;
‡ One patient with cerebrovascular accident and cerebral hemorrhage; both unrelated to G/P.

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

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)



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- 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,	1 (0.7)	0

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

Drug-drug interaction between DAA and antiretrovirals

Contraindicated/ Not recommended

Caution/Dose adjustment

No dose adjustment

	G/P	SOF/VEL	SOF/VEL/VOX
Concomitant drug	**Dosing recommendation**	**Dosing recommendation**	
Protease inhibitors			
Atazanavir	Contraindicated1	No dose adjustment2	Not recommended3
Darunavir	Not recommended1	No dose adjustment2,3	
Lopinavir	Not recommended4	No dose adjustment2	Not recommended3
Fosamprenavir Indinavir Saquinavir	Not recommended4	No dose adjustment4	Not recommended4
Tipranavir	Not recommended4	Not recommended4	Not recommended4

G/P: Glecaprevir/Pibrentasvir; SOF: Sofosbuvir; VEL: Velpatasvir; VOX: Voxilaprevir

1. Maviret SmPC 12/2017. 2. Epclusa SmPC 05/2017. 3. Vosevi SmPC 07/2017. 4. http://www.hep-druginteractions.org (accessed Nov 2017).

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Caution/Dose adjustment

No dose adjustment

	G/P	SOF/VEL	SOF/VEL/VOX
Concomitant drug	**Dosing recommendation**	**Dosing recommendation**	
Entry/integrase inhibitors Dolutegravir	No dose adjustment1	No dose adjustment2,3	
Elvitegravir/cobi/FTC/TAF	No dose adjustment1	No dose adjustment2,3	
Elvitegravir/cobi/FTC/TDF	No dose adjustment4	Close monitoring for tenofovir-associated adverse reactions is recommended2,3	
Maraviroc	No dose adjustment4	No dose adjustment4	
Raltegravir	No dose adjustment1	No dose adjustment2,3	

Cobi: Cobicistat; FTC: Emtricitabine; G/P: Glecaprevir/Pibrentasvir; SOF: Sofosbuvir; TAF: Tenofovir Alafenamide; TDF: Tenofovir disoproxil;
VEL: Velpatasvir; VOX: Voxilaprevir.

1. Maviret SmPC 12/2017. 2. Epclusa SmPC 05/2017. 3. Vosevi SmPC 07/2017. 4. http://www.hep-druginteractions.org (accessed Nov 2017).

Drug-drug interaction between DAA and antiretrovirals

	G/P	SOF/VEL	SOF/VEL/VOX
Concomitant drug	**Dosing recommendation**	**Dosing recommendation**	
NRTIs			
Abacavir	No dose adjustment1	No dose adjustment4	
Didanosine	No dose adjustment4	No dose adjustment4	
Emtricitabine	No dose adjustment1	No dose adjustment2,3	
Lamivudine	No dose adjustment1	No dose adjustment4	
TDF	No dose adjustment1	Close monitoring for tenofovir-associated adverse reactions is recommended2,3	
NNRTIs			
Efavirenz	Not recommended1	Not recommended2,3	
Etravirine	Not recommended4	Not recommended4	
Nevirapine	Not recommended4	Not recommended4	
Rilpivirine	No dose adjustment1	No dose adjustment2,3	

Contraindicated/ Not recommended

Caution/Dose adjustment

No dose adjustment

G/P: Glecaprevir/Pibrentasvir; SOF: Sofosbuvir; VEL: Velpatasvir; TDF: Tenofovir disoproxil; VOX: Voxilaprevir

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DAAs failures are rare

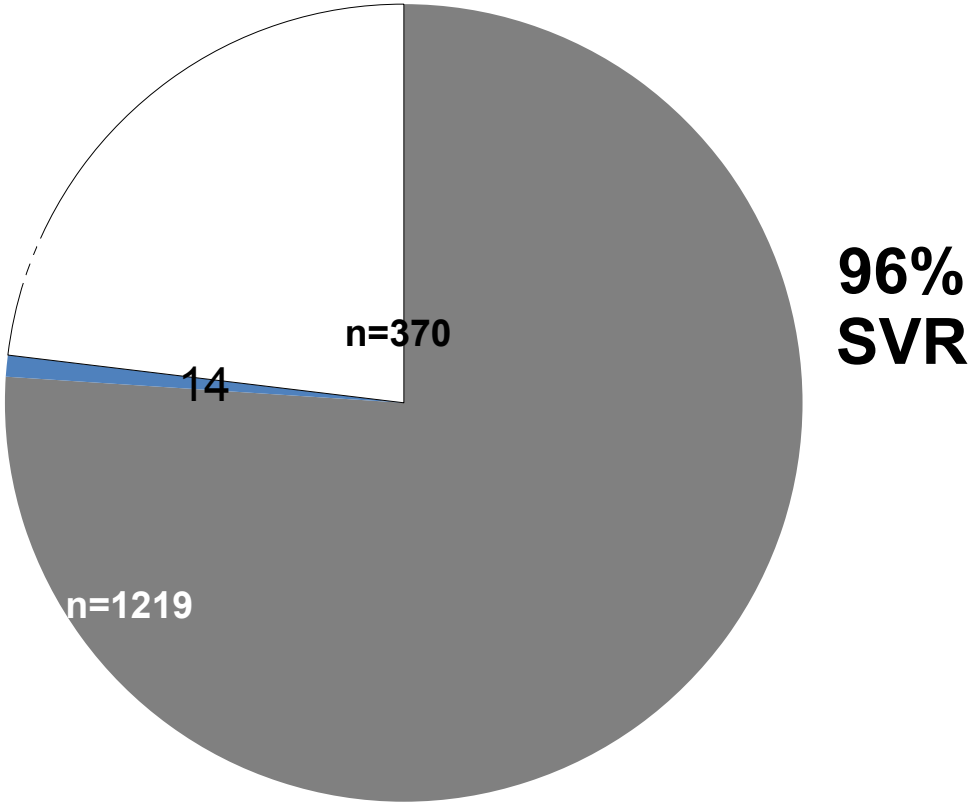
Summary of Phase 3 studies of IFN-free therapy in GT 1 patients published in the New England Journal of Medicine in 2014*

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)

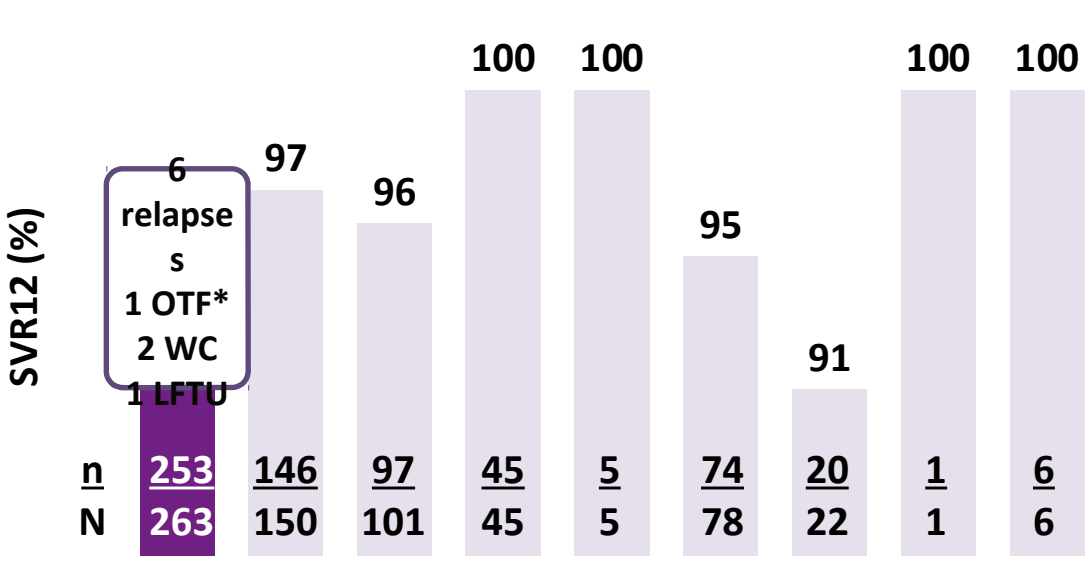


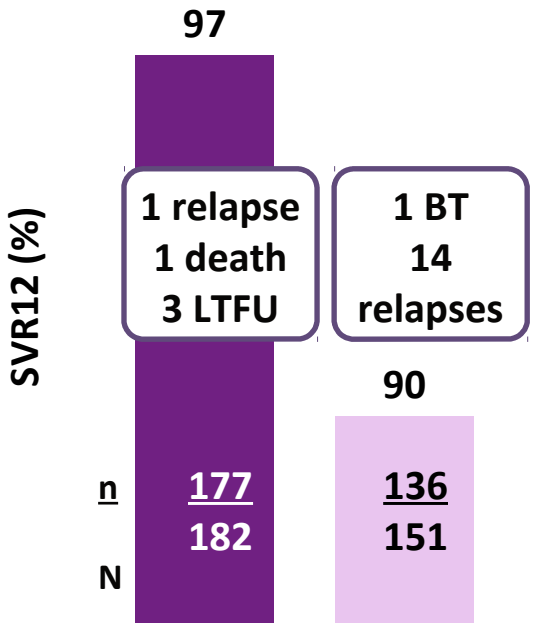
Gilead Sciences, Inc. Harvoni (ledipasvir/sofosbuvir), US PI, October 2014; Data on file.
Gilead Sciences, Inc; Gilead Sciences Europe Ltd; Harvoni (ledipasvir/sofosbuvir), SmPC, July 2015.

SOF/VEL/VOX or SOF/VEL in DAA-experienced patients with GT1–6 HCV infection: POLARIS-1 & -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

Safety of SOF/VEL/VOX or SOF/VEL in DAA-experienced patients with GT1–6 HCV infection: POLARIS-1 & -4

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

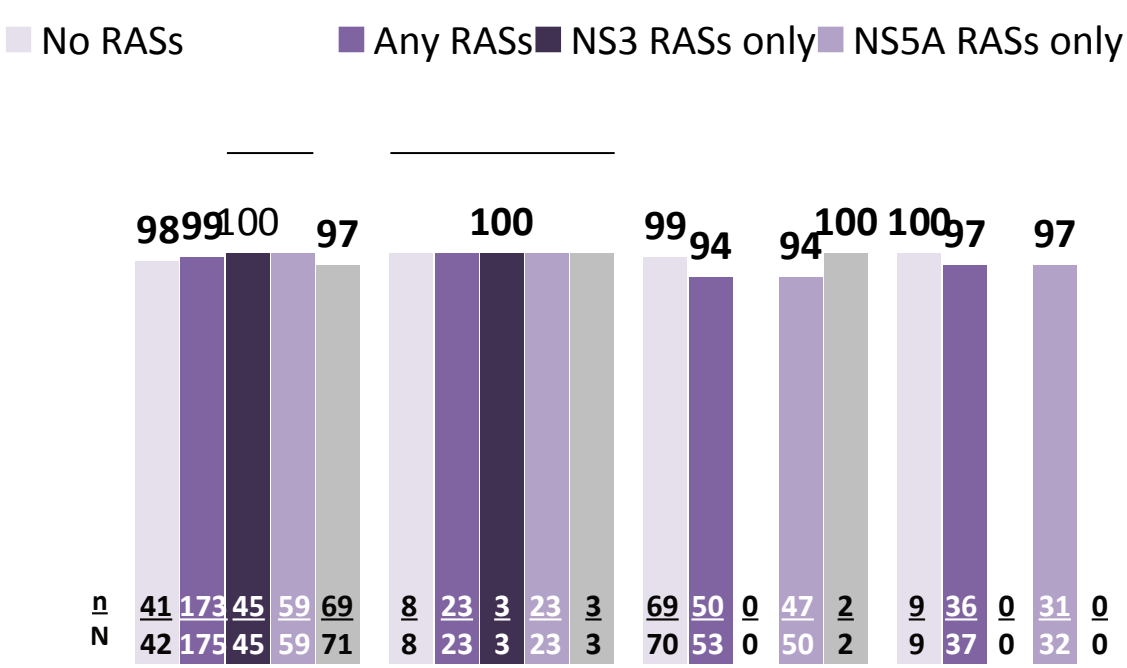
Safety summary Patients, n (%)	SOF/VEL/VOX n = 263
Any AE	206 (78)
SAE	5 (2)*
d/c due to AE	1 (<1)†
Death	0
Grade 3-4 lab abnormalities	18 (7)

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

Safety summary Patients, n (%)	SOF/VEL/VOX n = 182	SOF/VEL n = 151
Any AE	140 (77)	111 (74)
SAE	4 (2)	4 (3)
d/c due to AE	0	1 (<1)
Death	1 (<1)	0
Grade 3 lab abnormalities	10 (5)	9 (6)
Grade 4 lab abnormalities	1 (<1)	1 (<1)

Impact of RASs 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



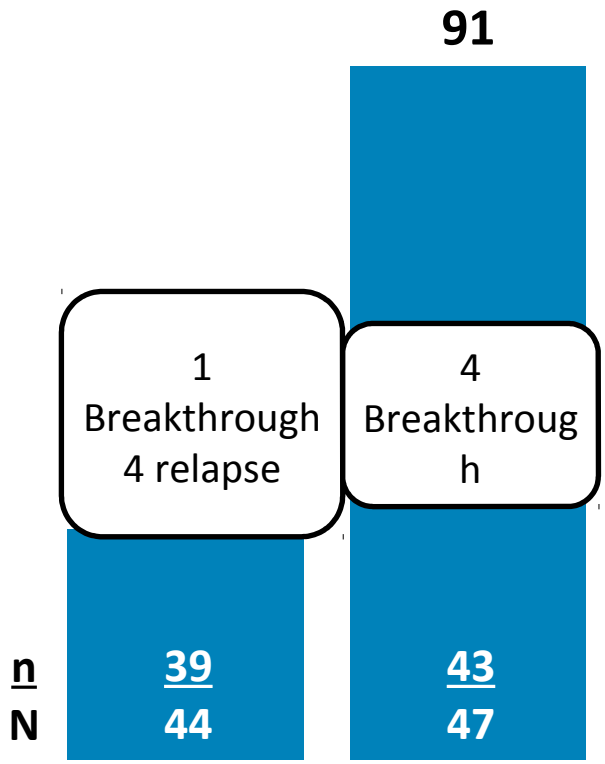
Study	HCV GT of patients who relapsed
POLARIS-1	1a
	3a
	3a
	3a
	3a
	4d
POLARIS-4	1a

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).

G/P for 12 or 16 Weeks in Patients with HCV GT1 or 4 Infection and Prior DAA Treatment Failure: MAGELLAN-1, PART 2



Prior Treatment History
PI: TVR, SMV, BOC
NS5A: LDV, DCV
NS5A + PI: OBV and PTV, or other combinations

- OTVF, on-treatment virologic failure

Poordad F, et al. Hepatology 2017

HCV treatment of special populations with pangenotypic drugs

- High & pangenotypic efficacy of the different regimens removed the « special populations »

- SOF/VEL or SOF/VEL/VOX and G/P may be easily used according to the patient profile

HCV treatment of special populations with pangenotypic drugs

Maviret (G/P)

- **GT1-6 infected patients** for

- 8 weeks (Non Cirrhotic)

- 12 weeks (Cirrhotic *and G1-6 NS3 failure in US*)

- 16 weeks (GT3 experienced cirrhotics; *G1-6 NS5A failure in US only*)

- **Preferred in CKD patients**
- **Not recommended or contraindicated in CPT B or C**

Vosevi (VOL/VEL/SOF)

- **GT1-6 infected patients** for

- 8 weeks (NC)

- 12 weeks (Cirrhotic and DAA-experienced)

- **Not recommended or contraindicated in CPT B or C**

  = SOF/VEL/RBV for 12 weeks