HCV treatment : are there still difficulties to treat patients ?

Stanislas Pol, MD, PhD

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

stanislas.pol@aphp.fr

Paris, France
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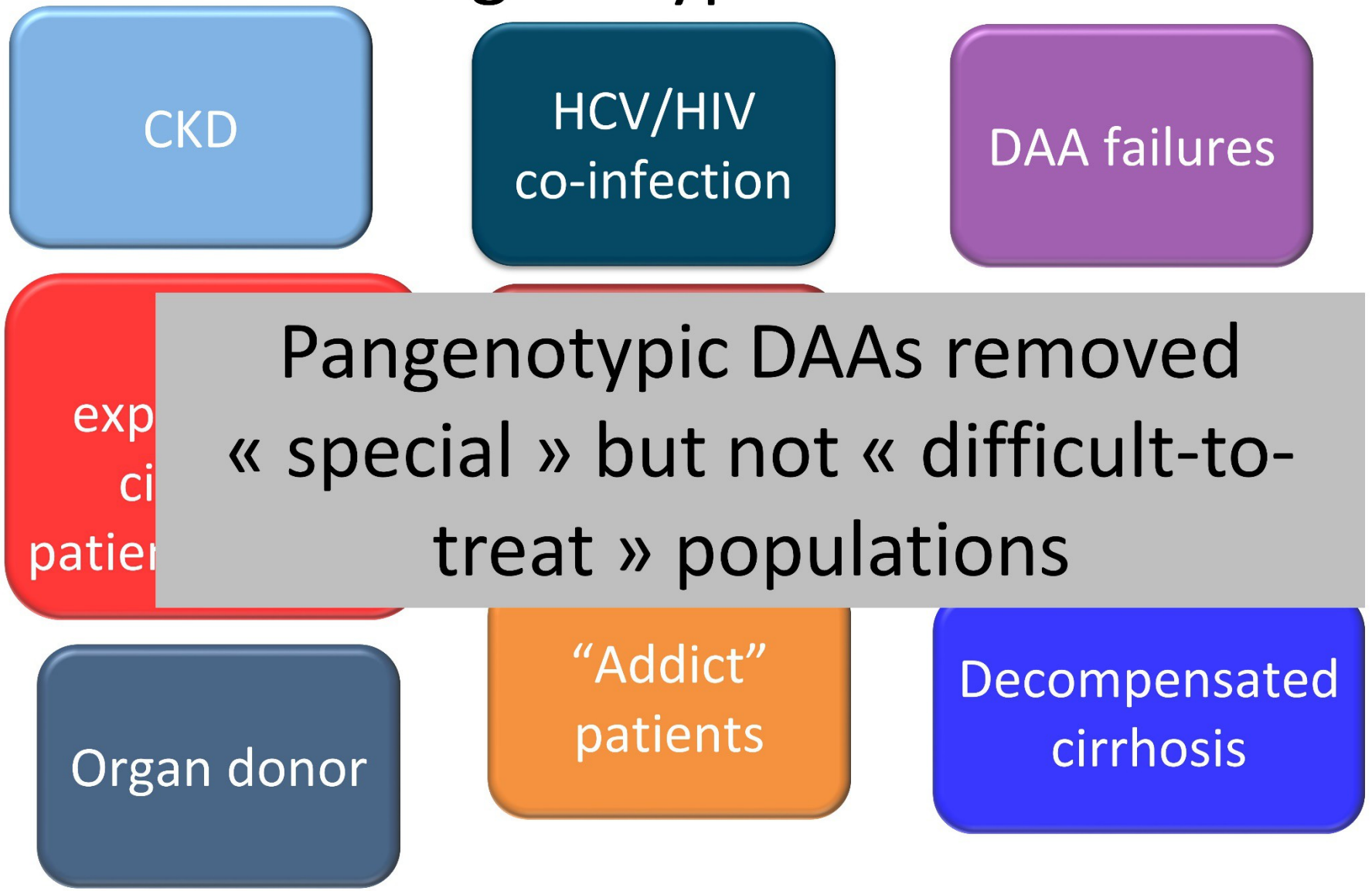
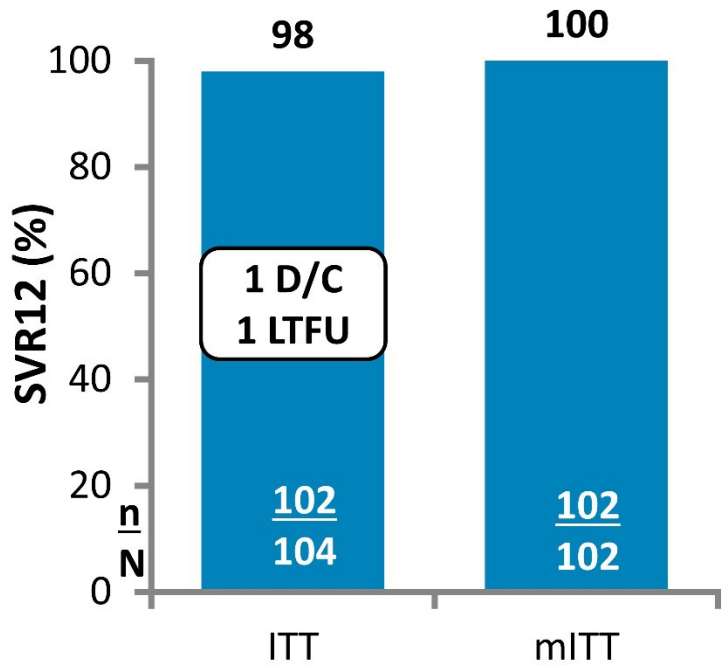
“Special Populations” in the Pan-genotypic Era



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)

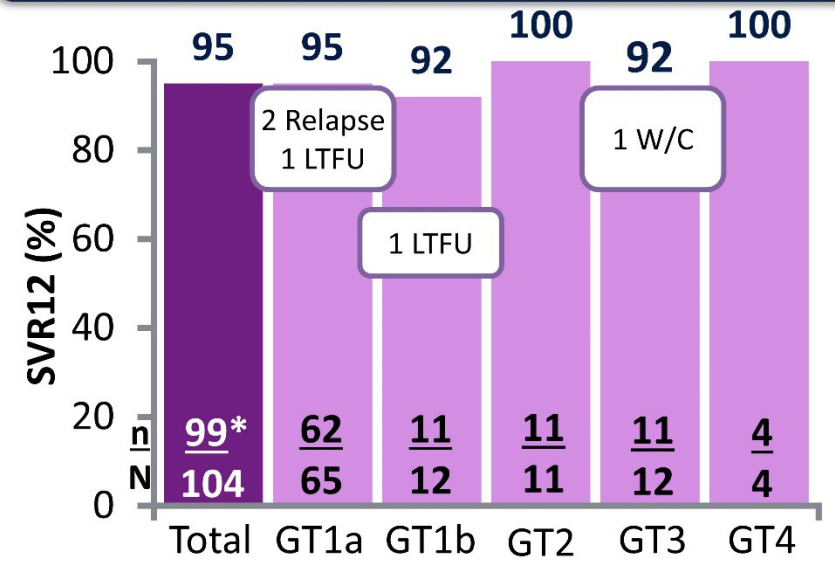


- CKD, chronic kidney disease; D/C, discontinued; LTFU, lost to follow up;
ITT, intent-to-treat; mITT, modified ITT (excludes patients who did not achieve SVR12 for non-virologic reasons).

Gane EJ, et al. NEJM 2017

HIV/HCV Coinfected patients

ASTRAL-5: SOF/VEL Phase 3, open-label, single-arm study, 12 weeks

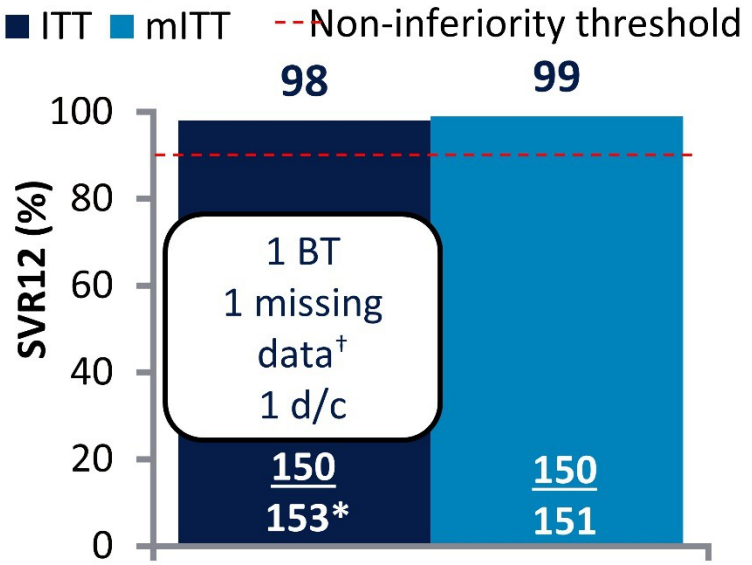


ARV use at baseline:

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

Wyles D, et al. Clin Infect Dis 2017.

EXPEDITION-2: Phase 3, G/P treatment for 8 weeks (non-cirrhotic) or 12 weeks (cirrhotic)



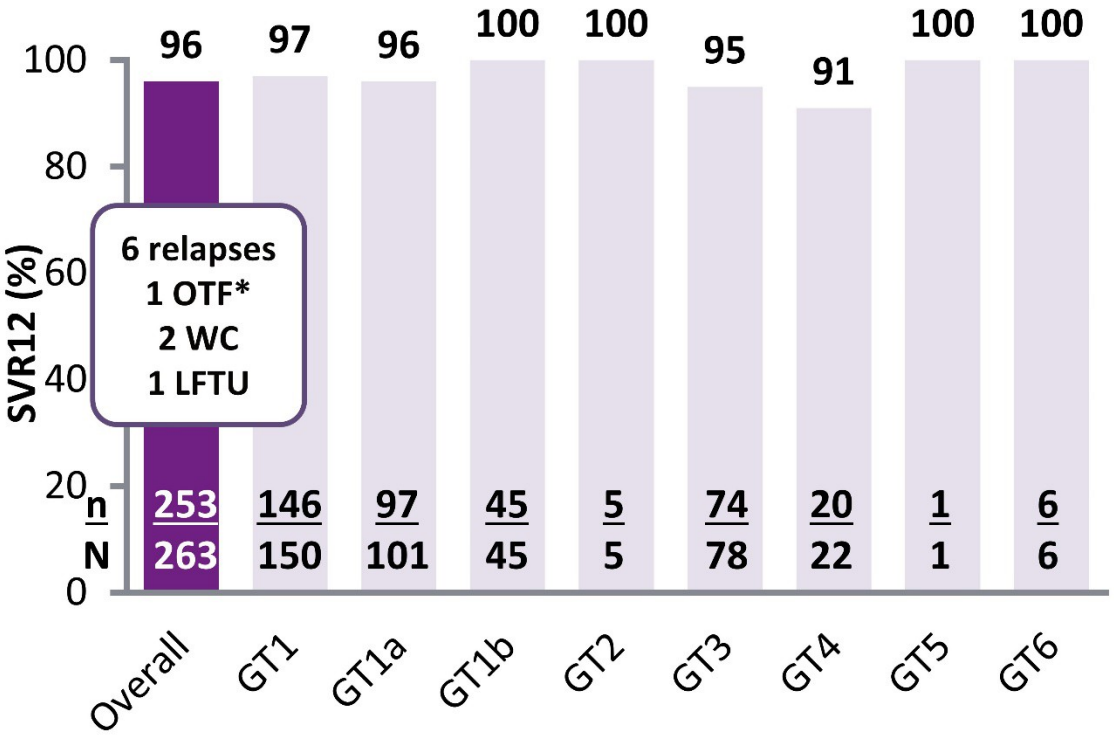
ARV use at baseline:

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

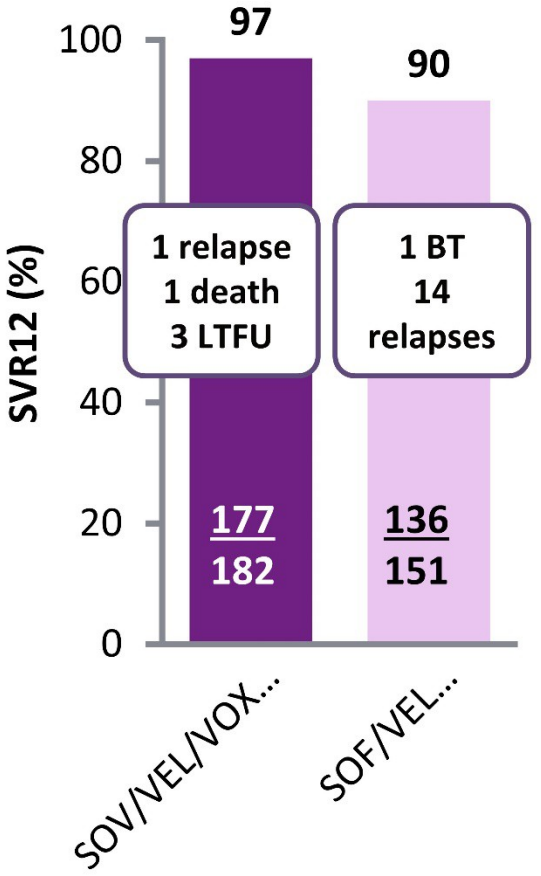
Rockstroh J, et al. J Hepatol 2017

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



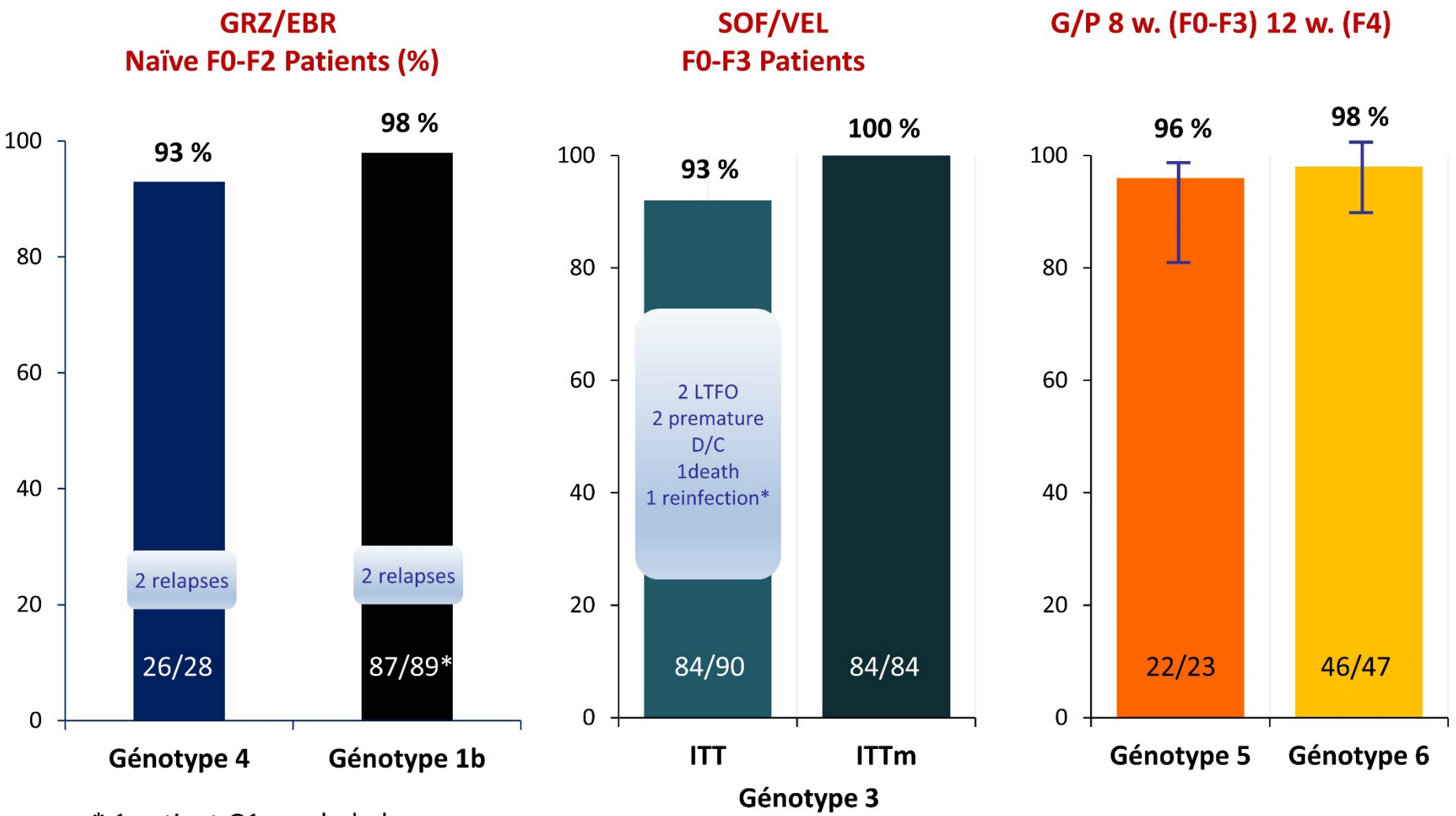
POLARIS-4
SOF/VEL/VOX or SOF/VEL for 12 weeks in DAA-experienced (non-NS5A) HCV GT1–6-infected patients



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

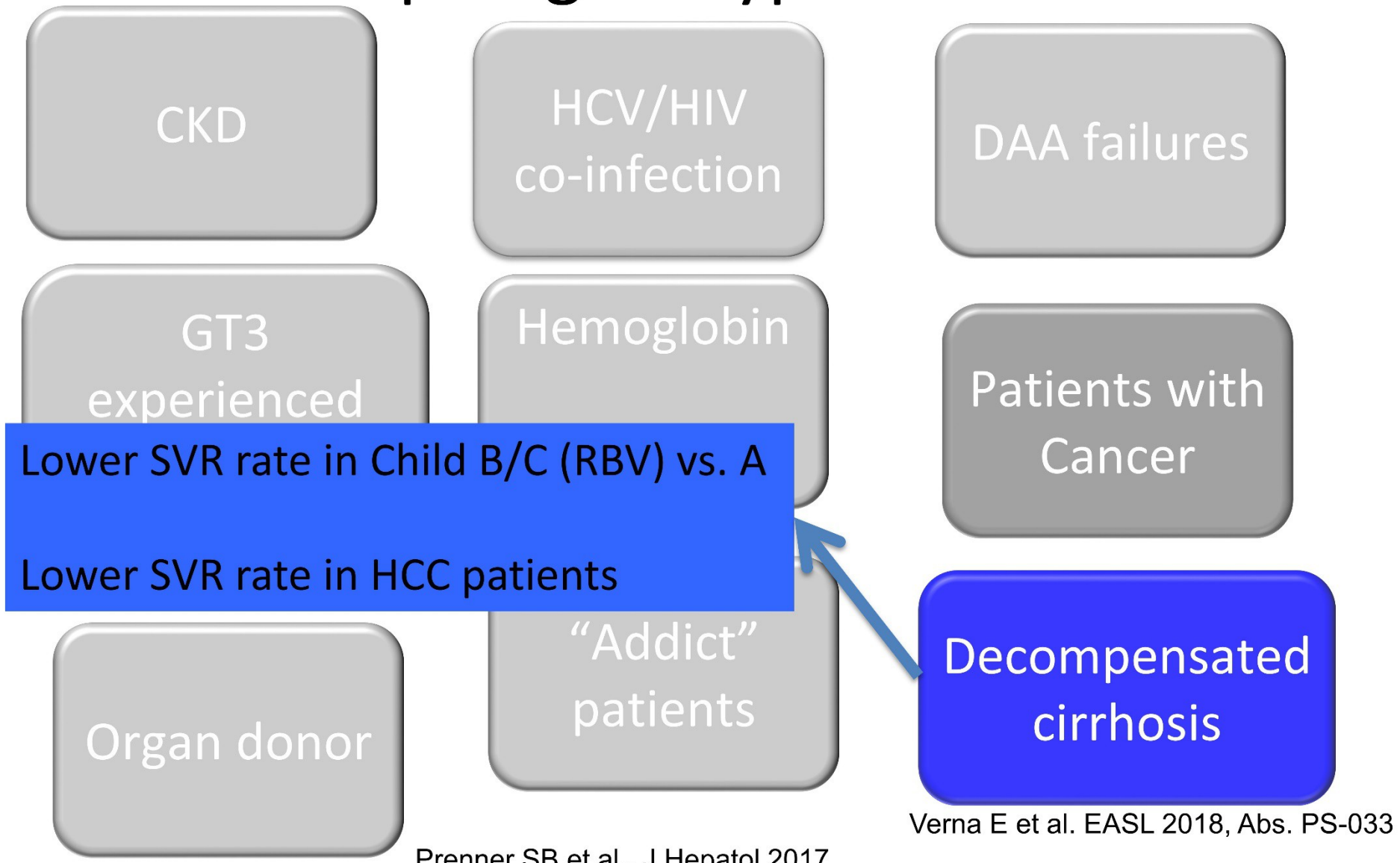
8 weeks : new standard in naïve non cirrhotics?



* 1 patient G1e excluded

Asselah T, et al. EASL 2018, Abs. GS-012 ; Abergel A, et al., EASL 2018, Abs. LBP-010 ;
Asselah T, et al. EASL 2018, Abs. GS-006 ; Boyle Aet al., EASL 2018, Abs. PS-034

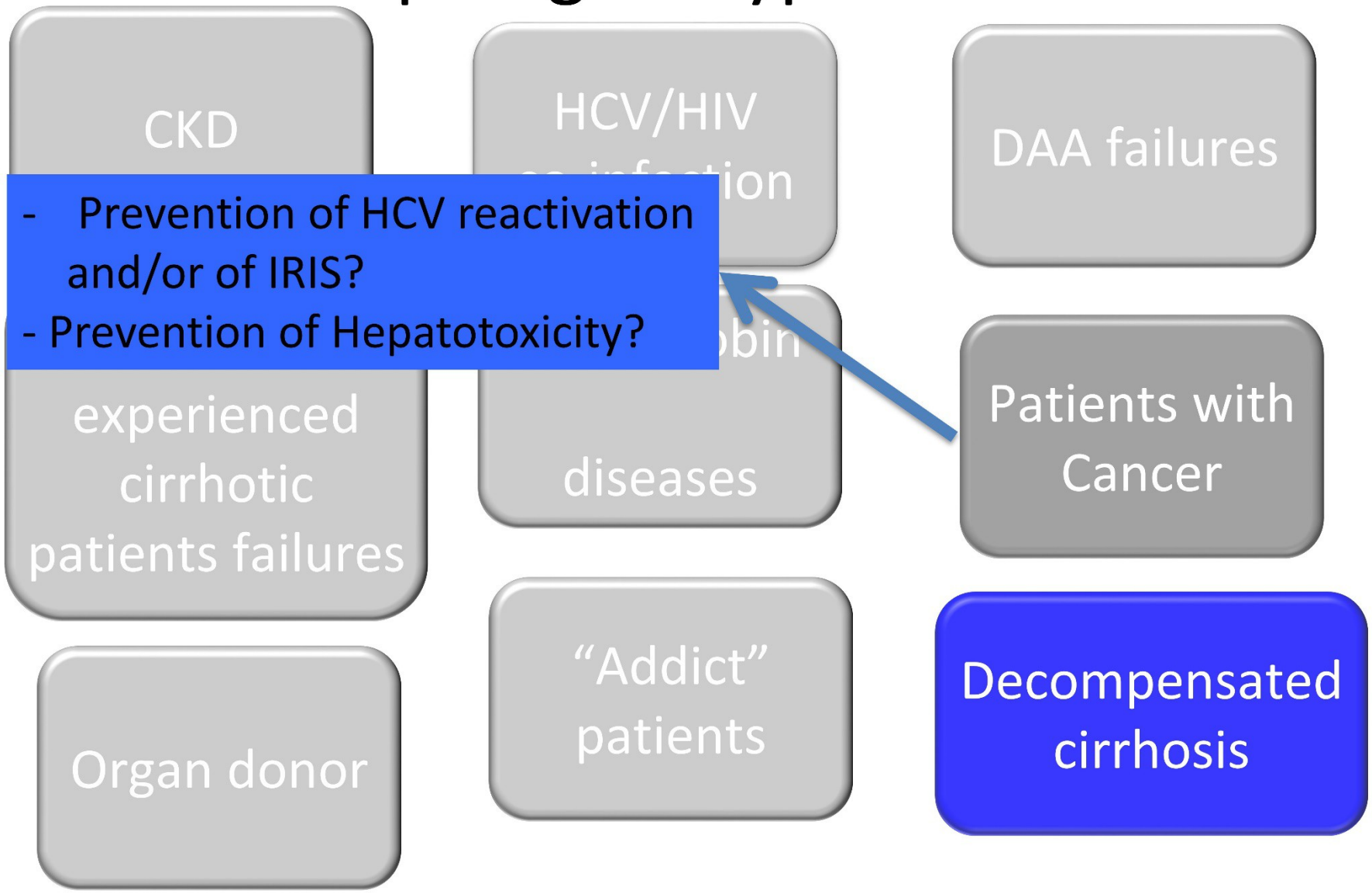
“Difficult-to-treat Populations” in the pan-genotypic era



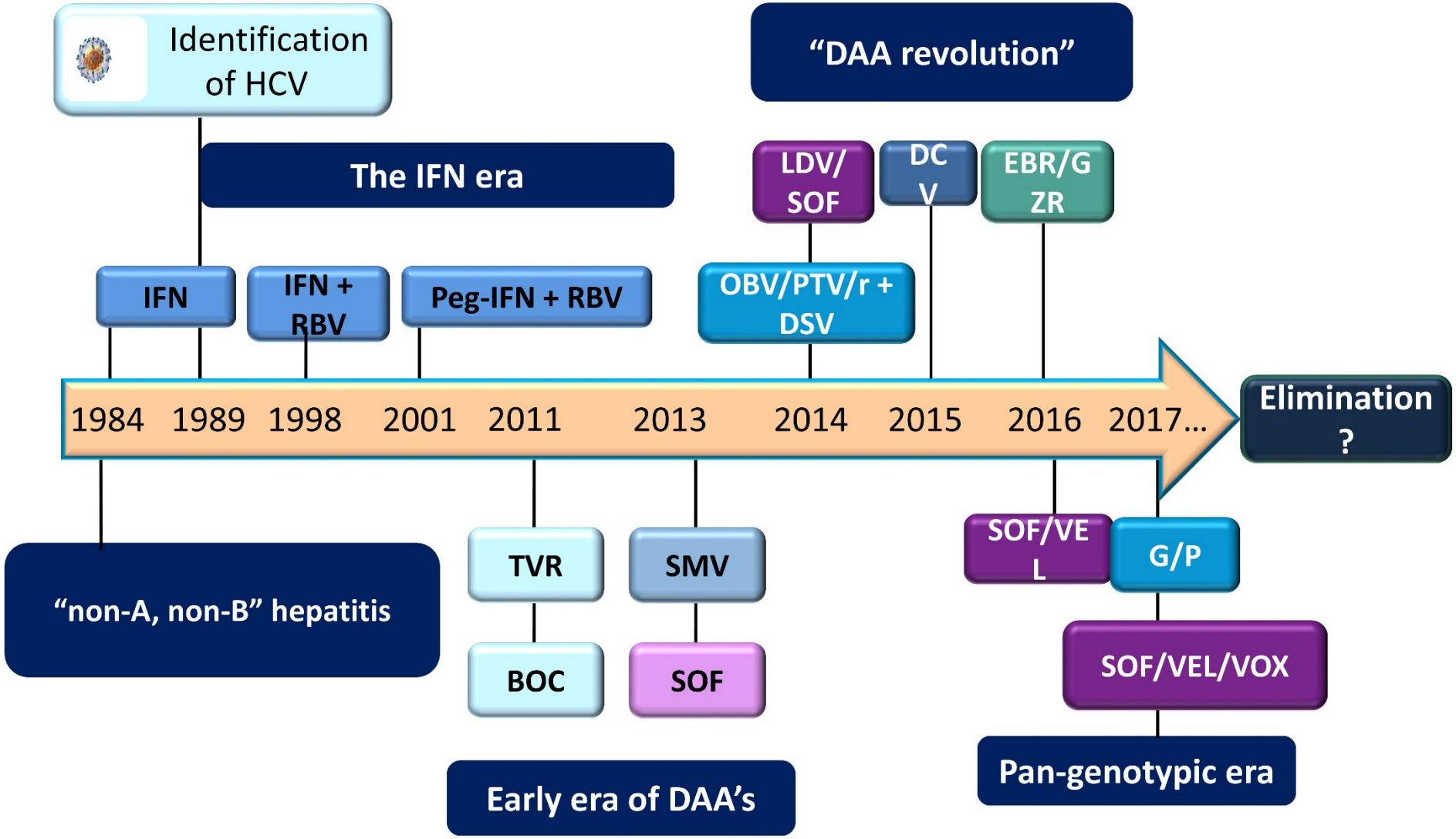
Verna E et al. EASL 2018, Abs. PS-033

Prenner SB et al., J Hepatol 2017

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



HCV Timeline: towards HCV Elimination



Pol S, et al. Nat Rev Dis Nephrol 2018

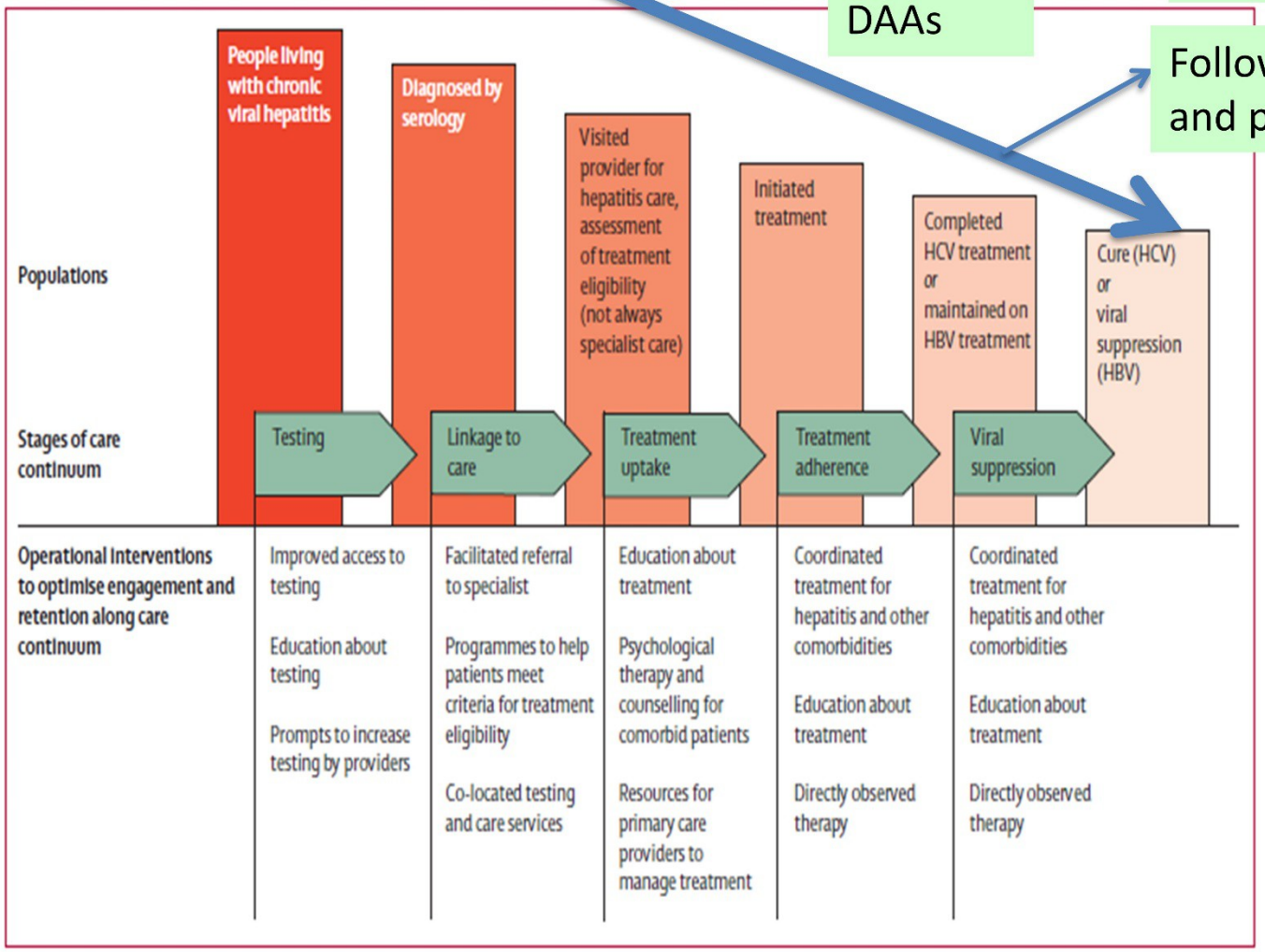
HCV cascade and Elimination

Screening

Access to care & DAAs

- Drug-drug interaction
- Adherence
- Safety

Follow-up of cured patients and prevention of re-infection



Zhou, Lancet Infect Dis 2016

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:**

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Ledipasvir/Sofosbuvir	Sofosbuvir/Velpatasvir
Lacosamide	◆	◆	◆	◆
Phenobarbital	●	●	●	●

- **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**

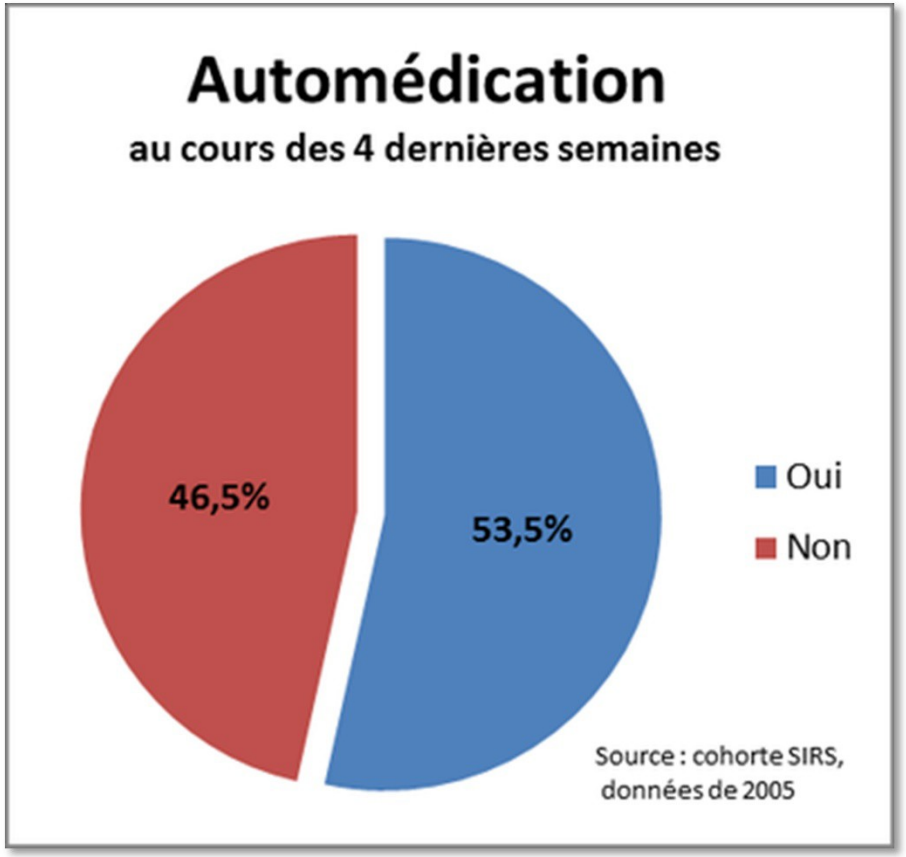
➢ **Dose-adjustment: limitation of the STR**

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

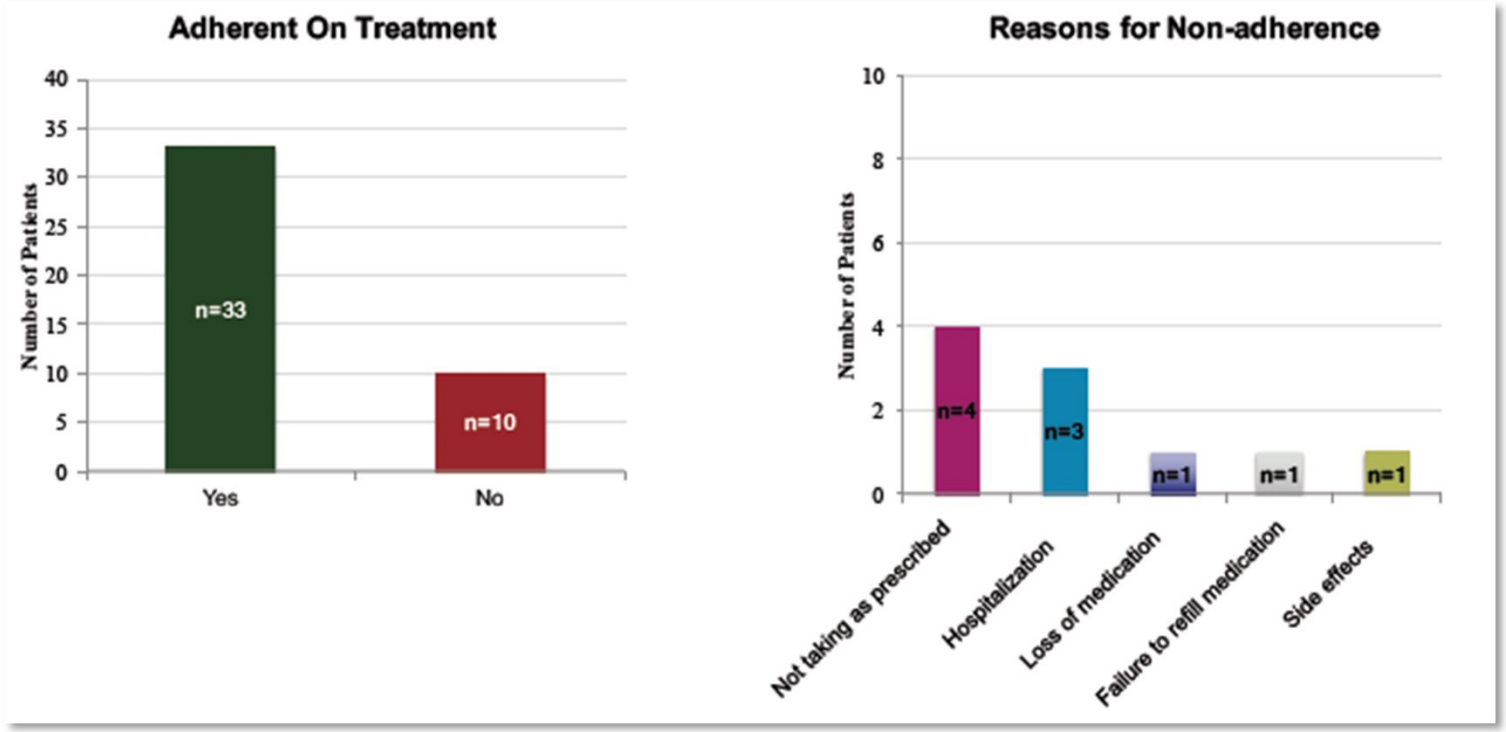
^ Data for 128 patients available

Sarpel D et al. AASLD 2016

Reasons of non-adherence

- Incapacity to take the drugs as prescribed

- Mean number of visits : lower in non-adherent patients



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

↓

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

Fontaine H et al. NEJM 2015

DAA and tolerance: HCC

France REcherche Nord & sud Sida-hiv Hépatites
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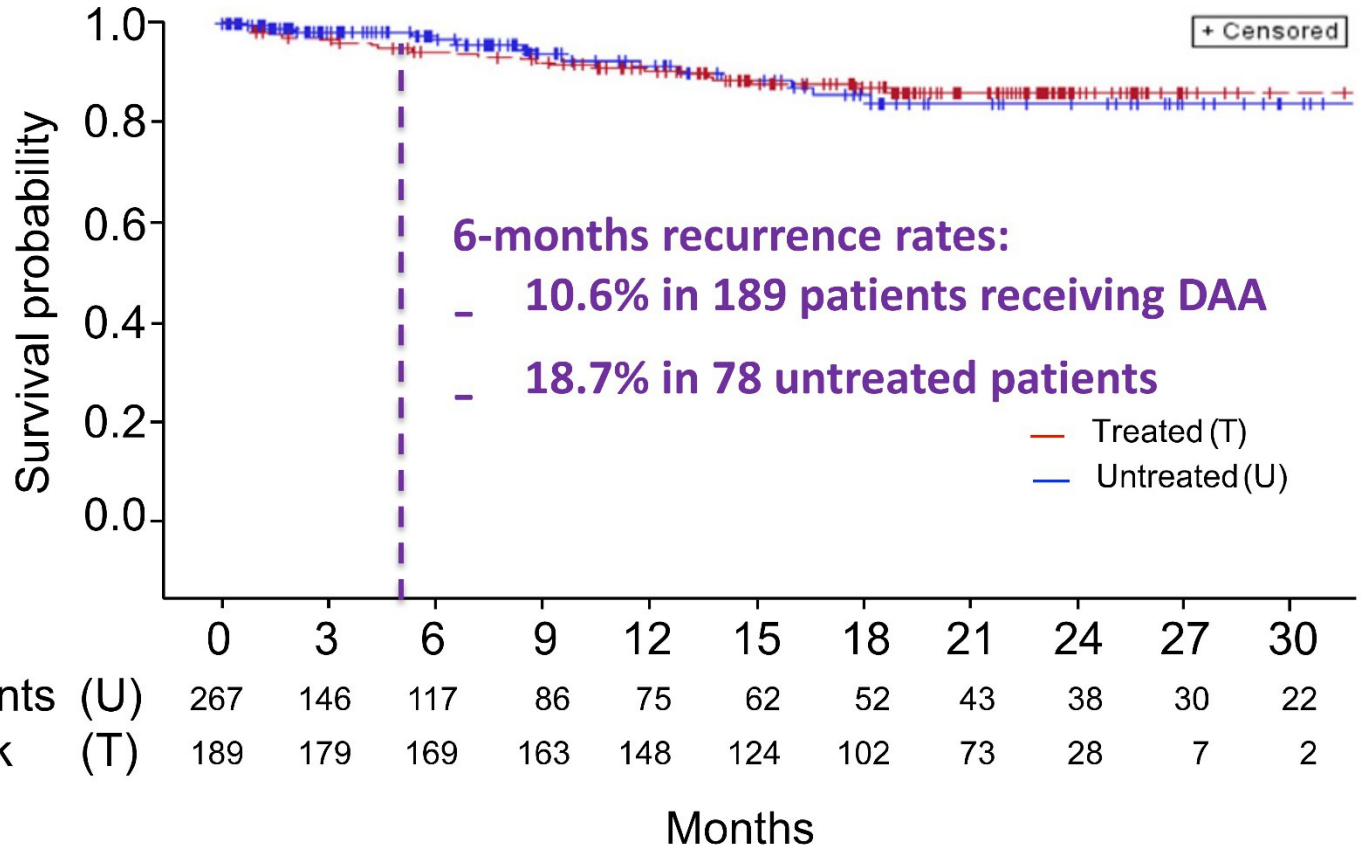
24 recurrences among 189 DAA+ patients (0.73/100 persons-month),

16 recurrences among 78 DAA- patients (0.66/100 persons-month)

P=0.8756

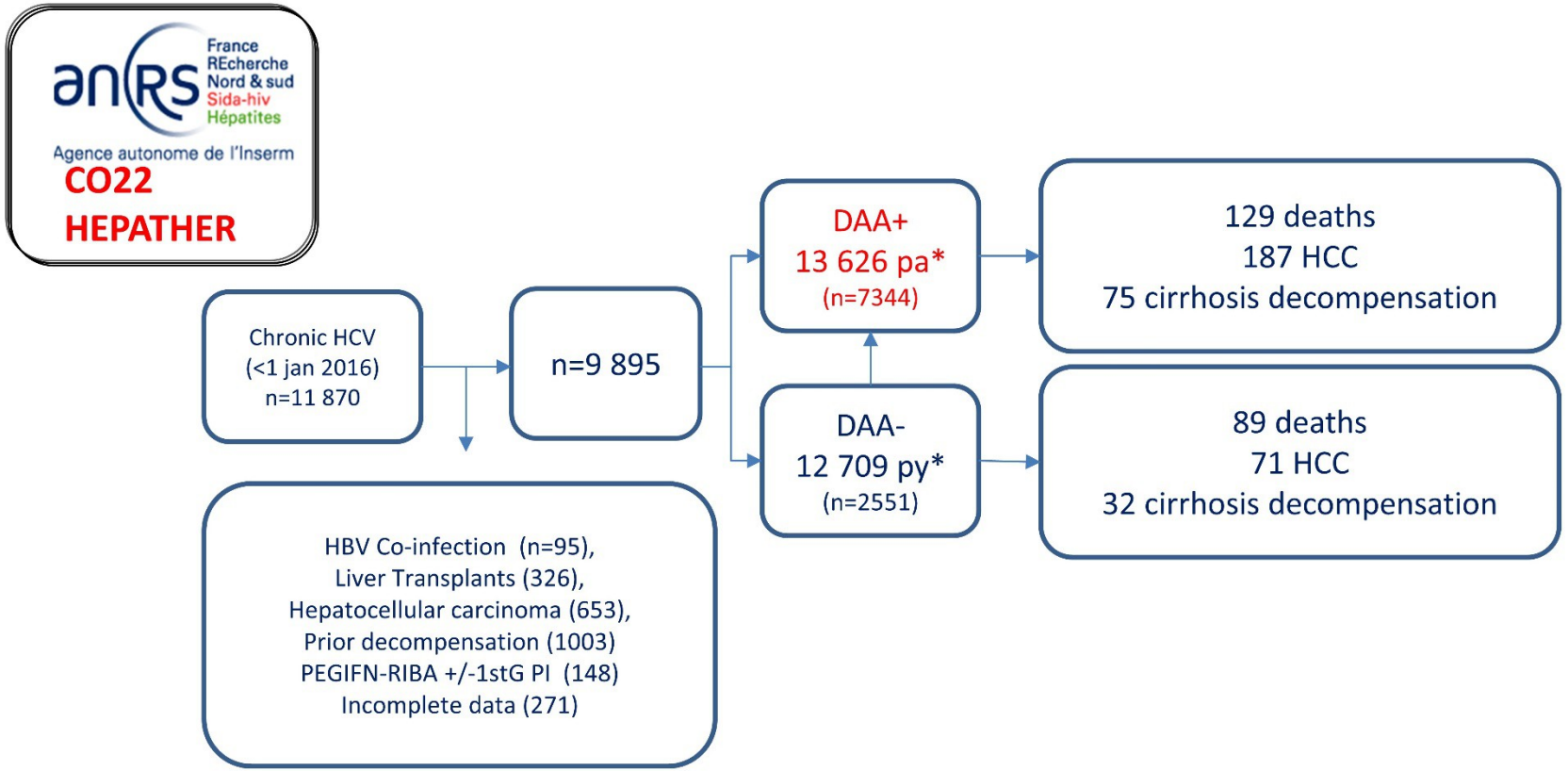
Recurrence of HCC according to DAA treatment



Multivariate adjusted HR for time-dependent DAA treatment (1.09 [95% CI 0.55–2.16], p =0.80)

AFEF/ANRS et al. J Hepatol 2016

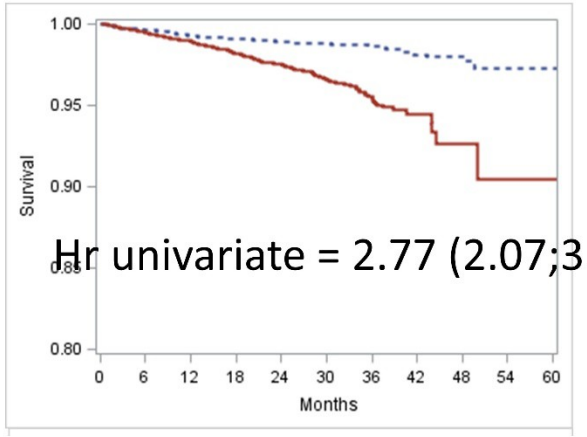
DAA and tolerance: HCC



*py = patients-year

Carrat F et al. The Lancet 2018 (In press)

DAA and tolerance: HCC



Hr univariate = 2.77 (2.07;3.71)

DAA+

DAA-

	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

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Carrat F et al. The Lancet 2018 (In press)

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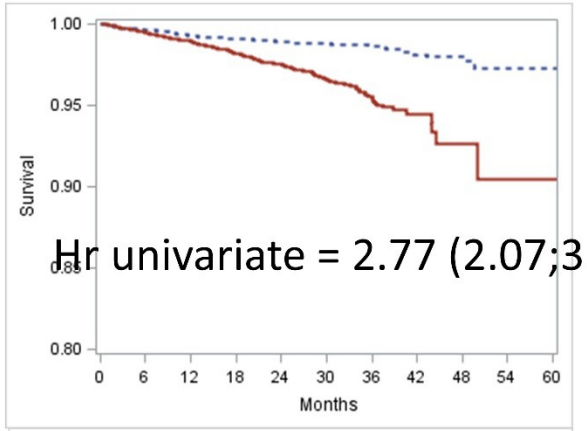
DAA and tolerance: HCC



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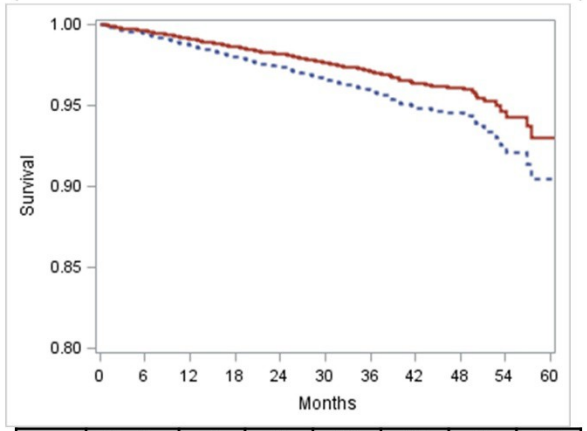

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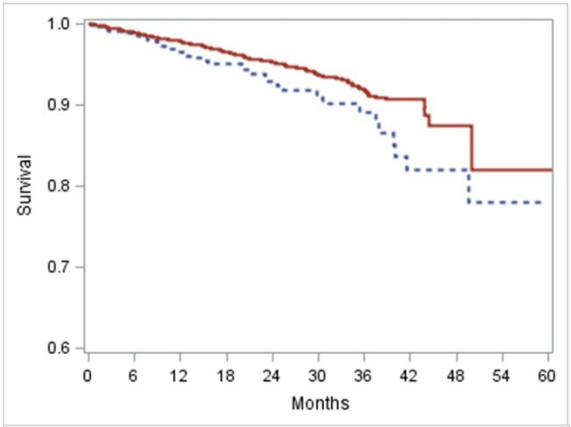
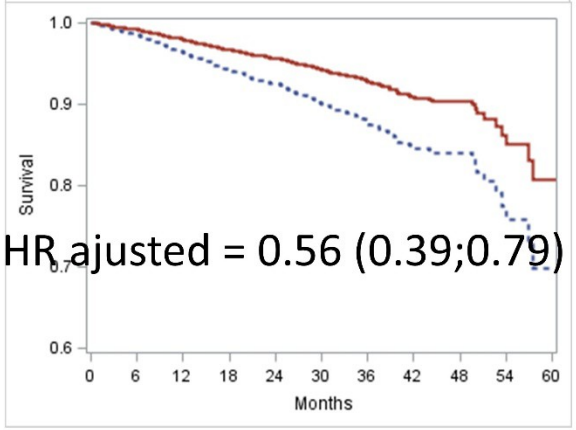
DAA+
DAA-





HR ajusted = 0.56 (0.39;0.79)

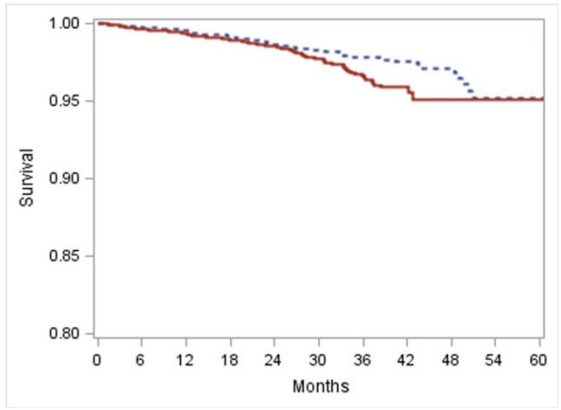
Risk of de novo HCC (all patients (n=9895) and cirrhotic patients (n=3039))

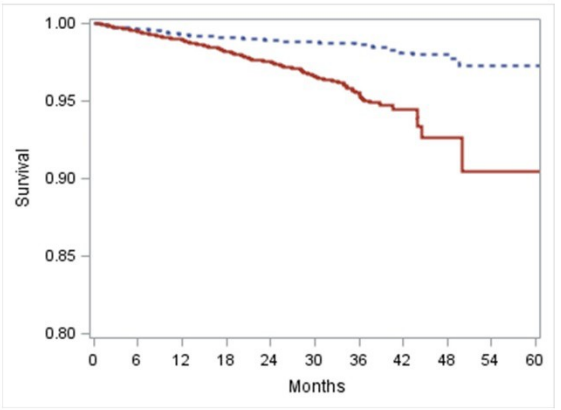
Carrat F et al. The Lancet 2018 (In press)

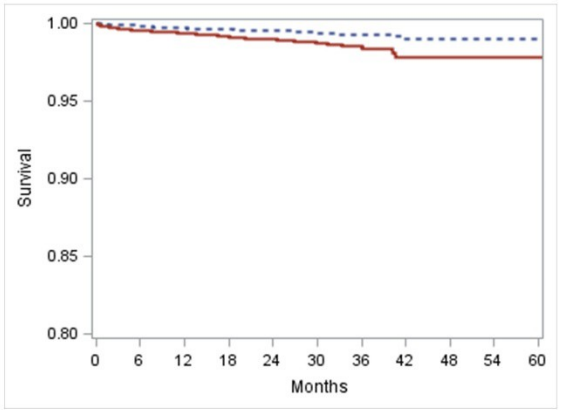
DAA and tolerance: HCC

All-cause mortality | Hepatocellular carcinoma | Decompensated cirrhosis

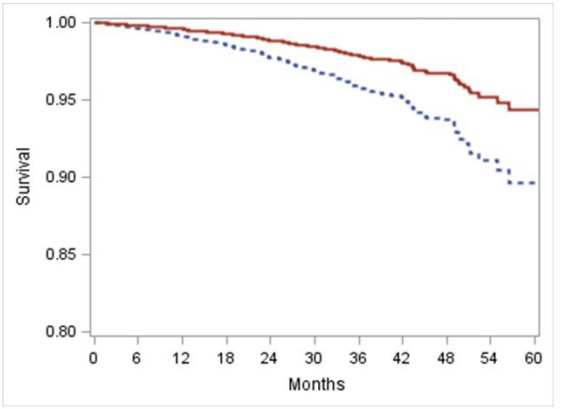
Unadjusted survival curves

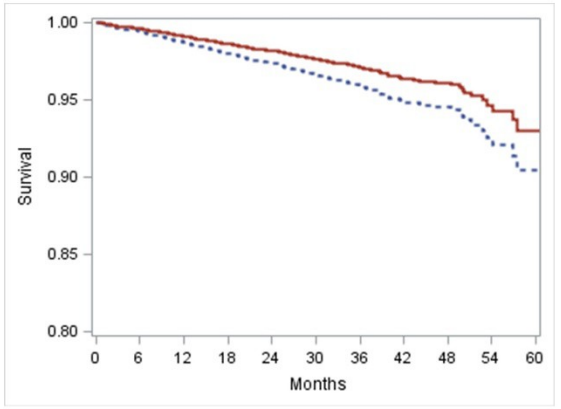


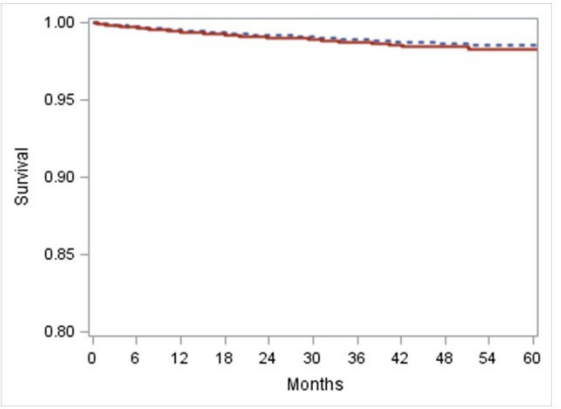




Multivariate-adjusted survival curves







	Months	0	12	24	36	48	60
N at risk	DAA+	7344	5448	3469	1012	59	6
	DAA-	9895	4774	2889	1344	360	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7308	5366	3368	977	57	6
	DAA-	9895	4751	2878	1337	355	10

	Months	0	12	24	36	48	60
N at risk	DAA+	7330	5408	3432	996	59	6
	DAA-	9895	4766	2888	1342	360	10

DAA+ DAA-

HCV treatment: : are there still difficulties to treat patients ?

- High & pangenotypic efficacy of the different regimens removed the « special » and almost the « difficult-to-treat » populations
- The 3 main remaining difficulties are mainly related to drug-drug interaction (including phytotherapy) and adherence
- Safety of DAAs is fair which does not exclude very rare and potentially severe adverse events nor their cautious prescription

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Stanislas Pol
Michelle Sizorn
Pierre Nahon
Linda Wittkop
Yazdan Yazdanpanah
Jean-Pierre Zarski
Fabien Zoulim