



SAHGEED

SOCIÉTÉ ALGÉRIENNE D'HÉPATO-GASTRO-ENTÉROLOGIE ET D'ENDOSCOPIE DIGESTIVE
ALGERIAN SOCIETY OF HEPATO-GASTRO-ENTEROLOGY AND DIGESTIVE ENDOSCOPY

الجمعية الجزائرية لأمراض الجهاز الهضمي والتنظير الهضمي

31 èmes Journées Nationales d'Hépato-Gastro-Enterologie

VHC : « Patients difficiles à traiter »
Conférence MSD

Pr Nabil DEBZI

Hépatologie

CHU Mustapha

EPIDÉMIOLOGIE

Population étudiée	Nombre de cas (n)	Séroprévalence (%)
Population à risque		
Les hémodialysés	68	36.8
Patients avec hémoglobinopathie	686	8.16
Les détenus (les personnes privées de liberté)	698	1.7
Les sujets infectés par le VIH	48	2.1
Les populations du Centre de dépistage Volontaire	4 715	3.11
Population générale		
La population du bilan prénuptial	12 849	0.74
Les donneurs de sang	43 189	0.23

Tableau 1 : Séroprévalence de l'hépatite virale C dans l'extrême Est Algérien [4]

L'Algérie est un pays de moyenne endémicité

La population des hémodialysés est la plus exposée Le génotype 1 est prédominant

Les patients difficiles à traiter

HEPATOLOGY, Vol. 62, No. 1, 2015

TERRAULT 5

Table 1. Difficult-to-Cure Patient Populations: Past and Present

	Past: Era of Peg-IFN and RBV	Present: Era of DAA Drug Combinations
Difficult to Cure	<ul style="list-style-type: none">• Genotype 1• High viral load, IL28B genotype TT• Treatment experienced• Cirrhosis• HIV coinfection• Elderly• Autoimmune diseases• Decompensated cirrhosis• Transplant recipients• Interferon intolerant• RBV intolerant• Noncompliant• Methadone maintenance• Active drug use• Mental health comorbidities• Underinsured	<ul style="list-style-type: none">• Cirrhosis, decompensated• Genotype 3, treatment-experienced cirrhosis• DAA failures
Difficult to Treat		<ul style="list-style-type: none">• ESRD/dialysis• Ribavirin intolerant• On medications that interact with HCV DAAs• Noncompliant
Difficulty with Access		<ul style="list-style-type: none">• Active drug use• Mild-to-moderate HCV disease• Underinsured

Les patients difficiles à guérir

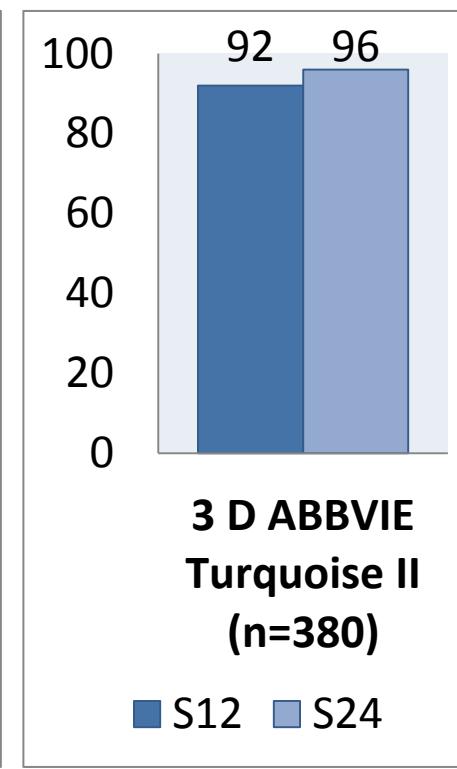
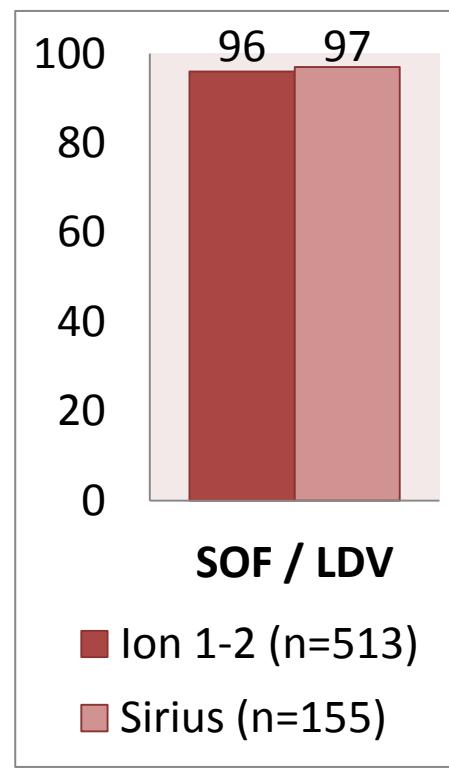
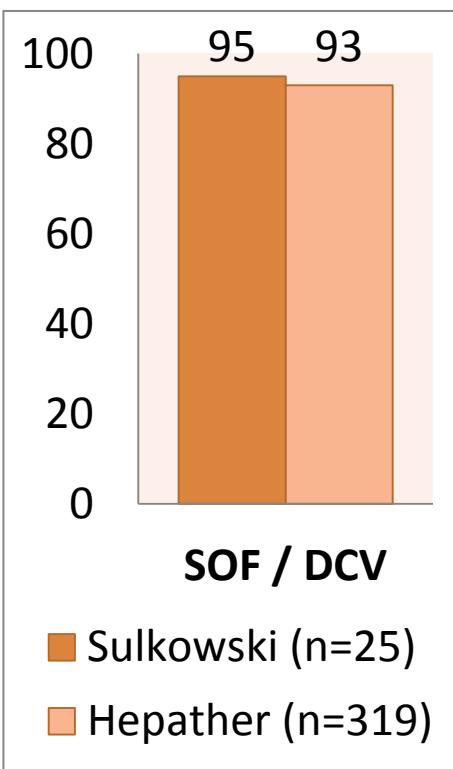
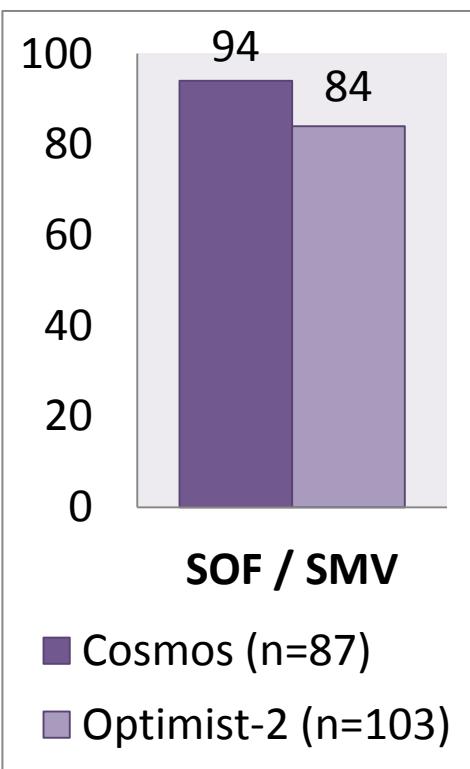
Cirrhoses décompensées

Les G3 , prétraités cirrhotiques

Échec AAD

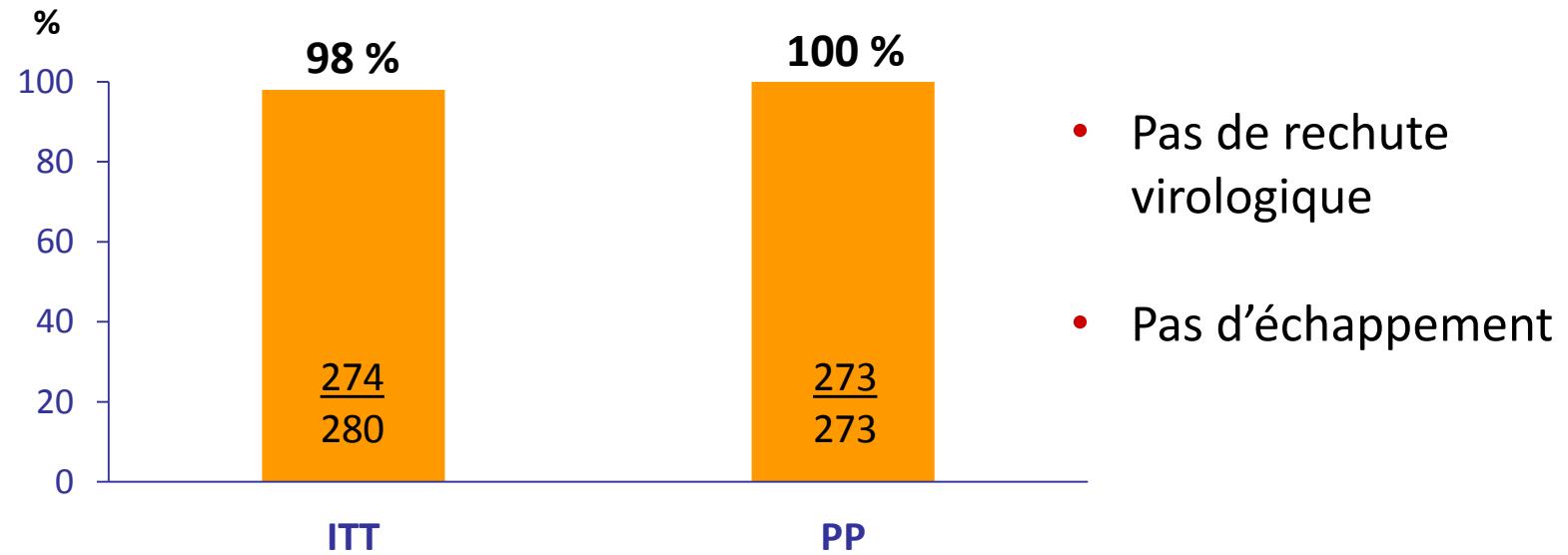
Efficacité anti-viraux directs en pré-greffe

Excellente en cas de cirrhose compensée
SVR 12 > 90%



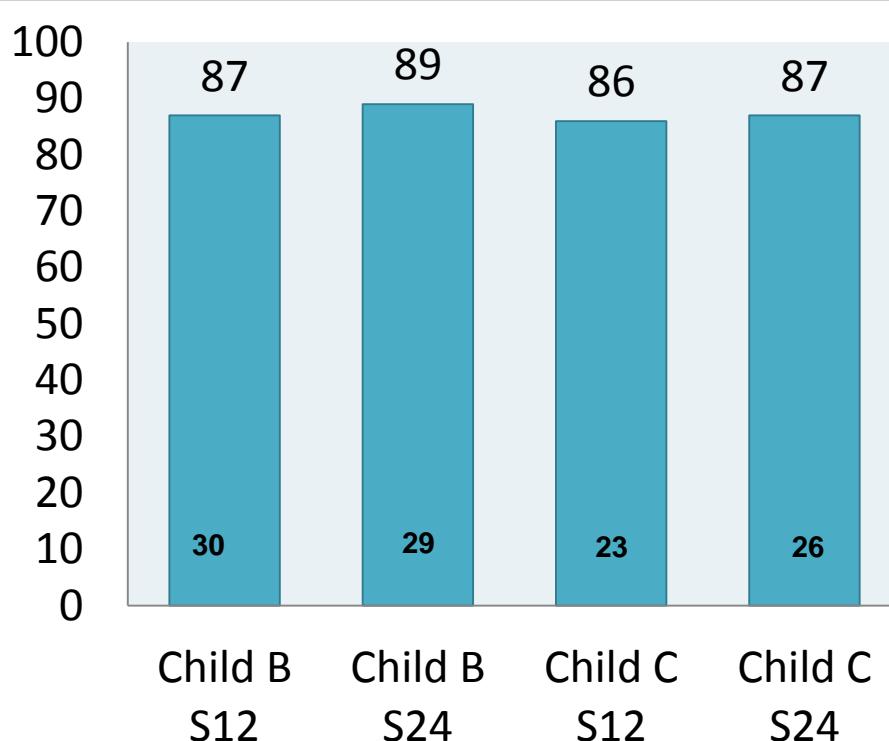
Glecaprevir/pibrentasvir 8 semaines chez les patients avec cirrhose de G1, G2, G4-6 (2)

Réponse virologique soutenue (RVS12)

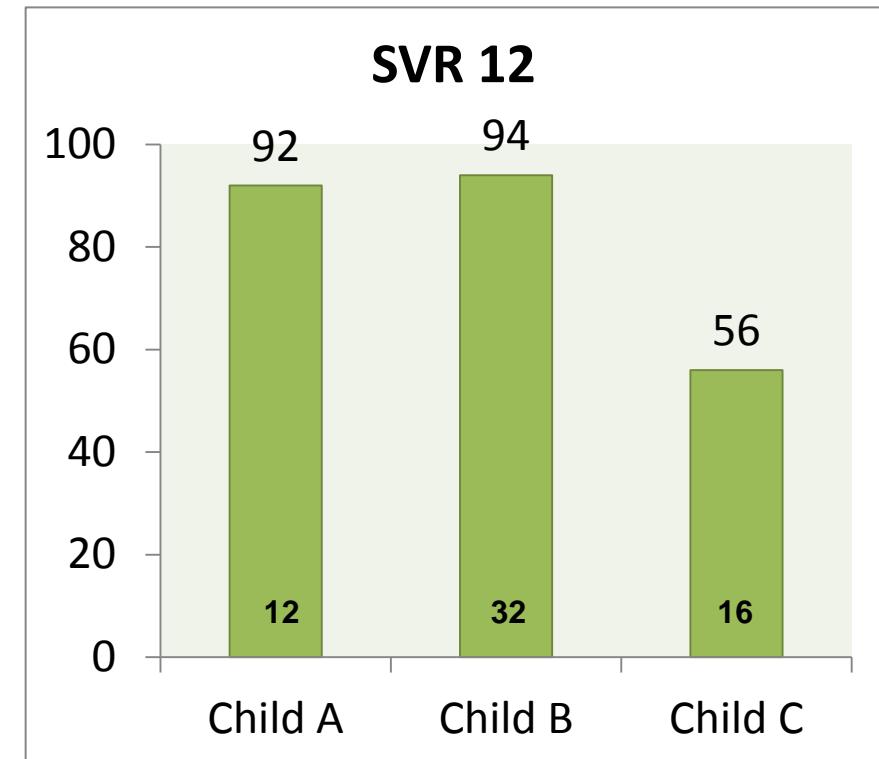


→ Excellente efficacité de la combinaison G/P 8 semaines chez les patients avec cirrhose naïfs de traitement de G1, G2, G4-6

... mais efficacité limitée en cas de cirrhose décompensée



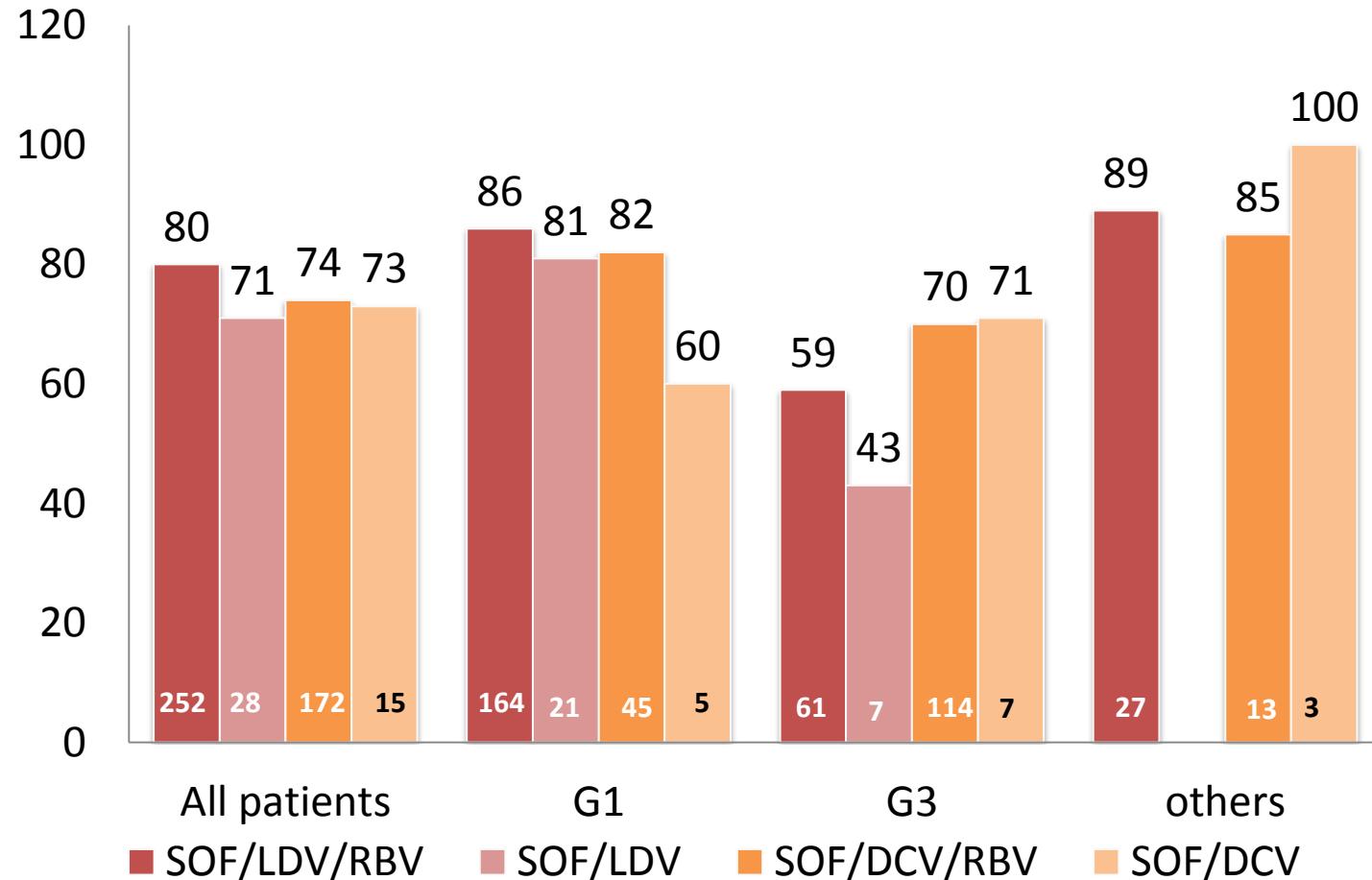
SOF + LDV +/- RBV – 12/24 semaines
SOLAR 1



SOF + DCV + RBV – 12 semaines
ALLY-1

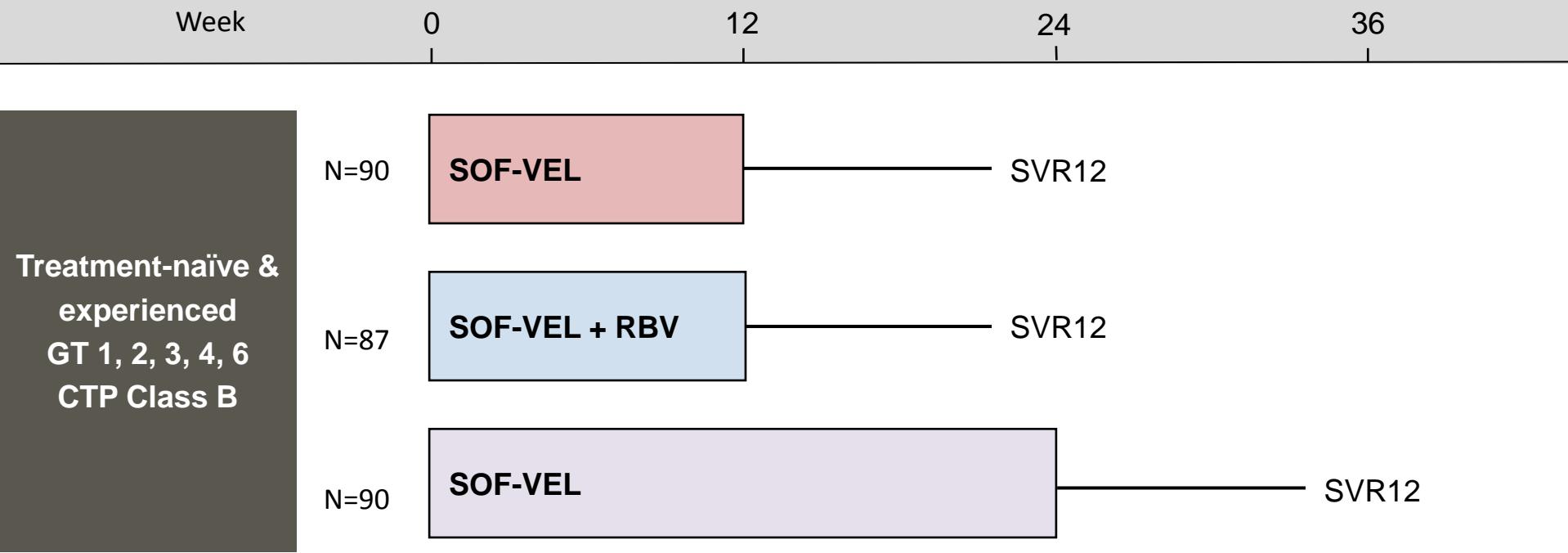
Les résultats de la « vraie vie » sur l'efficacité des AAD en cas de cirrhose Child B/C

12 semaines; CPT B 66%, CPT C 10%- MELD median 11,9; Ascite 38,1 % , RVO 27,2%, EH 17,1%



Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis

ASTRAL-4: Study Design



Abbreviations: SOF-VEL = sofosbuvir-velpatasvir; RBV = ribavirin

Drug Dosing

Sofosbuvir-velpatasvir (400/100 mg): fixed-dose combination; one pill once daily

Sofosbuvir: 400 mg once daily

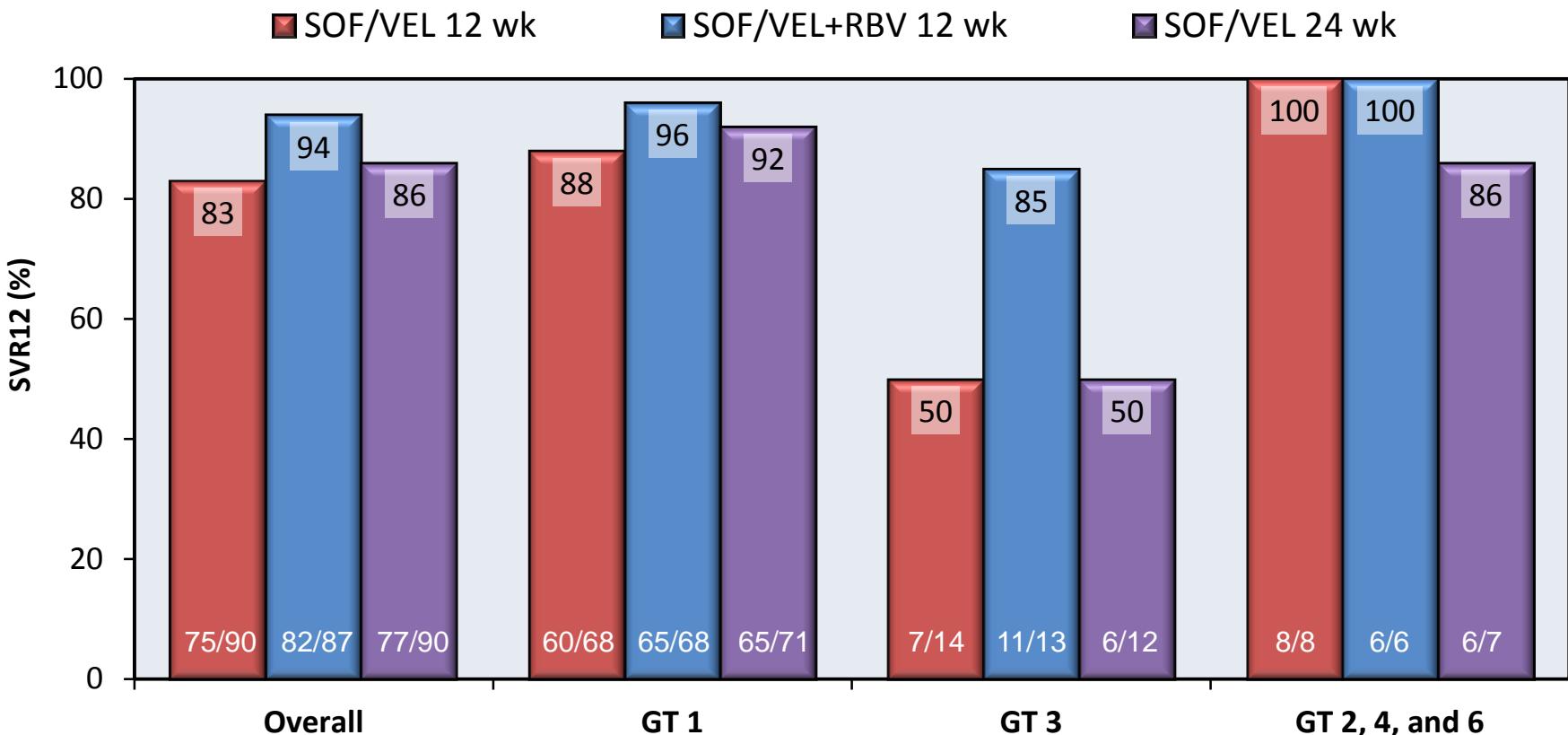
Ribavirin (weight-based and divided bid): 1000 mg/day if < 75 kg or 1200 mg/day if ≥ 75 kg

Source: Curry MP, et al. N Engl J Med. 2015;373:2618-28.

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis

ASTRAL-4: Results

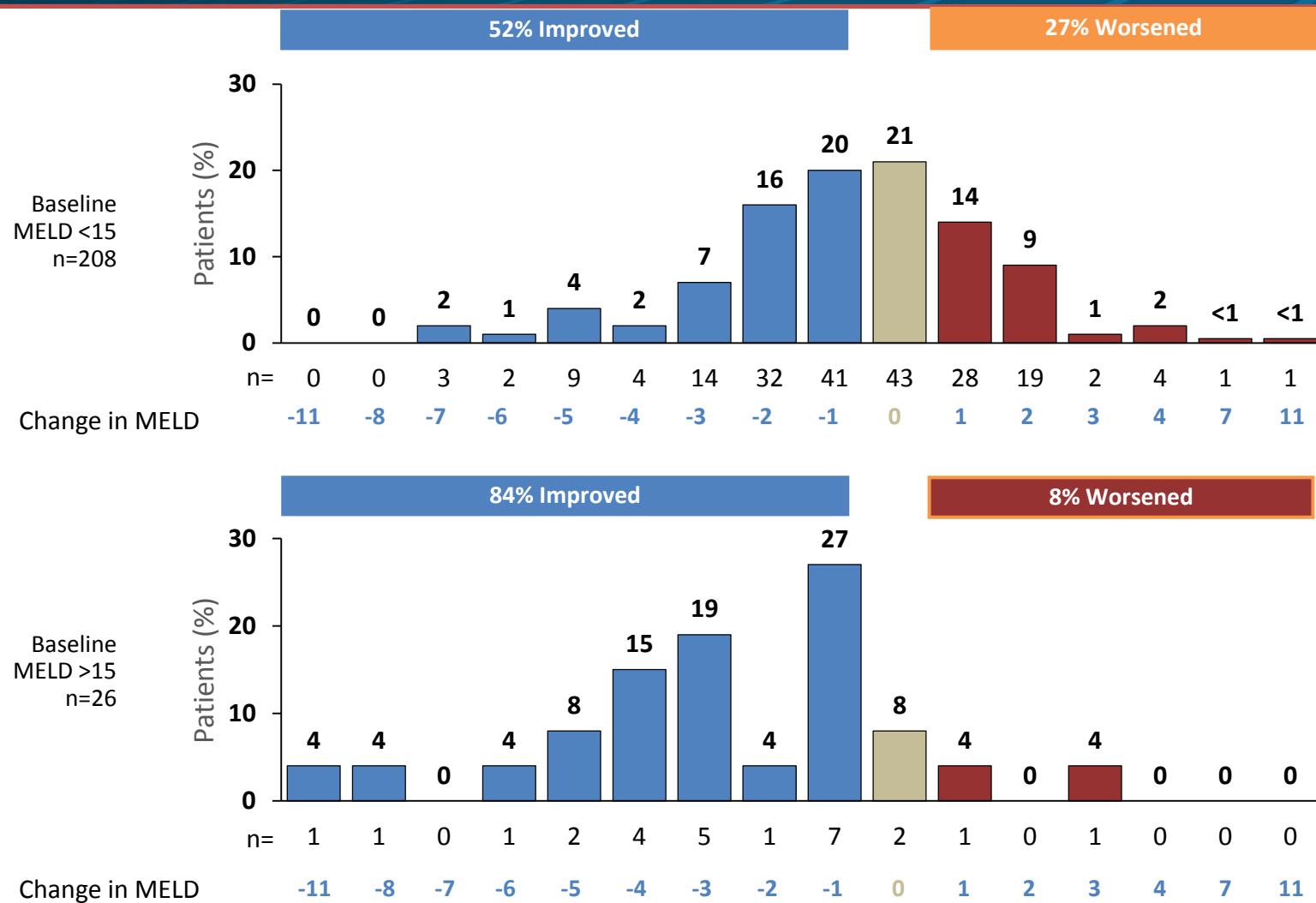
ASTRAL-4: SVR12 Results by Genotype



Source: Curry MP, et al. N Engl J Med. 2015;373:2618-28.

Sofosbuvir-Velpatasvir in Decompensated HCV Cirrhosis

ASTRAL-4: Change in MELD Scores on Treatment



Source: Curry MP, et al. N Engl J Med. 2015;373:2618-28.

Cirrhose décompensée

Durée attente sur liste attendue
> 3 mois

MELD < 20

Amélioration
MELD

Efficacité ++ /
Tolérance ++

MELD 20-25

Peu amélioration du
MELD

Efficacité + / Tolérance +

Durée attente sur liste
attendue < 2-3 mois

MELD > 25

Durée ARN indétectable <
30j

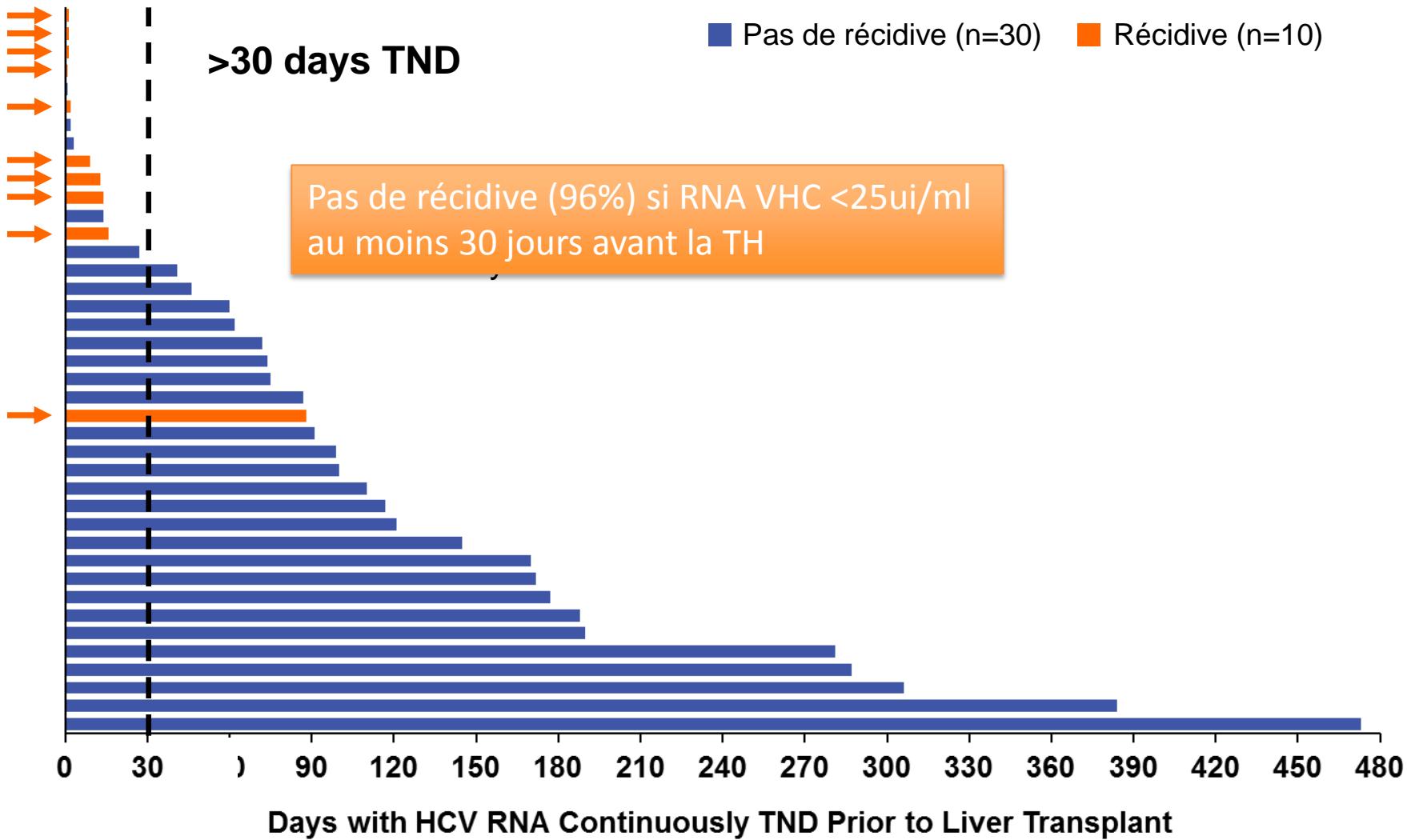
Efficacité –
/ Tolérance ?

Discussion au cas par cas

Traitements avant la greffe

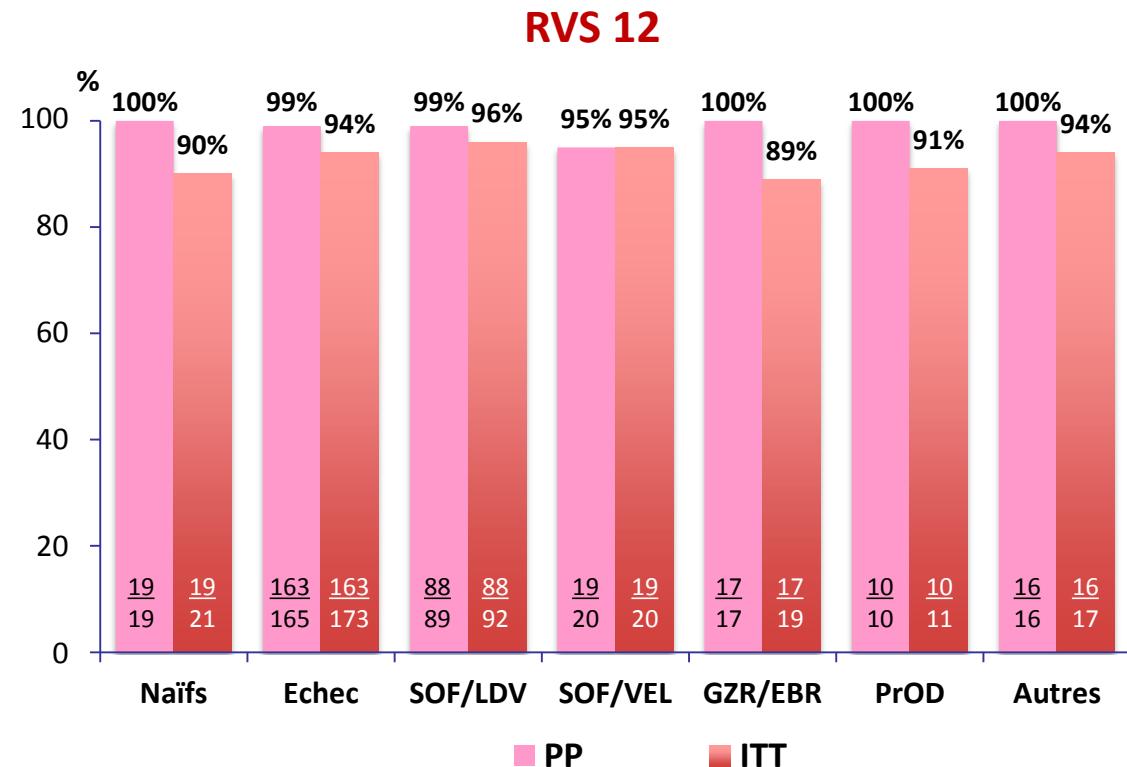
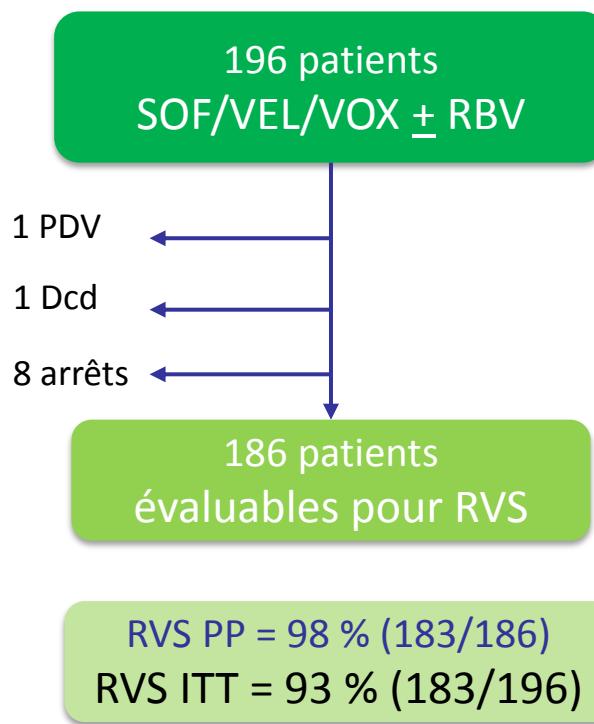
Traitements après la greffe

Le risque de récidive est inversement proportionnel au nombre de jours consécutifs d'indétectabilité du VHC avant la TH



SOF/VEL/VOX chez les patients en échec d'AAD

- Cohorte TRIO : 196 patients en échec d'AAD traités par SOF/VEL/VOX 12 sem.
 - Cirrhose : 42 % ; VIH+ : 3 % ; G1 : 78 % ; G3 : 16 % ; G2 : 3 % ; G4-6 : 3 % ; CKD stade 1-3 : 43 %
 - Diabète : 21 % ; HTA : 41 % ; dyslipidémie : 11 %

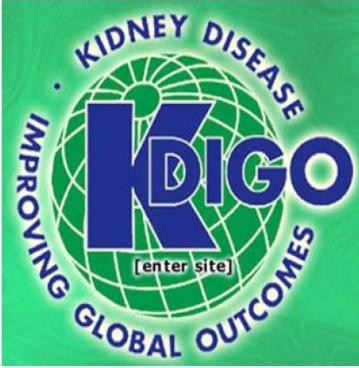


→ SOF/VEL/VOX efficace chez les patients en échec d'AAD

Les patients difficiles à traiter

IRC et dialysés

Interactions médicamenteuses



Dépistage

1.1.1 Il est suggéré de tester pour l'hépatite C les patients atteints de maladie rénale chronique (faible).

1.1.2 Les patients en hémodialyse chronique (MRC stade 5D) et les candidats à une transplantation rénale doivent être testés pour le VHC (forte).

1.2.1 Les patients en hémodialyse doivent être testés pour le VHC à l'initiation de l'hémodialyse ou lors du transfert d'une autre unité d'hémodialyse (forte).

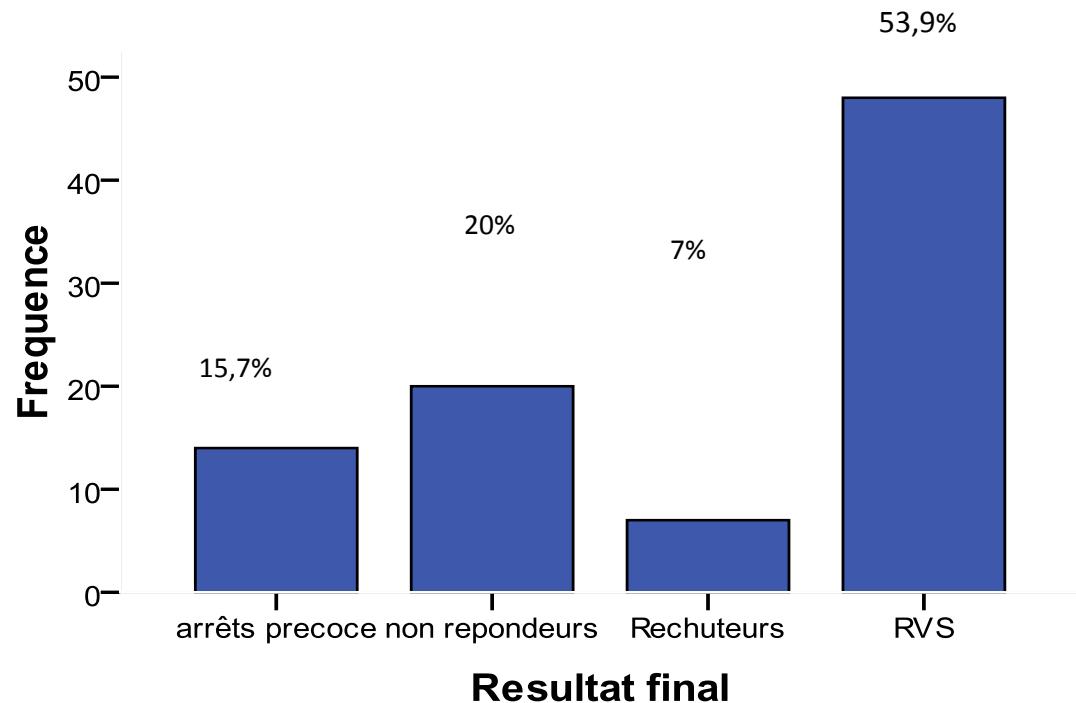
- **Dans les unités d'hémodialyse dont la prévalence VHC est basse, la recherche du VHC devrait être initiée par un test immuno-enzymatique (suivi en cas de positivité par un test moléculaire (à la recherche de l'ARN du VHC)) (modérée).**
- **Dans les unités d'hémodialyse dont la prévalence VHC est élevée, un test moléculaire doit être envisagé d'emblée (modérée).**

MSPRH 2008 – Hemodialysis

serology	Samples	%
Hbs Ag	788	10.50
Ab anti Hbc	757	10.08
Vaccine Ab Anti Hbs	1857	24.43
Immunity Ab anti Hbc Ab Anti Hbs	2075	27.72
AC anti VHC	7503	23.8

Résultats virologiques Thése DESM H.MAHIOU IFNPEG RBV

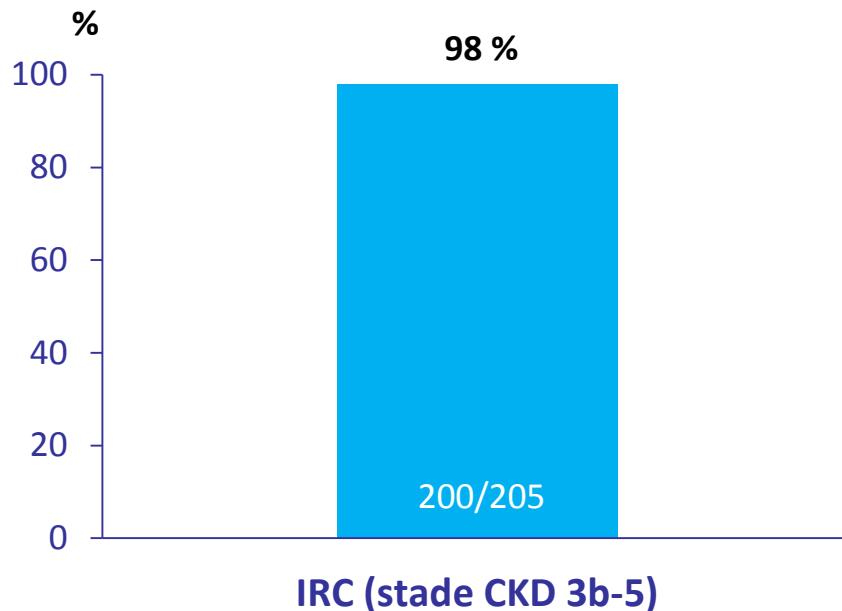
N=89, Sex ratio H/F =1,17,Age moyen $45,62 \pm 12,27$ (18-72)



Glecaprevir/pibrentasvir chez les patients VHC insuffisants rénaux (stade CKD 3b-5) (1)

- Analyse poolée des études EXPEDITION-4 et 5

RVS 12



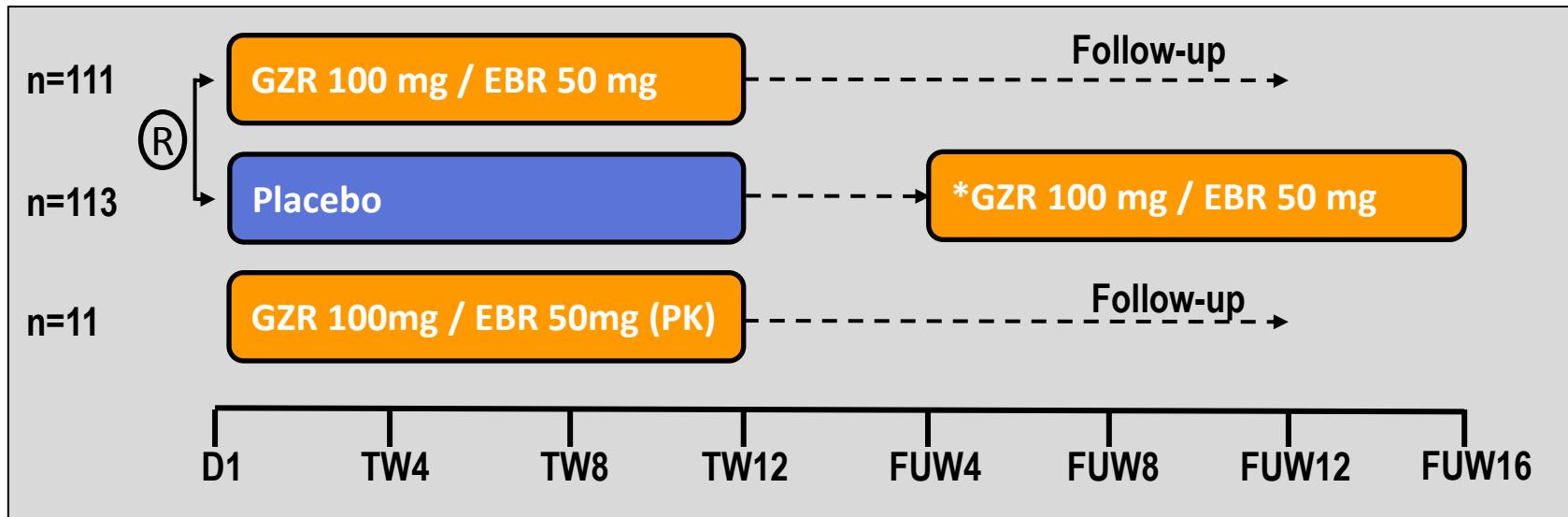
Cause de non réponse	n (%)
Echappement	0
Rechute	0
Arrêts prématurés	3 (1 %)
Perdus de vue	2 (1 %)*

* Les 2 patients étaient ARN VHC – à S2 pour le patient décédé et à S24 pour l'autre

→ L'association pan génotypique G/P est efficace chez les patients VHC avec IRC

C-SURFER STUDY DESIGN

Elbasvir
(50 mg) Grazoprevir
(100 mg)



- Background: <1% of EBR/GZR is renally excreted. A Phase 1 trial demonstrated no need for dose adjustments in patients with CKD
- Randomized, parallel-group, multi-site, placebo-controlled trial
- Stratification by diabetes (yes/no) and hemodialysis status (HD/non-HD)
- 224 patients randomized to immediate treatment with EBR/GZR or deferred treatment where patients received placebo for 12 weeks then open-label EBR/GZR starting at FUW4
- 11 patients in open-label GZR/EBR arm underwent intensive pharmacokinetic sampling

*Deferred open-label treatment arm. All randomized patients received blind treatment initially.

GZR and EBR were administered as separate entities in the immediate and PK arms, and as a fixed dose-combination in the deferred arm. CKD = chronic kidney disease; GT = genotype; HD = hemodialysis; R = randomized

C-SURFER BASELINE CHARACTERISTICS

Elbasvir
(50 mg)

Grazoprevir
(100 mg)

	GZR + EBR (ITG + PK group) 12 weeks (n = 122)	Placebo (DTG) 12 weeks (n = 113)
Gender, n (%)		
Male	92 (75)	80 (71)
Female	30 (25)	33 (29)
Race, n (%)		
White	61 (50)	48 (43)
African-American	55 (45)	53 (47)
Asian	5 (4)	9 (8)
Other	1 (<1)	3 (3)
HCV genotype, n (%)		
G1a	63 (52)	59 (52)
G1b	58 (48)	53 (47)
G1 other	1 (<1)	1 (<1)
Prior treatment history, n (%)		
Naive	101 (83)	88 (78)
Experienced	21 (17)	25 (22)
Cirrhosis, n (%)	7 (6)	7 (6)
Diabetes, n (%)	44 (36)	36 (32)
Dialysis, n (%)	92 (75)	87 (77)
CKD stage, n (%)		
stage 4	22 (18)	22 (19)
stage 5	100 (82)	91 (81)

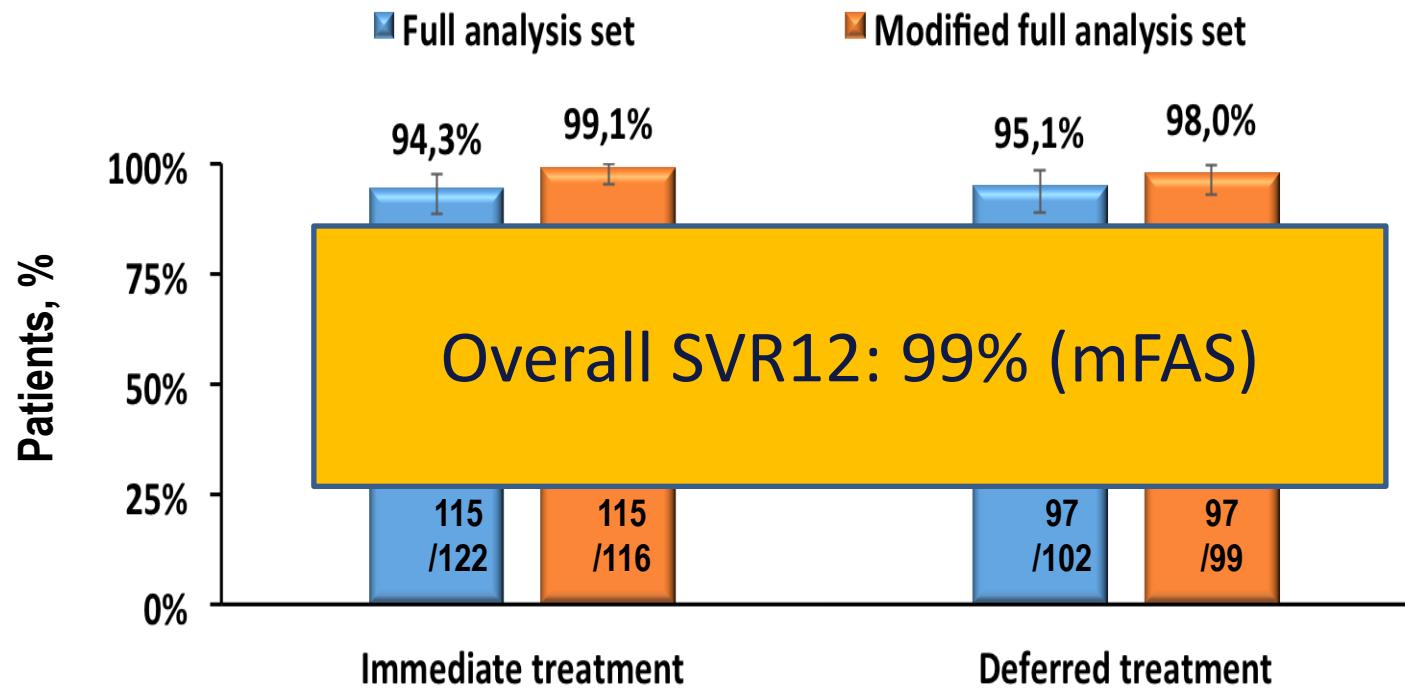
DTG = deferred treatment group; ITG = immediate treatment group; PK = intensive PK group

Roth D et al. *Lancet.* 2015;386:1537-1545; 2. Roth D et al. Poster presented at: Kidney Week 2015; November 2015; San Diego, CA.

C-SURFER SVR12: IMMEDIATE AND DEFERRED TREATMENT ARMS

Elbasvir
(50 mg)

Grazoprevir
(100 mg)



Relapse

1^a

1

2^c

2

D/c unrelated to treatment

6^b

0

3^d

0

MFAS = primary efficacy analysis; Tx = treatment.

FAS was a secondary analysis

^aNoncirrhotic, interferon-intolerant patient with HCV GT1b infection relapsed at

^bLost to follow-up (n = 2), n = 1 each for death, noncompliance, withdrawal by subject,

^cTwo patients in the DTG relapsed, both with G1a infection, relapsed at FW4 and FW12

^dWithdrawal by subject, n = 1; AE, n = 1; death, n = 1.

C-SURFER ADVERSE EVENTS

Elbasvir
(50 mg)

Grazoprevir
(100 mg)

	EBR/GZR (ITG) (n = 111)	EBR/GZR (DTG) (n = 102)	Placebo (DTG) (n = 113)	Difference in % Estimate ITG vs placebo (95% CI)
AEs, ^a n (%)	84 (75.7)	61 (59.8)	95 (84.1)	-8.3 (-18.9, 2.2)
Headache	19 (17.1)	7 (6.9)	19 (16.8)	0.3 (-9.6, 10.4)
Nausea	17 (15.3)	10 (9.8)	18 (15.9)	-0.6 (-10.3, 9.1)
Fatigue	11 (9.9)	9 (8.8)	17 (15.0)	-5.1 (-14.1, 3.7)
Insomnia	7 (6.3)	2 (2.0)	12 (10.6)	-4.3 (-12.2, 3.2)
Dizziness	6 (5.4)	5 (4.9)	18 (15.9)	-10.5 (-19.1, -2.6)
Diarrhea	6 (5.4)	5 (4.9)	15 (13.3)	-7.8 (-16.1, -0.2)
Serious AEs, n (%)	16 ^b (14.4)	13 ^c (12.7)	19 (16.8)	-2.4 (-12.1, 7.3)
Discont. due to an AE, n (%)	0 (0)	3 (2.9)	5 (4.4)	-4.4 (10.0, -1.0)
Deaths, ^d n (%)	1 (0.9)	0 (0)	3 (2.7)	-1.8 (-6.7, 2.5)

SAE = serious adverse event.

^aReported in ≥10% of patients in either treatment group (ASaT).

^b1 SAE in the DTG (placebo) was considered drug-related (elevated lipase level).

^c1 SAE in the DTG (EBR/GZR) was considered drug-related (interstitial nephritis).

^d1 ITG patient died of cardiac arrest and 3 DTG patients died of aortic aneurysm, pneumonia, and unknown cause.



Guide national pour la prise en charge VHC et VHB

L'association Grazoprevir-Elbasvir en cours d'enregistrement est le traitement approprié pour l'insuffisance rénale chronique et pour les contre-indications du sofosbuvir . Cette combinaison est indiquée pour les génotypes 1 et 4^[30].

Point of Reference on Drug-Drug Interactions

www.hep-drudinteractions.org

The image shows a composite screenshot. On the left is a large rectangular frame containing the University of Liverpool logo and the text "UNIVERSITY OF LIVERPOOL". Below this is a section titled "DRUG INTERACTION CHARTS" featuring a 3D-style grid of colored squares (blue, yellow, green) representing interaction data. To the right of the grid is the text "Access our comprehensive, user-friendly, free, drug interaction charts" and a red "CLICK HERE" button. At the bottom of this section is the text "Providing clinically useful, reliable, up-to-date, evidence-based information". A red arrow points from a box labeled "Online site" to the top-left corner of this frame. On the right side of the composite is a smaller rectangular frame showing a smartphone screen displaying the "Welcome to Liverpool HEP iChart" interface. The phone screen includes the university logo, the text "Welcome to Liverpool HEP iChart", "Providing summary data of drug interactions. Full details available at www.hep-drudinteractions.org", and buttons for "Sponsors", "Disclaimer", and "Start Drug Interactions". A red arrow points from a box labeled "Mobile app" to the top-right corner of this frame.

DDI: Estrogens

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir/Voxilaprevir
Estradiol	◆	▲	▲
Ethinylestradiol	◆	●	●

- Do Not Coadminister ■ Potential Interaction ▲ Potential Weak Interaction ◆ No Interaction Expected ✦ No Clear Data
- Do Not Coadminister □ Potential Interaction ▲ Potential Weak Interaction ◆ No Interaction Expected ✦ No Clear Data

DDI: Statins

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir/Voxilaprevir
Atorvastatin	■	●	●
Fluvastatin	■	■	●
Lovastatin	■	●	●
Pitavastatin	◆	■	●
Pravastatin	◆	■	■
Rosuvastatin	■	■	●
Simvastatin	■	●	●

● Do Not Coadminister ■ Potential Interaction ▲ Potential Weak Interaction ◆ No Interaction Expected ♦ No Clear Data

○ Do Not Coadminister □ Potential Interaction △ Potential Weak Interaction ◇ No Interaction Expected ♪ No Clear Data

DDI: Anticoagulants

	Elbasvir/Grazoprevir	Glecaprevir/Pibrentasvir	Sofosbuvir/Velpatasvir/ Voxilaprevir
Apixaban	■	■	■
Dabigatran	■	●	●
Edoxaban	■	■	●
Rivaroxaban	■	■	■
Warfarin	◆	■	■

● Do Not Coadminister

■ Potential Interaction

▲ Potential Weak Interaction

◆ No Interaction Expected

◆ No Clear Data

○ Do Not Coadminister

□ Potential Interaction

▲ Potential Weak Interaction

◆ No Interaction Expected

◆ No Clear Data

Les patients ayant un accès difficile au traitement

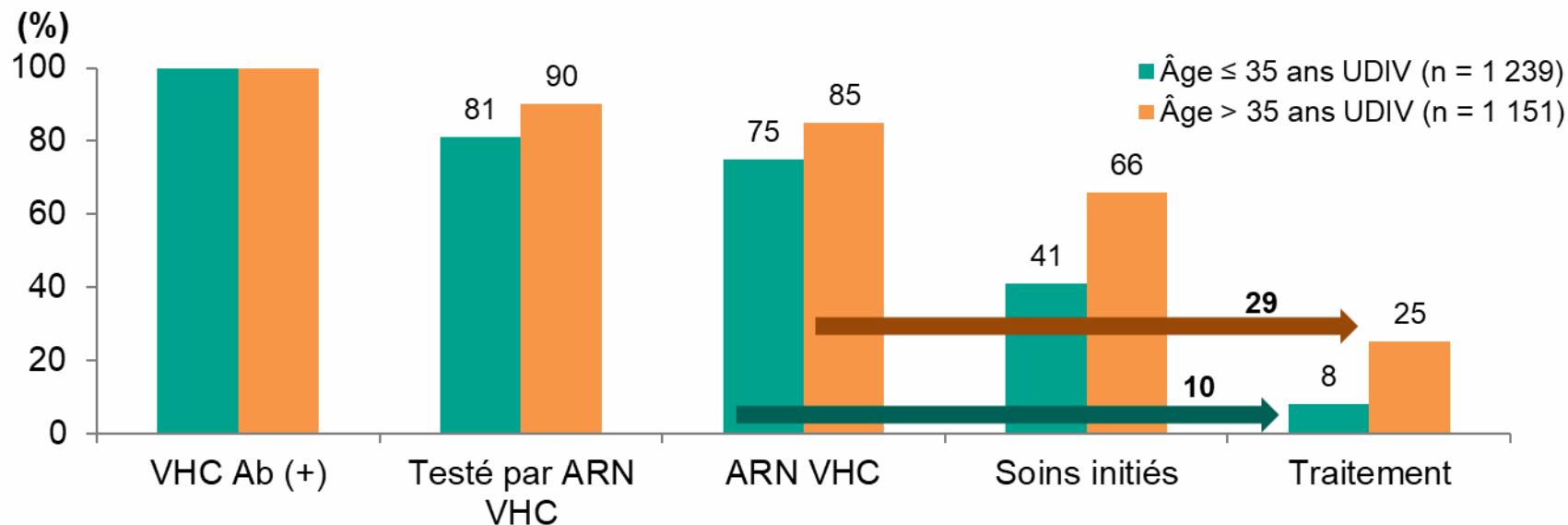
Usagers de drogue

Prisonniers

Pays à faible ressource

- Identification de 2 390 sujets usagers ou ex-usagers de drogues parmi 29 820 patients ayant été dépistés pour le VHC entre 2013 et 2017
- Analyse de la cascade de soins en fonction de l'âge chez les UDIV

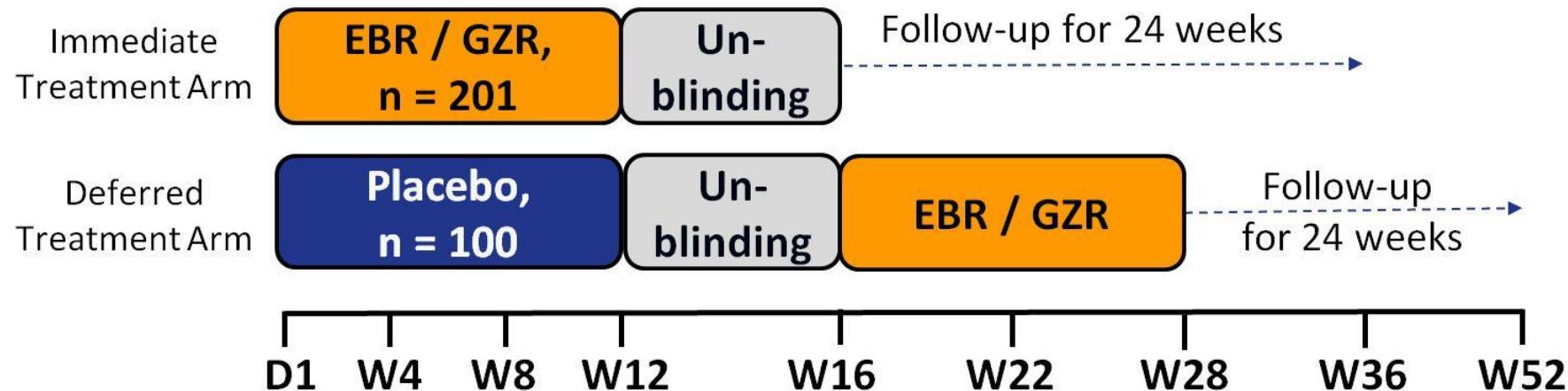
Cascade de soins chez des usagers de drogues (n = 2 390) à Philadelphie



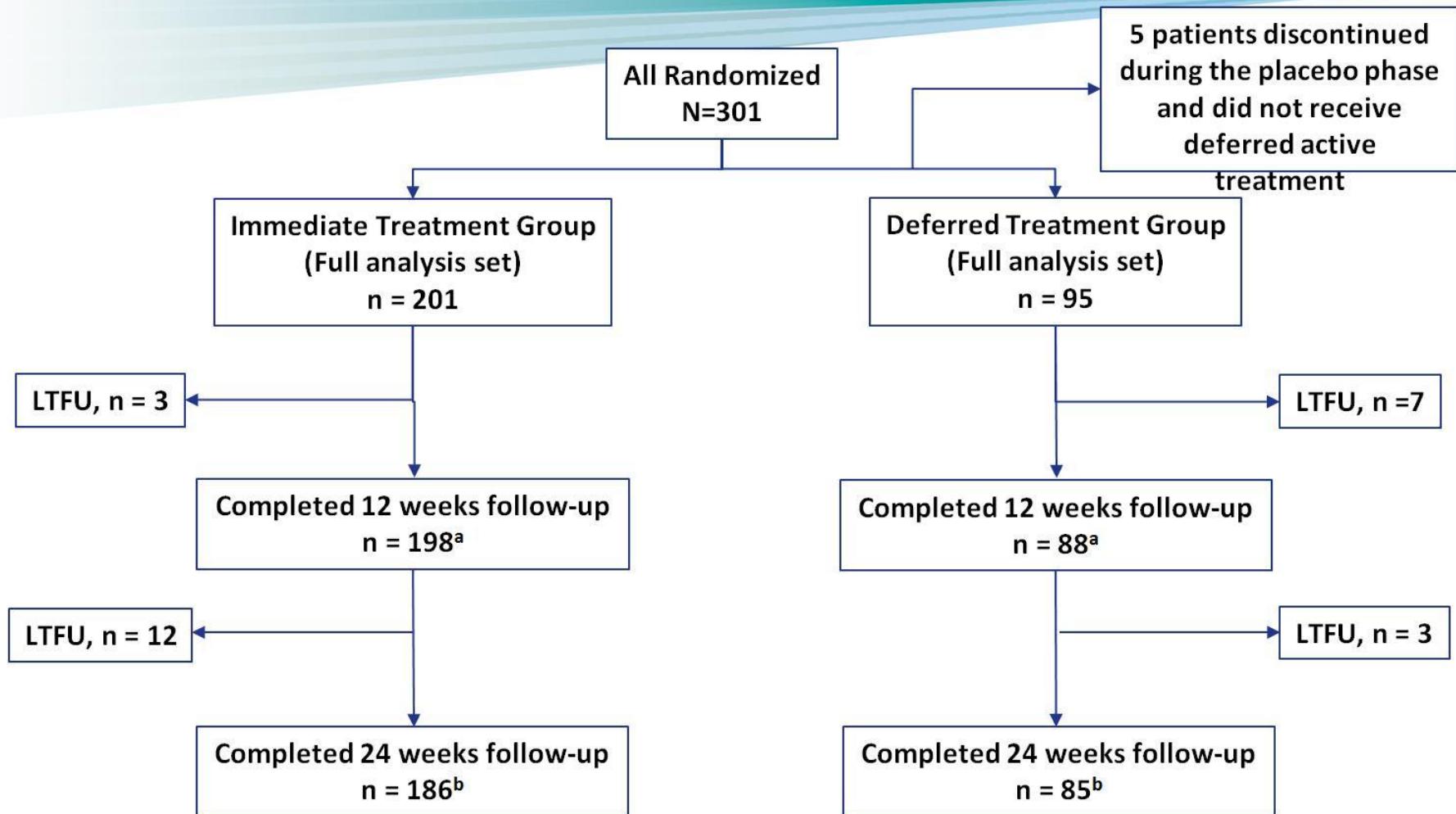
- L'accès aux soins et aux traitements reste très insuffisant chez les UDIV, en particulier chez les moins de 35 ans
- Ces résultats incitent à développer des programmes spécifiques chez ces patients

TRIAL DESIGN

- Phase 3, randomized, parallel-group, placebo-controlled, double-blind trial
- Treatment naïve, GT1, 4, 6; mixed genotypes of 1, 4, and 6 allowed
- On opiate agonist therapy (OAT) for at least 3 months, and consistently kept at least 80% of scheduled appointments while on OAT
- Goal of 20% with cirrhosis and may be co-infected with HIV



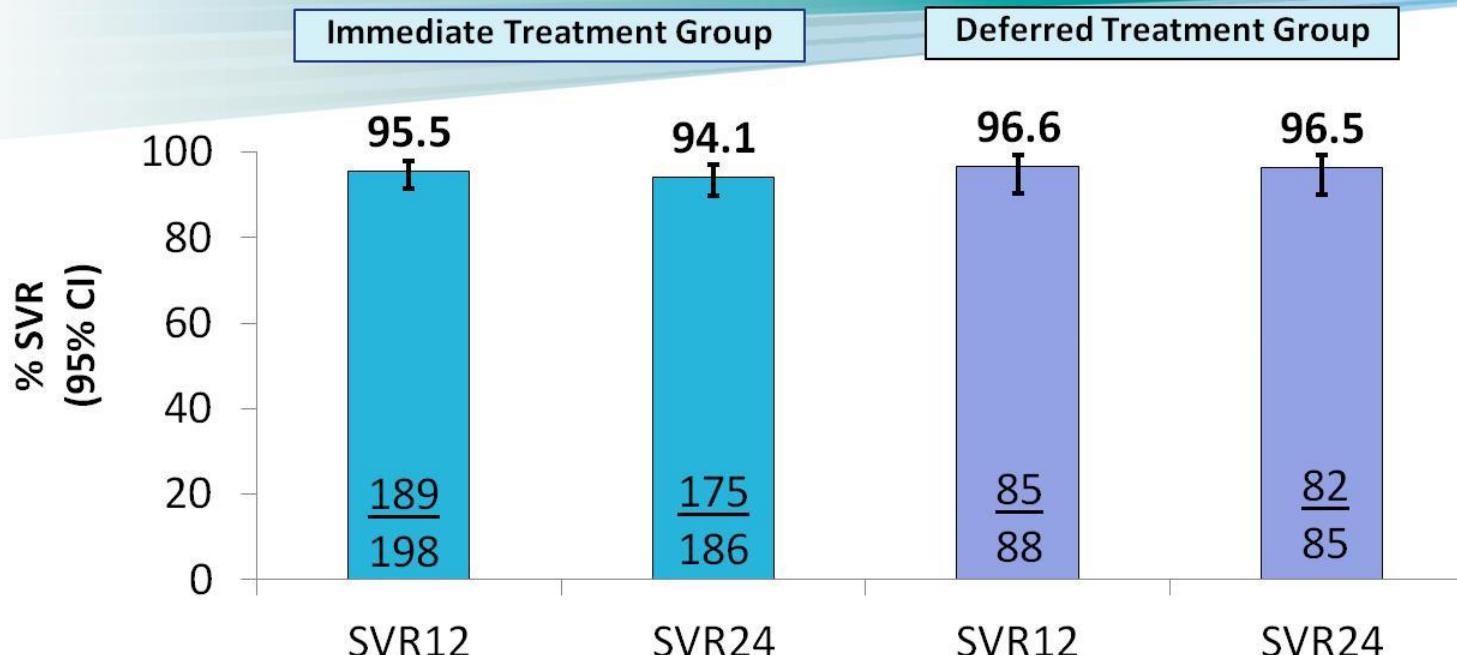
DISPOSITION



^amodified full analysis set for SVR12

^bmodified full analysis set for SVR24

EFFICACY: SUSTAINED VIROLOGIC RESPONSE MODIFIED FULL ANALYSIS SET (mFAS)



Reinfection – counted as success

	ITG	DTG	ITG	DTG
Failures	5	5	0	1
Relapse	7	9	1	1
Breakthrough	0	0	2	2
Discontinuation	2	2	0	0

In the FAS (where discontinuations were counted as failures), SVR12 was 91.5% in the ITG and 85.6% in the DTG, SVR24 was 89.5% in the ITG and 85.3% in the DTG.

HCV Seroprevalence in US State Correctional Departments, 2000-2012

State	Sex	Period of Observations	Median HCV Seroprevalence, %
Indiana	M & F	2003-2011	12.3
Michigan	M	2004-2009	11.0
	F		27.7
New Mexico	M	2010-2011	44.0
	F		35.4
New York	M & F	2000-2007	12.8
North Dakota	M & F	2008-2011	10.7
Oregon	M & F	2000-2005	26.7
Pennsylvania	M & F	2004-2010	18.3
Washington	M	2008-2011	17.6
	F		24.5

SToP-C: HCV Treatment as Prevention Trial in 4 Australian Correctional Centers

- Surveillance phase (Oct 2014 – Nov 2017): model number required to treat to show significant decrease in HCV incidence
- Treatment phase: 12 wks of SOF/VEL for all HCV-infected prisoners
- Current surveillance phase analysis includes 482 participants at risk of HCV (primary or reinfection) who had ≥ 1 follow-up visit; 388 py of follow-up

HCV Infection	Incidence/100 PY	95% CI	Factors Associated With HCV Risk*	aHR	95% CI
Overall	7.9	5.6-11.3			
Primary infection	6.4	4.0-10.1	Younger age, per 10 yrs	1.65	1.35-1.81
Reinfection	12.3	7.2-21.2			
In those w/IDU history but not during current imprisonment	11.4	5.4-23.9	History of injecting, but not in current imprisonment (vs no injecting)	8.16	1.64-40.76
In those injecting in current imprisonment	21.5	14.1-32.6	Injecting in current imprisonment (vs no injecting)	12.29	2.82-53.69

Hajarizadeh B, et al. EASL 2018. Abstract THU-134.

*Cox proportional hazard model. credit: [clinicaloptions.com](#)

Les Pays à faibles ressources

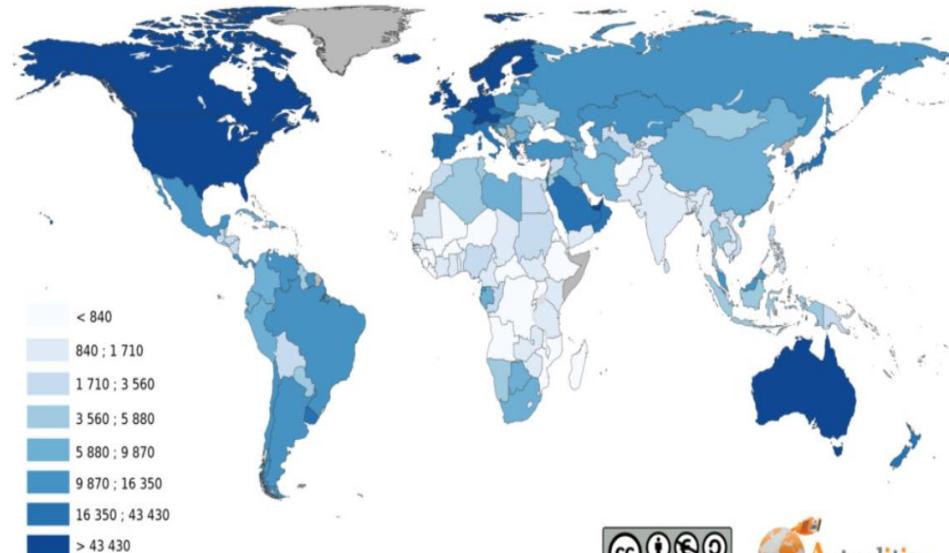
Les pays à faible revenu : pays dont le revenu national brut annuel par habitant est inférieur à 995 dollars (\$ US) ;

Les pays à revenu intermédiaire : pays dont le revenu national brut annuel par habitant est entre 996 dollars et 12 055 dollars (\$ US).

Les pays à revenu élevé : pays dont le revenu national brut annuel par habitant est supérieur à 12 055 dollars (\$ US).

58 pays
3,2 milliards

RNB par habitant (Revenu National Brut - \$)



Source
Worldbank.org



Access to medicines and hepatitis C in Africa: can tiered pricing and voluntary licencing assure universal access, health equity and fairness?

Table 1 Hepatitis C Virus burden, total health expenditure and cost of HCV treatment in seven African countries

Country	Total HCV population (000,000) ^a	Total expenditure on health as % of GDP (2014) (WHO) ^b	Total expenditure on health (000,000) (2014) (WHO) ^b	Cost of 12-weeks regimen of DAA per patient ^c		Total cost of 12-weeks regimen of DAA (000,000)				Cost of 12-weeks DAA as % of total health expenditure			
						For universal (100%) DAA coverage		For 80% DAA coverage		For universal (100%) DAA coverage		For 80% DAA coverage	
				Generic	Originator	Generic	Originator	Generic	Originator	Generic	Originator	Generic	Originator
Egypt	8.306	5.6%	18,524	\$684	\$1200	\$5681.3	\$9967.2	\$4545.0	\$7973.8	31%	54%	25%	43%
Ethiopia	0.676	4.9%	3015	\$750	\$1200	\$507.0	\$811.2	\$405.6	\$649.0	17%	27%	13%	22%
Nigeria	8.115	3.7%	17,800	\$750	\$1200	\$6086.3	\$9738.0	\$4869.0	\$7790.4	34%	55%	27%	44%
DRC	0.11	4.3%	1515	\$750	\$1200	\$82.5	\$132.0	\$66.0	\$105.6	5%	9%	4%	7%
Cameroon	1.473	4.1%	1197	\$750	\$1200	\$1104.8	\$1767.6	\$883.8	\$1414.1	92%	148%	74%	118%
Rwanda	0.475	7.5%	607	\$750	\$1200	\$356.3	\$570.0	\$285.0	\$456.0	59%	94%	47%	75%
South Africa	0.633	8.8%	27,519	\$750	\$1200	\$474.8	\$759.6	\$379.8	\$607.7	2%	3%	1%	2%

^a[13]

^bhttp://gamapserver.who.int/gho/interactive_charts/health_financing/atlas.html?indicator=i2

^c<http://apps.who.int/iris/bitstream/10665/250625/1/WHO-HIV-2016.20-eng.pdf?ua=1>

CONCLUSION

- L'avènement des DAA

1-Les patients difficiles à traiter : rare +++ < 5%

2-En Algérie Elimination du VHC : plan pour l'HD et l'IRC , Réservoir 1

3-Dans le monde : Accès au traitement pour les pays à faibles ressources