HCV and the kidney

Stanislas Pol, MD, PhD

Liver Department, Hôpital Cochin
Inserm UMS 20 & U-818, Institut Pasteur
Université Paris Descartes, Paris, France

stanislas.pol@aphp.fr

Paris, PHC, 11 January 2016

Disclosures

Consultant: BMS, Boehringer Ingelheim, Janssen, Gilead, Roche, MSD, Abbvie

Speaker: GSK, BMS, Boehringer Ingelheim, Janssen, Vertex, Novartis, Sanofi, Gilead, Roche, MSD, Abbvie

Grants: BMS, Gilead, Roche, MSD

Prevalence of HCV in dialysis and kidney transplantation

Authors	Reference year	Country	Patients, *n*	Anti-HCV positive, *n*
Pereira B., *et al.* (study 1)	1997	USA	103	21 (22.8%)
Pereira B., *et al.* (study 2)	1997	USA	103	23 (22.3%)
Legendre C., *et al.*	1998	France	499	112 (22.4%)
Batty D., *et al.*	2001	USA	28 692	1624 (5.7%)
Breitenfeldt M., *et al.*	2002	Germany	927	160 (17.2%)
Forman J., *et al.*	2004	USA	354	26 (7.3%)
Mahmoud I., *et al.*	2004	Egypt	133	80 (60.1%)
Bruchfeld A., *et al.*	2004	Sweden	571	51 (8.9%)
Aroldi A., *et al.*	2005	Italy	541	244 (45.1%)
Mitwalli A., *et al.*	2006	Saudi Arabia	448	286 (63.8%)
Einollahi B., *et al.*	2007	Iran	3028	NA
Ingsathit A., *et al.*	2007	Thailand	346	22 (6.3%)
Luan F., *et al.*	2008	USA	79 337	3708 (4.7%)
Gentil M., *et al.*	2009	Spain	3861	232 (6.7%)
Ridruejo E., *et al.*	2010	Argentina	542	180 (33.2%)
Morales J., *et al.*	2010	Spain	4304	587 (13.6%)
Scott D., *et al.*	2010	Australia, NZ	7572	140 (1.8%)
Singh N., *et al.*	2012	USA	2169	154 (7.1%)

Fabrizi F et al. J Viral Hepat 2014

Country	Anti-HCV Prevalence (%)	Anti-HCV–Positive Patients (*n*)	Reference
Belgium	11.8	51/433	Jadoul et al[8]
Netherlands	3.4	76/2286	Schneeberger et al[9]
Italy	22.5	2274/10097	Lombardi et al[3]
USA	22.3	88/394	Fabrizi et al[2]
France	16.3	216/1323	Salama et al[10]

Poordad F et al. Semin Liver Dis 2004

0.85% % in the general population

HCV infection is more frequent in patients with CKD

Prevalence of HCV in dialysis and kidney transplantation

Authors	Reference year	Country	Patients, *n*	Anti-HCV positive, *n*
Pereira B., *et al.* (study 1)	1997	USA	103	21 (22.8%)
Pereira B., *et al.* (study 2)	1997	USA	103	23 (22.3%)
Legendre C., *et al.*	1998	France	499	112 (22.4%)
Batty D., *et al.*	2001	USA	28 692	1624 (5.7%)
Breitenfeldt M., *et al.*	2002	Germany	927	160 (17.2%)
Forman J., *et al.*	2004	USA	354	26 (7.3%)
Mahmoud I., *et al.*	2004	Egypt	133	80 (60.1%)
Bruchfeld A., *et al.*	2004	Sweden	571	51 (8.9%)
Aroldi A., *et al.*	2005	Italy	541	244 (45.1%)
Mitwalli A., *et al.*	2006	Saudi Arabia	448	286 (63.8%)
Einollahi B., *et al.*	2007	Iran	3028	NA
Ingsathit A., *et al.*	2007	Thailand	346	22 (6.3%)
Luan F., *et al.*	2008	USA	79 337	3708 (4.7%)
Gentil M., *et al.*	2009	Spain	3861	232 (6.7%)
Ridruejo E., *et al.*	2010	Argentina	542	180 (33.2%)
Morales J., *et al.*	2010	Spain	4304	587 (13.6%)
Scott D., *et al.*	2010	Australia, NZ	7572	140 (1.8%)
Singh N., *et al.*	2012	USA	2169	154 (7.1%)

Fabrizi F et al. J Viral Hepat 2014

Country	Anti-HCV Prevalence (%)	Anti-HCV–Positive Patients (*n*)	Reference
Belgium	11.8	51/433	Jadoul et al[8]
Netherlands	3.4	76/2286	Schneeberger et al[9]
Italy	22.5	2274/10097	Lombardi et al[3]
USA	22.3	88/394	Fabrizi et al[2]
France	16.3	216/1323	Salama et al[10]

Poordad F et al. Semin Liver Dis 2004

7.6% in 2010, 3.72% in 2013

HCV infection is more frequent in patients with CKD but the prevalence is decreasing overtime

HCV and the kidney

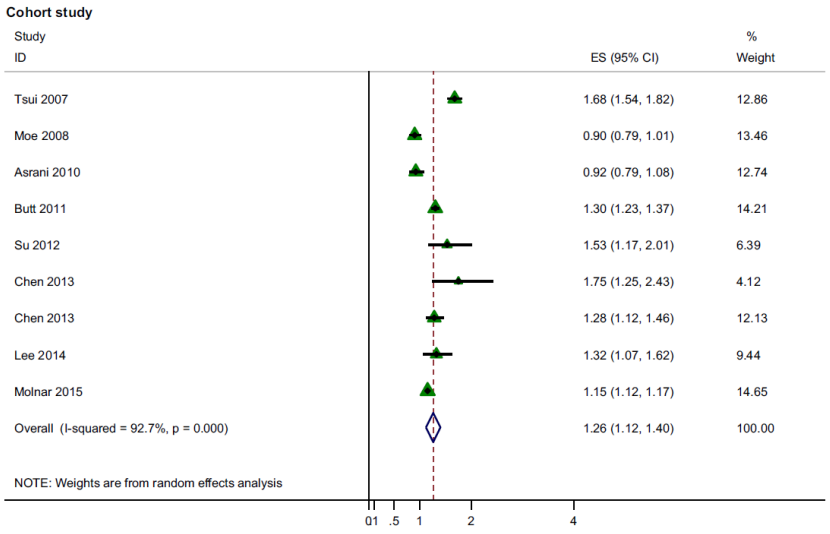
- Impact of chronic HCV on kidney function
- Impact of chronic HCV on survival
- Impact of kidney dysfunction on HCV therapy
- How to treat my CKD patients in 2016

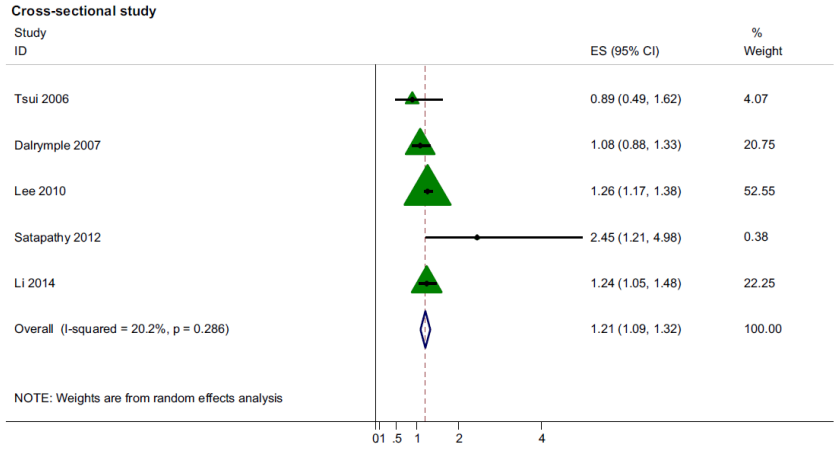
HCV and the kidney

- Impact of chronic HCV on kidney function
- Impact of chronic HCV on survival
- Impact of kidney dysfunction on HCV therapy
- How to treat my CKD patients in 2016

Chronic HCV infection impairs renal function

Increased risk of CKD in HCV+ (23%) vs. HCV-:
risk ratio = 1.23; 95% CI : 1.12-1.34



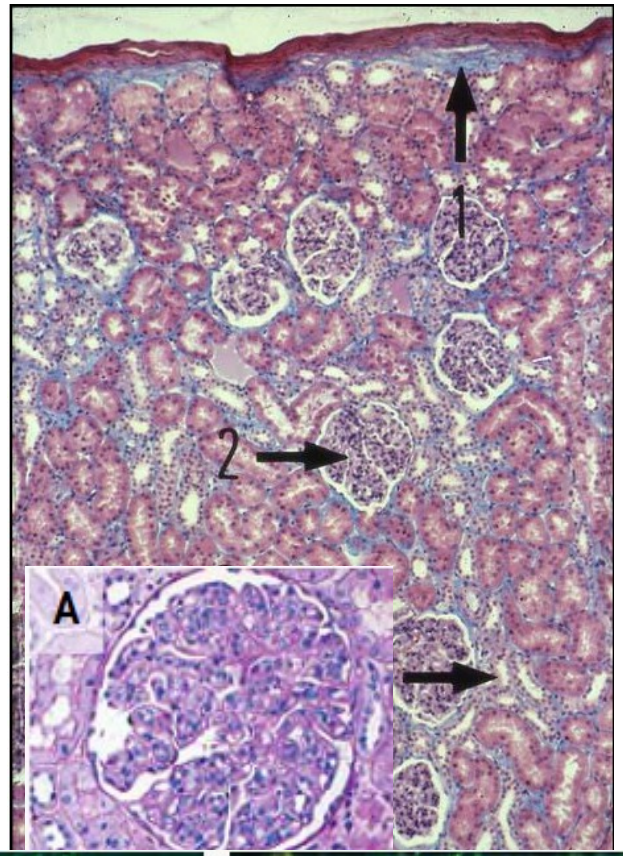


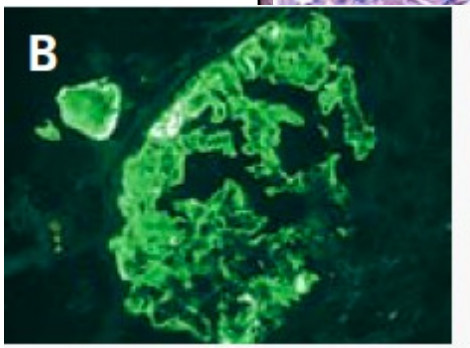
Molnar MZ et al. Hepatology 2015;61:1495

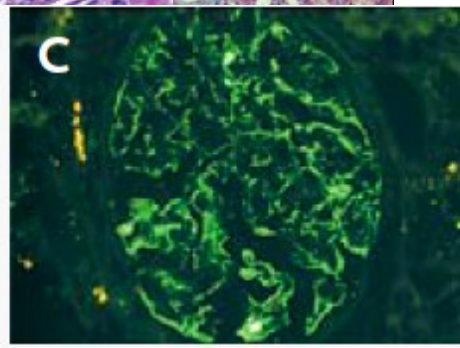
Park H et al. J Viral Hepat 2015

HCV infection may be associated with any kidney disease

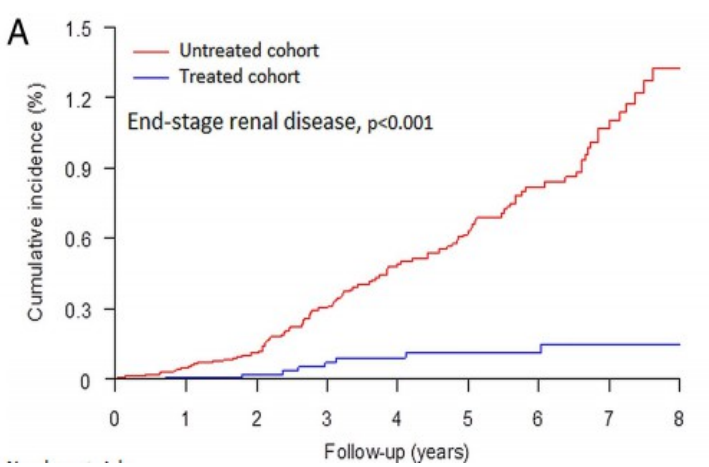
- Glomerulus :
  - Type II Cryoglobulinemia (MPGN)
  - GN with mesangial IgA deposits
  - Membranous GN
  - Hyalinosis
  - Fibrillar GN
  - Immunotactoïd GN
- Interstitium
  - Sjogren Syndrom
  - B Lymphoproliferation
- Vascular : thrombotic microangiopathy
- Rejection nephropathy

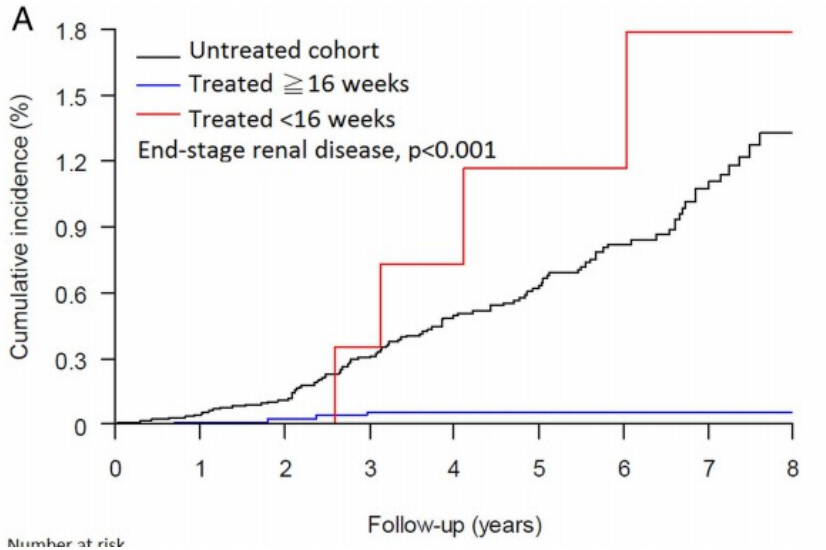






Reduction in CKD incidence in treated patients





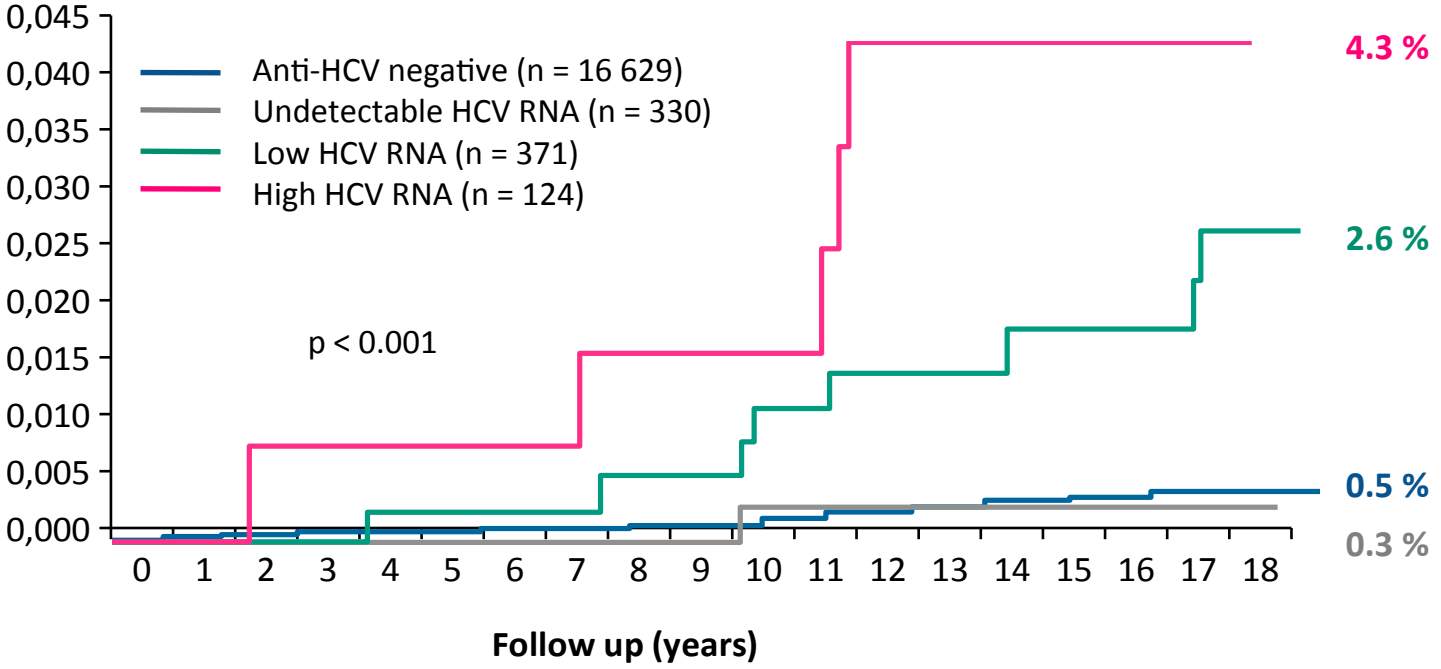
- Cumulated incidence of ESRD at 8 years in teated vs. untreated patients : 0.15% vs 1.32% (p<0.001)

- Reduction in CKD incidence in treated patients (HR 0.15; 95% CI 0.07– 0.31; p<0.001)

Hsu Y-C, et al. Gut 2015;64:495–503

Chronic HCV infection increases ESRD-related mortality

→Cumulative risk of death related to renal disease according to HCV status



Reveal HCV Longitudinal taïwanese study in 23 785 patients

HCV infection is associated with an increased risk of renal disease, ESRD and renal-related mortality

Lai TS et al., AASLD 2014 abstr. 172

HCV increases the risk of extra-hepatic mortality

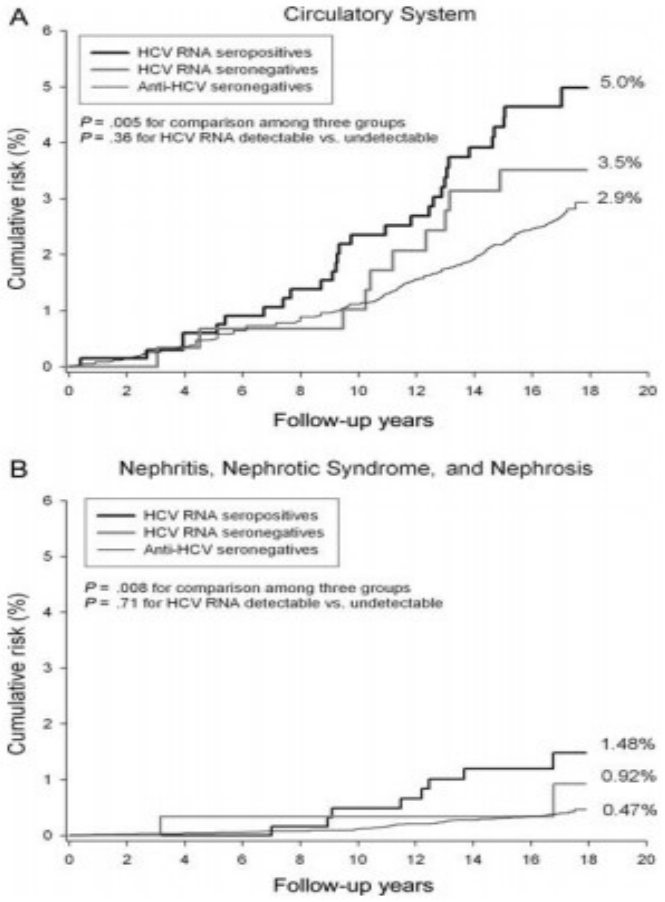


Figure 3. Cumulative mortality from circulatory diseases (*A*) and nephritis, nephrotic syndrome, and nephrosis (*B*) by serostatus of antibodies against hepatitis C virus (anti-HCV) and serum HCV RNA level at study entry.

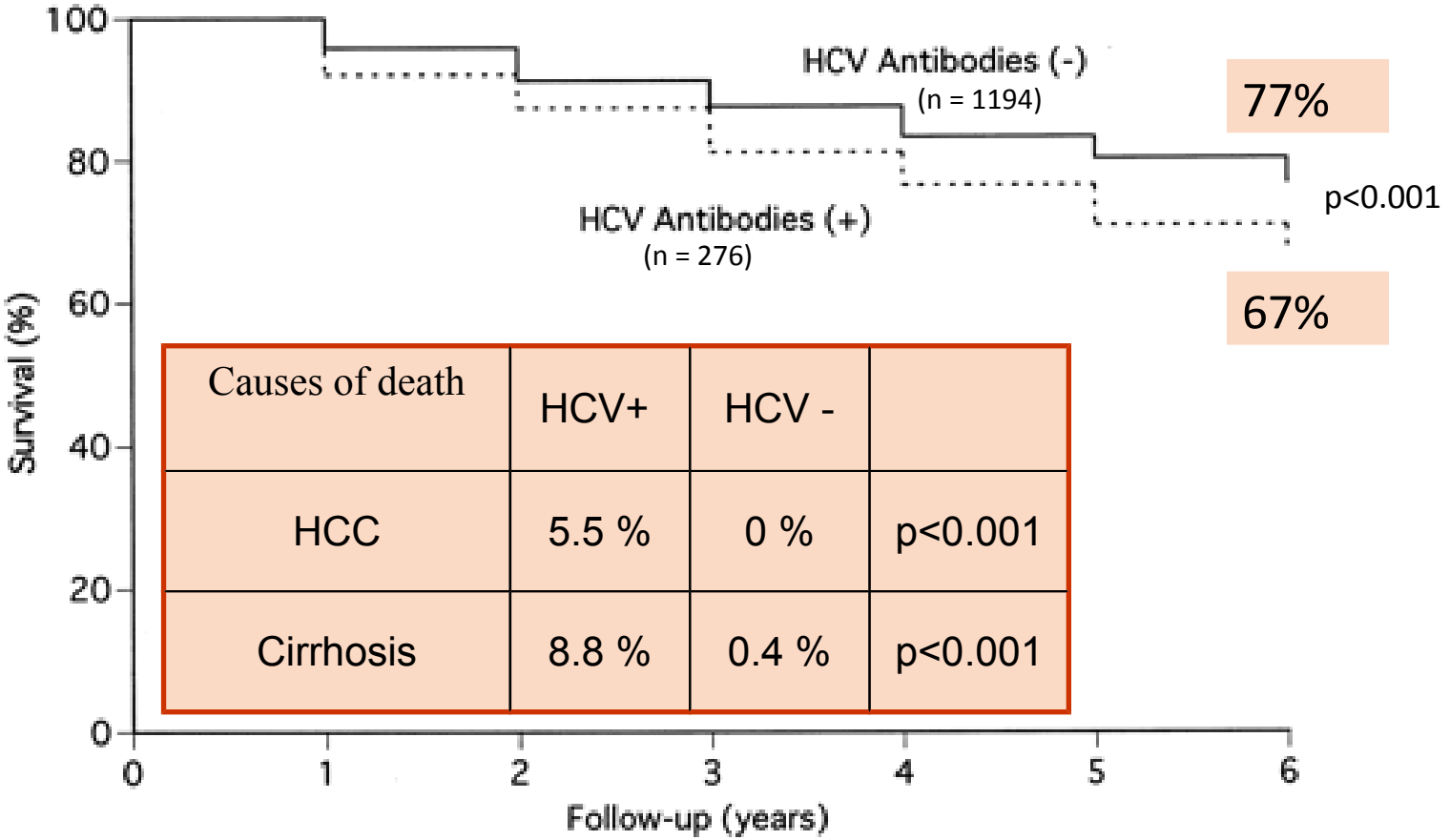
Hazard ratio [95% CI] for nephritis or nephrotic syndrome: 2.77 [1.49-5.15]

Mei-Hsuan Lee, et al. Chronic Hepatitis C Virus Infection Increases Mortality From Hepatic and Extrahepatic Diseases: A Community-Based Long-Term Prospective Study. J Infect Dis. (2012) 206 (4): 469-477

HCV and the kidney

- Impact of chronic HCV on kidney function
- Impact of chronic HCV on survival
- Impact of kidney dysfunction on HCV therapy
- How to treat my CKD patients in 2016

Harmful impact of HCV in hemodialysis patients



Causes of death	HCV+	HCV -	
HCC	5.5 %	0 %	p<0.001
Cirrhosis	8.8 %	0.4 %	p<0.001

Nakayama E, et al. J Am Soc Nephrol 2000

Harmful impact of HCV in kidney recipients

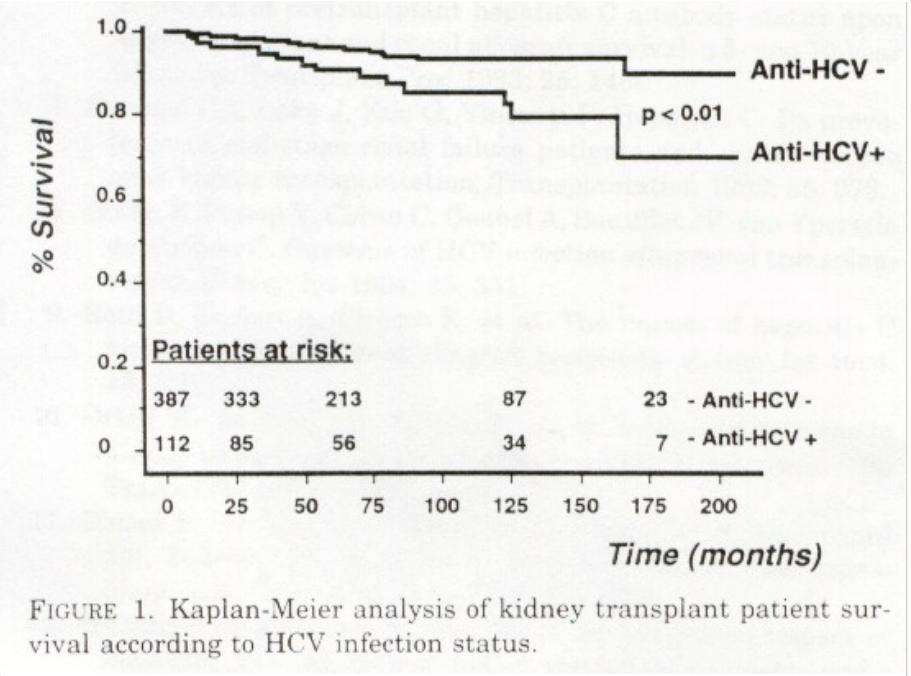
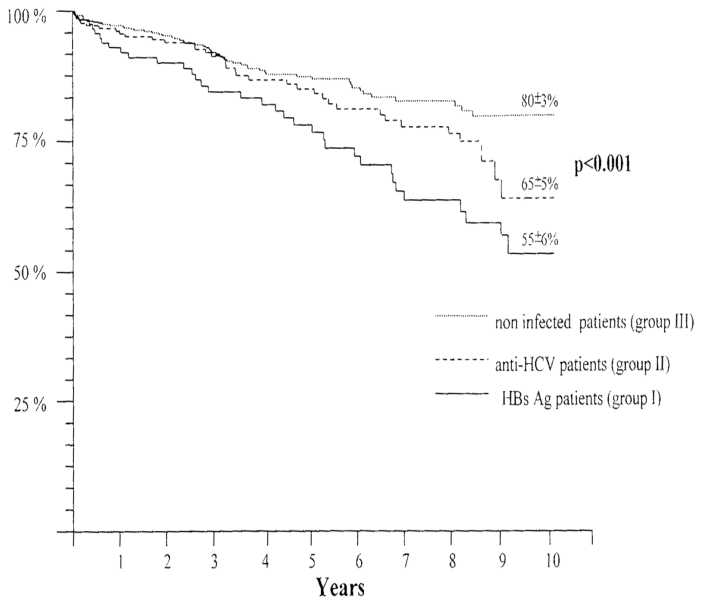


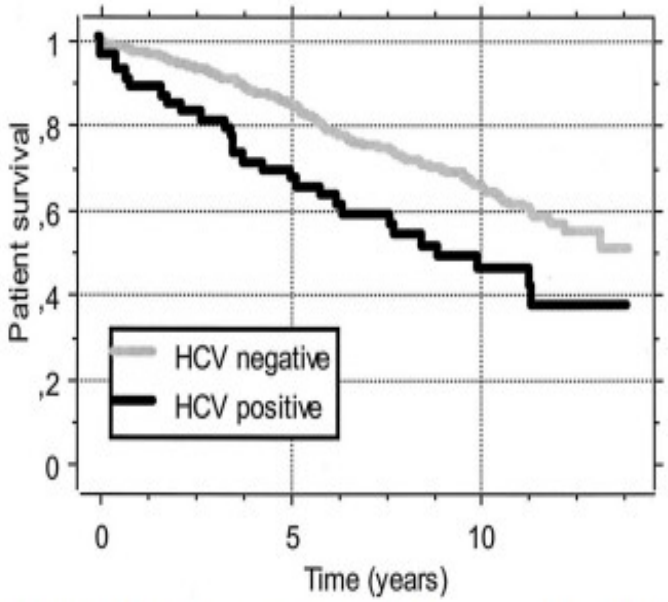
FIGURE 1. Kaplan-Meier analysis of kidney transplant patient survival according to HCV infection status.



Pol et al. Lancet 1991; Legendre C et al. Transplantation 1997; Mathurin P et al. Hepatology 1999; Bruchfeld A, et al. Transplantation 2004

Adjusted RR death : 1.79 [1.57-2.03]
Adjusted RR graft loss : 1.56 [1.35-1.8)

Fabrizi F et al. Am J Transplant 2005;5:1452-61



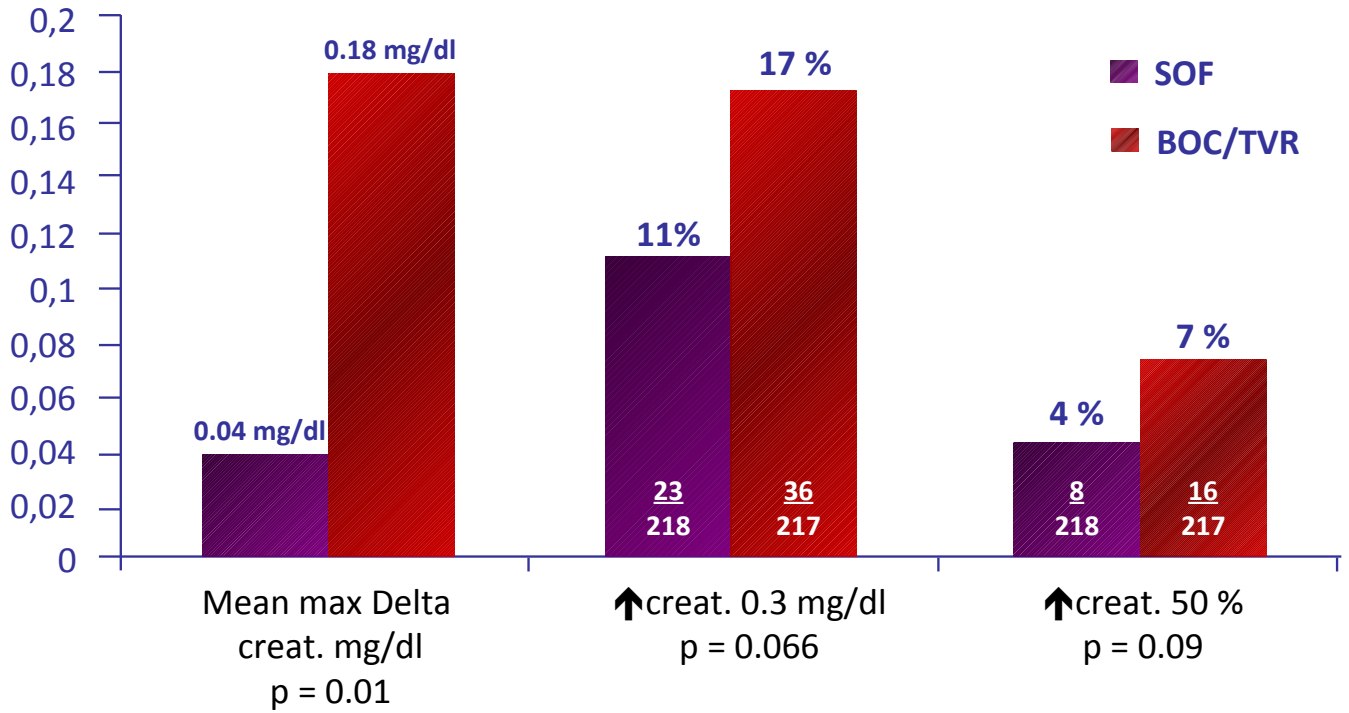
HCV and the kidney

- Impact of chronic HCV on kidney function
- Impact of chronic HCV on survival
- Impact of kidney dysfunction on HCV therapy
- How to treat my CKD patients in 2016

GFR may be affected by DAAs

- 219 patients with sofosbuvir-including regimen and 217 patients treated by boceprevir or telaprevir
- Renal impairement defined as an increase of creatinine ≥ 0.3 mg/dl or ≥ 50 % vs. baseline

Evolution of GFR under therapy (ClCr > 60 ml/min at beginning)

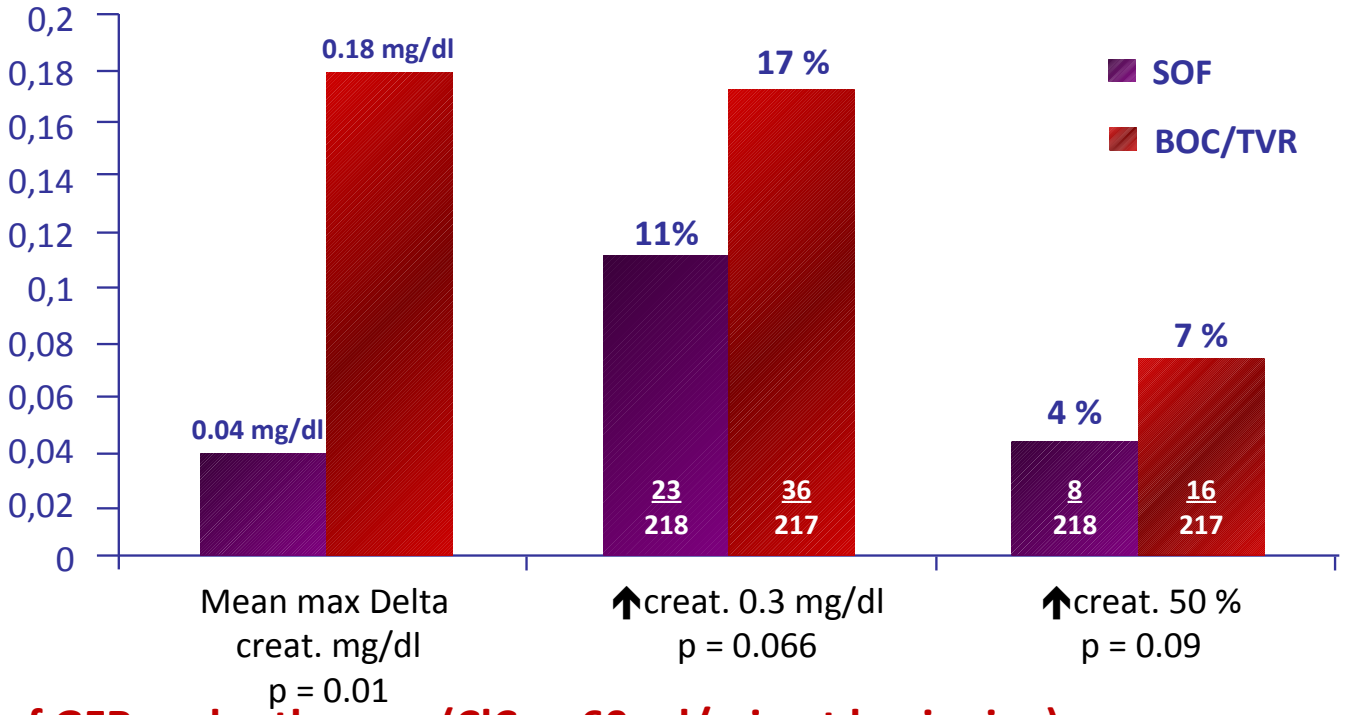


Almarzooqi S et al. , AASLD 2015, Abs. 1099

GFR may be affected by DAAs

- 219 patients with sofosbuvir-including regimen and 217 patients treated by boceprevir or telaprevir
- Renal impairement defined as an increase of creatinine ≥ 0.3 mg/dl or ≥ 50 % vs. baseline

No urine analysis: renal dysfunction or variations of reabsorption of creatinine?



Evolution of GFR under therapy (ClCr > 60 ml/min at beginning)

Almarzooqi S et al. , AASLD 2015, Abs. 1099

Pharmacokinetics of sofosbuvir and kidney dysfunction

PK Parameter	Normal Renal Function eGFR > 80 mL/min/1.73 m2 Mean (%CV) (n=6)	Severe Renal Impairment eGFR < 30 mL/min/1.73 m2 Mean (%CV) (n=6)	%GMR (90% CI) (n=6)
GS-331007 AUCinf, ng•h/mL	12,700 (19.1)	92,600 (85.9)	551 (313, 968)
GS-331007 Cmax, ng/mL	1360 (42.3)	1740 (23.0)	134 (98.6, 183)
SOF AUCinf, ng•h/mL	590 (29.9)	1580 (28.1)	271 (183, 402)

AUCinf=area under the curve; CI=confidence interval; Cmax=maximum observed plasma concentration of drug; CV=coefficient of variation, GMR=geometric mean ratio, PK=pharmacokinetic.

Cornpropst M, *et al. EASL* 2012. Barcelona, Spain. #1101

Pharmacokinetics of sofosbuvir and kidney dysfunction

	Normal Renal Function eGFR >80 mL/min /1.73 m2	ESRD: Period 1 (Dose Pre-Dialysis)		ESRD: Period 2 (Dose Post-Dialysis)	
PK Parameter	**Mean (%CV) (n=6)**	**Mean (%CV) (n=3 to 5)**	**%GMR (90% CI)**	**Mean (%CV) (n=3 to 5)**	**%GMR (90% CI)**
GS-331007 AUCinf, ng•h/mL	12,700 (19.1)	226,000 (78.6)	1380 (693, 2760)	358,000 (70.7)	2170 (1090, 4330)
GS-331007 Cmax, ng/mL	1360 (42.3)	1470 (39.5)	110 (81.0, 150)	2420 (35.0)	180 (132, 246)
SOF AUCinf, ng•h/mL	590 (29.9)	785 (42.7)	128 (84.5, 193)	948 (32.9)	160 (106, 242)

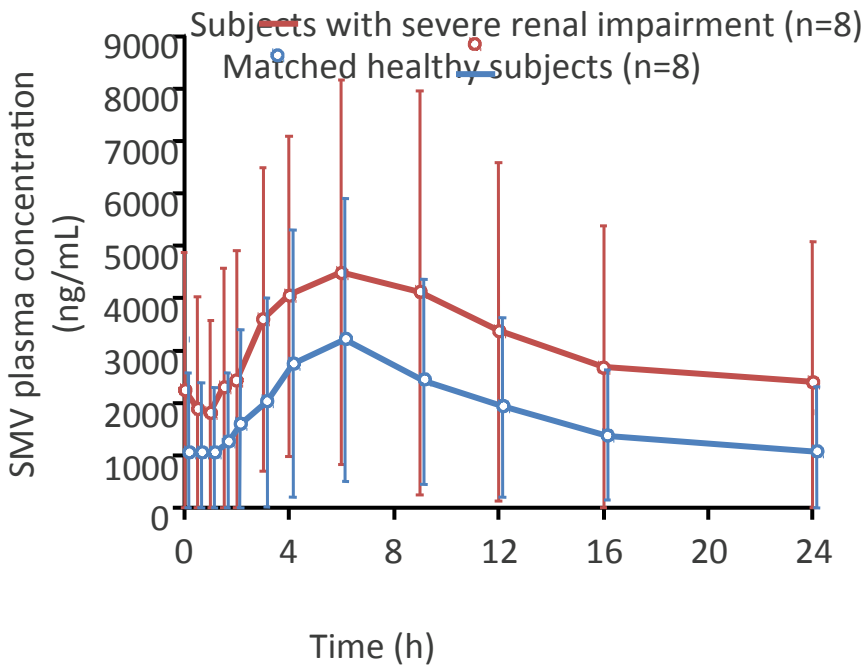
AUCinf=area under the curve; CI=confidence interval; Cmax=maximum observed plasma concentration of drug; CV=coefficient of variation, GMR=geometric mean ratio, PK=pharmacokinetic.

Cornpropst M, *et al. EASL* 2012. Barcelona, Spain. #1101

Pharmacokinetics of protease inhibitors and kidney dysfunction

Linear mean plasma concentration–time profiles of SMV

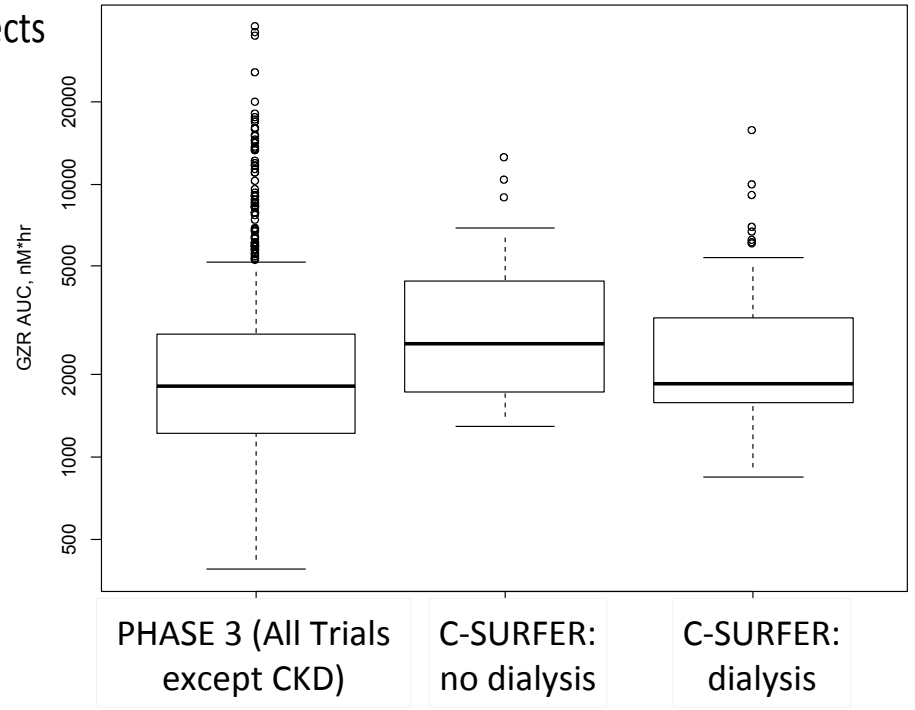
comparing severely renal impaired and matched healthy subjects



Bars represent SD

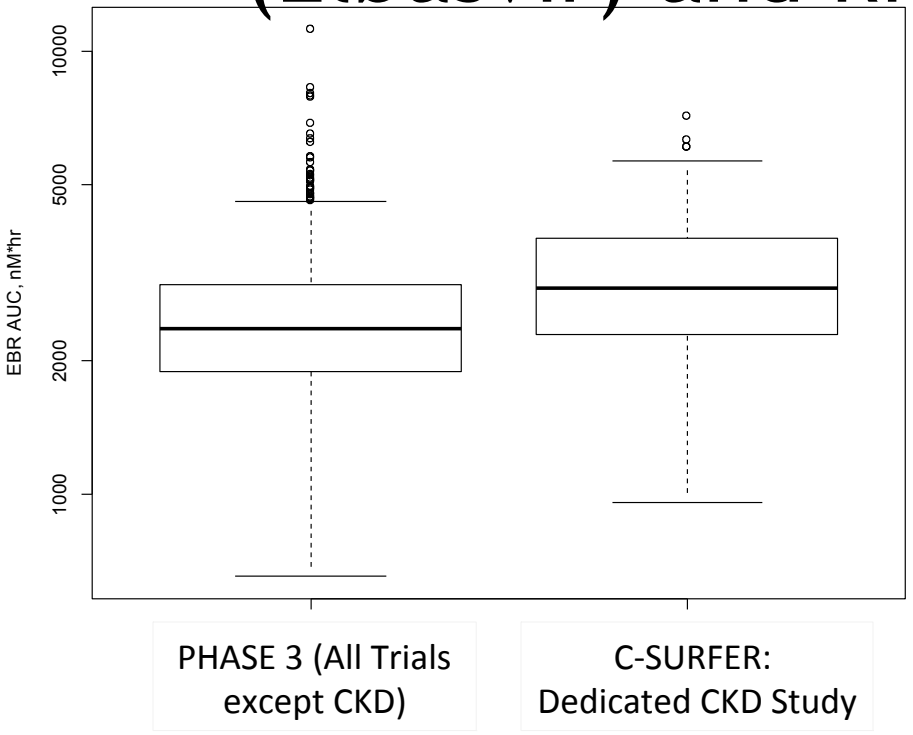
SMV, simeprevir

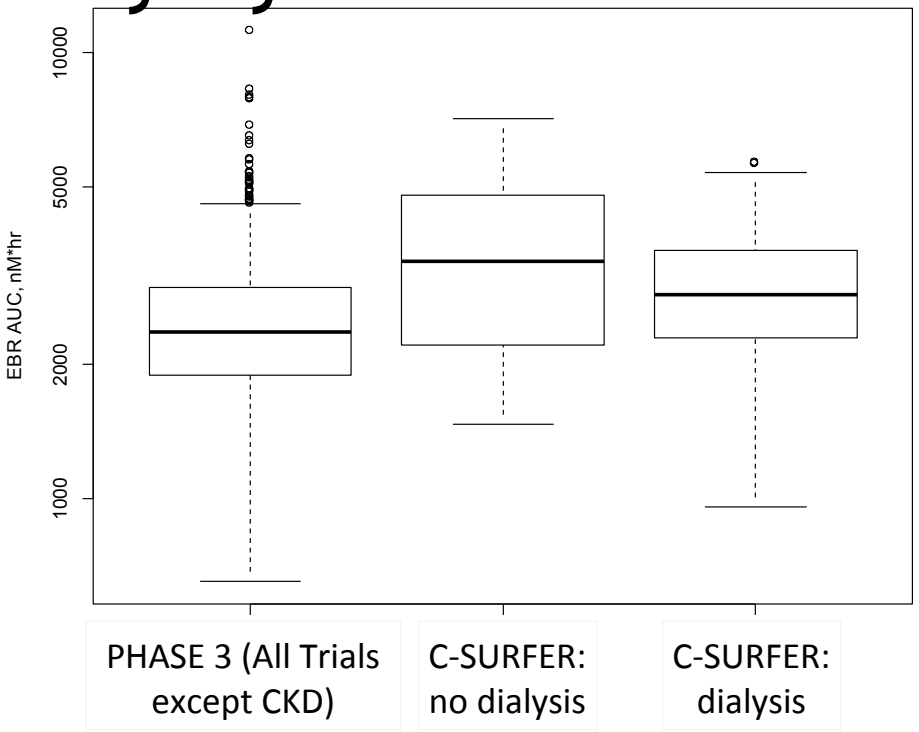
Simion *et al.* *HCV Clin Pharm Workshop* 2013



- GZR AUC compared between subjects in C-SURFER (with CKD) and other Phase 3 trials (C-EDGE; includes cirrhotic subjects)
- Overall, **GZR AUC is ~ 22% higher in patients with CKD compared to AUC in the other Phase 3 studies**

Pharmacokinetic of NS5A inhibitors (Elbasvir) and kidney dysfunction





	N	GM AUC (uM*hr)	Ratio vs no CKD
no CKD (P060, 061, 068)	950	2.38	--
CKD (P052)	116	2.96	1.24
CKD, no dialysis	30	3.31	1.39
CKD, dialysis	86	2.84	1.19

GM = geometric mean

- EBR AUC compared between subjects in C-SURFER (with CKD) and other Phase 3 studies (C-EDGE; includes cirrhotic subjects)
- Overall, **EBR AUC is ~ 24% higher in patients with CKD compared to AUC in the other Phase 3 studies**

ABT-450/r, ombitasvir +/- dasabuvir and kidney dysfunction

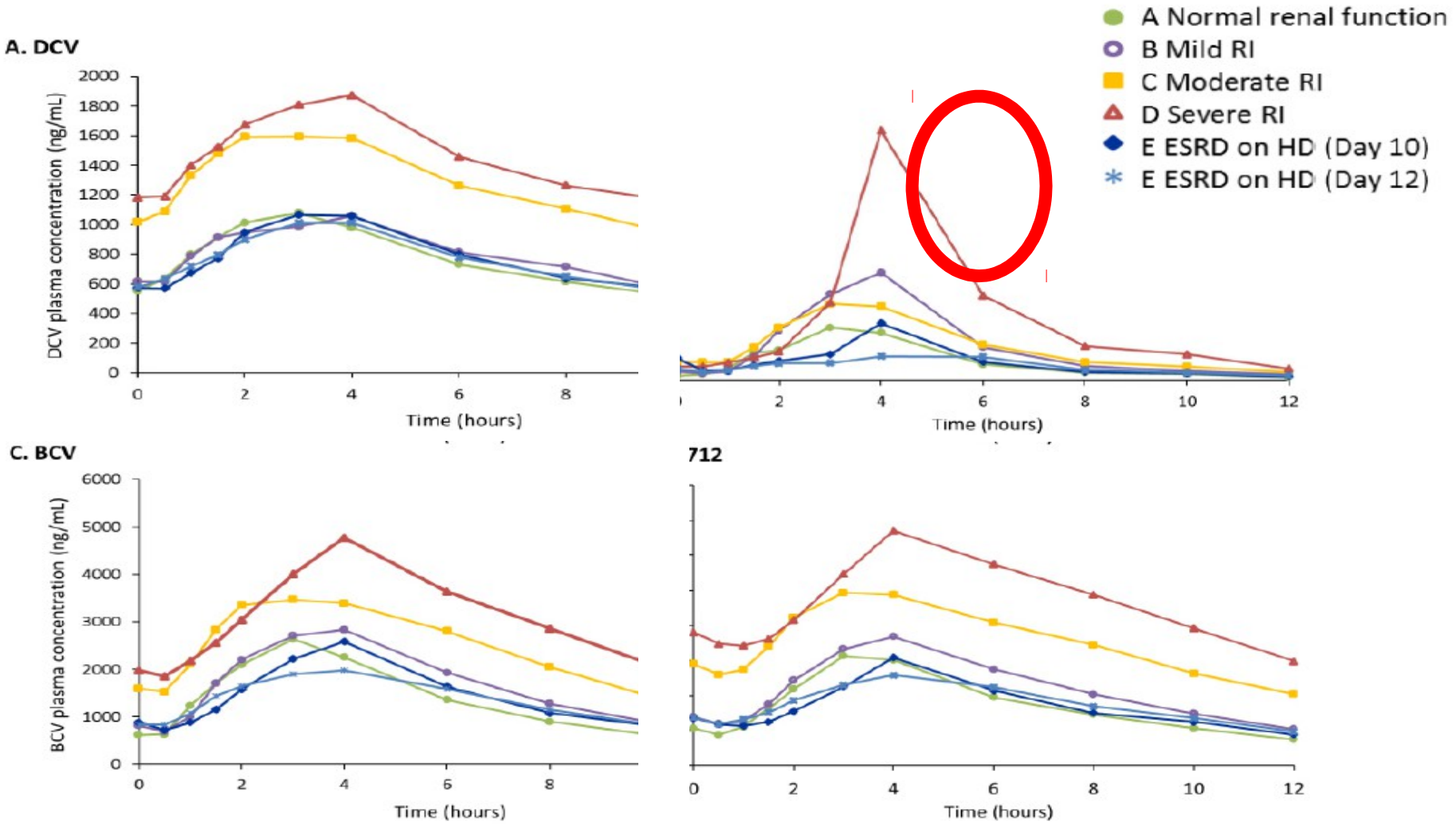
- Étude de Phase I study in 24 non infected subjects répartis en 4 groupes de 6 : fonction rénale normale (clairance de la créatinine ≥ 90 ml/mn, ou avec une insuffisance rénale minime (de 60 à 89), modérée (30 à 59) ou sévère (15 à 29)

By comparison with normal renal function	Minim renal impairement (GFR= 60-89)	Moderate renal impairement (GFR= 30-59)	Severe renal impairement (GFR= 15-29)
AUC ombitasvir	Unchanged	Unchanged	Unchanged
AUC ABT-450 and dasabuvir	↗ 20 %	↗ 37 %	↗ 50 %
AUC ritonavir	↗ 42 %	↗ 80 %	↗ 114 %

- No clinically relevant PK modification

Khatri A et al., AASLD 2014 abstr. 238

Asunaprevir/Daclatasvir/beclabuvir and kidney dysfunction



Adapted from: Adamczyk R. ILC 2015, #PO790

HCV DAAs and kidney function Summary

- Polymerase inhibitors: Sofosbuvir
- no dose adjustement for GFR> 30 mL/mn
- For GFR< 30 mL/mn: ?
  400 mg, 200mg/d or 400mg/2d

- NS5A inhibitors: - no dose adjustement
  - no adjustement of calcineurin inhibitors

- Protease inhibitors: - no dose adjustement
  - DDI with anticalcineurin drugs

HCV and the kidney

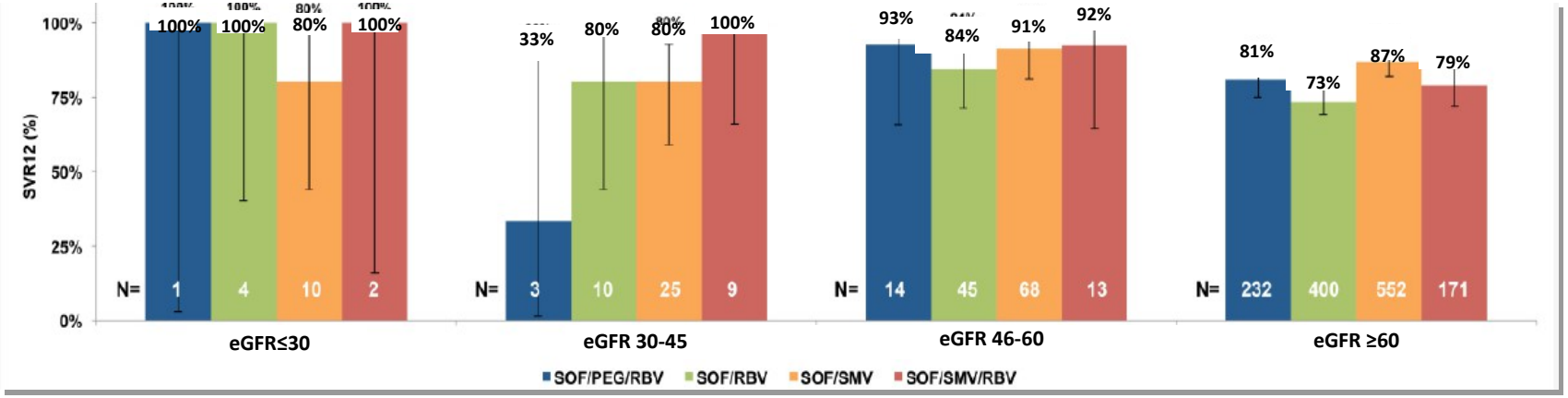
- Impact of chronic HCV on kidney function
- Impact of chronic HCV on survival
- Impact of kidney dysfunction on HCV therapy
- How to treat my CKD patients in 2016

Clinical Practice Guidelines for the Diagnosis, Prevention and Management of Hepatitis C in CKD

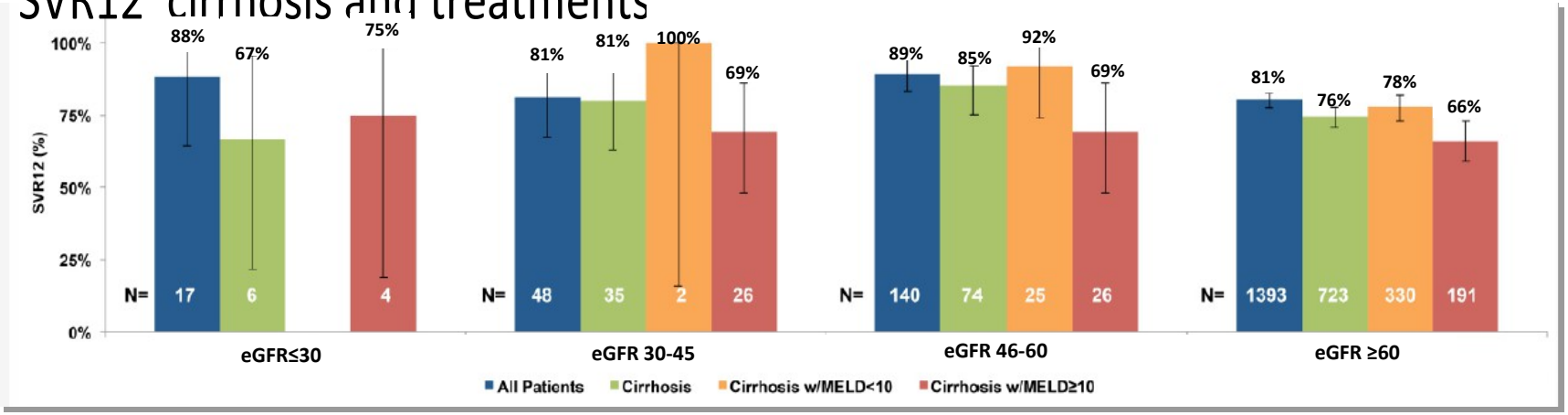
Outdated: Update in 2016

Real life: Sofosbuvir-including regimen and kidney function(Target)

SVR12 according to treatment and renal function



SVR12 cirrhosis and treatments



Adapted from: Saxena V. ILC 2015, #LP08

*Among patients with known outcomes

Real life: Sofosbuvir-including regimen and kidney function(Target)

Table 2: Safety Outcomes by Baseline eGFR*

Dichotomous = no (%) Continuous = mean (range)	eGFR ≤ 30 (N=17)	eGFR 30-45 (N=56)	eGFR 46-60 (N=157)	eGFR>60 (N=1,559)
Common AEs				
Fatigue	3 (18)	19 (34)	56 (36)	543 (35)
Headache	1 (6)	9 (16)	19 (12)	274 (18)
Nausea	3 (18)	8 (14)	33 (21)	247 (16)
Anemia AE	**6 (35)**	**16 (29)**	**37 (24)**	**246 (16)**
Required Transfusion(s)	2 (12)	5 (9)	3 (2)	31 (2)
Erythropoietin Start on Treatment	1 (6)	8 (14)	14(9)	50 (3)
RBV[§]				
Reduction in RBV due to Anemia	3 (38)	8 (30)	33 (42)	185 (19)
RBV Discontinuation	0 (0)	4 (15)	1 (1)	12 (1)
Worsening Renal Function[]	**5 (29)**	**6 (11)**	**4 (3)**	**14 (1)**
Renal or Urinary System AEs[Φ]	**5 (29)**	**6 (11)**	**13 (8)**	**84 (5)**
Any Serious AEs	**3 (18)**	**13 (23)**	**8 (5)**	**100 (6)**
Cardiac Serious AEs	**1 (6)**	**2 (4)**	**8 (5)**	**53 (3)**
Early Treatment Discontinuation	**1 (6)**	**4 (6)**	**6 (4)**	**68 (4)**
Early Treatment Discontinuation AE	**1 (6)**	**2 (3)**	**4 (2)**	**39 (3)**
Death[§]	**1 (6)**	**0 (0)**	**2 (1)**	**10 (1)**

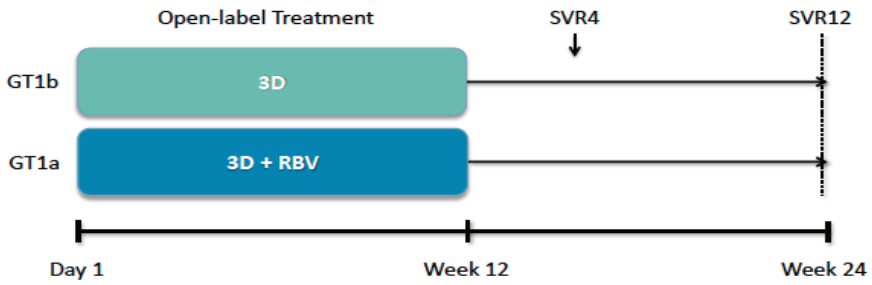
*Among all patients who completed therapy; [§] Among patients treated with RBV; [+] includes acute on chronic renal insufficiency, outcome abstracted from treatment documentation; [Φ] includes acute renal failure, dysuria, hematuria, urinary retention and other similar renal/urinary problems; [§] eGFR ≤ 30 patient that died: Liver transplant recipient with baseline MELD of 26 who died from worsening renal failure and hepatic decompensation

Adapted from: Saxena V. ILC 2015, #LP08

Ruby: 3D and renal failure

Multicenter, Open-label, Phase 3b Study

- 9 sites, all in the United States



- **3D**: Co-formulated OBV/PTV/r (25/150/100 mg QD) and DSV (250 mg BID)
- **For GT1a**: RBV 200 mg QD
- **For GT1b**: No RBV

	3D±RBV N=20
Male; n (%)	17 (85)
Black; n (%)	14 (70)
Age, years; median (range)	60 (49-69)
Hispanic or Latino ethnicity; n(%)	3 (15)
Degree of fibrosis*; n(%)	
F0-F1	10 (50)
F2	6 (30)
F3	4 (20)
HCV viral load, log_{10}(IU/mL); median (range)	6.6 (5.5-7.6)
GT1a; n (%)	13 (65)
Hemoglobin, g/dL; mean (SD)	12.6 (1.8)
CKD stage; n (%)	
4 (eGFR 15-30 mL/min/1.73m²)	7 (35)
5 (eGFR <15 mL/min/1.73m² or requiring dialysis)	13 (65)
On dialysis; n (%)	13 (65)
eGFR, mL/min/1.73m²; median (range)	10.9 (5.4-29.9)
Creatinine, mg/dL; median (range)	6.2 (2.2-10.8)

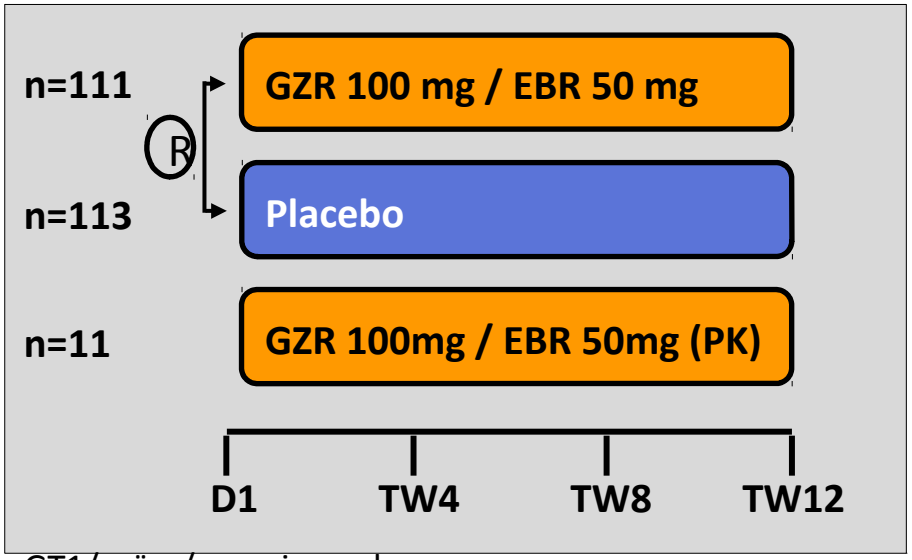
*Biopsy: 5 patients; Fibroscan: 10 patients; Fibrotest: 5 patients.

SVR12

➔ **2 failures : 1 death 14 days after the end of therapy (ventricular dysfunction) & 1 relapse (NS3 et NS5A RAVs)**

Pockros P et al. AASLD 2015, Abs. 1039

C-Surfer: Grazoprevir/Elbasvir in patients with GFR <30 mL/min

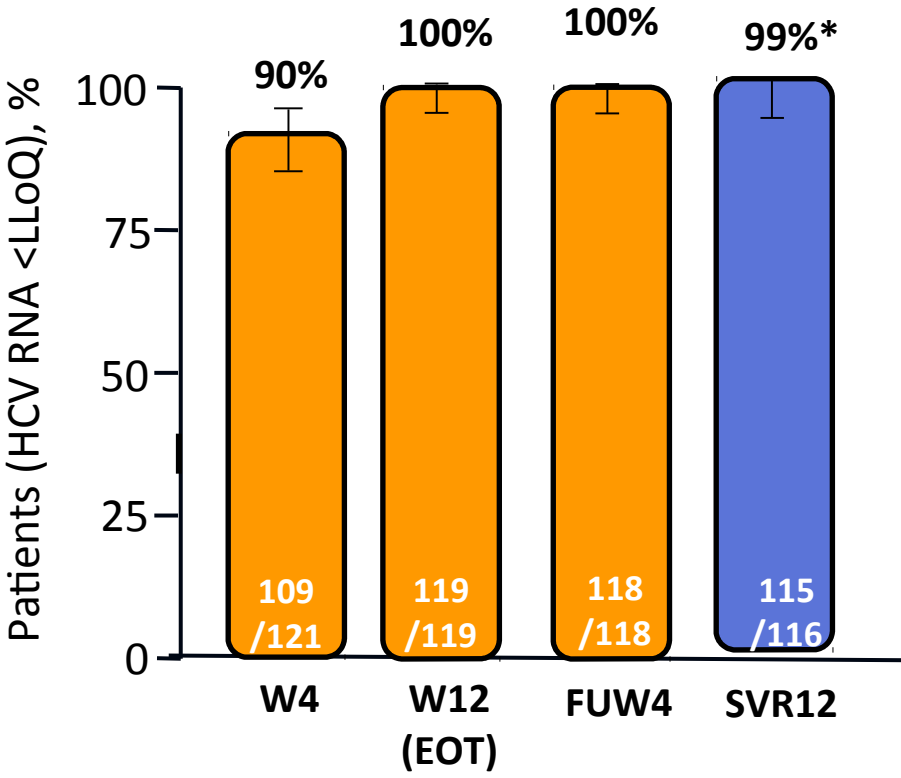


- GT1/naïve/experienced

- CKD stage 4/5 (eGFR 15-29 mL/min/1.73m2 ;

CKD stade 5: eGFR <15 mL/min/1.73m2 or dialysis)

1 noncirrhotic patient with HCV GT1b infection relapsed at FW12



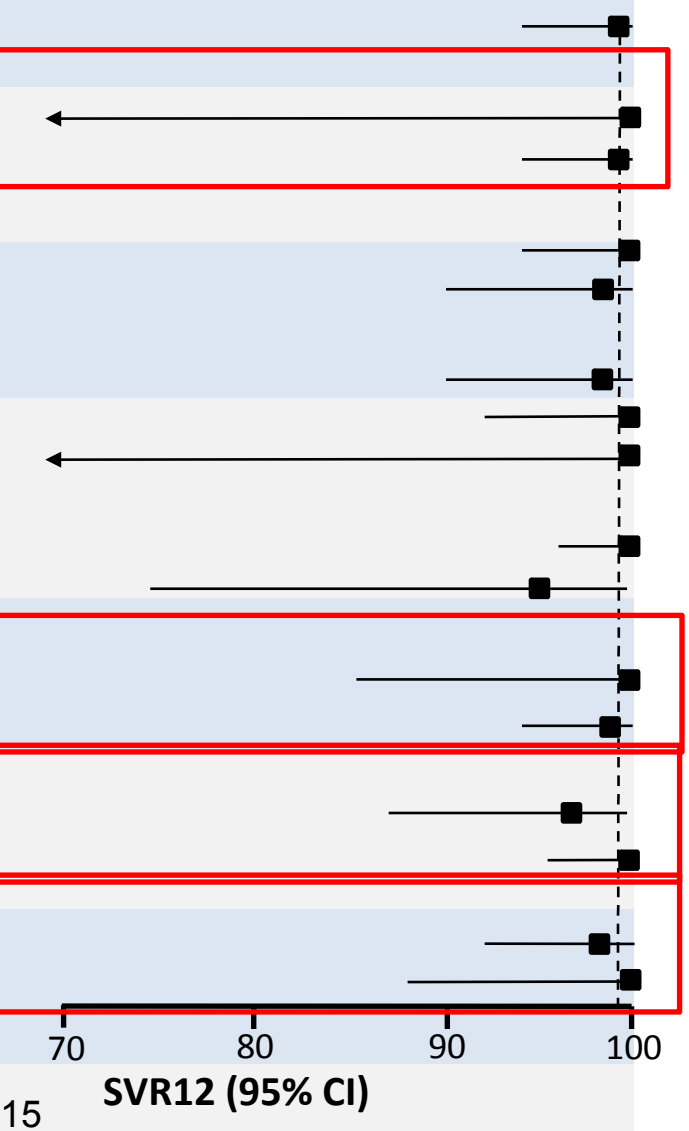
*Efficacy is presented for the modified full analysis set population (mFAS). Full Analysis set: patients with SVR12 94%

6 patients were excluded from the per protocol: lost to follow-up (n=2), n=1 each for death, non-compliance, withdrawal by subject, and withdrawal by physician (due to violent behavior)

Roth D et al. Lancet 2015

C-Surfer: Grazoprevir/Elbasvir in patients with GFR <30 mL/min)

ALL	**115/116**	**99.1 (95.3, 100)**
Cirrhosis		
Yes	**6/6**	**100 (54.1, 100)**
No	**109/110**	**99.1 (95.0, 100)**
HCV genotype		
G1a	**61/61**	**100 (94.1, 100)**
G1b	**54/55**	**98.2 (90.3, 100)**
Race		
White	**58/59**	**98.3 (90.9, 100)**
African American	**51/51**	**100 (93.0, 100)**
Asian	**5/5**	**100 (47.8, 100)**
Previous treatment		
Naive	**96/96**	**100 (96.2, 100)**
Experienced	**19/20**	**95.0 (75.1, 99.9)**
CKD stage		
Stage 4	**22/22**	**100 (84.6, 100)**
Stage 5	**93/94**	**98.9 (94.2, 100)**
Diabetes		
Yes	**40/41**	**97.6 (87.1, 99.9)**
No	**75/75**	**100 (95.2, 100)**
Hemodialysis		



*modified full analysis set population (mFAS)

Roth D et al. Lancet 2015

DAAs in CKD in practice

- GFR> 30 ml/mn: all the therapeutic options
- GFR < 30 ml/mn, including dialysis patients:
  GT1 or 4: GZP/EBV 12 weeks
  GT1b: 3D 12 weeks
  GT2/3/5/6: SOF (200 mg/d or 400 mg/d or each 2 days ???) + NS5A
  SOF/LDV?
- Kidney recipients: Few or No data

- GFR > 30 ml/mn* GT1, 2, 4-5: SOF+LDV 12 weeks
  GT1 or 4: GZP/EBV 12 weeks/3D with adjustments of calcineurin inhibitors
  GT3: SOF + DCV
- GFR < 30 ml/mn GT1 or 4: GZP/EBV 12 weeks
  GT1b 3D with adjustments of calcineurin inh.
  GT2/3/5/6: SOF (200 mg/d or 400 mg/d or each 2 days?) + NS5A each day

* Kamar et al. AJKD 2015; Harvoni Gilead trial 2016

HCV in dialysis patients and kidney recipients: conclusions

- HCV hepatitis may be associated with a risk of
  - severe disease (immunosuppression)
  - liver-related overmortality
  - decreased patients and grafts survival

- Thus requiring:
  - prevention
  - evaluation of fibrosis
  - antiviral therapies by DAAs

- Different options for oral combinations of DAAs are available:
  - treat after as well as before kidney transplantation (derogatory allografts?)
  - inactive cirrhosis does not contra-indicate renal Tx.

Acknowledgments

- Anaïs Vallet-Pichard
  Marion Corouge
  Hélène Fontaine
  Liver Department, Hôpital Cochin, Paris, France

- Corinne Isnard-Bagnis, Hôpital Pitié-Salpétrière
  Eric Thervet, Hôpital Européen Georges Pompidou
  Christophe Legendre, Alain Debure, Hôpital Necker
  Nephrology Departments, Paris, France

- Michel Jadoul, Nephrology Department, Brussels, Belgium
- Paul Martin, Hepatology Department, Miami, FL, USA

Instituts thématiques Inserm
Institut national de la santé et de la recherche médicale

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

UNIVERSITÉ PARIS DESCARTES

Institut Pasteur

anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES
KDIGO