Hepatitis C Virus Infection in Patients With Chronic Kidney Disease

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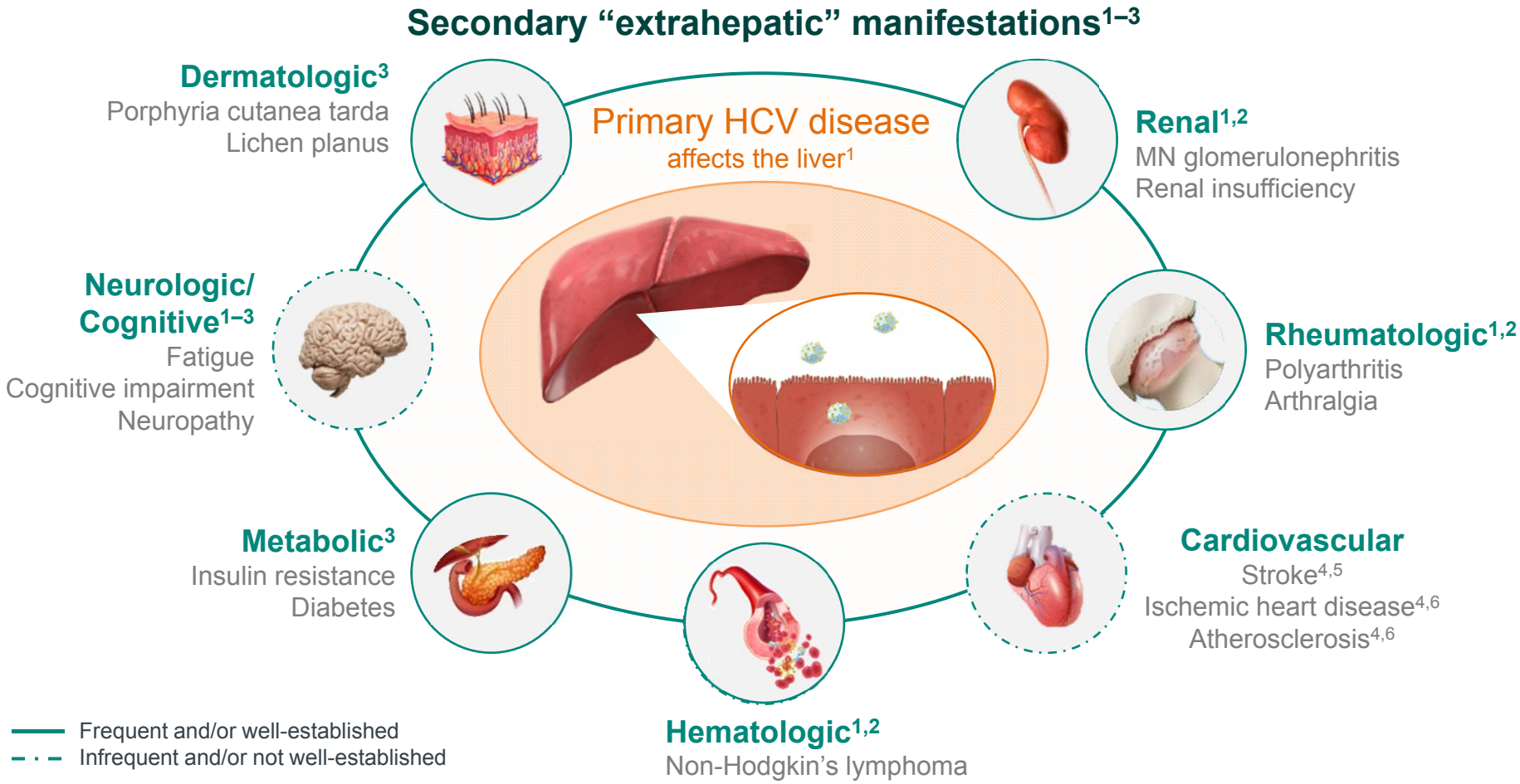
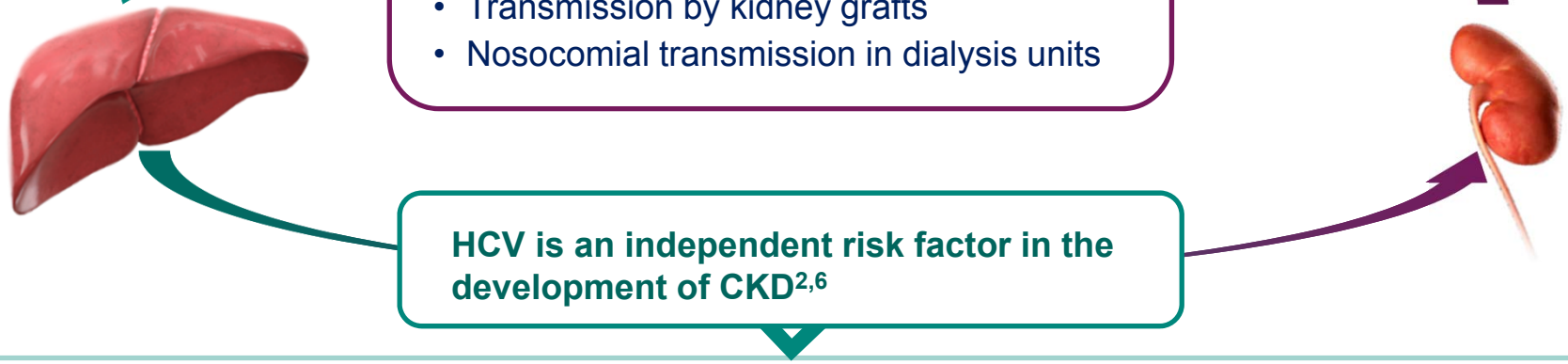
The Relationship Between CKD and Chronic HCV Infection

Chronic HCV Infection Is a Systemic Disease[1]



HCV Is a Cause and Complication of CKD[1]



- HCV is a significant cause of renal disease, especially MN glomerulonephritis[1,7]
- HCV infection has been linked to ~80% of cases of mixed cryoglobulin-related vasculitis and associated MN glomerulonephritis[7]

HCV: CAUSE

Atteintes rénales

- Associées à la CM:
  - 20 % à 30%
  - A rechercher systématiquement
  - HTA: 80% des cas symptomatiques ➡ prise TA!
  - Syndrome néphrotique: 25 % ➡ BU!
  - Evolution vers insuffisance rénale: 10 à 20% sur 10 ans

➡ PBR

Glomérulonéphrite aiguë ou chronique membrano-proliférative de type 1 avec dépots sous endothéliaux

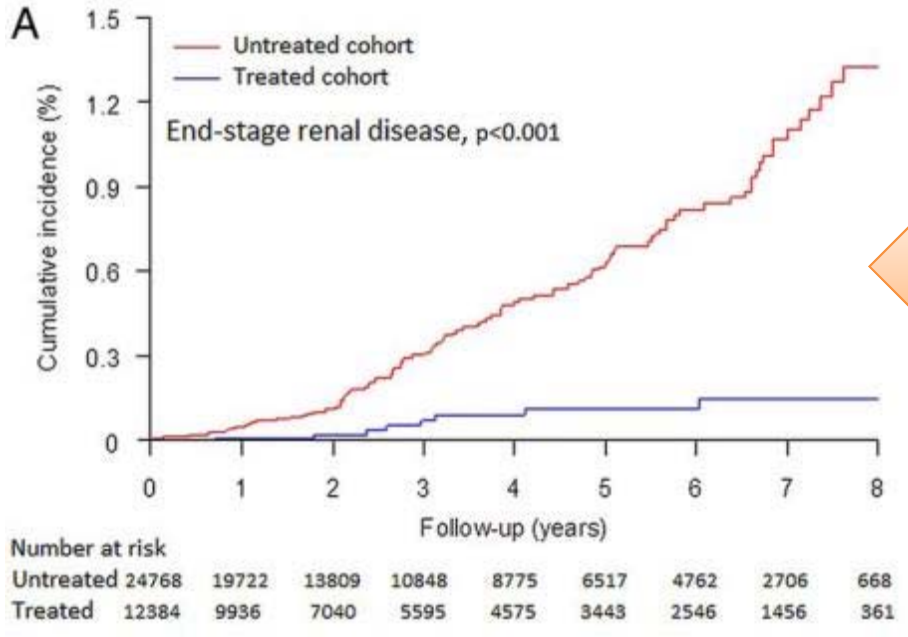
Atteintes rénales

- non associées à la CM:
  - Plus rares
  - Facteurs rhumatoïdes absents et Complément normal
  - PBR: glomérulonéphrite membranaire, glomérulo-sclérose segmentaire et focale, glomérulonéphrite proliférative, néphropathie à IgA, microangiopathie thrombotique, néphrite intersticielle
  - Evolution vers insuffisance rénale: 10 à 20% sur 10 ans

HCV Infection is Associated with an Increased Risk of CKD Progression

Large Taiwanese prospective chronic HCV cohort study: 12,384 patients treated with pegIFN/RBV and 24,768 untreated matched controls were followed up for a mean of 3.3 years and 3.2 years, respectively[1]

Cumulative incidence of ESRD



Patients with chronic renal impairment at baseline were excluded from the study

Antiviral treatment was associated with an **85% lower risk** for ESRD (HR 0.15; 95% CI = 0.07–0.31; *P* < 0.001)

Proposed mechanism for HCV-induced renal injury is deposition of circulating immune complexes (cryoglobulinemia)[2]

CKD, chronic kidney disease; ESRD, end-stage renal disease.

1. Hsu YC, *et al*. *Gut* 2015; **64:**495–503;
2. Gill K, *et al*. *Hepatol Int* 2016; **10:**415–423.

The Association Between HCV and CKD May Be Mediated by Comorbidities and Other Factors

Comorbidities associated with ↑ risk of CKD development or progression that are common among HCV-infected persons[1-5]:

- **HIV Coinfection**
- **Diabetes**
- **Atherosclerosis**
- **Hypertension**

HCV ⋯▶ **CKD**

Risk of Developing CKD Among HCV-infected Persons With and Without Comorbidities Compared With Healthy Controls[2]	Comorbidity Status	HR for CKD Development
	HCV Alone	1.92
	HCV + **Diabetes**	**4.33**
	HCV + **Hypertension**	**2.90**
	HCV + **Hyperlipidemia**	**3.84**
	HCV + **Cirrhosis**	**3.31**

Chronic HCV Infection Is Independently Associated With Renal Function Impairment

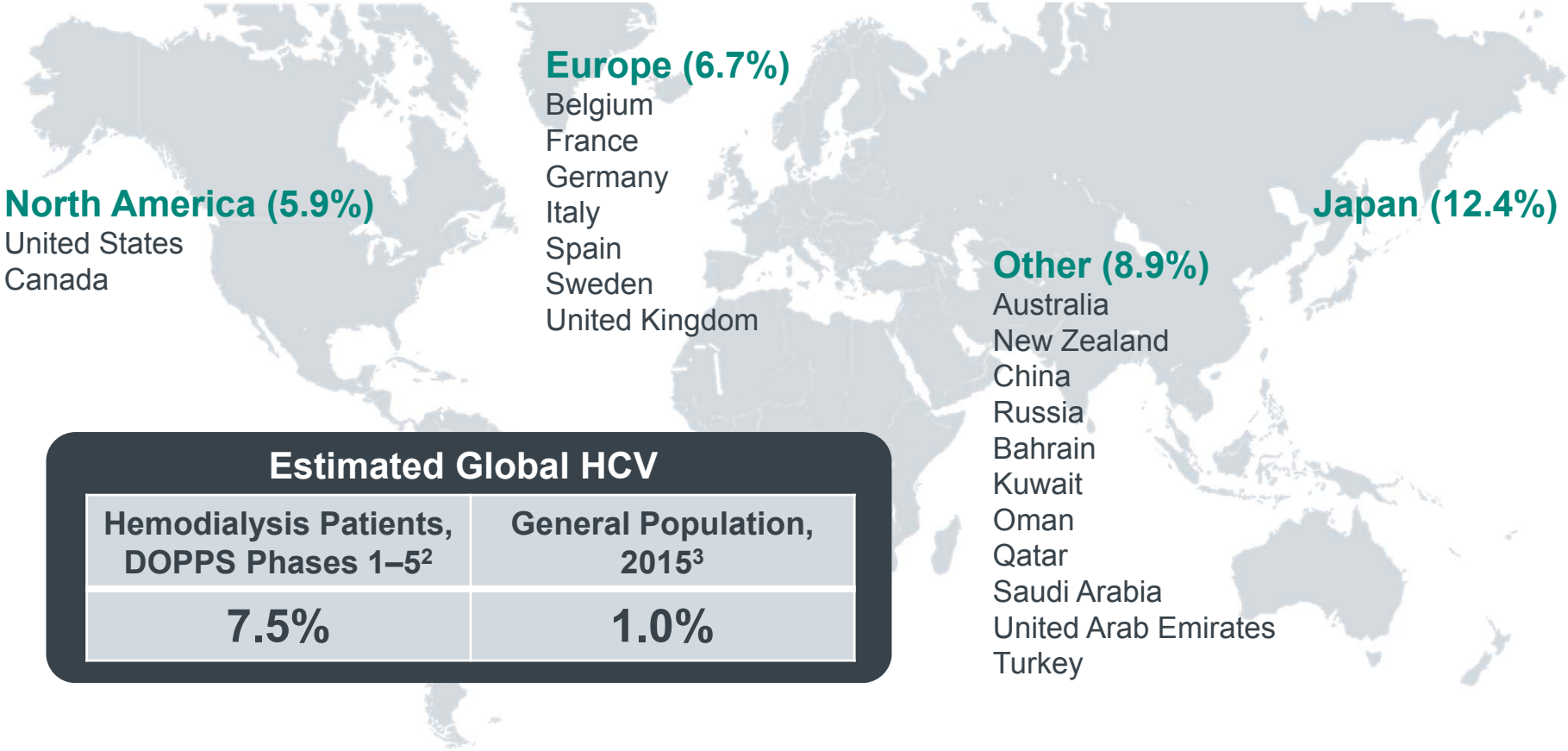
The Independent Association of Renal Disease and HCV Has Been Observed in Several Large Analyses

Condition	N	Adjusted Risk	95% CI
Membranoproliferative glomerulonephritis[1]	171,020	OR = 4.53	3.11–6.6
Reduced eGFR[2,a]	890,560	RR = 1.70	1.20–2.39
Renal insufficiency[3,b]	25,782	OR = 1.40	1.11–1.76

HCV: CONSEQUENCE

HCV Infection Is More Prevalent Among Persons on Hemodialysis Than in the General Population[1]

Prevalence of HCV Infection in Hemodialysis Patients of DOPPS Phases 1–5 (1996–2015) by Region[2]



Estimated Global HCV

Hemodialysis Patients, DOPPS Phases 1–5[2]	General Population, 2015[3]
7.5%	1.0%

The **DOPPS** is a prospective cohort study of hemodialysis practices based on the collection of observational longitudinal data for a random sample of patients from dialysis facilities in a representative and random sample of units in twenty countries.

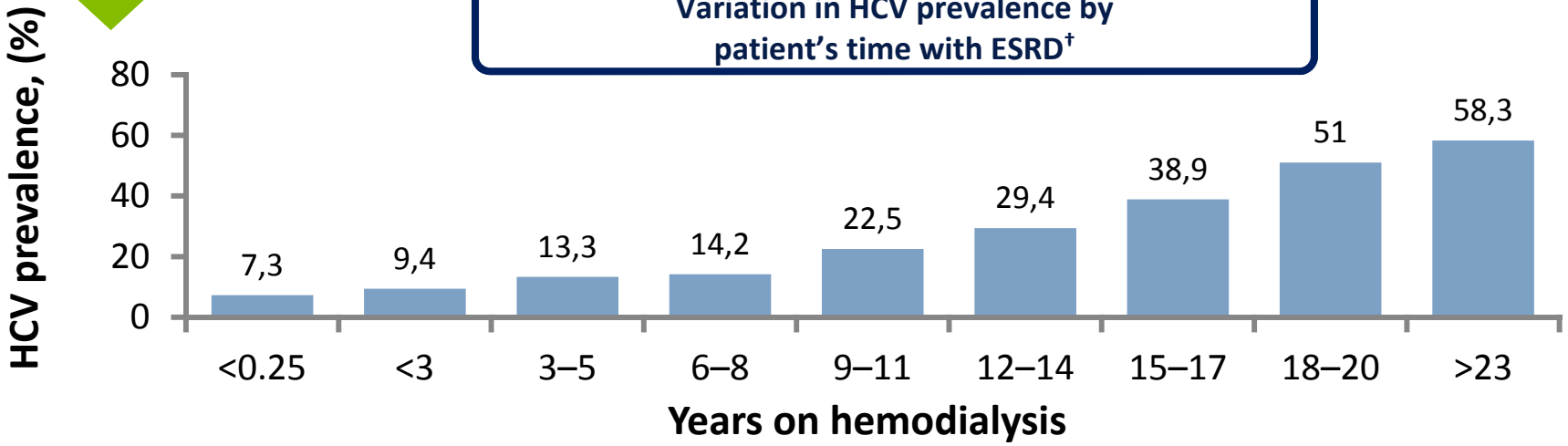
Patients with CKD on Hemodialysis are at Risk of Contracting HCV

Hemodialysis increases risk of HCV exposure and nosocomial transmission

Mean anti-HCV prevalence of **13.5%** in patients on hemodialysis in France, Germany, Italy, Japan, Spain, UK and US*

Risk factors: number of transfusions, duration of hemodialysis, type of hemodialysis, lack of compliance with universal precautions

Variation in HCV prevalence by patient's time with ESRD†



CKD, chronic kidney disease.

* Hemodialysis Outcomes and Practice Patterns Study 2004.

† The mean time on ESRD was 4.9 years, with a standard deviation of 5.4 years.

Fissell RB, *et al. Kidney International* 2004; **65:**2335–2342;
Aguirre Valadez J, *et al. Ther Clin Risk Manag* 2015; **11:**329–338.

HCV et IRC : Augmente la morbi-mortalité

HCV Infection in Patients on Hemodialysis Increases Risk of Mortality

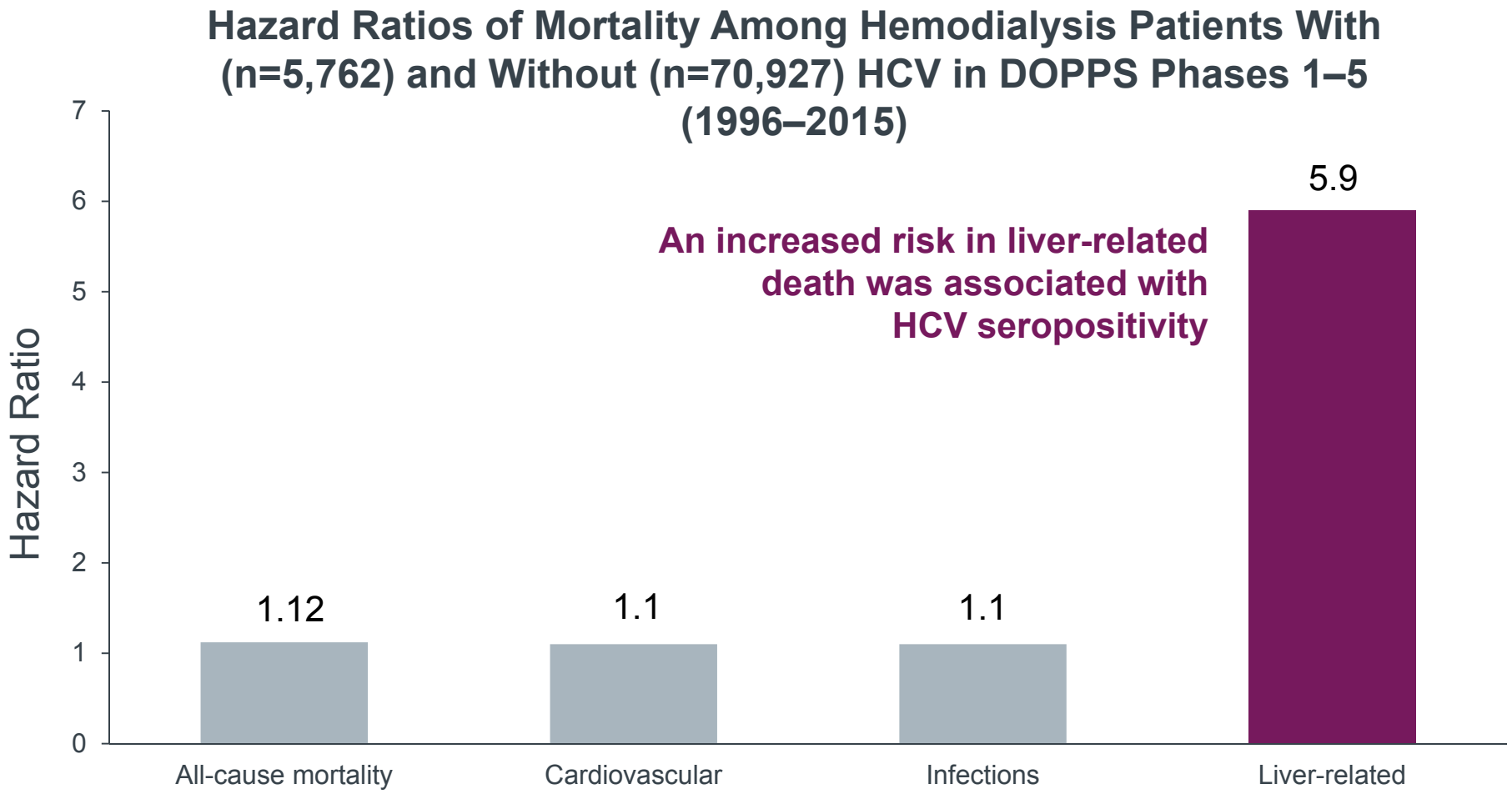
Meta-analysis of observational studies evaluating the impact of HCV on mortality in patients on maintenance hemodialysis

Risk with HCV among hemodialysis patients	Number of studies	Random effects adjusted relative risk (95% CI)
All-cause mortality	14	1.35 (1.25–1.47)
Liver disease-related mortality	4	3.82 (1.82–7.61)
Cardiovascular-related mortality	3	1.26 (1.10–1.45)
Infectious disease-related mortality	2	1.53 (1.11–2.12)

Cardiovascular- and liver-related mortality are major causes of death in patients with HCV on hemodialysis

Fabrizi F, *et al. J Viral Hepat* 2012; **19:**601–607.

HCV Increases the Risk of Liver Damage and Liver-Related Deaths Among Hemodialysis Patients[1]



Patients with HCV and CKD Increased Risk of Cardiovascular Disease and All-Cause Mortality

Kaiser Permanente electronic records were used to compare cardiovascular outcomes in HCV-infected patients without (n = 16,145) and with (n = 2,179) CKD

	HCV only			HCV + CKD			
Outcome	**N**	**PY**	**aIR (95% CI)**	**N**	**PY**	**aIR (95% CI)**	**Rate ratio (95% CI)**
Congestive heart failure	427	69,270	6.1 (5.5–6.8)	445	5,365	23.7 (20.2–27.9)	**3.9 (3.3–4.6)**
Cardio-myopathy	192	69,895	2.8 (2.4–3.2)	133	6,107	8.2 (6.2–10.7)	**3.0 (2.2–3.9)**
Acute myocardial infarction	349	69,702	4.7 (4.2–5.4)	165	6,161	11.3 (9.0–14.2)	**2.4 (1.9–3.0)**
Death	1,603	70,517	21.5 (20.3–22.8)	680	6,462	34.6 (30.9–38.8)	**1.6 (1.4–1.8)**

HCV-infected patients with CKD also had significantly increased risk for arrhythmia, bradyarrhythmia, acute coronary syndrome, and transient ischemic attack

CKD increased the risk of cardiovascular events and all death in patients with chronic HCV infection

aIR, adjusted incidence rate; CKD, chronic kidney disease; PY, person years.

Tartof SY, *et al. J Hepatol* 2016; **64**(suppl):S624.

KDIGO Guidelines: Recommendations for the Treatment of HCV Infection in Patients with CKD

All patients to be assessed for kidney disease at the time of HCV diagnosis with urinalysis and eGFR. If there is no evidence of kidney disease at initial evaluation, patients who remain NAT positive should undergo repeat screening for kidney disease

All CKD patients and kidney transplant recipients infected with HCV to be evaluated for antiviral therapy

- Patients to be treated with an IFN-free regimen
- Choice of specific regimen to be based on HCV genotype (and subtype), viral load, drug–drug interactions, eGFR category, stage of hepatic fibrosis, kidney and liver transplant candidacy, and comorbidities

CKD, chronic kidney disease;
eGFR, estimated glomerular filtration rate;
NAT, nucleic acid test(ing);
KDIGO, Kidney Disease: Improving Global Outcomes.

KDIGO 2018 Kidney International Supplements (2018) 8, 91-165

AASLD/EASL Guidelines: Recommendations for the Treatment of Patients with Renal Insufficiency

Owing to high risk of severe complications, patients with CKD require special consideration for treatment[1]

Cryoglobulinemia proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis

Treatment must be delivered without delay[2]

Patients with clinically significant extrahepatic manifestations (e.g. HCV-related cryoglobulinemia)

Persons at elevated risk of HCV transmission and in whom HCV treatment may yield transmission reduction benefits: persons on long-term hemodialysis[1,2]

Increased risk for nosocomial transmission

+

Substantial clinical impact of HCV infection in those on hemodialysis

=

Compelling arguments for HCV therapy as effective antiviral regimens that can be used in advanced renal failure become available

CKD, chronic kidney disease.

1. AASLD Recommendations for Testing, Managing, and Treating Hepatitis C. Available at: http://www.hcvguidelines.org/fullreport (accessed Dec 2018);
2. EASL Recommendations on Treatment of Hepatitis C. *J Hepatol* 2018; *in press*.

HCV Screening Recommendations

WHO	EASL	KDIGO	CDC	AASLD

HCV screening for populations at increased risk of infection is universally recommended[1–6]

All CKD patients should be screened for HCV

at the time of initial evaluation of CKD and as indicated by specific risk[2,4]

Routine HCV screening is recommended for hemodialysis patients

- Upon initiation of HD or transfer to another HD facility or modality
- At the time of evaluation for kidney transplantation
- **Every 6 months**

An IFN-free therapy should be considered for all HCV-infected patients[1–3]

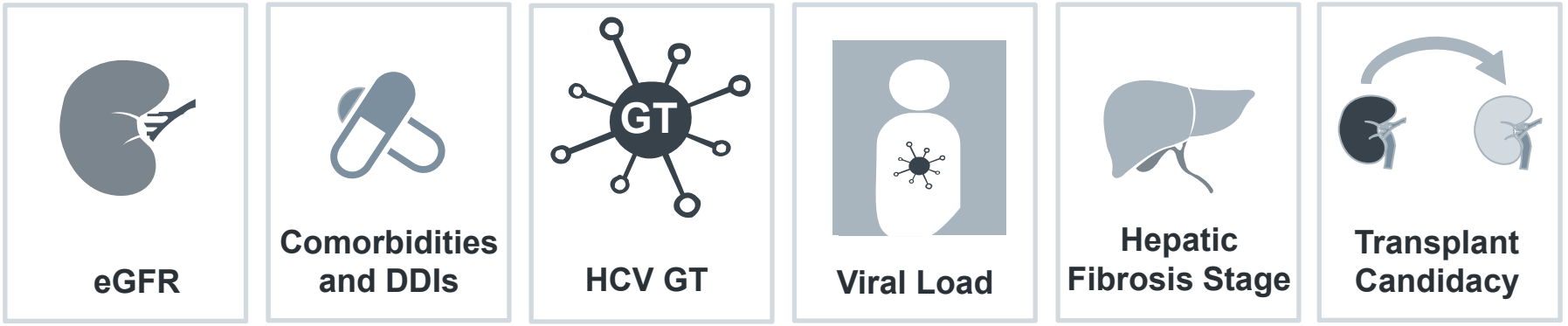
HCV = hepatitis C virus; WHO = World Health Organization; EASL = European Association for the Study of the Liver; KDIGO = Kidney Disease: Improving Global Outcomes; CDC = Centers for Disease Control and Prevention; AASLD = American Association for the Study of Liver Diseases; CKD = chronic kidney disease; HD = hemodialysis; IFN = interferon.

1. World Health Organization guidelines for the screening, care and treatment of persons with hepatitis C infection. World Health Organization Web site. http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/. Accessed April 7, 2017. **2.** KDIGO 2017 Draft clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. Kidney Disease: Improving Global Outcomes Web site. www.kdigo.org/clinical_practice_guidelines/Hep%20C/KDIGO%202017%20Hep%20C%20GL%20Public%20Review%20Draft%20FINAL.pdf. Accessed March 7, 2017. **3.** European Association for the Study of the Liver. *J Hepatol*. 2017;66:152–194. **4.** Urging dialysis providers and facilities to assess and improve infection control practices to stop hepatitis C virus transmission in patients undergoing hemodialysis. Centers for Disease Control and Prevention Web site. www.emergency.cdc.gov/han/han00386.asp. Accessed February 2, 2017. **5.** Hepatitis C FAQs for health professionals. Centers for Disease Control and Prevention Web site. www.cdc.gov/hepatitis/hcv/hcvfaq.htm#b1. Accessed February 2, 2017. **6.** HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. American Association for the Study of Liver Diseases Web site. http://www.hcvguidelines.org/sites/default/files/full-guidance-pdf/HCVGuidance_April_12_2017_b.pdf. Accessed July 6, 2017.

Special Considerations for HCV Treatment in Patients With Renal Impairment[1]

All CKD patients with chronic HCV infection should be considered for treatment with an IFN-free DAA therapy.[1–4]

Considerations for Selection of HCV Regimen[1–3,5]



Key Treatment Guidelines for Chronic HCV GT1 or GT4 Infected Patients With Impaired Kidney Function

eGFR ≥30 mL/min/1.73 m² — **General guidelines may be followed**[1,2]

eGFR <30 mL/min/1.73 m² — **The EASL and AASLD guidelines recommend select DAA regimens for patients** [1,2]

	CKD patients (G1-G6)
EASL[1]	• EBR/GZR for 12 weeks (G1 & G4) • GLE/PIB for 12 weeks (G1-G6)
AASLD[2]	• EBR/GZR for 12 weeks (G1 & G4) • GLE/PIB for 12 weeks (G1-G6)

Completion of DAA Therapy is Associated with Reduced Risk of End-stage Renal Disease

Retrospective observational cohort study using the US administrative claims Quintiles/IMS PharMetrics Plus database to examine the risk of ESRD among HCV patients completing DAA regimens compared with untreated patients

Baseline patient characteristics

- DAA-treated patients were older, male, and more likely to have cirrhosis at baseline
- Chronic renal insufficiency was similar between groups (7.0% vs 6.5%)

- Patients completing therapy had a substantial reduced risk of ESRD after adjusting for age, gender, cirrhosis, prior renal insufficiency, and other baseline comorbidities
- In patients with prior CKD, a similar reduction in risk was observed (RR = 0.76, 95% CI: 0.55–1.04)

Incidence rates of ESRD

	N	# of events	Total person-time (years)	Unadjusted rate, per 100 person-years (95% CI)
Untreated*	138,058	1,104	160,854.2	0.69 (0.65– 0.73)
DAA-treated†	19,606	131	22,233.3	0.59 (0.49– 0.70)

	Unadjusted IRR		Adjusted IRR	
	IRR	(95% CI)	IRR	(95% CI)
Untreated	1.00	(ref)	1.00	(ref)
DAA-treated	0.86	(0.72–1.03)	0.56	(0.46–0.67)

CI, confidence intervals; CKD, chronic kidney disease;
ESRD, end-stage renal disease; IRR, incidence rate ratio; RR, relative risk.
* Untreated HCV patients: ICD code for HCV diagnosis but no evidence of treatment;
† DAA-completing HCV patients received at least 12 weeks of DAA therapy.

Singer AW, *et al. Hepatology* 2017; **64**(Suppl 1):519A (Poster presentation #970).

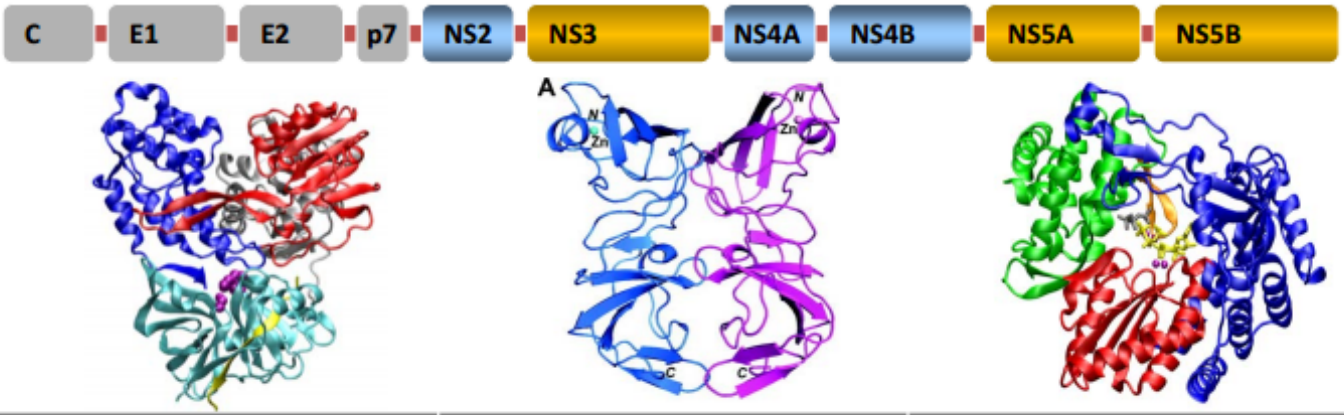
Summary

- Chronic HCV is a known cause and a complication of CKD
- Patients with CKD, especially those on hemodialysis, have a higher prevalence of HCV infection compared with the general population
- Chronic HCV infection increases the risk of developing ESRD and the risk of adverse outcomes in patients with ESRD
- DOPPS estimated that only 1.5% of patients with chronic HCV on hemodialysis who were enrolled in the study received HCV antiviral treatment between 1998 and 2015 worldwide
- The WHO, EASL, AASLD, CDC, and KDIGO guidelines recommend HCV screening for persons with increased risk, including CKD patients
- All chronic HCV-infected patients should be considered for HCV antiviral treatment

HCV Treatment in CKD

Les Antiviraux Directs du VHC

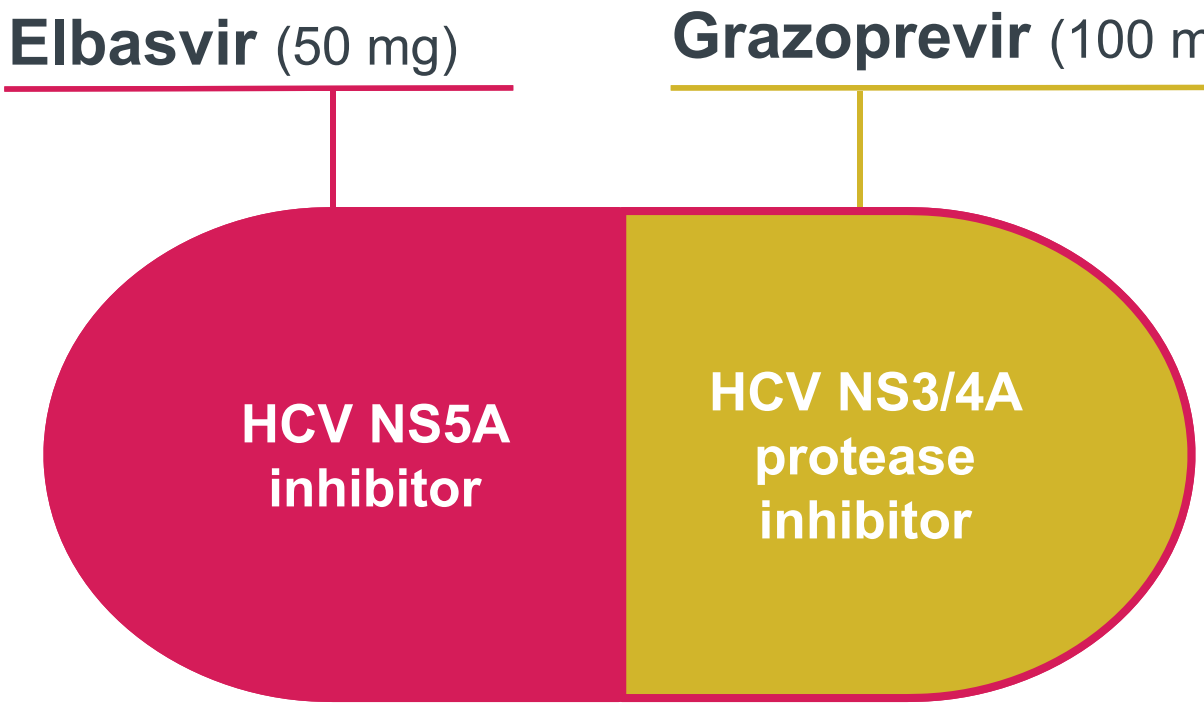
Cibles Virales | **Cibles d'Hôte**



NS3	NS5A	NS5B	Cyclophilin A
Protéase sérine NS3/4A essentielle au processing post-traductionnel de la polyprotéine du VHC	Phosphoprotéine multifunctionnelle essentielle au complexe de réplication de l'ARN VHC	ARN Polymérase ARN dépendante NS5B spécifique du VHC	Protéine de l'hôte impliquée dans la réplication du VHC via l'interaction avec la protéine NS5A et la polymérase
-PREVIR **Boceprevir** **Telaprevir** **ABT-450/r, ACH-1625** **Asunaprevir,** **Simeprevir, BI-201335** **MK-5172**	**-ASVIR** **-Daclatasvir** **Ledipasvir (GS-5885)** **GS-5816** **ABT-267 (Ombitasvir)** **PPI-668** **Elbasvir**	**-BUVIR** **-<u>Nucleos(t)ide analogue</u>** **Sofosbuvir,** **IDX-184*** **<u>Non-nucleoside analogue</u>** **ABT-333 (Dasabuvir)** **ABT-072, BMS-791325**	**Alisporivir** **SCY-635**

ZEPATIER™ (elbasvir and grazoprevir) Treatment Outcomes in HCV Genotype 1-Infected Subjects With Advanced Chronic Kidney Disease

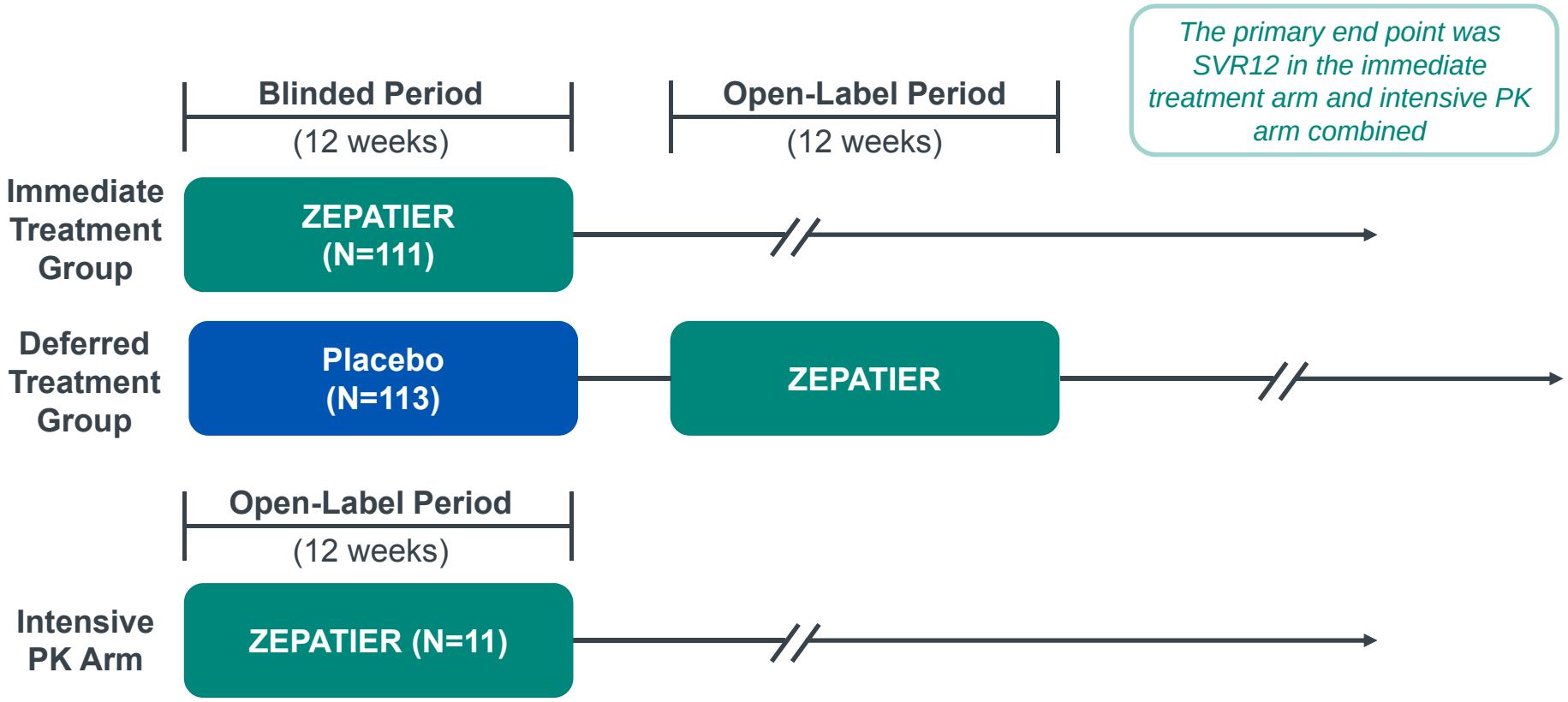
ZEPATIER™ (elbasvir and grazoprevir) Is a Fixed-Dose Combination of Elbasvir and Grazoprevir[1]



ZEPATIER is indicated for the treatment of chronic hepatitis C GT1 and GT4 infection in adults

ZEPATIER™ (elbasvir and grazoprevir): C-SURFER Study Design[1]

Treatment-Naïve or Treatment-Experienced[a] HCV GT1 Patients With or Without Cirrhosis With Advanced Chronic Kidney Disease (Stage 4 or 5)[b]



HCV = hepatitis C virus; GT = genotype; PK = pharmacokinetic; IFN = interferon; pegIFN = peginterferon alfa; RBV = ribavirin; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SVR12 = sustained virologic response 12 weeks after the cessation of treatment.

[a]Patients who failed treatment with IFN or pegIFN +/- RBV.

[b]Stage 4 CKD was defined as eGFR 15-29 ml/min/1.73 m^2. Stage 5 CKD was defined as eGFR <15 ml/min/1.73 m^2.

1. Roth D et al. *Lancet*. 2015;386:1537–1545.

Demographics for Patients Treated With ZEPATIER™ (elbasvir and grazoprevir) in C-SURFER[1]

Selected Patient Demographics From C-SURFER Pooled Immediate-Treatment Group and Intensive Pharmacokinetic Group (N=122)

Patient Demographics	
Gender	
Male	75%
Female	25%
Race	
White	50.0%
African-American	45.1%
Asian	4.1%
Other	0.8%
HCV genotype	
1a	51.6%
1b	48.4%
HCV treatment history	
Naive	82.8%
Experienced	17.2%

Patient Demographics	
Cirrhosis status	
No cirrhosis	94.3%
Compensated cirrhosis	5.7%
Diabetes status	
Diabetes	36.1%
No diabetes	63.9%
Hemodialysis status	
On hemodialysis	75.4%
Not on hemodialysis	24.6%
Chronic kidney disease	
Stage 4	18.0%
Stage 5	82.0%

HCV = hepatitis C virus.

1. Roth D et al. *Lancet*. 2015;386:1537–1545.

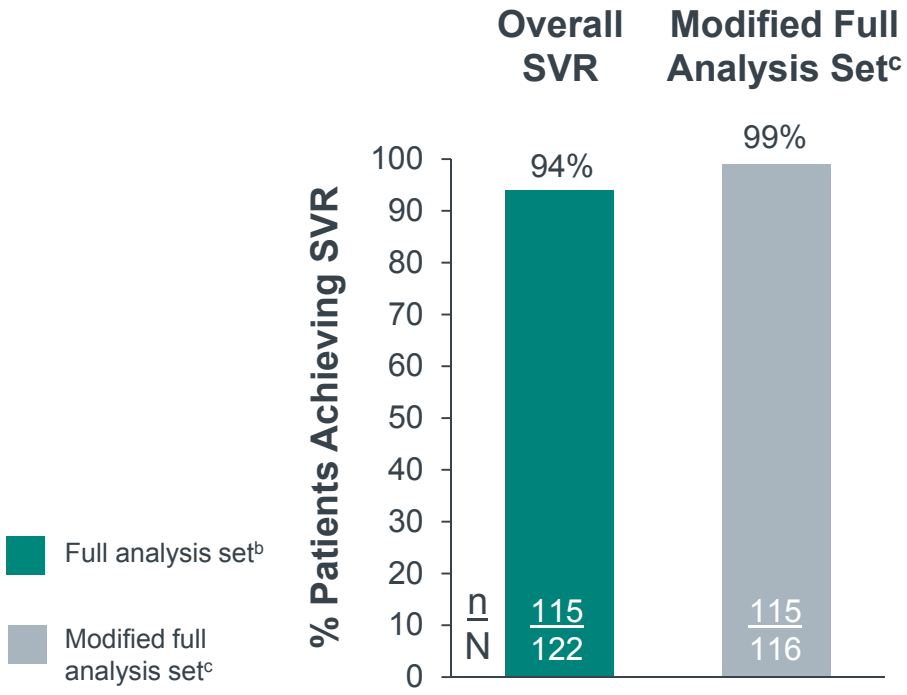
Demographics for Patients Treated With ZEPATIER™ (elbasvir and grazoprevir) in C-SURFER[1] (*continued*)

Primary Etiology of Renal Disease for Patients in the C-SURFER Pooled Immediate-Treatment Group and Intensive Pharmacokinetic Group (N=122)

Primary etiology of renal disease	
Hypertension	41.0%
Type 1 diabetes	4.9%
Type 2 diabetes	17.2%
Congenital cystic kidney disease	3.3%
Chronic autoimmune glomerulonephritis	9.0%
Pyelonephritis	1.6%
Urinary tract obstruction	3.3%
Cryoglobulinemia	3.3%
Other	16.4%

ZEPATIER™ (elbasvir and grazoprevir): Efficacy in HCV GT1-Infected Patients With CKD Stage 4 or 5—C-SURFER[a] (Full and Modified Analysis Sets)[1]

SVR Rates for CKD Stage 4 or 5 Patients Receiving 12 Weeks of ZEPATIER



HCV = hepatitis C virus; GT = genotype; CKD = chronic kidney disease; SVR = sustained virologic response.

[a]Immediate treatment and pharmacokinetic arm results are presented.

[b]Full analysis set was a secondary analysis which included all patients who received at least one dose of study drug.

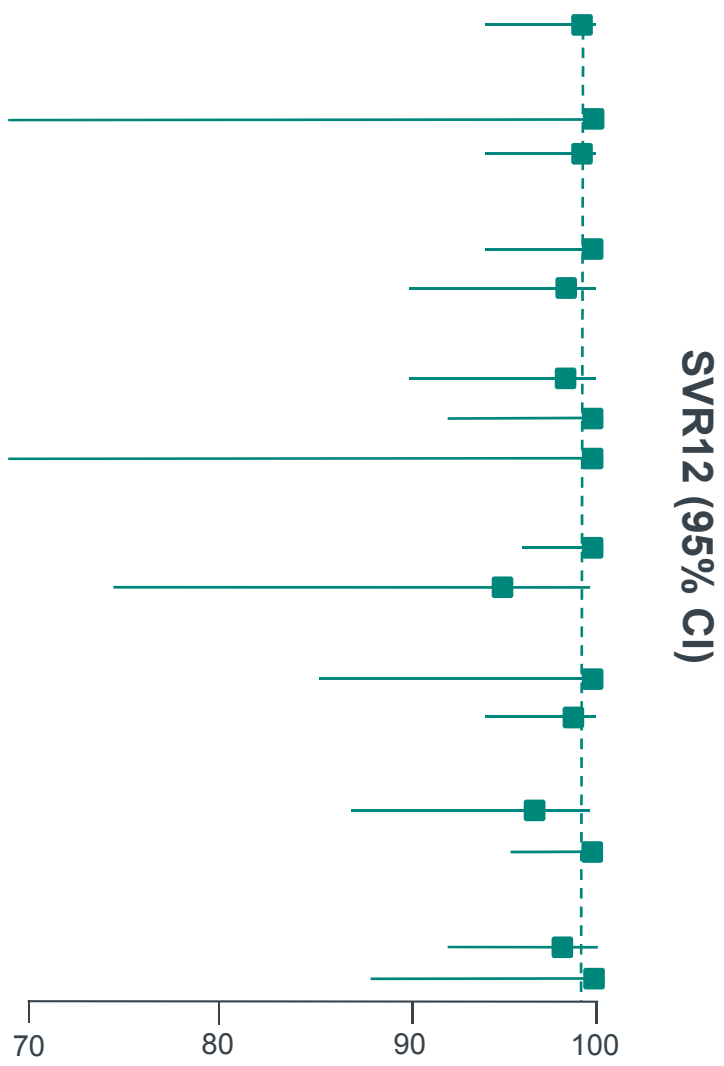
[c]Modified full analysis set was a primary analysis in a prespecified population, which excluded patients not receiving at least 1 dose of study treatment, and those with missing data because of death or early study discontinuation for reasons unrelated to treatment response.

[d]Includes genotype 1 subtypes other than 1a or 1b.

1. Roth D et al. *Lancet*. 2015;386:1537–1545.

ZEPATIER™ (elbasvir and grazoprevir): Efficacy in HCV GT1-Infected Patients With CKD Stage 4 or 5—C-SURFER[a] (Modified Full Analysis Set)[1]

SVR	n/N	% (95% CI)
Overall	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		
1a	61/61	100 (94.1, 100)
1b	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		
Yes	86/87	98.9 (93.8, 100)
No	29/29	100 (88.1, 100)

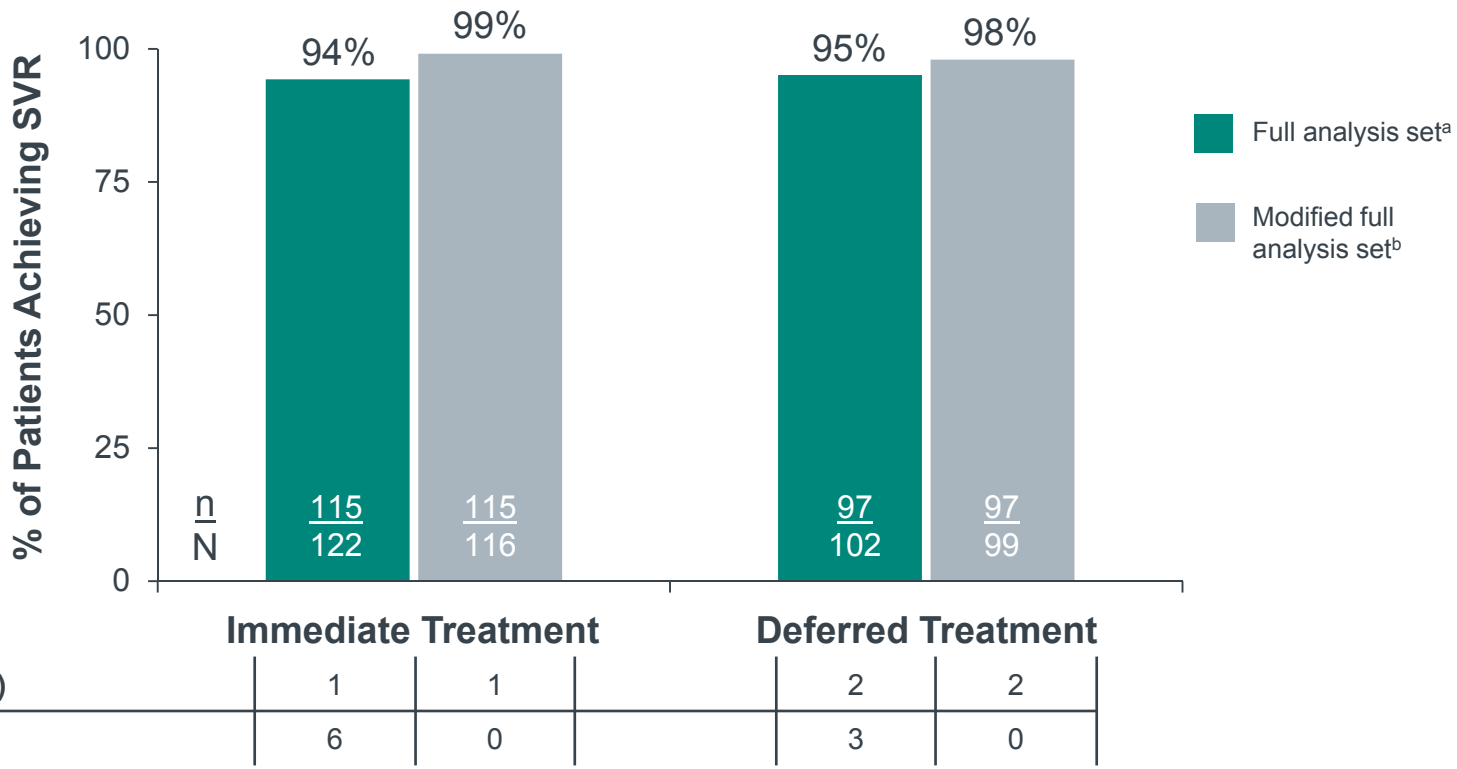


HCV = hepatitis C virus; GT = genotype; CKD = chronic kidney disease; SVR = sustained virologic response; CI = confidence interval.

1. Roth D et al. *Lancet*. 2015;386:1537–1545.

ZEPATIER™ (elbasvir and grazoprevir): Efficacy in HCV GT1-Infected Patients With CKD Stage 4 or 5—C-SURFER[a] (Full and Modified Analysis Sets)

SVR in Immediate and Deferred Treatment Groups[1]



	Immediate Treatment		Deferred Treatment	
Relapse (n)	1	1	2	2
Other[c] (n)	6	0	3	0

HCV = hepatitis C virus; GT = genotype; CKD = chronic kidney disease; SVR = sustained virologic response.

[a]Full analysis set was a secondary analysis.

[b]Modified full analysis set was a primary analysis in a prespecified population, which excluded patients not receiving at least 1 dose of study treatment, and those with missing data because of death or early study discontinuation for reasons unrelated to treatment response.

[c]Includes patients who discontinued for reasons unrelated to treatment response, including death, noncompliance, and withdrawal by patient or physician.

1. Roth D et al. Kidney Week 2015, Poster TH-PO667.

ZEPATIER™ (elbasvir and grazoprevir): Adverse Reactions in HCV GT1-Infected Patients With CKD Stage 4 or 5—C-SURFER[1,a]

Adverse Reactions Occurring at ≥5% Frequency in Patients With Advanced CKD and Chronic HCV Treated With ZEPATIER in C-SURFER

Adverse Reaction	ZEPATIER[a] (N=111) % (n)	Placebo (N=113) %(n)
Headache	17% (19)	17% (19)
Nausea	15% (17)	16% (18)
Fatigue	10% (11)	15% (17)
Insomnia	6% (7)	11% (12)
Dizzinness	5% (6)	16% (18)
Diarrhea	5% (6)	13% (15)
Drug-related SAE	0% (0)	1% (1)
Discontinuation due to AE	0% (0)	4% (5)

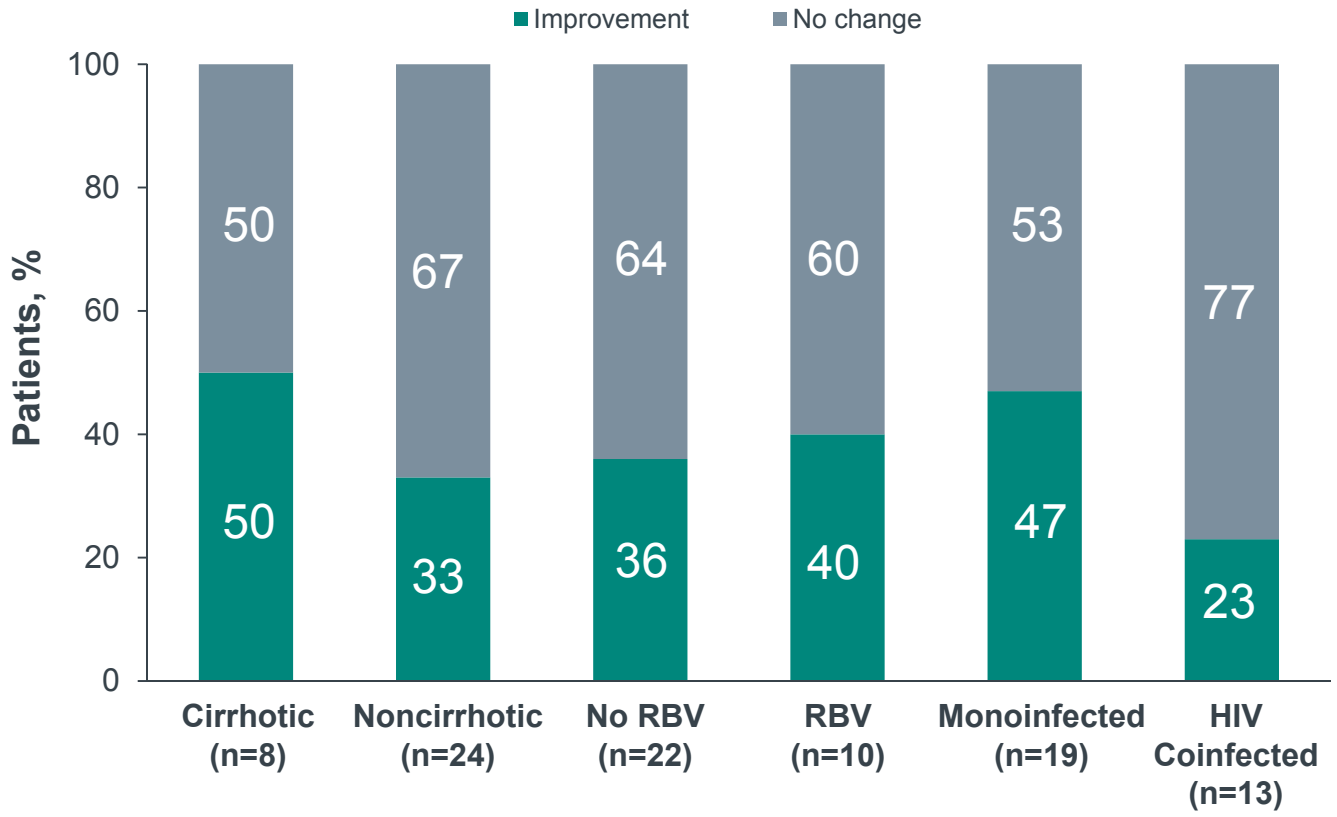
HCV = hepatitis C virus; GT = genotype; CKD = chronic kidney disease; SAE = serious adverse event.

[a]Immediate treatment and pharmacokinetic arm results are presented.

1. Roth D et al. *Lancet*. 2015;386:1537–1545.

ZEPATIER™ (elbasvir and grazoprevir): eGFR in Patients With Stage 3 CKD in Phase 2/3 Clinical Trials (Full Analysis Set)[1]

Change in CKD Stage Between Baseline and EOT in Selected Subgroups Among Patients With CKD Stage 3[a] at Baseline (n=32)



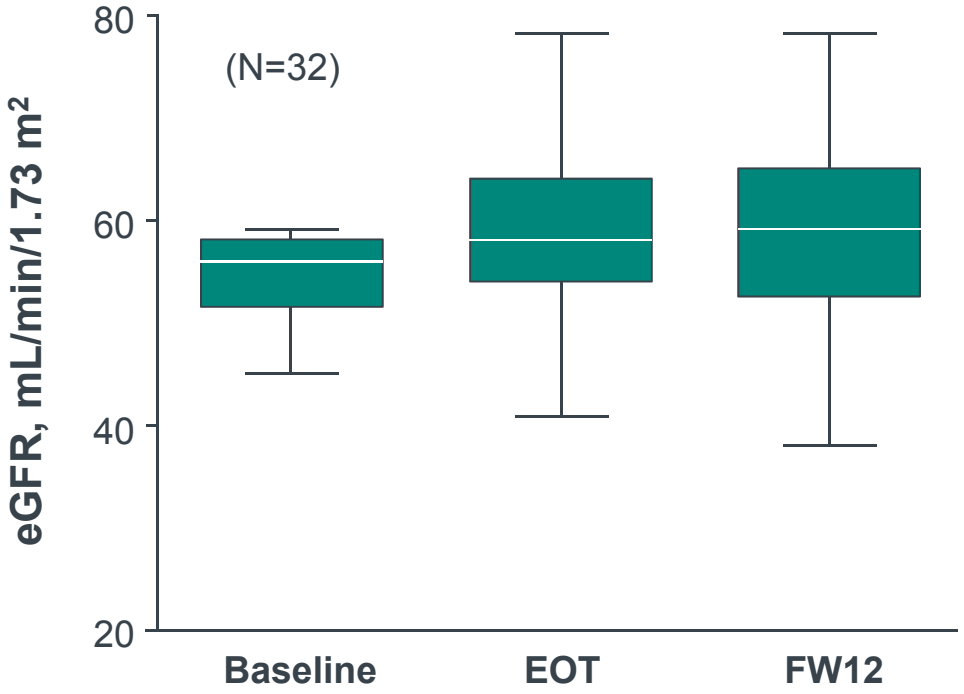
eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; EOT = end of treatment; RBV = ribavirin; HIV = human immunodeficiency virus.

[a]CKD stage 3 defined as baseline eGFR <60 to ≥30 mL/min/1.73 m^2.

1. Reddy KR et al. *Hepatology.* 2017; doi: 10.1111/hepr.12899.

ZEPATIER™ (elbasvir and grazoprevir): eGFR in Patients With Stage 3 CKD in Phase 2/3 Clinical Trials (Full Analysis Set) (*continued*)[1]

Median eGFR[a] During Treatment and Follow-up in Patients With CKD Stage 3



Elbasvir/grazoprevir does not worsen renal function in patients with HCV infection and preexisting renal disease[1]

CKD stage 3 defined as baseline eGFR <60 to ≥30 mL/min/1.73 m^2.

[a]eGFR assessed using the Modification of Diet in Renal Disease equation.

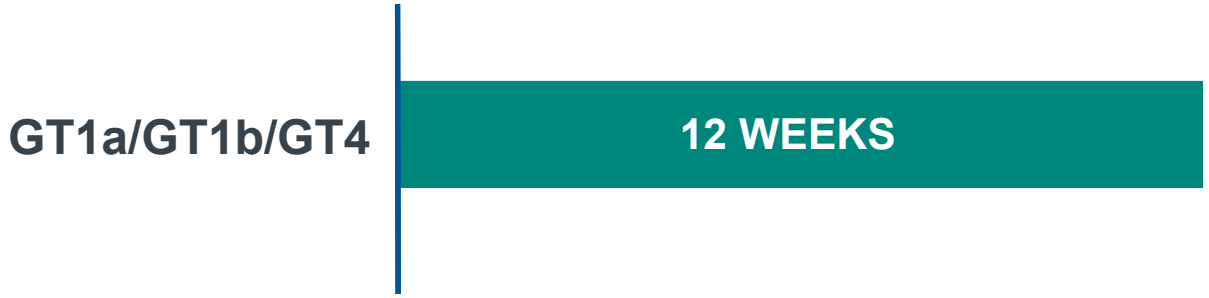
eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; EOT = end of treatment; FW = follow-up week; RBV = ribavirin.

1. Reddy KR et al. *Hepatology.* 2017; doi: 10.1111/hepr.12899.

Indication and Dosing Regimens for ZEPATIER™ (elbasvir and grazoprevir)

Recommended Regimens and Treatment Durations for ZEPATIER™ (elbasvir and grazoprevir)[1]

One pill, once-daily, 12-week regimen recommended for most patients with chronic HCV infection with or without compensated cirrhosis



- **GT1a:** ZEPATIER for 16 weeks plus RBV[a] should be considered in patients with baseline HCV RNA level >800,000 IU/mL and/or the presence of specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimize the risk of treatment failure
- **GT4:** ZEPATIER for 16 weeks plus RBV[a] should be considered in patients with baseline HCV RNA level >800,000 IU/mL to minimize the risk of treatment failure

Recommended Regimens and Treatment Durations for ZEPATIER™ (elbasvir and grazoprevir): Renal and Hepatic Considerations[1]

Renal Impairment	
Any degree of renal impairment including patients receiving hemodialysis or peritoneal dialysis	No dosage adjustment recommended
Hepatic Impairment	
Mild hepatic impairment: Child-Pugh class A	No dosage adjustment recommended
Moderate or severe hepatic impairment: Child-Pugh class B or C	Contraindicated

ZEPATIER™ (elbasvir and grazoprevir): Safety and Tolerability[1]

Safety and Tolerability of ZEPATIER in Patients With Chronic HCV Infection Across Phase 2 and 3 Trials

	ZEPATIER (N=1,033)	ZEPATIER + RBV (N=657)	Placebo (N=105)
≥1 Adverse Event(s)	71%	84%	69%
Fatigue	16%	29%	17%
Headache	18%	21%	18%
Nausea	8%	15%	8%
Insomnia	4%	11%	6%
Drug-related AE[a]	40%	68%	39%
Serious AE	2%	3%	3%
Serious drug-related AE	<1%	<1%	0%
Death[b]	<1%	<1%	0%

HCV = hepatitis C virus; RBV = ribavirin; AE = adverse event.

[a]Determined by the investigator.

[b]There were 3 deaths: ZEPATIER (post-appendectomy complication, n=1; coronary artery disease, n=1); ZEPATIER + RBV (motor vehicle accident, n=1).

1. Dusheiko GM et al. AASLD 2015, #712.

Drug-Drug Interactions for ZEPATIER™ (elbasvir and grazoprevir)

Drugs That Do Not Require Dose Adjustment With ZEPATIER™ (elbasvir and grazoprevir)[1,a]

Within Drug Class	Drug Name
Acid-reducing agents	antacids | H2 receptor antagonists | proton pump inhibitors
Antiarrhythmics	digoxin
Asthma agents	montelukast
HBV antivirals	entecavir
HCV antivirals	sofosbuvir
HIV medications	dolutegravir | raltegravir | abacavir | emtricitabine | lamivudine | rilpivirine | tenofovir disoproxil fumarate
Statins	pitavastatin | pravastatin
Immunosuppressants	mycophenolate mofetil | prednisone
Opioid substitution therapy	buprenorphine/naloxone | methadone
Oral contraceptives	ethinyl estradiol | levonorgestrel
Phosphate binders	calcium acetate | sevelamer carbonate
Sedatives	midazolam

Contraindicated Drugs and Other Potentially Significant Drug Interactions With ZEPATIER™ (elbasvir and grazoprevir)[1]

Contraindicated With ZEPATIER		
OATP1B inhibitors		rifampicin | atazanavir | darunavir | lopinavir | saquinavir | tipranavir | cobicistat | ciclosporin
CYP3A or P-gp inducers		efavirenz | phenytoin | carbamazepine | bosentan | etravirine | modafinil | St. John's wort
OATP1B and CYP3A inhibitors		elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (fixed-dose combination)
Not Recommended With ZEPATIER		
CYP3A inhibitor		ketoconazole
Other Clinical Considerations for Coadministered Drugs		
Anticoagulants	**dabigatran etexilate**	Concentrations of dabigatran may increase when coadministered with elbasvir, with possible increased bleeding risk. Clinical and laboratory monitoring is recommended.
Statins	**atorvastatin**	Dose of atorvastatin should not exceed 20 mg/day
	rosuvastatin	Dose of rosuvastatin should not exceed 10 mg/day
	fluvastatin | lovastatin | simvastatin	Dose of fluvastatin, lovastatin, or simvastatin should not exceed 20 mg/day
Tacrolimus		Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events is recommended

www.hep-druginteractions.org

GLE/PIB: Maviret

Glecaprevir/Pibrentasvir (*Mavyret*)

Next Generation Direct-Acting Antivirals

Glecaprevir
(formerly ABT-493)
pangenotypic NS3/4A protease inhibitor

Collectively: G/P

Pibrentasvir
(formerly ABT-530)
pangenotypic NS5A inhibitor

In vitro:[1,2]

- High barrier to resistance
- Potent against common NS3 polymorphisms (eg, positions 80, 155, and 168) and NS5A polymorphisms (eg, positions 28, 30, 31 and 93)
- Additive/synergistic antiviral activity

Clinical PK & metabolism:

- Once-daily oral dosing
- Minimal metabolism and primary biliary excretion
- Negligible renal excretion (<1%)

G/P is coformulated and dosed once daily as three 100 mg/40 mg pills for a total dose of 300 mg/120 mg
Glecaprevir was identified by AbbVie and Enanta

1. Ng TI, et al. Abstract 636. CROI, 2014. 2. Ng TI, et al. Abstract 639. CROI, 2014.

EXPEDITION-4: Study Design

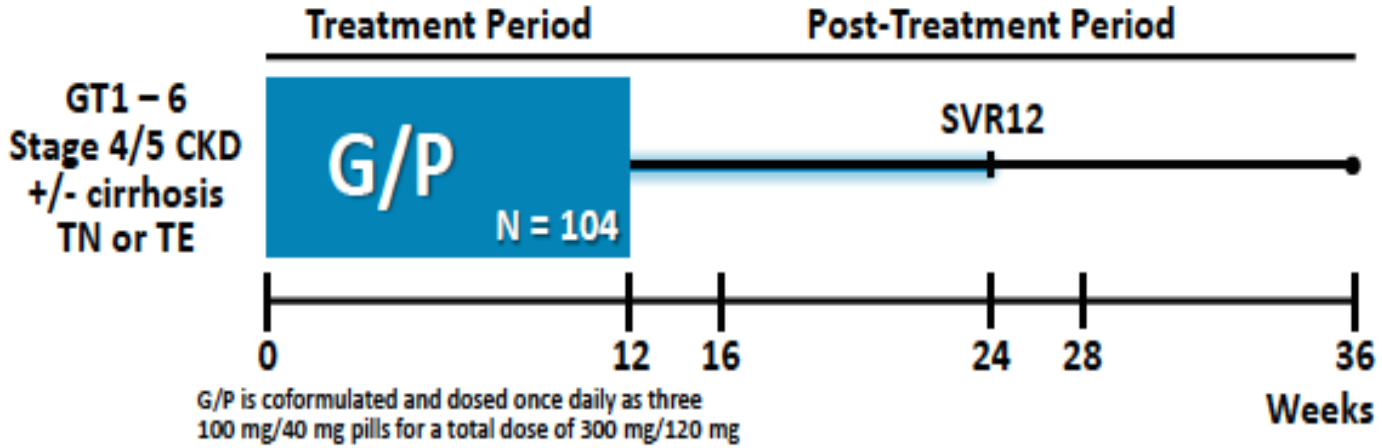
EXPEDITION 4 was a single-arm, multicenter, open-label, phase 3 study investigating the efficacy and safety of 12 weeks MAVIRET® in adults (N=104) with chronic HCV infection (GT1–6) and renal impairment, with (N=20) or without (N=84) compensated cirrhosis. The primary endpoint was sustained virologic response at 12 weeks after the end of treatment in the intention-to-treat population.*,[1]

GT: Genotype; HCV: Hepatitis C Virus; SVR: Sustained Virologic Response.
*patients who received at least one dose of study drug.
Reference: **1.** Gane et al. EXPEDITION-4, N Engl J Med 2017 Oct12;377(15)1448-1455.

MAVIRET
glecaprevir/pibrentasvir

Efficacy and Safety of GLE/PIB in Renally Impaired Patients With HCV GT1-6: Expedition 4[1]

EXPEDITION-4: Objective and Study Design



Objective

- Determine the efficacy and safety of pangenotypic G/P for 12 weeks in patients with HCV GT1-6 and stage 4 or 5 chronic kidney disease (CKD)

EXPEDITION-4: Baseline demographics

Baseline demographics[1]

Prior treatment history, n (%)	
Naïve	60 (58)
IFN/pegIFN ± RBV	42 (40)
SOF + RBV ± pegIFN	2 (2)
Compensated cirrhosis, n (%)	
Yes	20 (19)
No	84 (81)
CKD stage, n (%)	
Stage 4	14 (13)
Stage 5	90 (87)
Hemodialysis	85 (82)

CKD: Chronic Kidney Disease; IFN: Interferon; pegIFN: pegylated Interferon; RBV: Ribavirin; SOF: Sofosbuvir.

Reference: **1.** Gane et al. EXPEDITION-4, N Engl J Med 2017 Oct12;377(15)1448-1455.

MAVIRET
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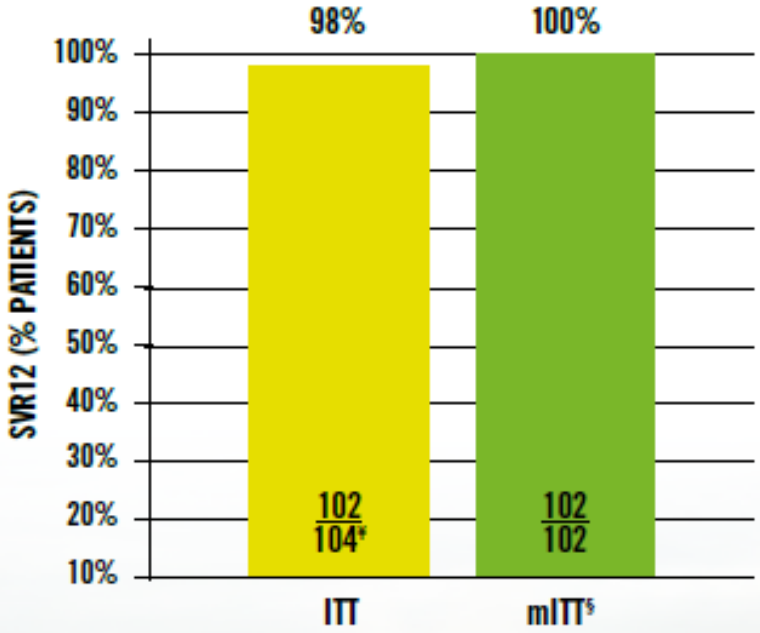
EXPEDITION-4

MOVE AHEAD WITH A TREATMENT REGIMEN APPROVED FOR ALL LEVELS OF RENAL IMPAIRMENT[1,2]

Baseline demographics[2]

Prior treatment history, n (%)	
Naive	60 (58)
IFN/pegIFN ± RBV	42 (40)
SOF + RBV ± pegIFN	2 (2)
Compensated cirrhosis, n (%)	
Yes	20 (19)
No	84 (81)
CKD stage, n (%)	
Stage 4	14 (13)
Stage 5	90 (87)
Hemodialysis	85 (82)

GT1–6 RENALLY IMPAIRED PATIENTS (CKD STAGE 4 AND 5) TREATED FOR 12 WEEKS



12 weeks is not the recommended treatment duration for non-cirrhotic patients[1].

CKD: Chronic Kidney Disease; GT: Genotype; IFN: Interferon; pegIFN: pegylated Interferon; RBV: Ribavirin; SOF: Sofosbuvir.
¥: 1 discontinuation and 1 lost to follow-up.
§ mITT = ITT population modified to exclude subjects who did not achieve SVR12 for reasons other than virologic failure.
Reference: **1.** SmPC MAVIRET® 06/2018. **2.** Gane et al. EXPEDITION-4, N Engl J Med 2017 Oct12;377(15)1448-1455.

MAVIRET
glecaprevir/pibrentasvir

Efficacy and Safety of GLE/PIB in Renally Impaired Patients With HCV GT1-6: Expedition 4[1]

Summary of Adverse Events (AE)

Event, n (%)	G/P N = 104
Any AE	74 (71)
Serious AE	25 (24)
Serious AE related to DAA*	0
AEs leading to study drug d/c†	4 (4)
Death‡	1 (1)
AEs occurring in ≥10% of patients	
Pruritus	21 (20)
Fatigue	15 (14)
Nausea	12 (12)

*As assessed by study physician

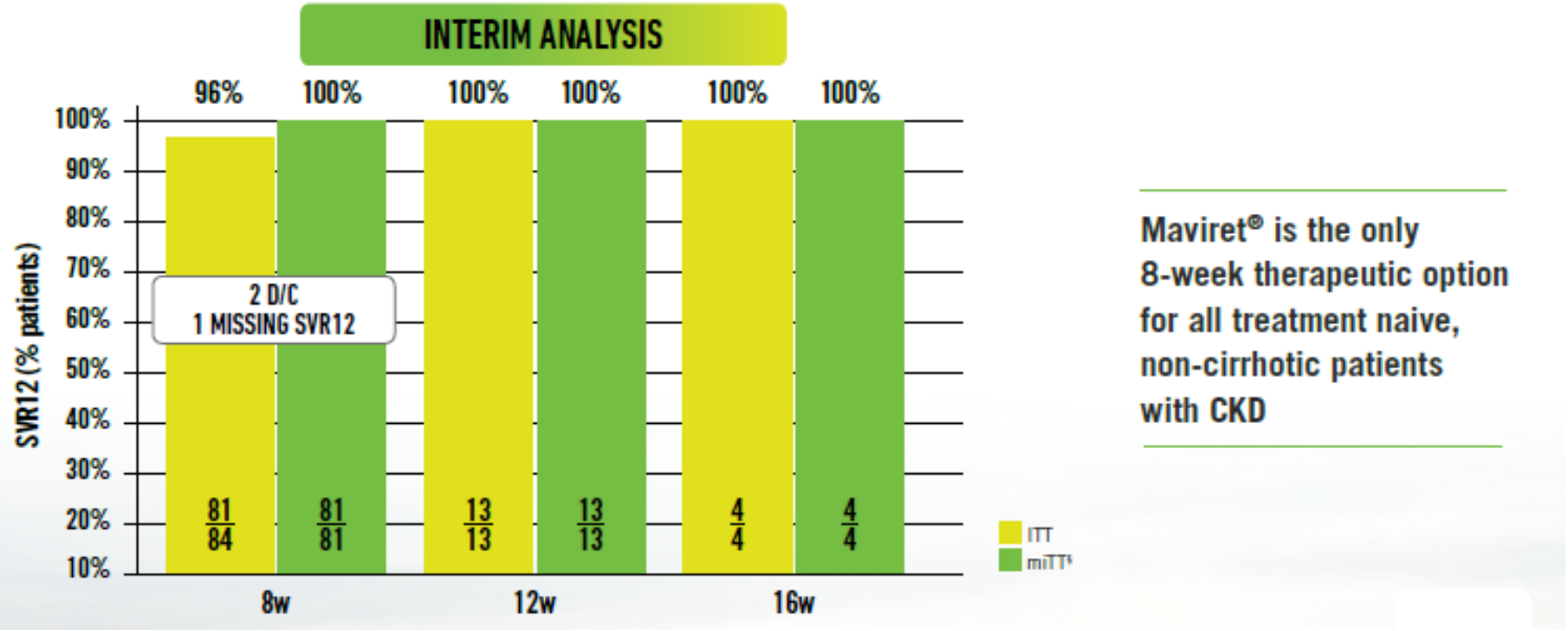
†AEs for 4 subjects were: 1)diarrhea, 2) pruritis, 3) pulmonary edema, hypertensive cardiomyopathy with congestive failure and 4) hypertensive crisis

‡Patient who died experienced SAE of cerebral hemorrhage, not related to study drug, at post-treatment week 2

EXPEDITION-5

EFFICACY OF MAVIRET® IN GT 1–6 INFECTED PATIENTS WITH RENAL IMPAIRMENT: EXPEDITION-5[1]

EXPEDITION-5: TN or PRS* experienced HCV GT1-6-infected patients with CKD stage 3b, 4, or 5.



Maviret® is the only 8-week therapeutic option for all treatment naive, non-cirrhotic patients with CKD

* Treatment naive or PRS experienced (pegIFN + RBV ± SOF, or SOF + RBV)

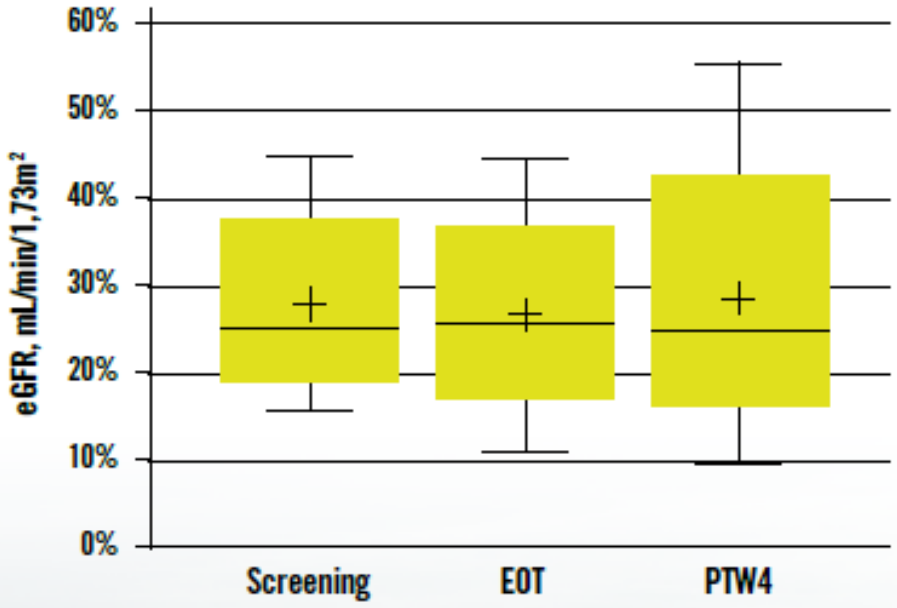
§ mITT analysis excluded all patients that failed to achieve SVR12 for reasons other than just virologic failure, including those who failed due to non-compliance

CKD: Chronic Kidney Disease; d/c: discontinuation; GT: Genotype; HCV: Hepatitis C Virus; ITT: Intention To Treat; pegIFN: pegInterferon; RBV: Ribavirin; SOF: Sofosbuvir; SVR: Sustained Virologic Response; TN: Treatment-Naïve; w: weeks.

MAVIRET glecaprevir/pibrentasvir

EXPEDITION-5

EFFICACY AND SAFETY OF MAVIRET® IN GT 1–6 INFECTED PATIENTS WITH RENAL IMPAIRMENT: EXPEDITION-5[1]



Of the 24 patients with CKD 3b/4 and available data, mean eGFR remained unchanged from screening to EOT to PTW4

No patient experienced an AE of worsening renal function or started dialysis during or post treatment

AE: Adverse Event; CKD: Chronic Kidney Disease; eGFR: estimated Glomerular Filtration Rate; EOT: End Of Treatment; GT: Genotype; m: meter; min: minute; mL: milliliter; PTW4: post-treatment week 4.

Reference: **1.** THU-363, Persico; presented at EASL 2018; Paris.

MAVIRET glecaprevir/pibrentasvir

Glecaprevir-Pibrentasvir (Mavyret) Indications: Treatment-Naïve Patients

Glecaprevir-Pibrentasvir in HCV Treatment-Naïve Patients		
HCV Genotype	Treatment Duration	
	No Cirrhosis	Compensated Cirrhosis (Child-Pugh Class A)
Genotype 1	8 weeks	12 weeks
Genotype 2	8 weeks	12 weeks
Genotype 3	8 weeks	12 weeks
Genotype 4	8 weeks	12 weeks
Genotype 5	8 weeks	12 weeks
Genotype 6	8 weeks	12 weeks

Source: *Mavyret* Prescribing Information. AbbVie. Slide courtesy David Spach,MD

Glecaprevir-Pibrentasvir (Mavyret) Indications: Treatment Experienced-Patients

Glecaprevir-Pibrentasvir in HCV Treatment-Experienced Patients			
HCV Genotype	Patients Previously Treated With a Regimen Containing:	Treatment Duration	
		No Cirrhosis	Compensated Cirrhosis (Child-Pugh Class A)
1	An NS5A inhibitor[1] without prior treatment with an NS3/4A protease inhibitor	16 weeks	16 weeks
	An NS3/4A PI[2] without prior treatment with an NS5A inhibitor	12 weeks	12 weeks
1, 2, 4, 5, or 6	PEG + RIB +/- sofosbuvir (NS5B inhibitor)[3]	8 weeks	12 weeks
3	PEG + RIB +/- sofosbuvir (NS5B inhibitor)[3]	16 weeks	16 weeks

[1]In clinical trials, subjects were treated with prior regimens containing ledipasvir and sofosbuvir or daclatasvir with pegylated interferon and ribavirin.

[2]In clinical trials, subjects were treated with prior regimens containing simeprevir and sofosbuvir, or simeprevir, boceprevir, or telaprevir with pegylated interferon and ribavirin

[3]Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor.

Source: *Mavyret* Prescribing Information. AbbVie.

SOF-Based Regimens (Epclusa)

Safety of SOF- Based Regimens in Renally Impaired Patients

Retrospective analysis of 45 Phase 2 and 3 studies of SOF-based regimens[1]

- SOF + RBV, LDV/SOF ± RBV, and SOF/VEL ± RBV
- Analysis grouped by use of RBV and degree of renal and hepatic impairment
- Evaluated the renal function (eGFR) using Cockcroft-Gault equation

- Patients with **moderate renal impairment (30-49 mL/min)** had fluctuations in eGFR ≥10mL/min
  - 22% (27/123) had least one postbaseline decrease
  - 25% (31/123) had least one postbaseline increase
  - 3% (4/123) had both increases and decreases
- Changes in eGFR were sporadic and usually transient
- Most patients with an increase or decrease were in the post-kidney or post-liver transplant studies

Standardized case reports from 8 US-based medical practices were summarized for the following:[2]

- The use of LDV/SOF in patients with eGFR ≤30 mL/min at baseline
- eGFR recalculated for all patients using CDK-Epi to capture

- 100% (9/9) patients with **severe renal impairment** achieved SVR12
- Of the patients with severe renal impairment and post treatment follow-up, 2 had increased eGFR and 5 had decreased eGFR

KDIGO Guidelines on the Prevention, Diagnosis, Evaluation and Treatment of HCV in CKD

Mild to Moderate disease (eGFR >30 mL/min/1.73 m^2)

Patients to be treated with any licensed DAA-based regimen (1A)

Severe renal disease (eGFR<30 mL/min/1.73 m^2)

Patients to be treated with DAA-based regimens, preferentially RBV-free

- **GT1a: EBR/GZR (1B)* or GLE/PIB (1B)**
- **GT1b: EBR/GZR (1B) or GLE/PIB (1B)**
- **GT2,3: GLE/PIB (1B)**
- **GT4: EBR/GZR (2D)* or GLE/PIB (1B)**
- **GT5,6: GLE/PIB (2D)**

* Addition of RBV or extension of therapy to 16 weeks should be considered in patients with baseline RASs.

KDIGO CKD Work Group. 2017; Public review draft. Available at: http://www.kdigo.org/clinical_practice_guidelines/Hep%20C/KDIGO%202017%20Hep%20C%20GL%20Public%20Review%20Draft%20FINAL.pdf (Accessed May 2018).

Patients with renal impairment, including haemodialysis

Recommendations	Grade of evidence	Grade of recommendation
Mild to moderate renal impairment (eGFR ≥30 mL/min/1.73 m^2)		
• Treat according to the general recommendations • No dose adjustments are needed • Patients should be carefully monitored	A	1
Severe renal impairment (eGFR <30 mL/min/1.73 m^2 or ESRD*)		
• Treat in expert centres with close monitoring by a MDT	B	1
• GLE/PIB for 8 or 12 weeks (all GT)	A	1
• GZR/EBR for 12 weeks (GT 1a, 1b and 4)†	A	1
• OBV/PTV/r + DSV for 12 weeks (GT 1b)	A	1
• Use SOF with caution, only if an alternative treatment is not available	B	1
• Risk/benefit of treating patients with ESRD and an indication for kidney transplant before or after renal transplantation require individual assessment	B	1

*ESRD on haemodialysis (CKD stage 4/5) without an indication for liver transplant; †With HCV RNA level ≤800,000 IU/mL (GT 1a/4)

EASL CPG HCV. J Hepatol 2018;69:461–511.

EASL™ The Home of Hepatology

EASL Guidelines for the Treatment of HCV-Infected Patients with Renal Insufficiency

Mild to Moderate disease
(eGFR ≥30 mL/min/1.73 m²)

No dose adjustments of HCV DAAs are needed, but these patients should be carefully monitored (A1)

Severe renal disease
(eGFR< 30 mL/min/1.73 m²)
or end-stage renal disease on haemodialysis without an indication for kidney transplantation

All genotypes: G/P for 8 or 12 weeks (A1)

GT1a*: EBR/GZR for 12 weeks (A1)

GT1b: EBR/GZR for 12 weeks or OBV/PTV/r + DSV for 12 weeks (A1)

GT4 TN†: EBR/GZR for 12 weeks (A1)

SOF should be used with caution only if an alternative treatment is not avaliable, because no dose recommendation can be given (B1)

Patients with severe renal impairment, or those with ESRD on haemodialysis, should be treated for their HCV infection, and SOF-free regimens must be preferred. If there is no other choice than a SOF-based regimen, close monitoring is required and treatment should be rapidly interrupted if renal function deteriorates.

*with an HCV RNA level ≤800,000 IU/ml (5.9 Log10 IU/ml);
†with an HCV RNA level ≤ 800,000 IU/ml (5.9 Log10 IU/ml).

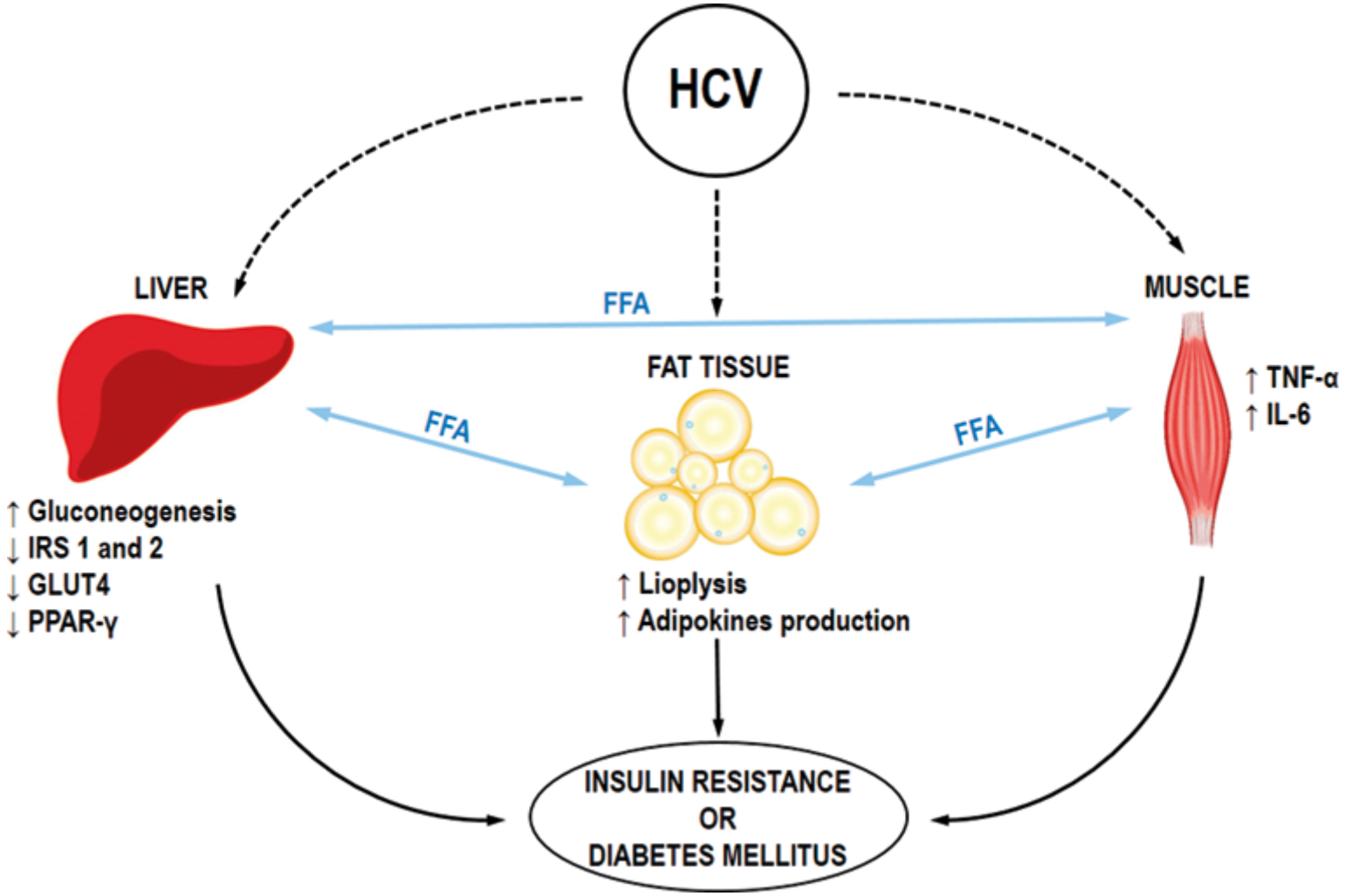
EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol* 2018. Available at: https://doi.org/10.1016/j.jhep.2018.03.026 (accessed June 2018).

Take Home Message

- Dépister IRC chez HCV
- Dépister HCV chez IRC
- On peut traiter (quasi) tous les patients!
- 98% SVR!
- Peu d'effets secondaires
- **Maviret** 3cp 1x/j 8semaines (12semaines si cirrhose)
- **Zepatier** 1cp 1x/j 12semaines G1b (G1a et G4 LVL)
- Epclusa (velpatasvir-sofosbuvir) avec précaution

Merci de votre attention

HCV et Diabète



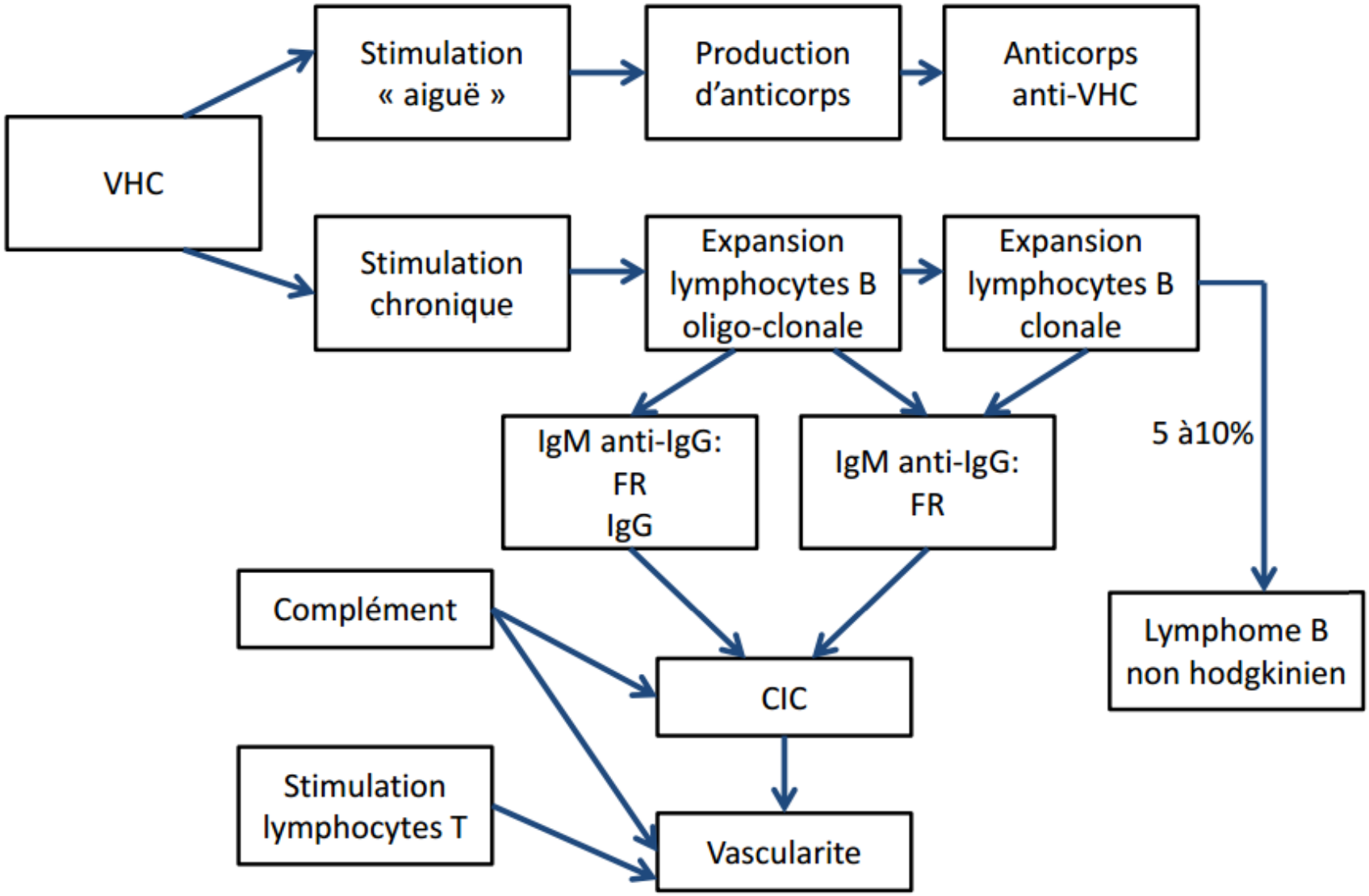
HCV et Diabète

- Selon le niveau de l'atteinte hépatique, on évalue entre 10 % à 30 % le nombre de patients porteurs d'une infection chronique par le VHC qui présente un diabète sucré. Le risque augmente avec le niveau de fibrose hépatique. Les troubles métaboliques associés à l'infection par le VHC seraient liés à une action directe du virus C sur les voies de signalisation de l'insuline. L'infection par le VHC augmente le niveau d'insulinorésistance indépendamment des autres anomalies du syndrome métabolique. Le VHC a également une action inhibitrice sur la *microsomal transfert triglyceride protein*, une enzyme impliquée dans la synthèse et la sécrétion des *very low density lipoproteins*. Cela se traduit par une hypobêtalipoprotéinémie et un taux de triglycérides normal ou bas en cas d'infection virale C. En conséquence, les patients diabétiques séropositifs pour l'infection par le VHC présentent un profil clinique particulier avec un poids plus faible et un profil lipidique et tensionnel moins altéré que ceux des diabétiques séronégatifs. Les troubles métaboliques sont susceptibles d'influencer l'histoire naturelle de l'infection par le VHC. L'obésité et l'insulinorésistance sont associées à une progression plus rapide de la fibrose en cas d'infection par le VHC. De même, le diabète et l'insulinorésistance sont des facteurs de mauvaise réponse aux thérapeutiques antivirales C

Cryoglobulinémie mixte: CM

- VHC: principale cause de CM avec prévalence de 30 à 50%
- CM: immunoglobuline (Ig) précipitant in vitro si température inférieure à 37°C
- Surtout de type II: Ig G polyclonales et IgM monoclonales avec activité facteur rhumatoïde
- Manifestations cliniques liées à vascularite des petits et moyens vaisseaux
- Triade clinique typique: asthénie, purpura, arthralgies

VHC et stimulation des lymphocytes B



MEH, CM et VHC

Manifestations extra-hépatiques	Fréquence %
Asthénie	90
Purpura	90
Arthralgies	80
Axonopathie sensitivo-motrice	65
HTA	45
Syndrome de Raynaud	35
Glomérulonéphrite	35
Altérations neuro-cognitives	30
Ulcères des membres inférieurs	20
Prurit	15
Myalgies	15
Syndrome néphrotique	15
Thrombopénie	10

Atteintes cutanées

- Associées à la CM:
  - purpura vasculaire: 30% à 100% CM symptomatique
  - surtout purpura des extrémités +/- ulcères cutanés malléolaires
  - pas d'atteinte de la face
  - évolution par poussées => dermite ocre
  - rares: syndrome de Raynaud, acrocyanose

Biopsie cutanée

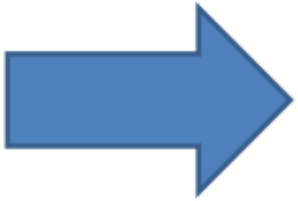
Vascularite leucocytoclasique des petits vaisseaux du derme avec infiltrat inflammatoire de cellules mononuclées

Atteintes cutanées

- Non associées à la CM:
  - –Porphyrie cutanée tardive:
    - lésions vésiculo-bulleuses
    - prédominent au niveau des zones découvertes
    - cicatrisation en macules +/- grains de millium
    - diagnostic: porphyrines selles et urines, déficit sanguin en urocarboxylase
  - –Prurit
    - Très fréquent
    - Quelles que soient les lésions cutanées
  - –Lichen plan
    - Association discutée

Atteintes neurologiques périphériques

- Associées à la CM:
  - Au moins un tiers des patients
  - A rechercher systématiquement
  - Soit minime: purement sensitive distale
  - Soit plus sévère: sensitivo-motrice
  - Absence de déficit moteur



EMG

Atteinte dégénérative axonale avec altération des potentiels sensitifs sans anomalie des vitesses de conduction

Asthénie

- Asthénie
  - Prévalence: 50 à 70%
  - Altération de la qualité de vie
  - Eliminer hypothyroïdie
- Dépression
  - Un quart des patients avant traitement anti VHC
- VHC peut atteindre directement le SNC
  - Altérations des neurotransmetteurs sérotoninergiques and dopaminergiques