Simposio de Hepatitis Virales y Trasplante de Organos Sólidos
Hospital El Cruce-FUNDIEH-AbbVie-
23 de marzo 2021

Tratamiento de la Hepatitis C en Recetores de Trasplante de Organos Sólidos

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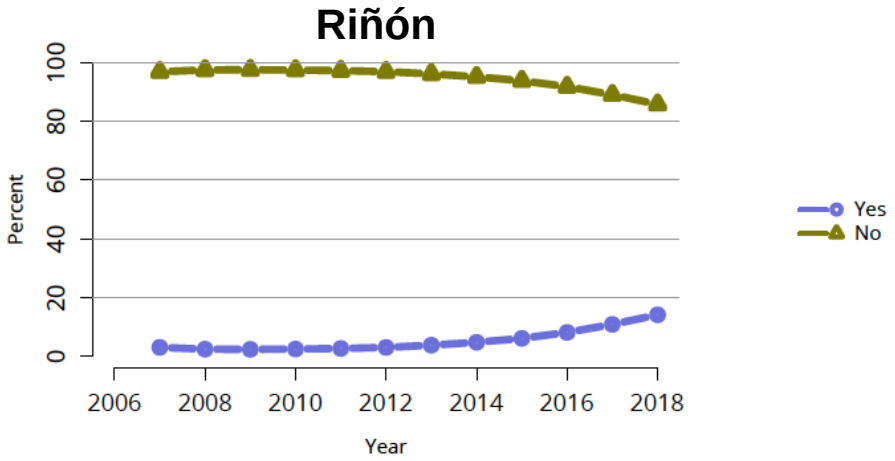
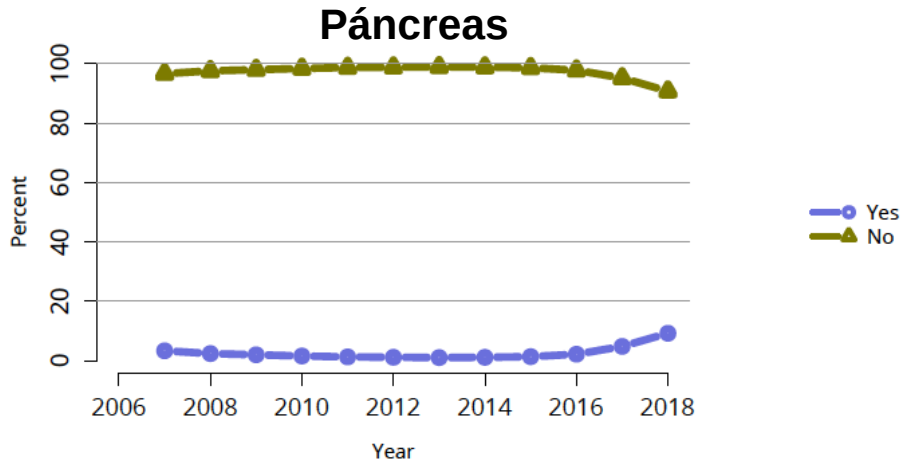
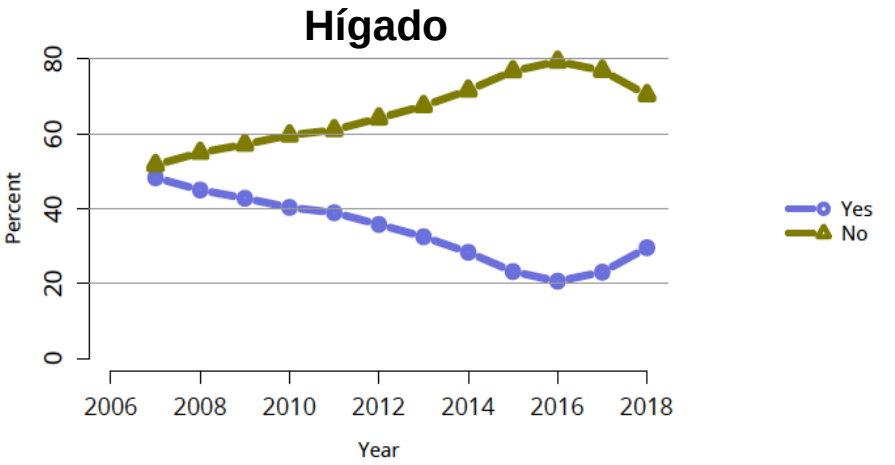
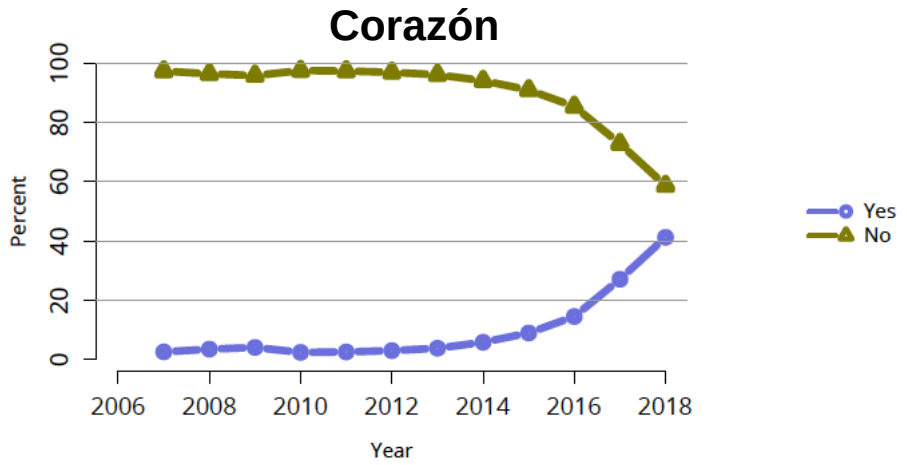
Pacientes en Lista de Espera que Aceptan un Organo HCV+. SRTR





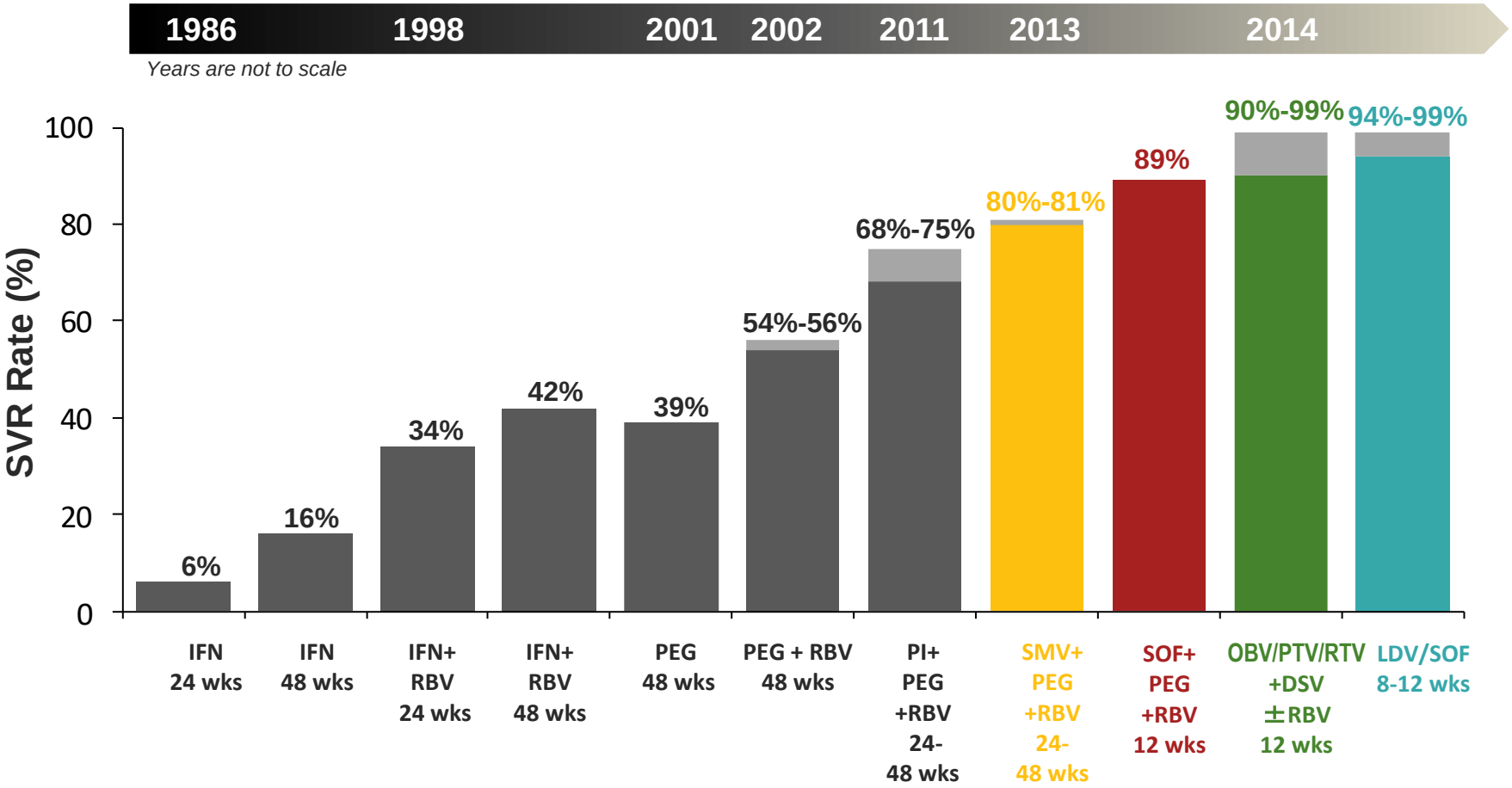




¿ Tratamientos eficaces? ¿Menor tiempo en lista de espera?

OPTN/SRTR 2018 Annual Data Report: Hepatitis C J.H. Wang, Am J Transplant. 2020

SVR Rates for Approved Therapies in HCV Genotype 1 Treatment-Naïve Patients



Efficacy rates are not directly comparable, due to differing study designs

Adapted from Strader DB, et al. Hepatology 2004;39:1147-71. INCIVEK [PI]. Cambridge, MA: Vertex Pharmaceuticals; 2013. VICTRELIS [PI]. Whitehouse Station, NJ: Merck & Co; 2014. Jacobson I, et al. EASL 2013. Amsterdam. The Netherlands. Poster #1425. Manns M, et al. EASL 2013. Amsterdam. The Netherlands. Oral #1413. Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02; Afdhal N, et al. *N Engl J Med* 2014; 370: 1889-98; Kowdley K, et al. *N Engl J Med* 2014; 370: 1879-88. Feld JJ, et al. *N Engl J Med* 2014;370:1594-603. Ferenci et al. *N Engl J Med* 2014; 370:1983-92.

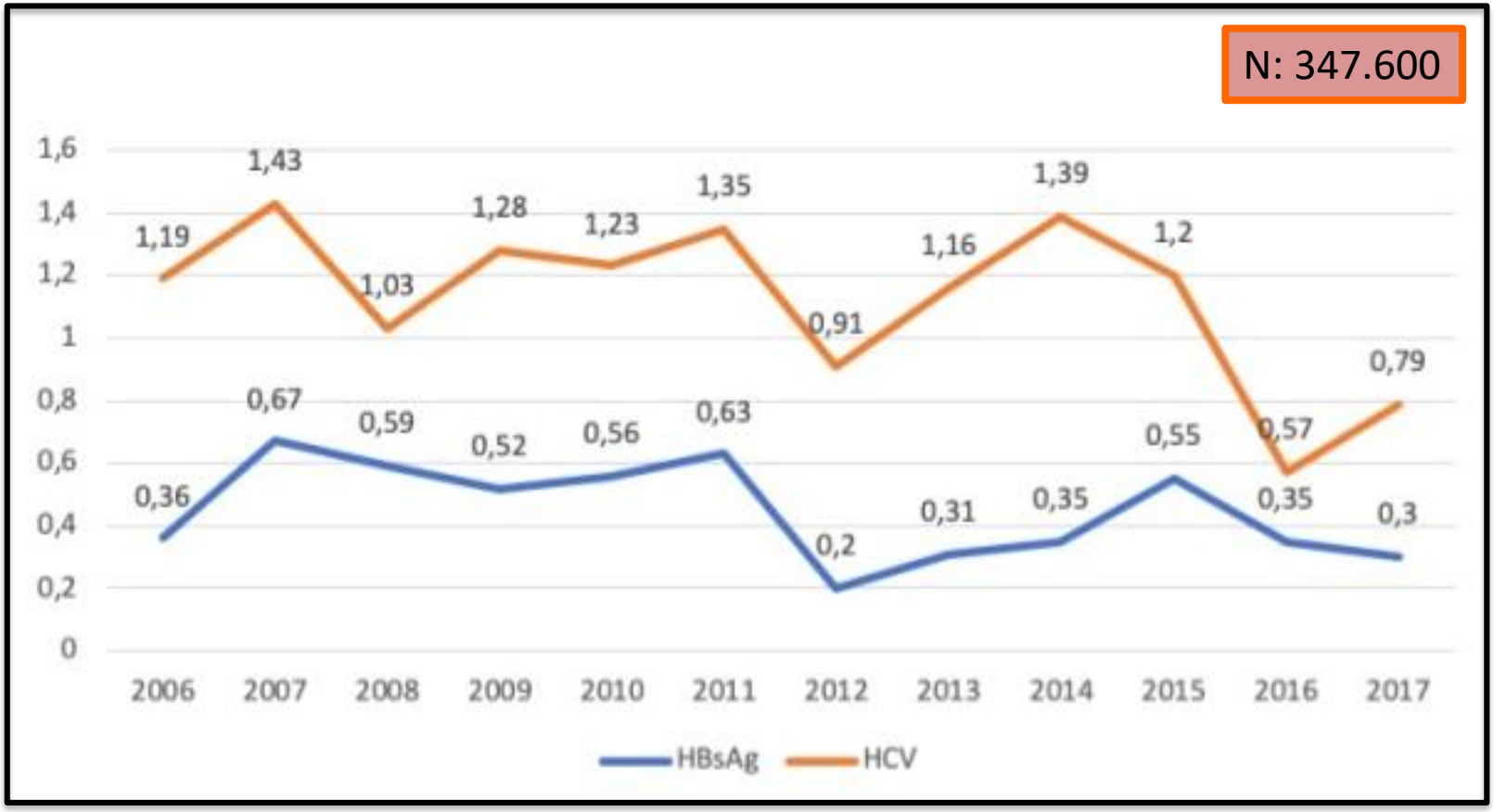
Aplicabilidad de SOT con uso de Donantes antiHCV+

Tipo de Organo	Tiempo en lista aceptando HCV+	Tiempo en lista NO aceptando HCV+
Riñón	76% (menos de un año)	55% (menos de un año)
Corazón	76% (menos de un año)	55% (menos de un año)
Pulmón	76% (menos de un año)	55% (menos de un año)
Hígado	80% (menos de un año)	78% (menos de un año)

Utilizando órganos HCV+ se reduce entre 2 y 26% el tiempo de lista de espera

OPTN/SRTR 2018 Annual Data Report: Hepatitis C J.H. Wang, Am J Transplant. 2020

Prevalencia de serologia HCV y HBV en Potenciales Donantes de Organos. INCUCAI



Anders M, et al. XX Congreso AAEEH 2019

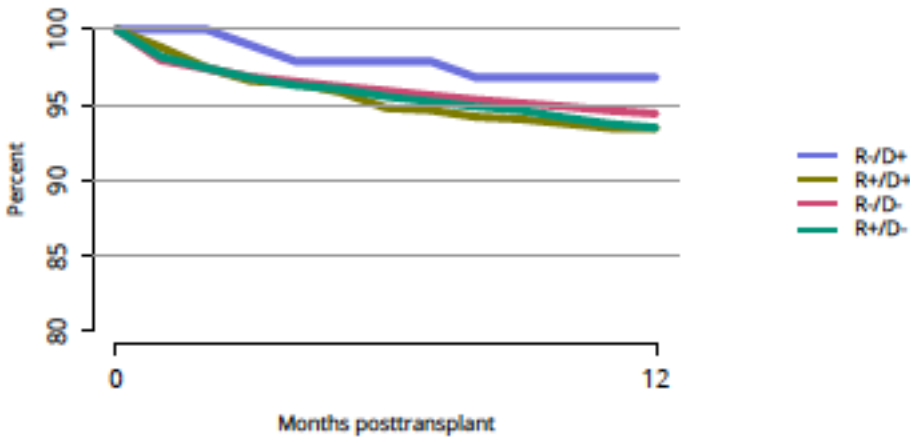
Prevalencia de serologia HCV y HBV en Donantes de Organos. INCUCAI

Total donantes	**11421**
Edad	**49 ± 19 años**
Masc/femenino	**1,6:1**
HCV	**1,12% (IC 0,9-1,3%; n=124)**
HBsAg	**0,4% (IC 0,3-0,5%; n= 49)**
Anti HBc	**2,6% (IC 2,3-2,9%; n=287)**
HIV	**0,26% (IC 0,1-0,4%; n=26)**
Chagas	**3,7% (IC 3,4-4,1%; n= 420)**

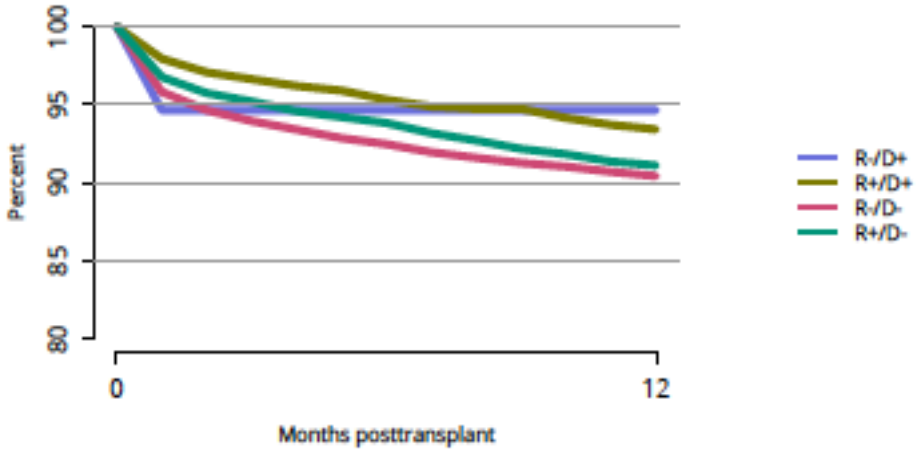
Anders M, et al. XX Congreso AAEEH 2019

Sobrevida del Injerto Según Status HCV RNA Donante y Receptor

Riñón

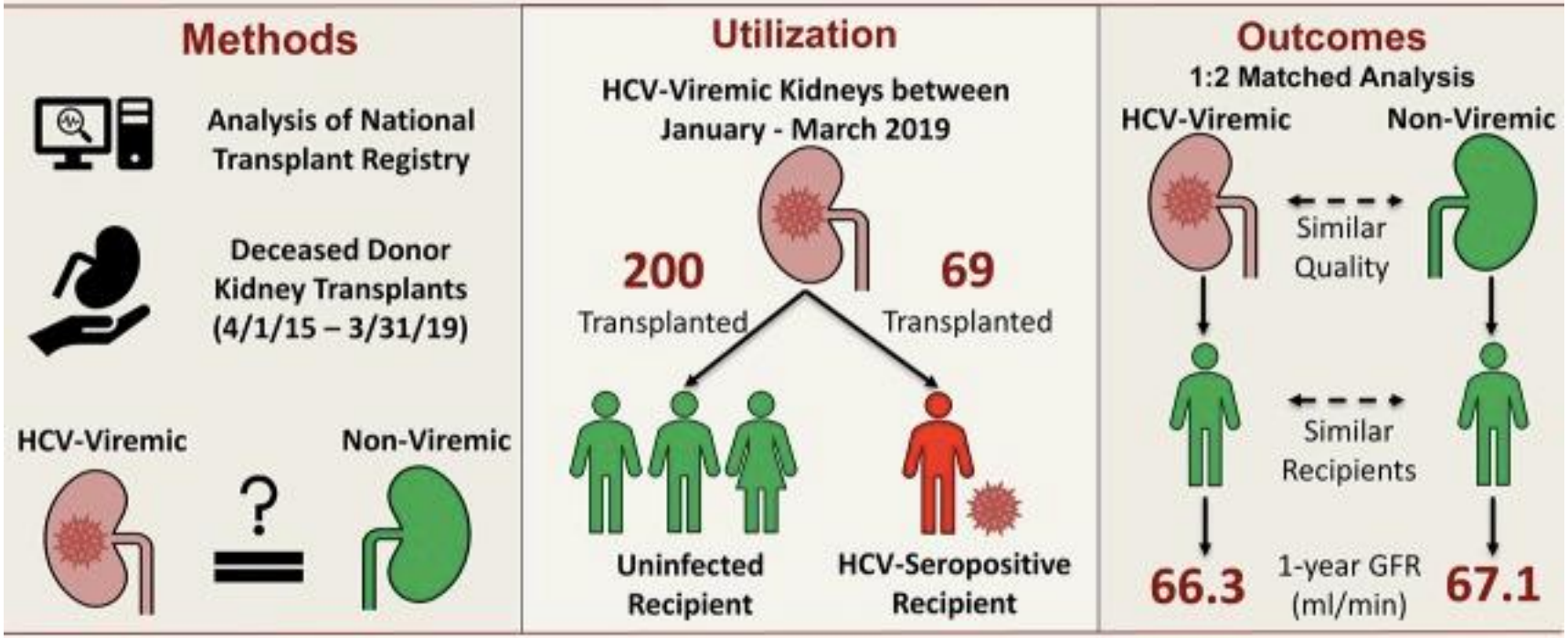


Hígado



OPTN/SRTR 2018 Annual Data Report: Hepatitis C J.H. Wang, Am J Transplant. 2020

Trends in Utilization and One-Year Outcomes with Transplantation of HCV-Viremic Kidneys



CONCLUSION Most HCV-Viremic kidneys are now transplanted into uninfected recipients. HCV-Viremic kidneys have similar function compared to nearly-identical uninfected kidneys at the end of 1-year. HCV-Viremic kidneys are a valuable resource for transplantation.

Vishnu S Potluri , J Am Soc Nephrol . 2019

Recomendaciones Sobre Uso de Donantes HCV + en Receptores HCV-

Donante HCV Ab + / HCV RNA –	Riesgo de Transmisión BAJO

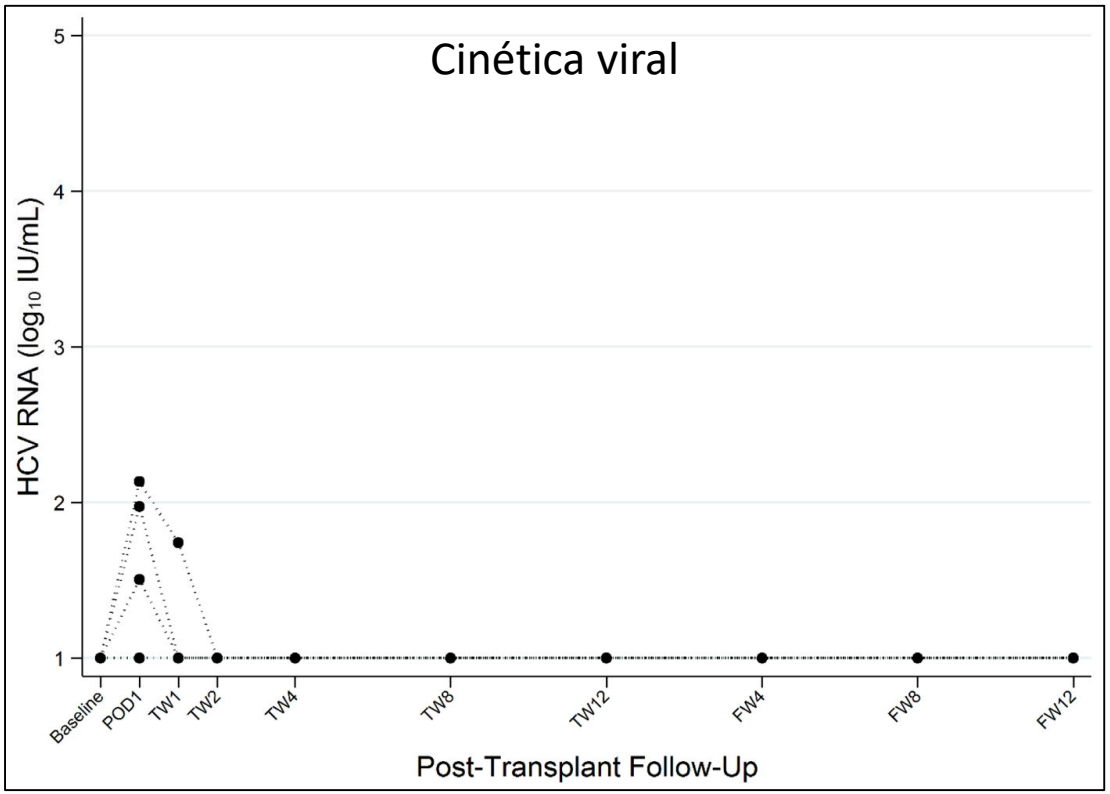
- Riguroso consentimiento informado
- Monitoreo periódico de HCV RNA en receptor

Donante HCV Ab + / HCV RNA +	Riesgo de Transmisión ALTO

- Riguroso consentimiento informado
- Realizar tratamiento profiláctico (asegurar acceso)
- Seguimiento post SVR

Levitsky J, Am J Transplant. 2017. Bari K, Hepatology. 2018

DAA Profilaxis o Tratamiento en Trasplante Renal de Donante HVC RNA+ a Receptores HCV -

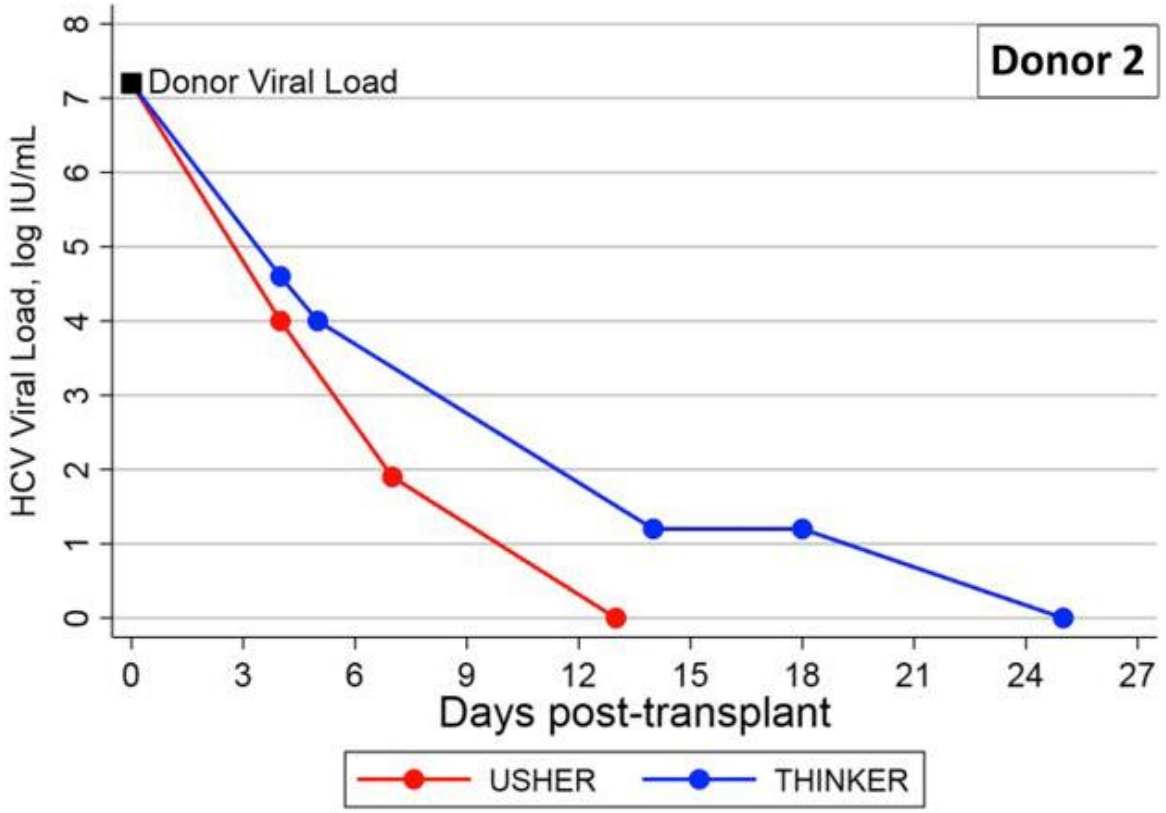


Tratamiento:
-(THINKER TRIAL) EBR-GZR 12 SEM
-SOF agregado en genotipo 2 o 3 y continuaron el tto por 12 semanas con triple combinación.
SVR:100%

- glecaprevir and pibrentasvir pre tx inmediato hasta 8 semanas (SVR100%)
- SOF/LED (8 SEM), SOF/VEL (12 SEM) desde dia 7 post Tx (SVR 100%)

Christine M. Durand, Ann Intern Med. 2018. Antonio Franco, Transpl Int. 2019. Justa Friebus-Kardash Transpl Infect Dis. 2019

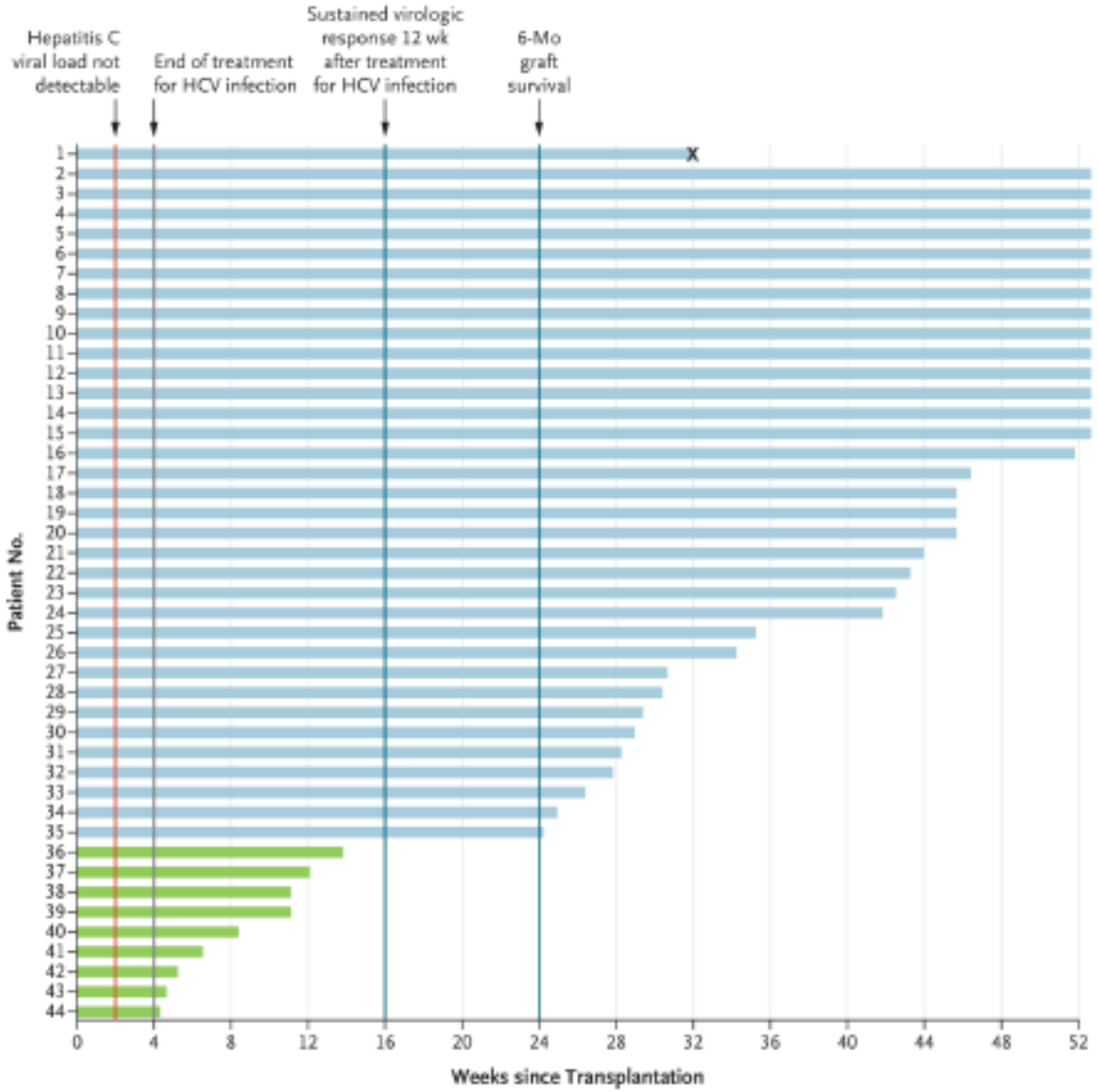
Tratamiento De Receptores Cardiacos HCV- Que Recibieron Un Organo HCV+



elbasvir/grazoprevir therapy to 16 weeks.

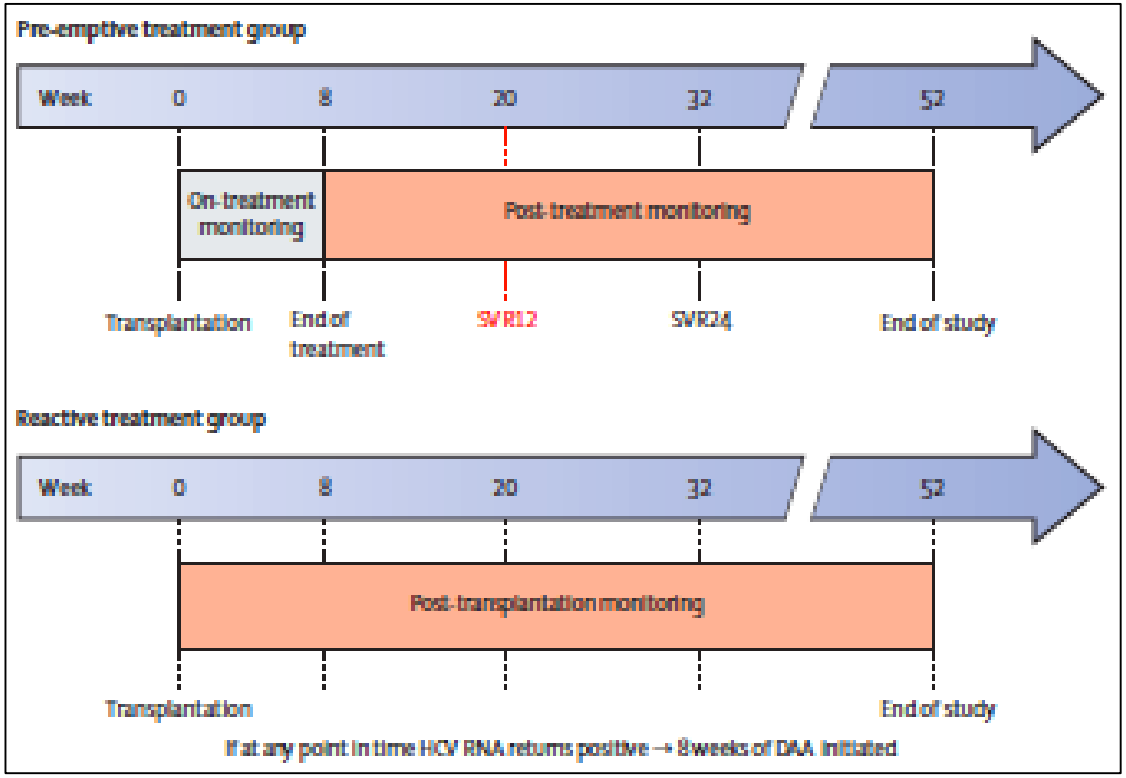
Rhondalyn C McLean, Am J Transplant 2019.

Tratamiento con SOF/VPV por 4 Semanas En Receptores HCV- de Corazón y Pulmón HCV +



Ann E Woolley, N Engl J Med 2019

Pre-emptive GP en Receptores HCV- de Corazón HCV+

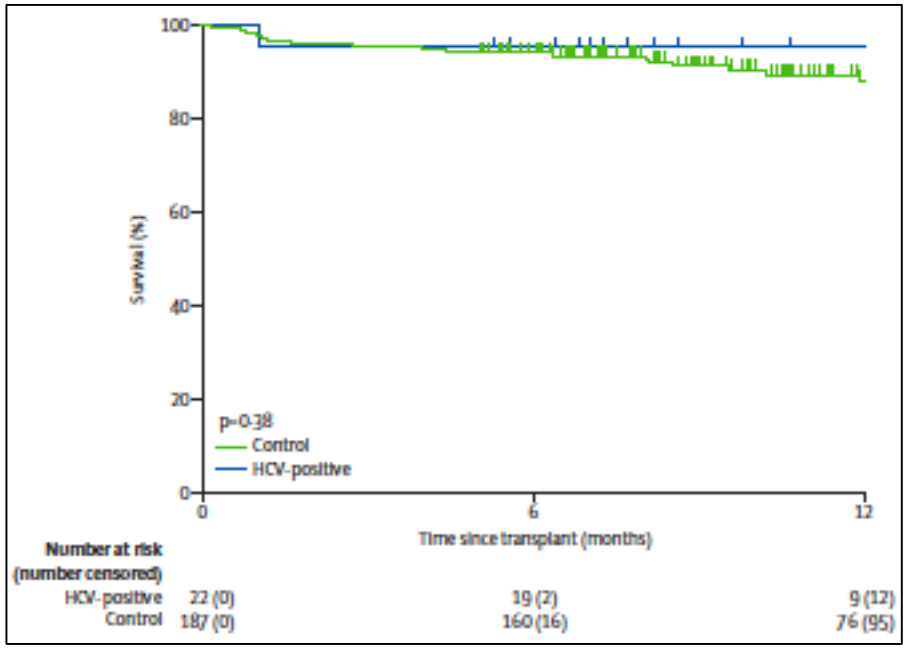


SVR: 100%

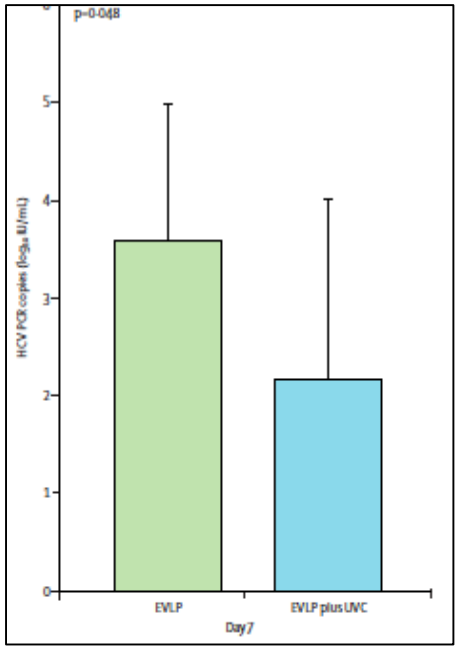
Emily D Bethea, Lancet Gastroenterol Hepatol 2019

Prevención De Transmisión de HCV en Trasplante Pulmonar de Donantes HCV + a Recepetores -

Sobrevida en donantes HCV+ o -



CV basal en terapia UV pre Tx



SOF/VEL 12 semanas (2 colestasicas post tto) respondieron a SOF/VEL/VOX

Marcelo Cypel, Lancet Respir Med. 2020

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Non-Liver Solid Organ Transplant

RECOMMENDED	RATING
Prophylactic[a]/preemptive[b] treatment with a pangenotypic DAA regimen is recommended.	II, B

[a] Prior to HCV RNA results, typically immediately pre-transplant or day 0 post-transplant
[b] Day 0 to within the first week post-transplant, typically as soon as the patient is deemed clinically stable

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Non-Liver Organs from HCV-Viremic Donors

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C

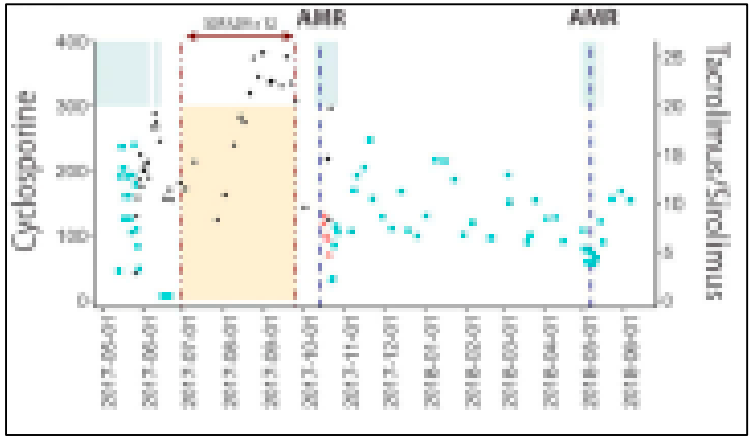
[a] Other considerations in selection of the DAA regimen:

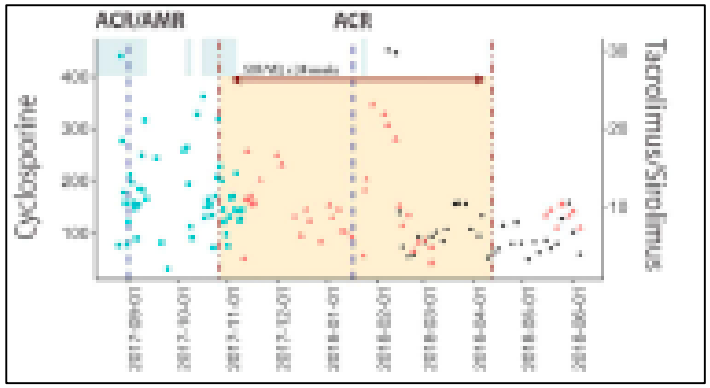
- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided
- Specific drugs that are contraindicated or not recommended with specific DAA agents, including but not limited to:
  - High-dose antacid therapy (eg, twice daily proton pump inhibitor)
  - Amiodarone (contraindicated with sofosbuvir-inclusive regimens; see prescribing information)
  - Specific statins (eg, atorvastatin)
- Consideration of immunosuppressive drugs and DAA interactions (see below)

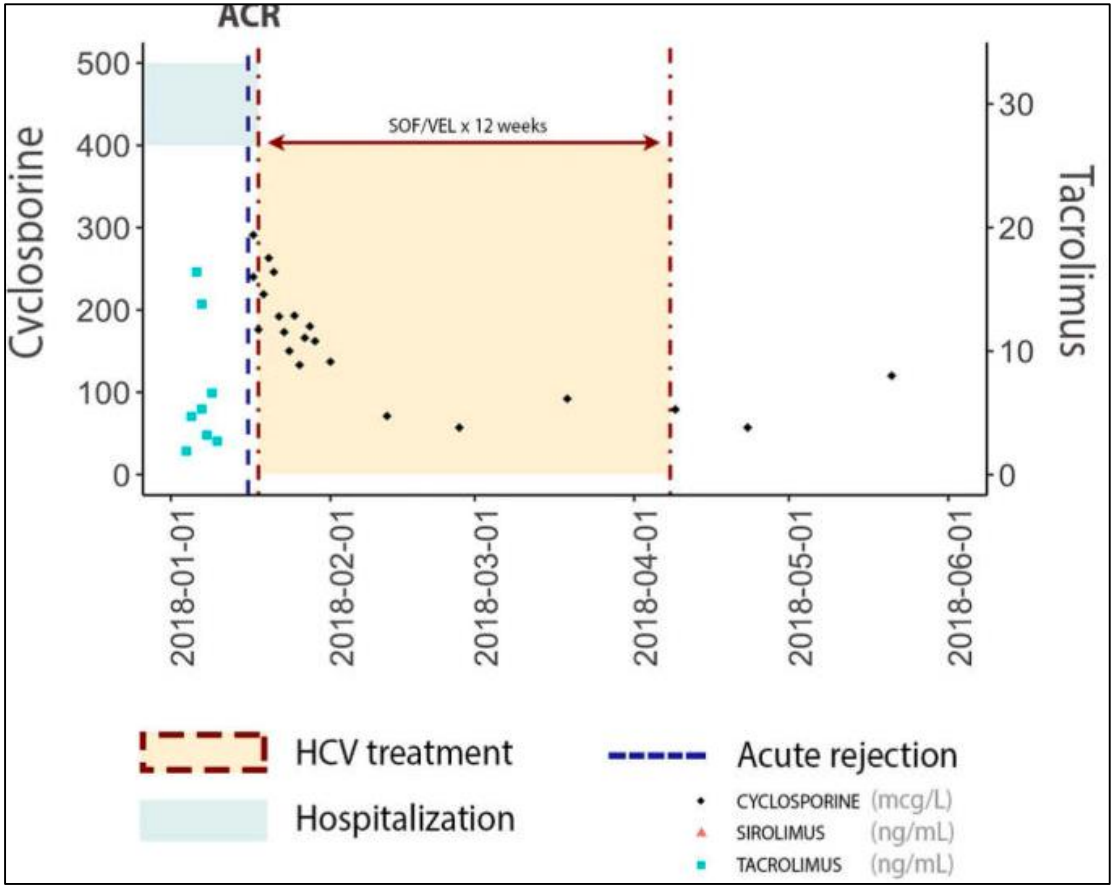
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the

www.hcvguidelines.org. January 21, 2021

Trasplante Hepático en receptores HCV- con donantes HCV virémicos







Six patients received sofosbuvir/velpatasvir-based therapy, 3 patients received ledipasvir/sofosbuvir-based therapy, and 1 patient received sofosbuvir/daclatasvir- 12 W- **SVR 100%**

Kwong AJ, Am J Transplant. 2019

Recommendation Regarding Timing of DAA Therapy for HCV-Negative Recipients of HCV-Viremic Liver Transplant

RECOMMENDED	RATING
Early[a] treatment with a pangenotypic DAA regimen is recommended when the patient is clinically stable.	II, B

[a] Early treatment refers to starting within the first month after liver transplant but preferably within the first week when the patient is clinically stable.

Recommended[a] regimens listed by evidence level and alphabetically for:

Treatment of HCV-Uninfected Recipients of Liver Grafts from HCV-Viremic Donors

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, C
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, C

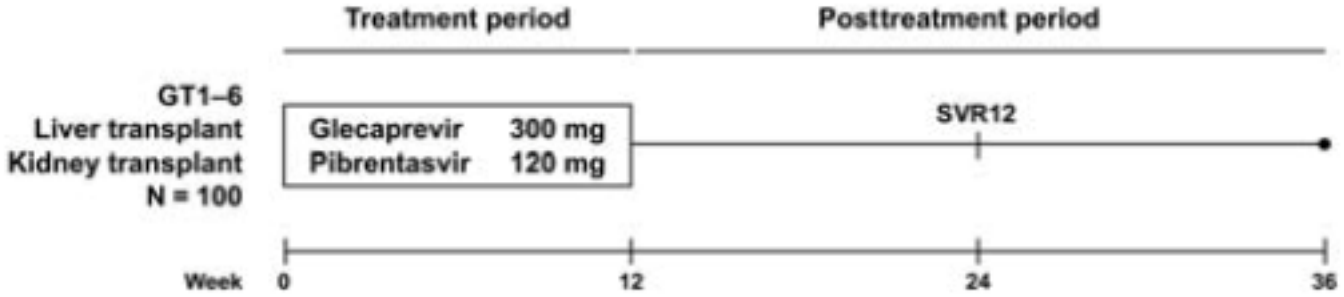
[a] Other considerations in selection of the DAA regimen:

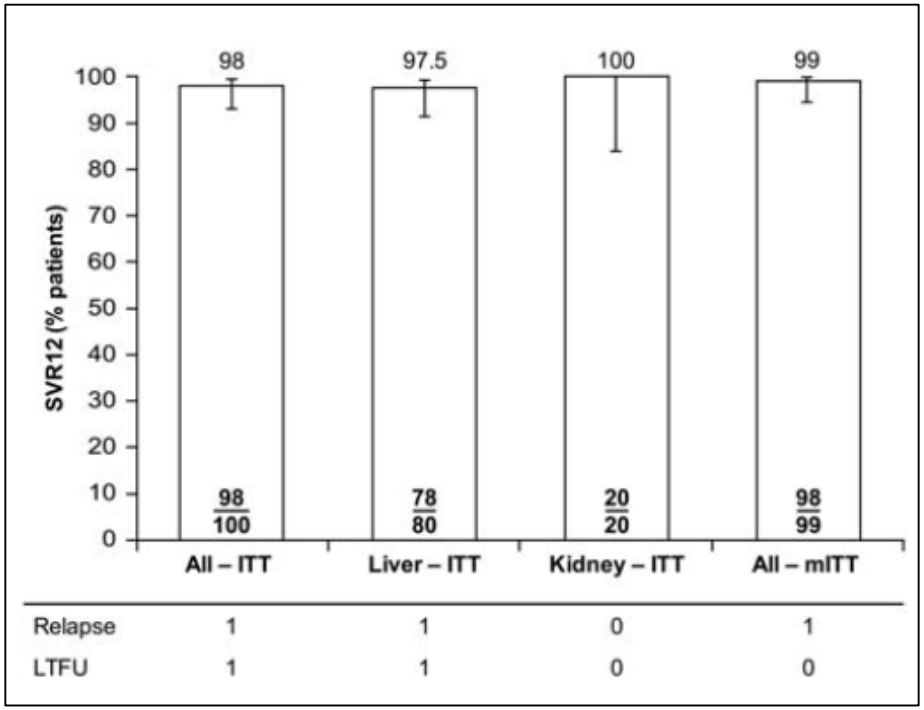
- Presence of liver dysfunction (eg, elevated bilirubin) as protease inhibitors should be avoided

www.hcvguidelines.org. January 21, 2021

MAGELLAN-2

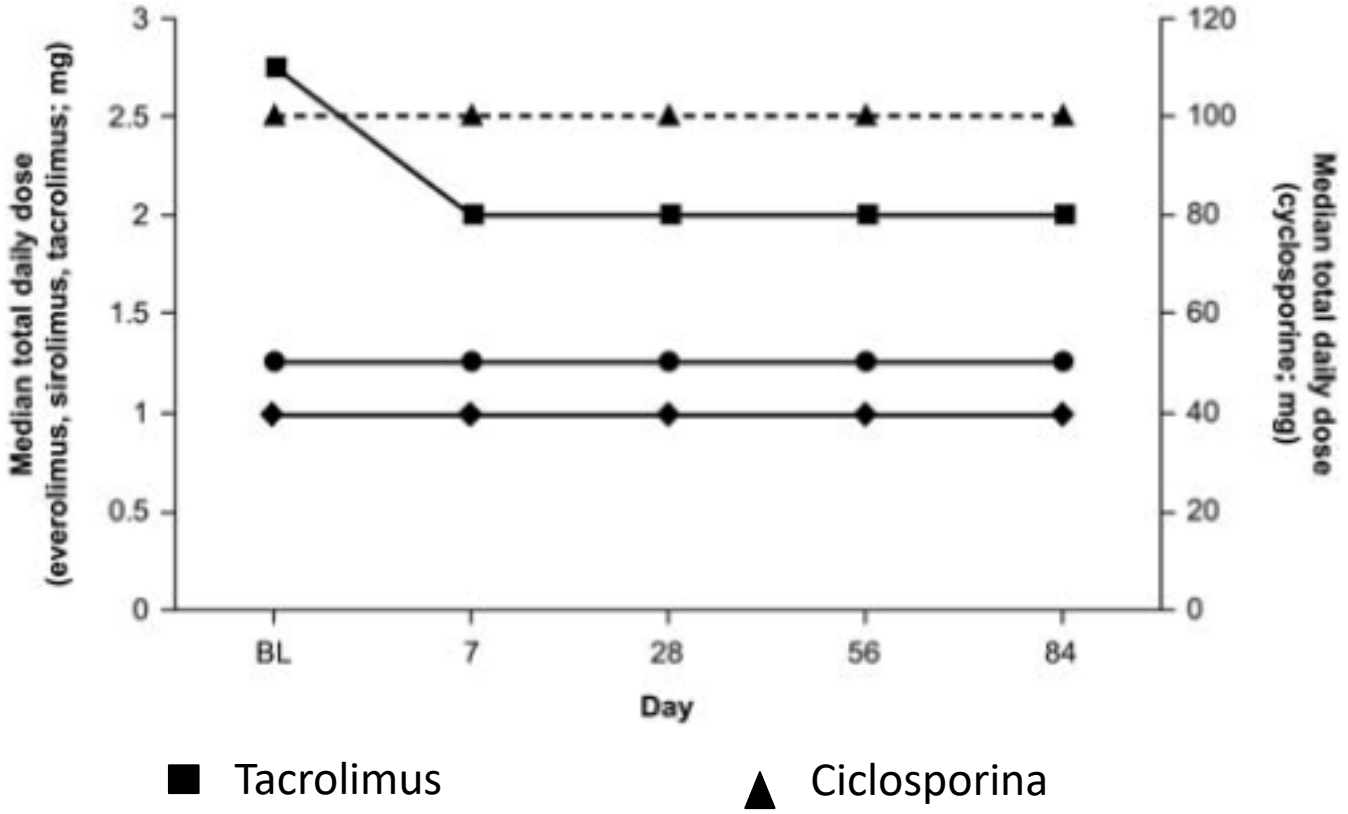
Pacientes trasplantados de hígado o riñón con mas de 3 meses de seguimiento (HCV+) todos los genotipos y sin cirrosis.





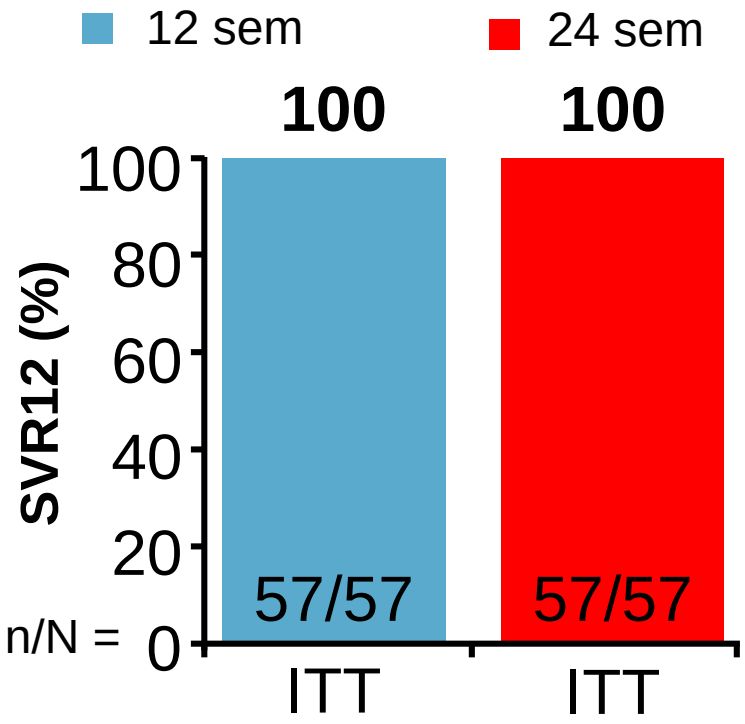
Reau N, Hepatology. 2018

MAGELLAN-2: Interacción entre IP e ICN



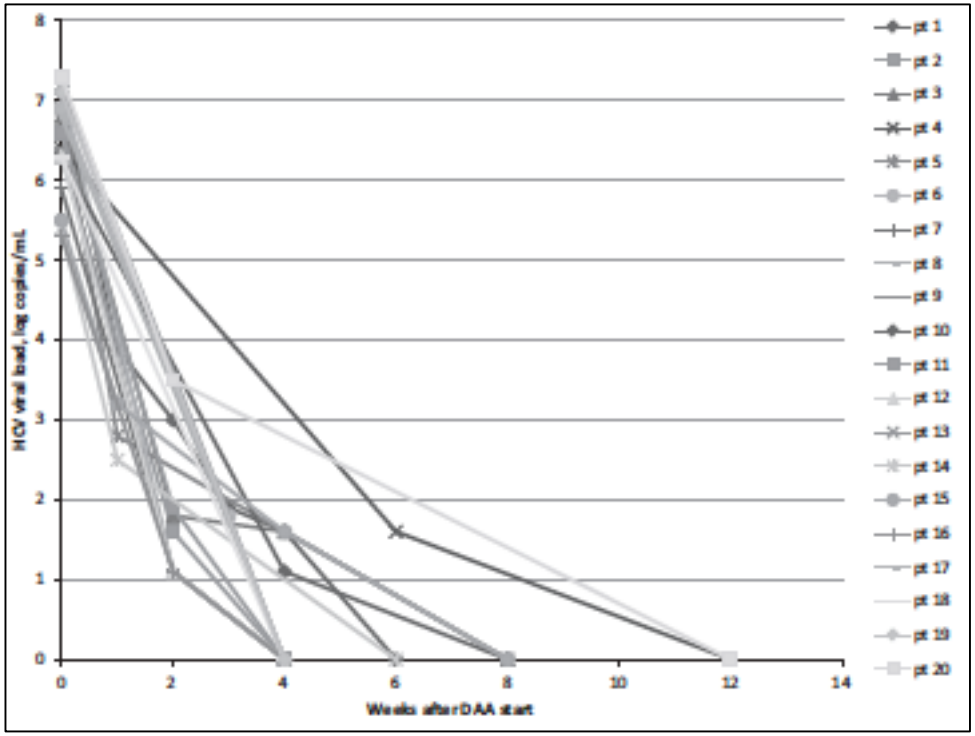
Reau N, Hepatology. 2018

Tratamiento con SOF-LPV por 12 o 24 Semanas en Trasplantados Renales con HCV + genotipo 1 o 4 (eGFR >30 mL/min)



Colombo M. Ann Intern Med. 2017

Tratamiento con AAD en receptores renales HCV+

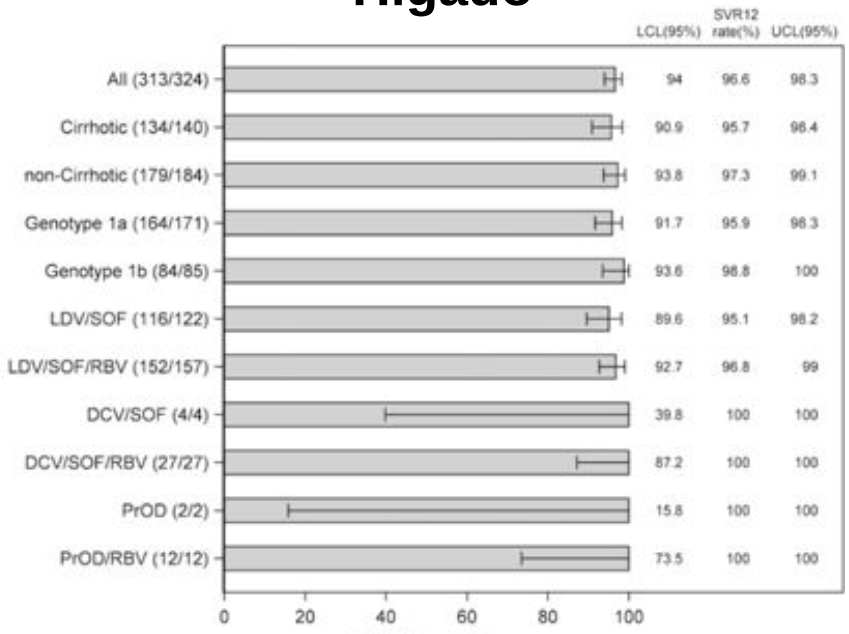


- simeprevir plus sofosbuvir (n=9); ledipasvir/sofosbuvir (n=7); sofosbuvir plus ribavirin (n=3); and daclatasvir plus sofosbuvir (n=1). **SVR12 100%**
- 45% tuvo que reducir inmunospuresión

Sawinski D, Am J Transplant. 2016

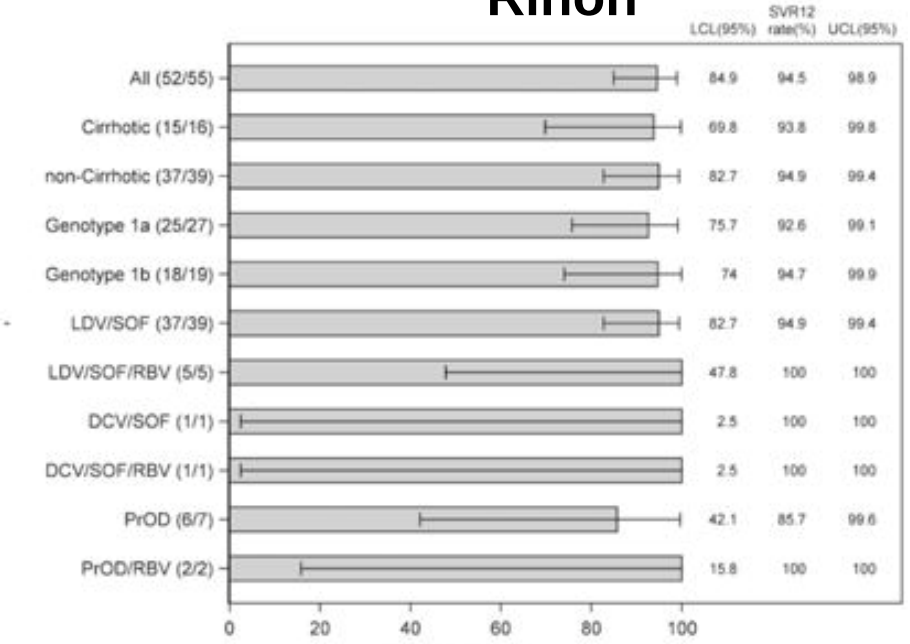
Seguridad y eficacia de AAD en receptores de trasplante de hígado y riñón HCV+: resultados del estudio HCV-TARGET

Hígado



SVR: 96%

Riñón



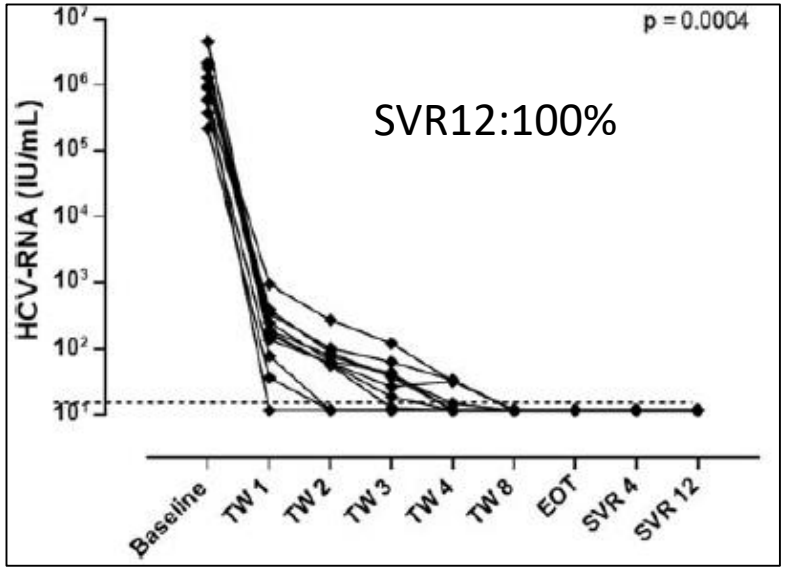
SVR:95%

sofosbuvir/ledipasvir (SOF/LDV) ± RBV(85%), sofosbuvir + daclatasvir (SOF + DAC) ± ribavirin (9%) and ombitasvir/paritaprevir/ritonavir + dasabuvir (PrOD) ± RBV (6%)

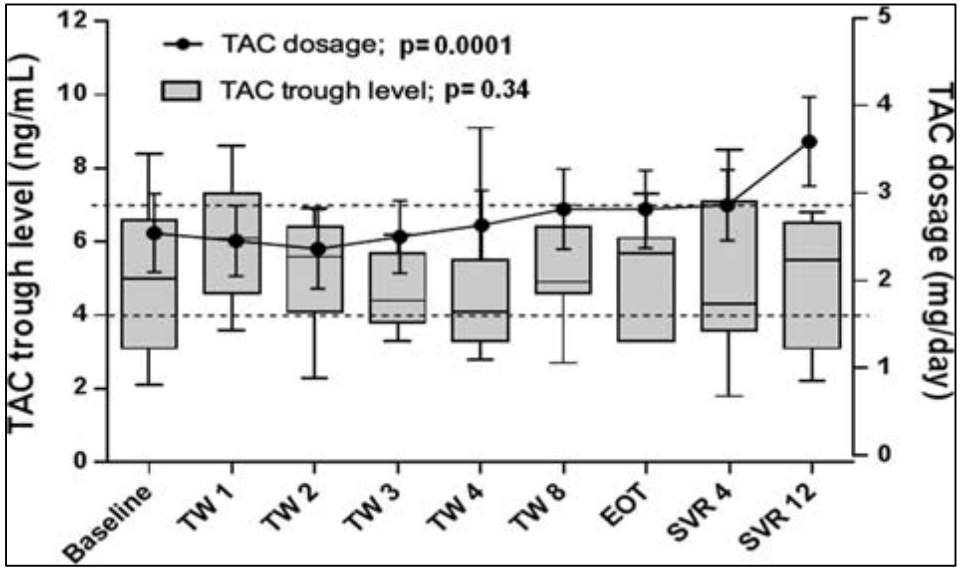
Saxena V, Hepatology. 2017

Tratamiento de Receptores Renales HCV+ con Grazoprevir/Elbasvir

Cinética Viral intra TTO



Niveles de TaC intra TTO



Eisenberger U, Transplant Direct. 2019

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive and Non-DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A[c] IIa, C[d]
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	IIa, C
ALTERNATIVE	**DURATION**	**RATING**
Genotype 1 or 4 only: Daily fixed-dose combination of elbasvir (50 mg)/ grazoprevir (100 mg) for patients without baseline NS5A RASs[e] for elbasvir	12 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.
[c] Based on evidence for patients without cirrhosis.
[d] Based on evidence for patients with compensated cirrhosis.
[e] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

www.hcvguidelines.org. January 21, 2021

Recommended regimen for:

DAA-Experienced Kidney Transplant Patients With Genotype 1-6 Infection, With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg), with or without ribavirin[b]	12 weeks	IIa, C

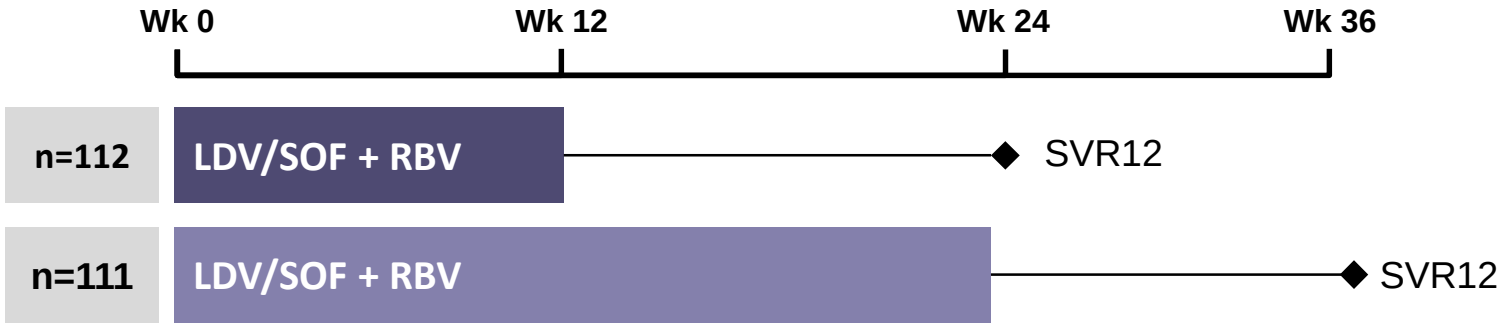
[a] Excludes CTP class B and class C patients. For decompensated cirrhosis, please refer to the appropriate section.
[b] For patients with cirrhosis and multiple negative baseline characteristic, consideration should be given to adding ribavirin. If renal dysfunction is present, a lower starting dose is recommended. Maximum ribavirin dose is 1000 mg/d for patients who weigh <75 kg and 1200 mg/d for those who weigh ≥75 kg.

For additional information on treatment of DAA failures post transplant, treatment of decompensated cirrhosis following transplantation, treatment of transplant recipients from HCV-positive donors, and post-transplant drug-drug interactions, please see Patients Who Develop Recurrent HCV Infection Post Liver Transplantation.

Post-Transplant Antiviral Therapy: SOLAR 1

Sofosbuvir + Ledipasvir + RBV

Cohort B



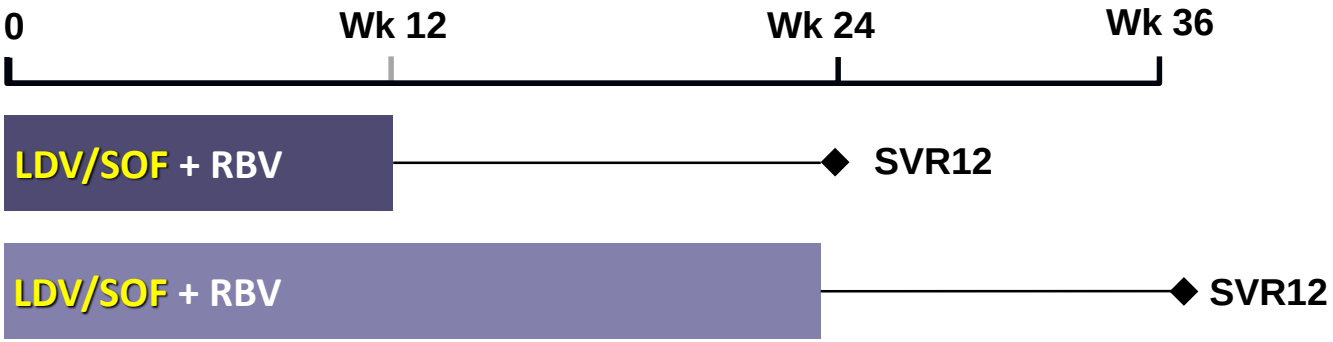
- 223 post transplant patients
- Genotype 1 or 4 , naïve or experienced
- F0-F3 (n=111)
- Cirrhosis CTP A (n=51), B (n=52) y C (n=9)
- FCH (n=6)
- Weight adjusted RBV (F0–F3); progressive (cirrhosis)

Charlton et al, Gastro 2015

Post-Transplant Antiviral Therapy: SOLAR 2

Sofosbuvir + Ledipasvir + RBV

Cohort B

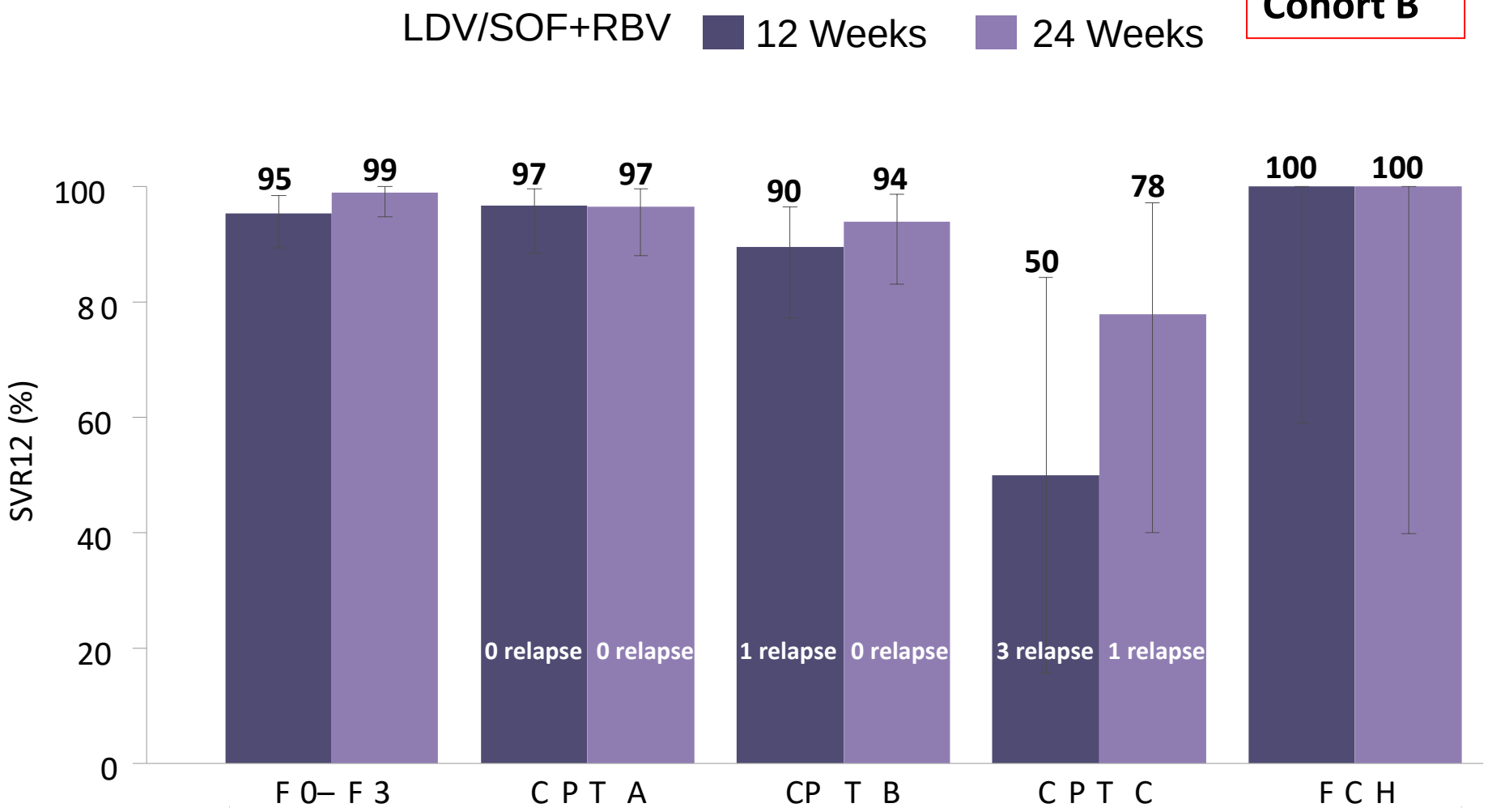


- 226 post- transplant patients
- Genotype 1 and 4, naïve or experienced
- No cirrhosis
- Compensated and decompensated cirrhosis
- FCH
- Hemoglobin ≥ 10 g/dL, Cr Cl ≥ 40 mL/min, platelets > 30,000

Manns et al, Lancet 2016

SOLAR 1 and 2 - SVR12 Post Transplant

Cohort B



	F 0– F 3		C P T A		CP T B		C P T C		F C H	
Overall:	102/107	104/105	58/60	56/58	43/48	46/49	4/8	7/9	7/7	4/4
GT1:	94/99	99/100	55/56	51/53	41/46	43/45	4/7	7/9	7/7	4/4
GT4:	8/8	5/5	3/4	5/5	2/2	3/4	0/1	0	0	0

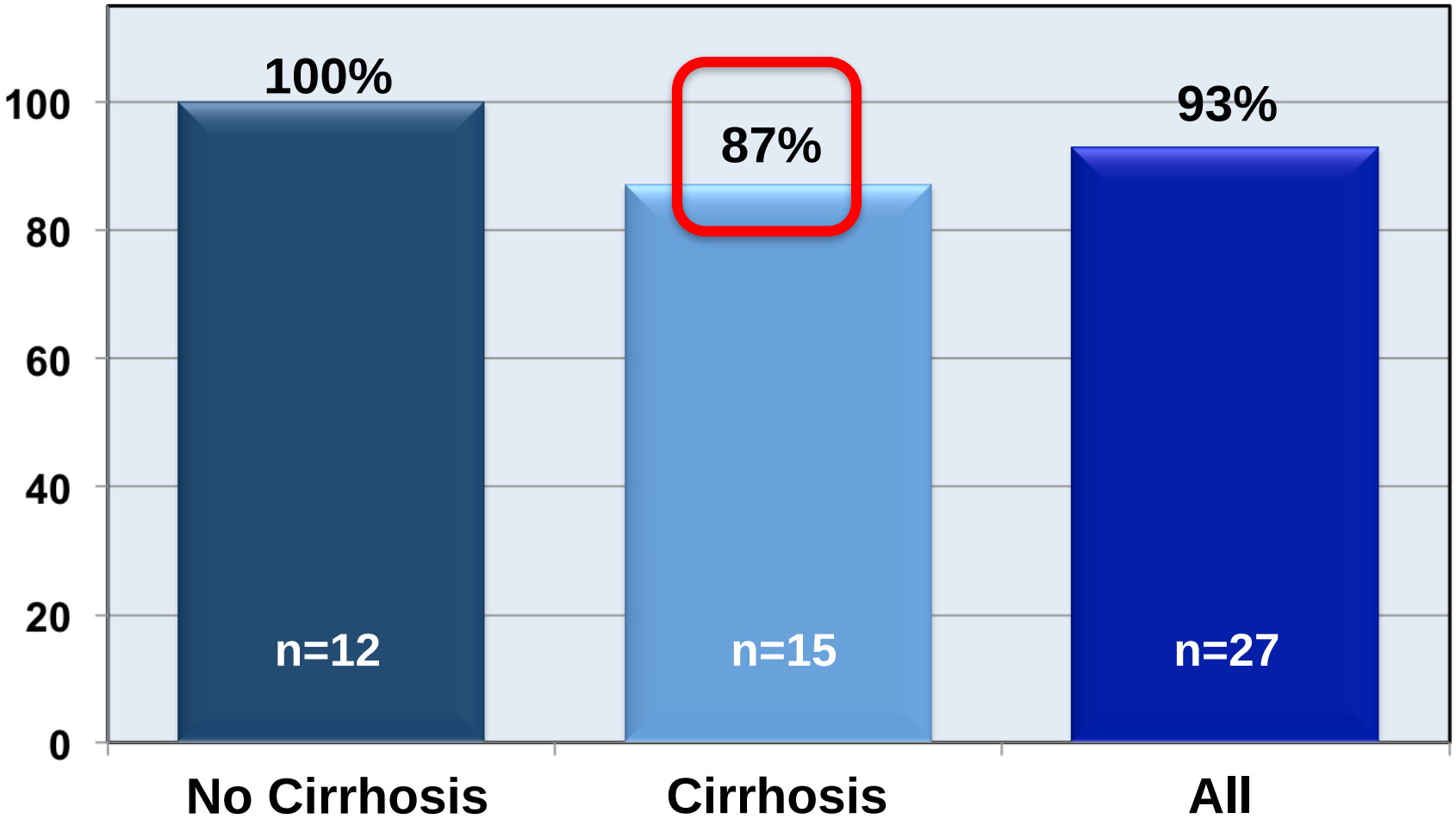
Analysis excluded 13 patients transplanted prior to FU-12 with HCV RNA <LLOQ at last measurement prior to transplant, 13 patients with other virologic outcome (death, lost to follow-up, etc) and 3 pretransplant patients who were CPT A at baseline. *Error bars* represent 95% CIs.

Post-Transplant Antiviral Therapy

Genotype 4

Cohort B

LDV + SOF + RBV (12 + 24 wk)

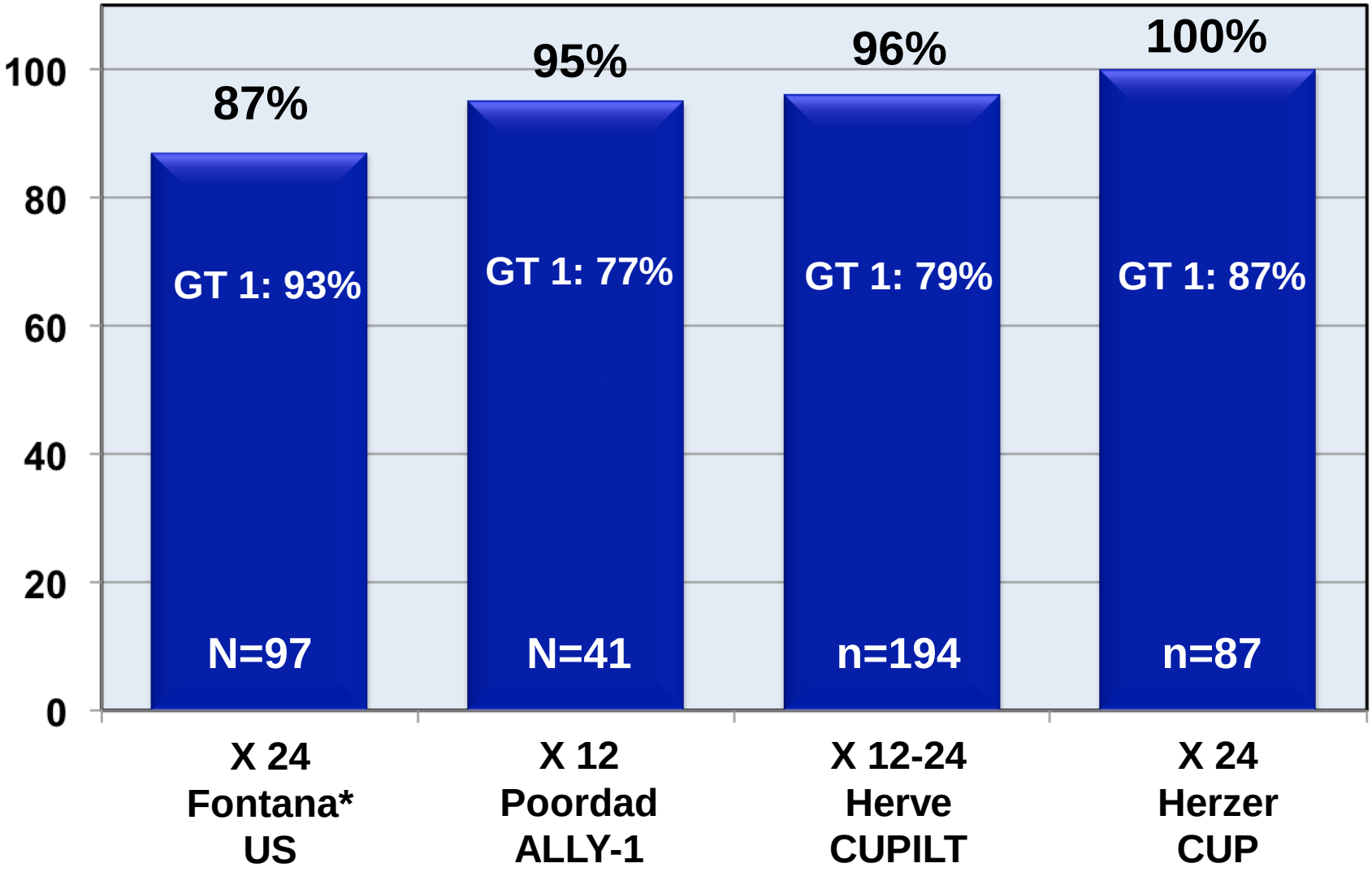


SOLAR-2

Manns et al, Lancet 2016

Post-Transplant Antiviral Therapy

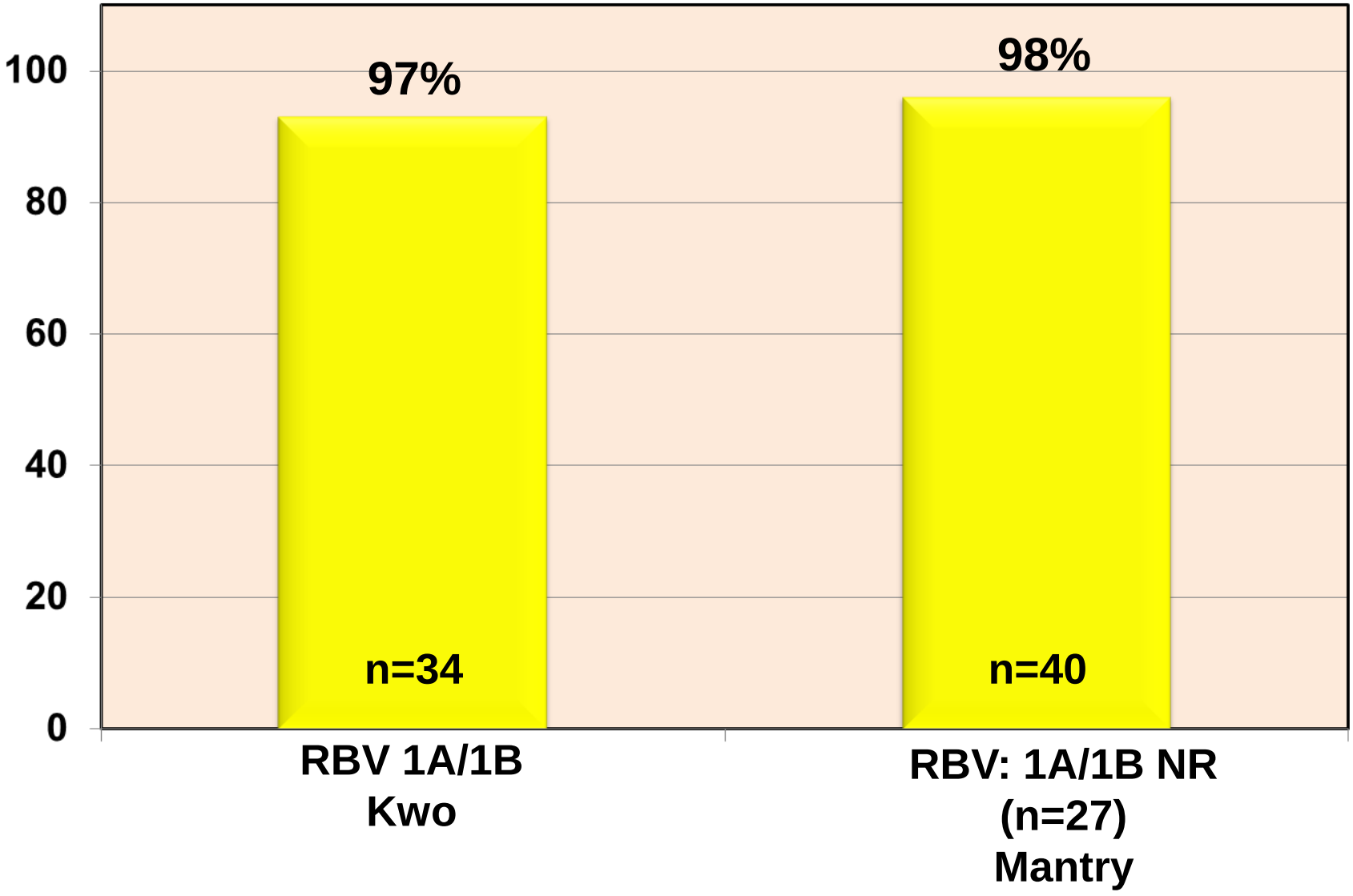
GT1: DCV + SOF ± RBV



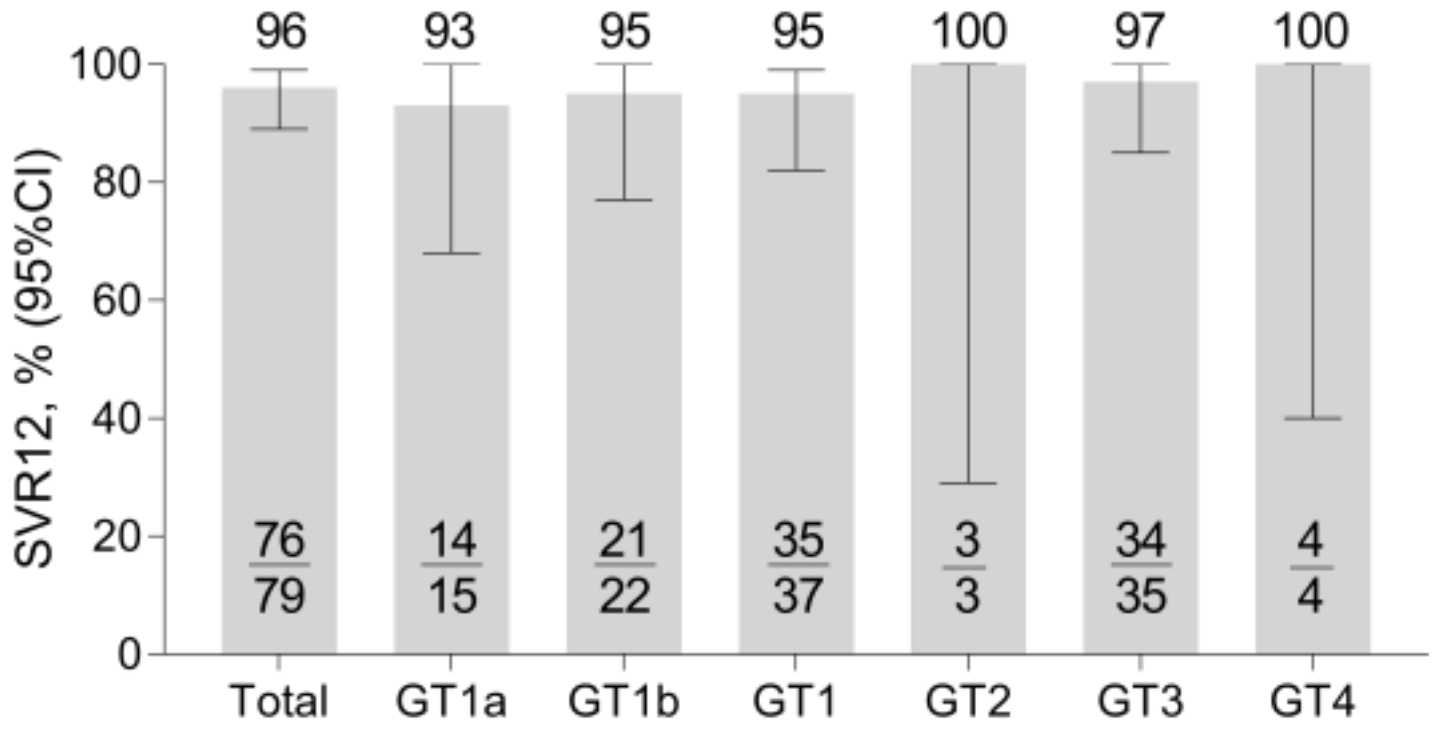
**DAC/SOF - DAC/SIM - DAC/SOF/SIM*

Tratamiento Antiviral Post-Trasplante

GT1: 3D ± RBV



Sofosbuvir/Velpatasvir por 12 semanas en Receptores de Hígado HCV Genotio 1-4

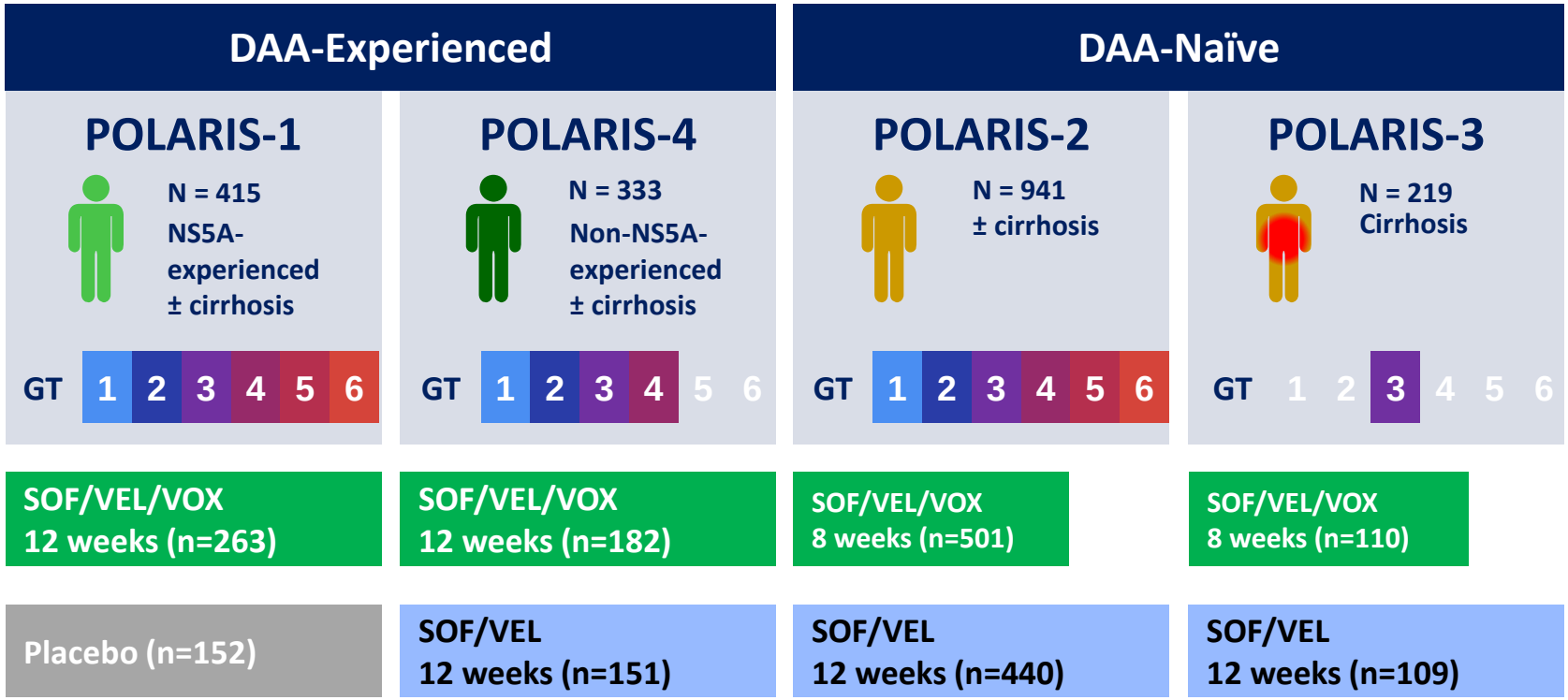


No change in calcineurin inhibitor dose is needed for patients receiving sofosbuvir/velpatasvir

Agarwal K, J Hepatol. 2018

POLARIS Phase 3 Program

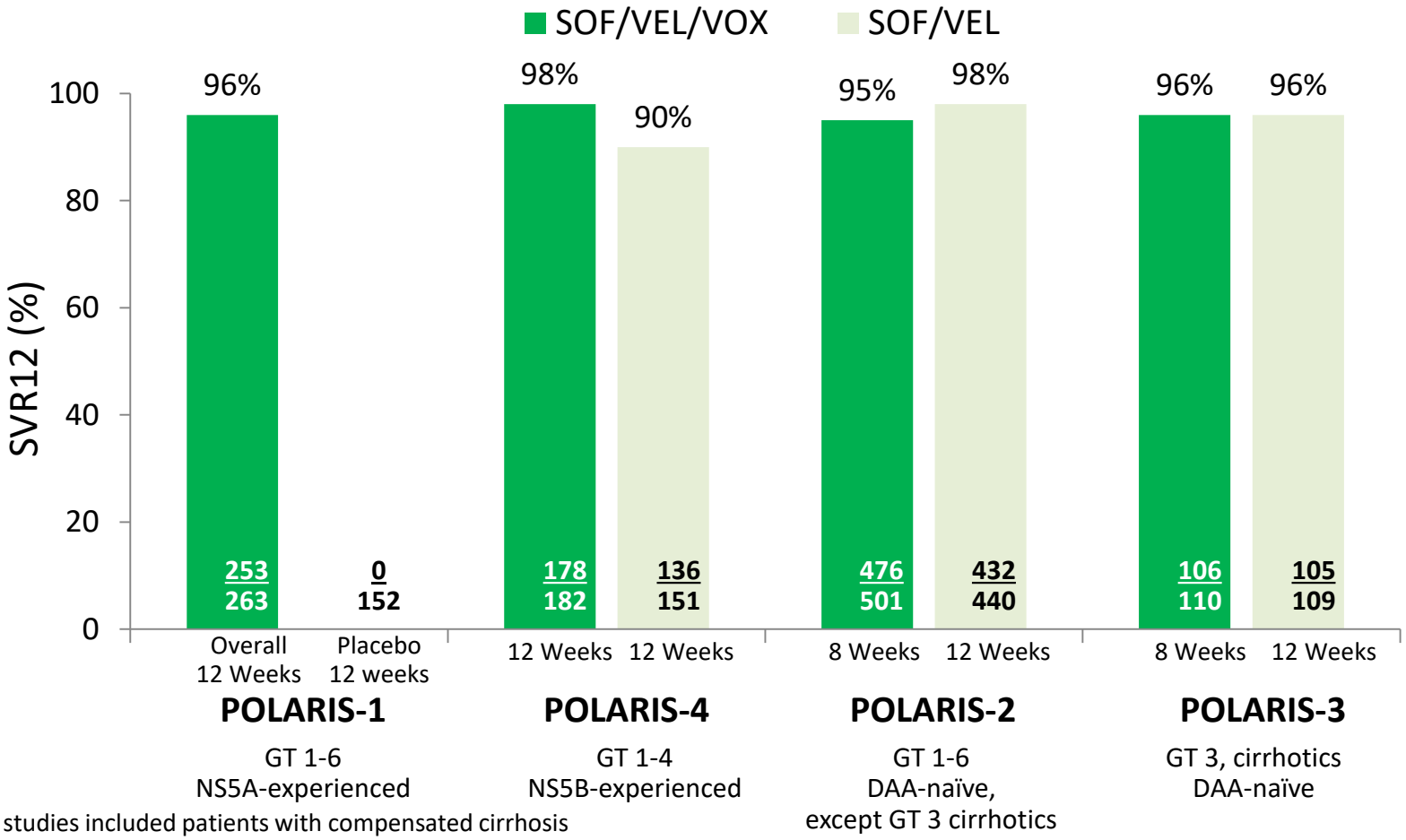
Pacientes difíciles de curar por no SVR a AAD (5%)



Bourliere M, et al. N Engl J Med 2017;376:2134-46; Jacobson I, et al. Gastroenterology 2017, doi: 10.1053/j.gastro.2017.03.047.

POLARIS Phase 3 Program (POLARIS-1, POLARIS-4, POLARIS-2, POLARIS-3)

Eficacia (ITT Analysis)



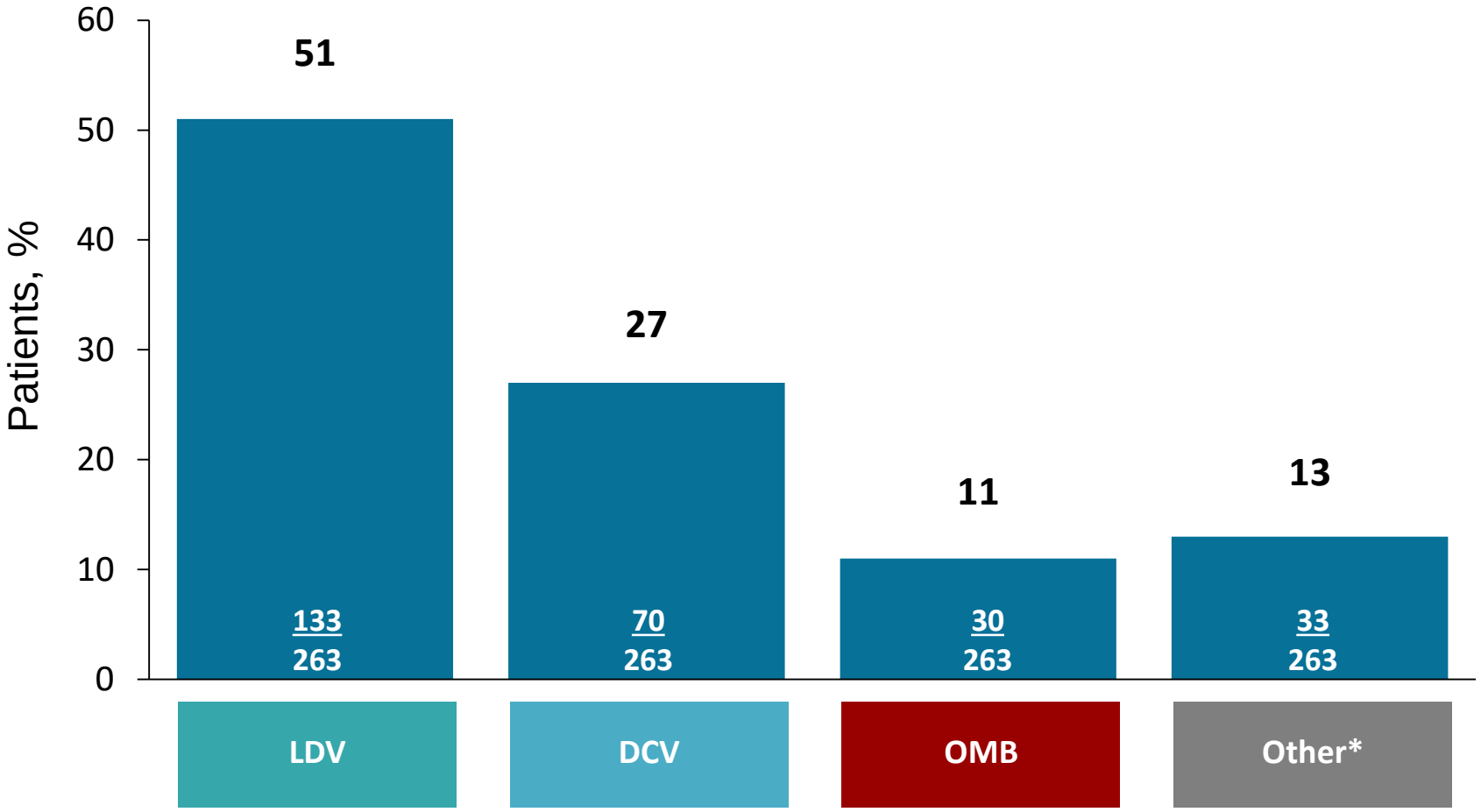
*All studies included patients with compensated cirrhosis

SOF/VEL/VOX for 12 weeks provides a STR for DAA-experienced patients and SOF/VEL for 12 weeks provides a STR for DAA-naive patients regardless of cirrhosis status

Bourliere M, et al. N Engl J Med 2017;376:2134-46; Jacobson I, et al. Gastroenterology 2017, doi: 10.1053/j.gastro.2017.03.047.

POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6

Experimentados a NS5A (%)

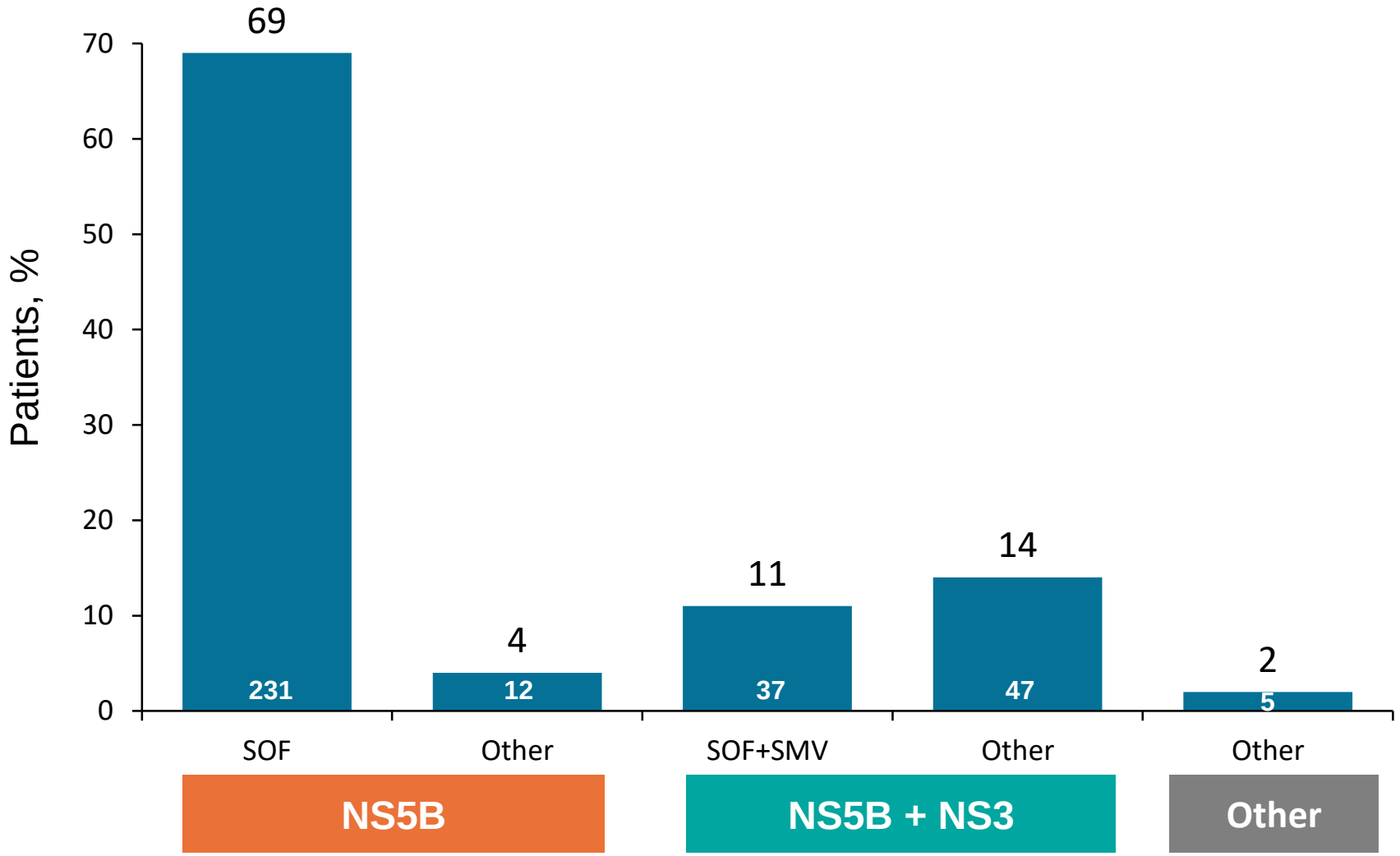


*Other included SOF/VEL experienced, EBR/GZR experienced, and other investigational combinations and/or medications from discontinued programs.
DCV, daclatasvir; LDV, ledipasivir; OMB, ombitasvir.

Bourliere M, AASLD 2016, Oral 194

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

Tratamiento Previo con DAA

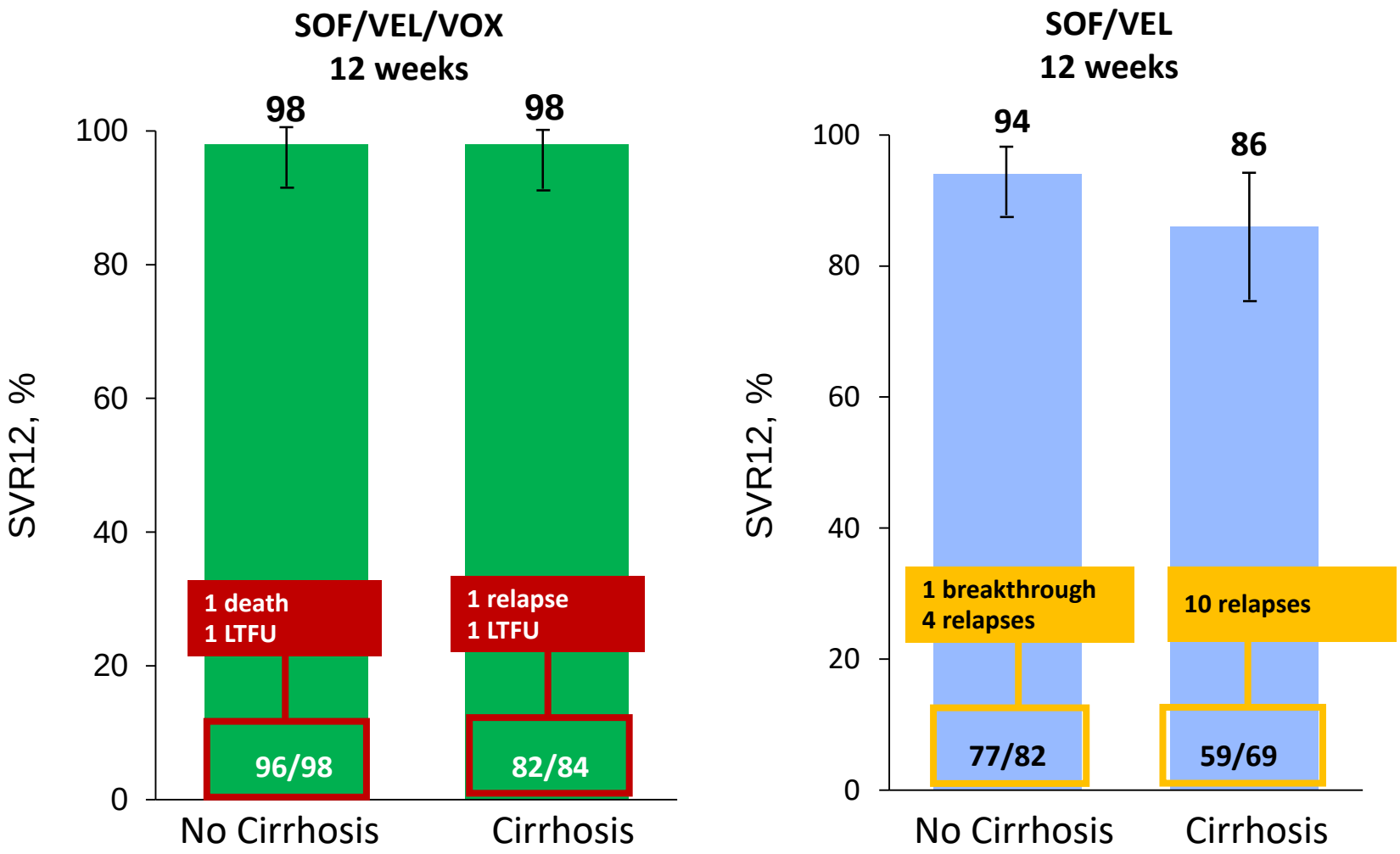


Other NS5B included mericitabine (n=7); other NS5B+NS3 included deleobuvir+faldaprevir (n=14), mercitabine+danoprevir (n=8), and SOF+telaprevir (n=6); SMV, simeprevir; SOF, sofosbuvir.

Bourliere M, et al. N Engl J Med 2017;376:2134-46;; Zeuzem S, AASLD 2016, Oral 109.

POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

SVR12 Cirrosis vs No-cirrosis



Bourliere M, et al. N Engl J Med 2017;376:2134-46

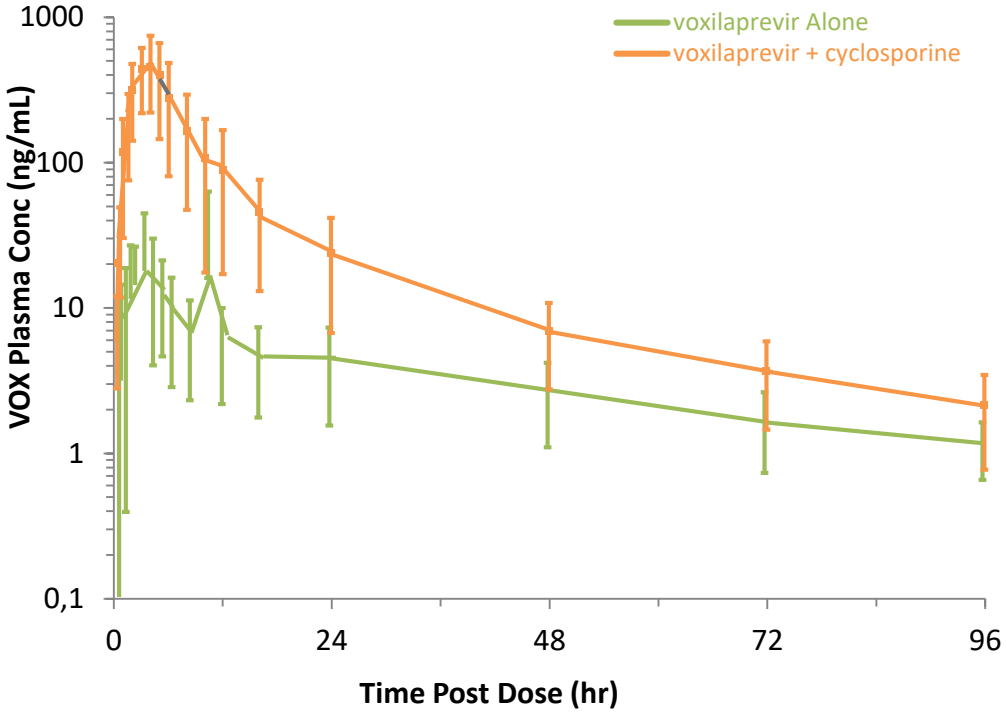
Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction[a]

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Effect/Recommendation
Immunosuppresants:		
cyclosporine[c]	↑ voxilaprevir	Coadministration of voxilaprevir with cyclosporine has been shown to substantially increase the plasma concentration of voxilaprevir, the safety of which has not been established. Coadministration of VOSEVI with cyclosporine is not recommended.

a. This table is not all inclusive.
b. ↓ = decrease, ↑ = increase
c. These interactions have been studied in healthy adults.

Vosevi™ [PI]. Gilead Sciences, Inc. Foster City, CA

Effect of Cyclosporine on VOX PK



VOX PK Param.	Cyclosporine
AUC_{inf}	940 (737, 1200)
AUC_{last}	1100 (854, 1420)
C_{max}	1900 (1410, 2560)

- VOX exposure significantly increased by potent hepatic OATP inhibition by cyclosporine (AUC_{inf} ↑8.4-fold, C_{max} ↑18-fold)

Kirby B, et al. 17th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy 2016

SOF/VEL/VOX and Immunosuppressants

Perpetrator	Object	AUC, %	C_{max}, %
Tacrolimus 5 mg	**SOF**	↑13	↓4
	GS-331007	↔	↔
SOF 400 mg	**Tacrolimus**	↑9	↓27
SOF 400 mg	**Cyclosporine**	↔	↔
VEL 100 mg		↔	↔
VOX 100 mg		↔	↔

- SOF, VEL, and VOX had no impact on cyclosporine exposure
- No significant interactions expected between SOF/VEL/VOX and tacrolimus (CYP3A4 substrate)

Garrison K, et al. EASL 2017; P_187

Tratamiento Antiviral Post-Trasplante

RVS en Hepatitis Colestásica C

Autor	N	Régimen	RVS
Fontana	31	DCV-SOF	86%
Leroy	15 8	DCV-SOF PEG-SOF	100% 88%
Charlton	6	LDV-SOF	100%
Manns	5	LDV-SOF	100%
Pungpapong	13	SMV-SOF	100%
Forns	10	SOF-RBV	80%

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, B
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive and -Experienced Patients With Genotype 1-6 Infection in the Allograft With Compensated Cirrhosis

RECOMMENDED	DURATION	RATING
Genotype 1, 4, 5, or 6 only: Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	I, C

[a] Dosing is 3 coformulated tablets (glecaprevir [100 mg]/pibrentasvir [40 mg]) taken once daily. Please refer to the prescribing information.

www.hcvguidelines.org. January 21, 2021

Inmunosupresión

We suggest that blood concentrations of immunosuppressive medications are monitored regularly during DAA treatment, and following completion of treatment until SVR12 is achieved.

Quality/Certainly of evidence: Moderate
Strenght of Recommendation: Strong

Interacción Entre los Antivirales y los Inmunosupresores

Inhibidor (Clase)	Droga	Interacción con CNI	
		Si	No
Proteasas	GLECAPREVIR	XXX	
	VOXILAPREVIR	XXX	
	GRAZOPREVIR	X (CsA)	
	PARITAPREVIR/r	XX	
Polimerasas (nucleos(t)ídico)	SOFOSBUVIR		X
Polimerasas (no nucleosídico)	DASABUVIR		X
NS5A	DACLATASVIR		X
	LEDIPASVIR		X
	VELPATASVIR		x

Tischer S et al (2014); AALSD/IDSA. Available at: http://www.hcvguidelines.org.