Hepatitis B and Hepatitis C Virus in non-Liver Transplant Recipients

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Financial Disclosures

- Research Grants

  Merck, Gilead, Abbvie, Intercept, Bristol Myers Squibb

- Advisory Boards

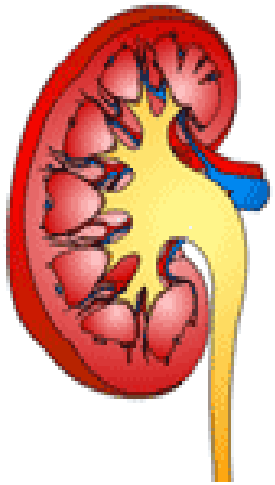
  Merck, Gilead and Bristol Myers Squibb

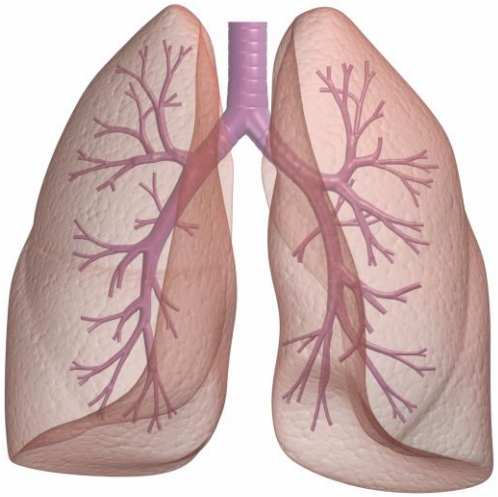
- Consultancy Agreements

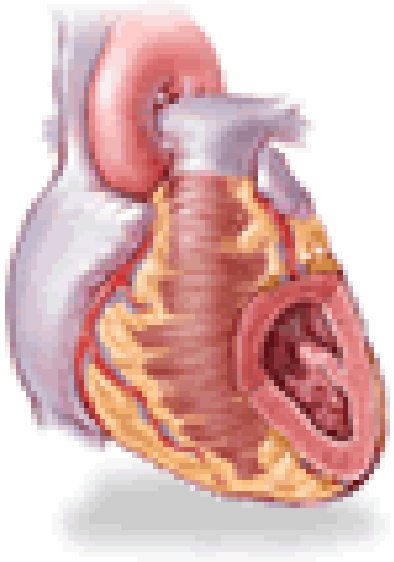
  Merck, Gilead Sciences, Intercept and Bristol Myers Squibb

Introduction

Discuss management and role of Antiviral therapy against Hepatitis B and C in non-liver transplant recipients







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Introduction

It is a **DNA virus**

It belongs to the

Family: ***Hepadnaviridae***

Genera: ***Orthohepadnaviridae***

Other members of

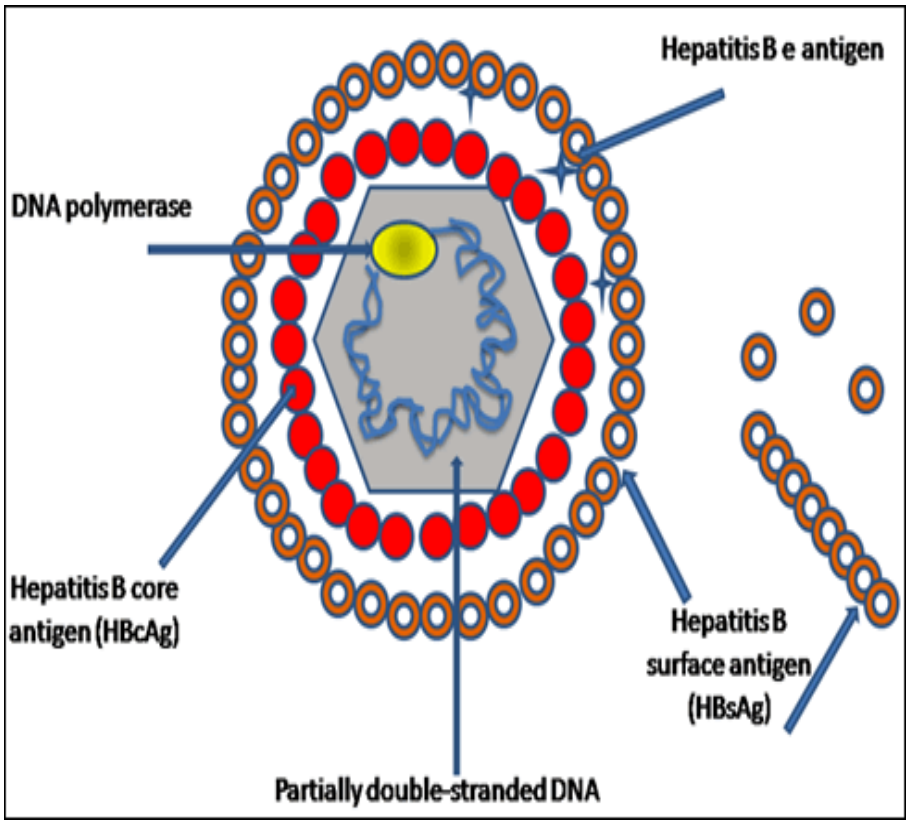
Orthohepadnaviridae are

Woodchuck hepatitis virus

Ground squirrel hepatitis virus

GENOTYPE A-H

A1 & D in INDIA



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HBV and Solid Organ Transplant

- HBV can cause liver-related morbidity and mortality in non-liver transplant recipients

- Active HBV occurs
  - Pre-Transplant HBsAg+
  - Transmitted by donor organ
  - Reactivation (post transplant) induced by immunosuppression

HBV and Solid Organ Transplant

Hepatitis B Serology (Donor/Recipient)

	HBsAg	HBsAb	HBcAb
Active HBV	**+**	**-**	**+**
Immunity	**-**	**+**	**+/-**
low level	**-**	**-**	**+**

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HBV and Solid Organ Transplant

Donor : HBsAg +

- Organs from HBsAg + donors universally transmits HBV, and has been associated with HBV liver-related morbidity and mortality

- Use of these donor organs remains a relative contraindication

  - Occasional HBsAg+ donors have been transplanted into naïve heart and kidney recipients and also into HBsAg+ liver recipients with minimal morbidity

  - These organs can be used with the utilization of HBV prophylaxis (Nucleos(t)ide Analogues, Lam/TDF/ENT : +/- HBIG)

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QUESTION: A donors kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At your center we would?

a) Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient

b) Not use any organs from this donor as I never did understand any of that HBV serology

c) Transplant the liver only into HBV immune recipients, a high status HBsAg+ or a HBV non-immune recipient, with NA and HBIG coverage

d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described

HBV and Solid Organ Transplant

Donor : HBcAb +

- Donors with HBcAb(+) status are not uncommon

* Canada (79/1656)	4.7%
* US Population	5.4%
* UNOS	3.8%

- Low HBV endemic areas (US, Canada) : 1-5%

HBV and Solid Organ Transplant

Donor : HBcAb +

- Isolated HBcAb(+) donors:
  - Potentially infectious (low level active infection)
  - Immunity (low Ab titer)

- Is there an organ specific risk?
- Is the recipient HBV status important?
- Is recipient therapy/prophylaxis required?

HBV and Solid Organ Transplant

Donor : HBcAb +

		No. HBV Infected / No. Recipients			
Krieger	**2001**			**Renal**	**1/26 (3.8%)**
Madayag	**1997**			**Renal**	**0/45**
Satterthwaite	**1997**			**Renal**	**0/38**
Paletta	**1996**	**Heart**	**0/8**	**Renal**	**0/28**
Wachs	**1995**	**Heart**	**0/7**	**Renal**	**1/42 (2.4%)**
Radomski	**1995**			**Renal**	**0/10**
Cirocco	**1994**			**Renal**	**0/16**
Kadian	**1994**	**Heart**	**0/13**	**Renal**	**0/19**
Miller	**1993**	**Heart**	**0/12**	**Renal**	**0/19**

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HBV and Solid Organ Transplant

Donor : HBcAb +

(HBcAb+ donors to Liver Allograft Recipients)

Dodson *(Transplantation,1997)* :118 donors

	Recip. status	*%HBV*
48 cAb-, sAb+,	cAb+/-, sAb+/-	0%
70 cAb+. sAb+/-	cAb-, sAb-	72%
	cAb-, sAb+	0%
	cAb+, sAb-	13%

- No restriction on sAb+ donors
- No need to test donor sAb

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QUESTION: A donors kidneys, heart, lungs, and liver are offered. The donor is found to have HBsAg(-), HBsAb(+), and HBcAb(+). At your center we would?

a) Transplant the kidneys, heart and lungs into any suitable recipient because the risk of transmission of HBV is very low but if possible select a HBsAb+ recipient

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d) Use all organs from this donor since the risk of HBV transmission in this setting has not been described

HBV and Solid Organ Transplant

Recipient : HBsAg +

High risk of HBV reactivation if aviremic +/- rapid progressive liver disease

- Prior to effective HBV therapy --- Death
- Currently nucleos(t)ide analogues are used
  - Lamivudine, Entecavir, Tenofovir (TDF / TAF)
- Regardless of HBV DNA at baseline

HBV and Solid Organ Transplant

Recipient : HBcAb +

- Isolated HBcAb +
  - Reactivation can occur
  - Monitor at regular intervals (serology, DNA)

- HBcAb +, HBsAb +
  - Reactivation (serologically or clinically) can occur secondary to low level viral replication in the liver, even years after loss of HBsAg
  - Prophylactic vs Preemptive therapy with NA

HBV and Solid Organ Transplant

Recipient : Summary

- HBsAg(+) recipient:
  - Initiate LAM/Tenofovir
- HBcAb(+) and HBsAb(-) recipient:
  - Potential for reactivated HBV disease
  - Monitor serology (HBsAg/HBV DNA), treatment with NA
- HBcAb(+) and HBsAb (+) recipients:
  - Low risk of reactivation

HBV and Solid Organ Transplant

Summary

KIDNEY/HEART/PANCREAS			Recipient				
Donor			HBsAg +	HBsAg – HBcAb + HBsAb +	HBsAg – HBcAb + HBsAb –	HBsAg – HBcAb – HBsAb +	HBsAg – HBcAb – HBsAb –
HBsAg	HBcAb	HBsAb					
+	+	+/–	Transplant (C)	Do Not Use	Do Not Use	Do Not Use	Do Not Use

Legend:
Transplant (A) – consider for transplant – **no concerns**
Transplant (B) – consider for transplant and **monitor recipient** post transplant for HBV
Transplant (C) – consider for transplant and **treat recipient** for HBV accordingly / consult hepatology

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HBV and Solid Organ Transplant

Summary

KIDNEY/HEART/PANCREAS			Recipient				
Donor			HBsAg +	HBsAg – HBcAb + HBsAb +	HBsAg – HBcAb + HBsAb –	HBsAg – HBcAb – HBsAb +	HBsAg – HBcAb – HBsAb –
HBsAg	HBcAb	HBsAb					
+	+	+/–	Transplant (C)	Do Not Use	Do Not Use	Do Not Use	Do Not Use
–	+	+	Transplant (C)	Transplant (B)	Transplant (B/C)	Transplant (B)	Transplant (B)

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HBV and Solid Organ Transplant

Summary

KIDNEY/HEART/PANCREAS			Recipient				
Donor			HBsAg +	HBsAg – HBcAb + HBsAb +	HBsAg – HBcAb + HBsAb –	HBsAg – HBcAb – HBsAb +	HBsAg – HBcAb – HBsAb –
HBsAg	HBcAb	HBsAb					
+	+	+/–	Transplant (C)	Do Not Use	Do Not Use	Do Not Use	Do Not Use
–	+	+	Transplant (C)	Transplant (B)	Transplant (B/C)	Transplant (B)	Transplant (B)
–	+	–	Transplant (C)	Transplant (B)	Transplant (C)	Transplant (B)	Transplant (B/C)

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HBV and Solid Organ Transplant

Summary

KIDNEY/HEART/PANCREAS			Recipient				
Donor			HBsAg +	HBsAg – HBcAb + HBsAb +	HBsAg – HBcAb + HBsAb –	HBsAg – HBcAb – HBsAb +	HBsAg – HBcAb – HBsAb –
HBsAg	HBcAb	HBsAb					
+	+	+/–	Transplant (C)	Do Not Use	Do Not Use	Do Not Use	Do Not Use
–	+	+	Transplant (C)	Transplant (B)	Transplant (B/C)	Transplant (B)	Transplant (B)
–	+	–	Transplant (C)	Transplant (B)	Transplant (C)	Transplant (B)	Transplant (B/C)
–	–	+	Transplant (C)	Transplant (A)	Transplant (B)	Transplant (A)	Transplant (A)

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HBV and Solid Organ Transplant

Summary

KIDNEY/HEART/PANCREAS			Recipient				
Donor			HBsAg +	HBsAg – HBcAb + HBsAb +	HBsAg – HBcAb + HBsAb –	HBsAg – HBcAb – HBsAb +	HBsAg – HBcAb – HBsAb –
HBsAg	HBcAb	HBsAb					
+	+	+/–	Transplant (C)	Do Not Use	Do Not Use	Do Not Use	Do Not Use
–	+	+	Transplant (C)	Transplant (B)	Transplant (B/C)	Transplant (B)	Transplant (B)
–	+	–	Transplant (C)	Transplant (B)	Transplant (C)	Transplant (B)	Transplant (B/C)
–	–	+	Transplant (C)	Transplant (A)	Transplant (B)	Transplant (A)	Transplant (A)
–	–	–	Transplant (C)	Transplant (A)	Transplant (B)	Transplant (A)	Transplant (A)

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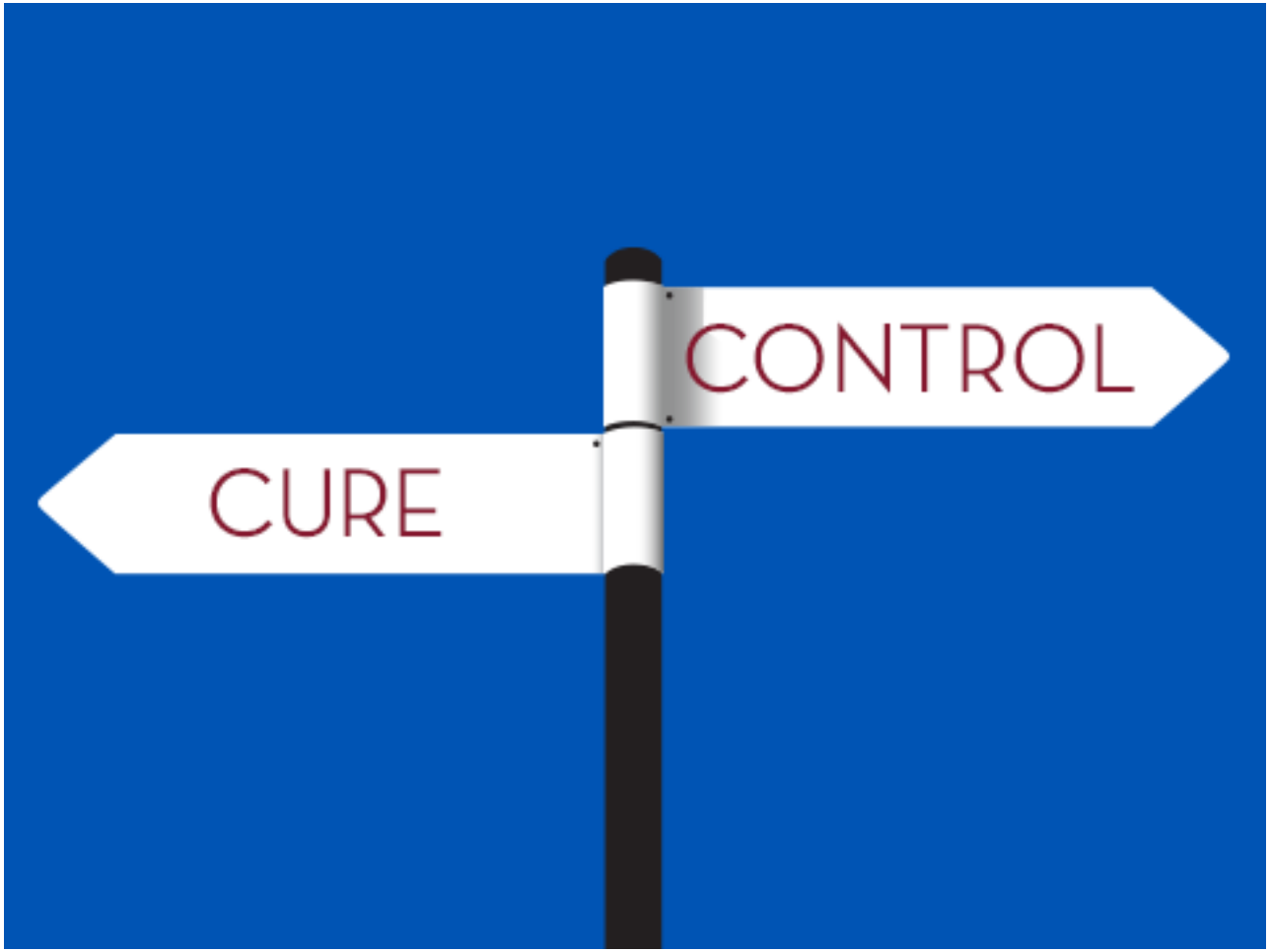

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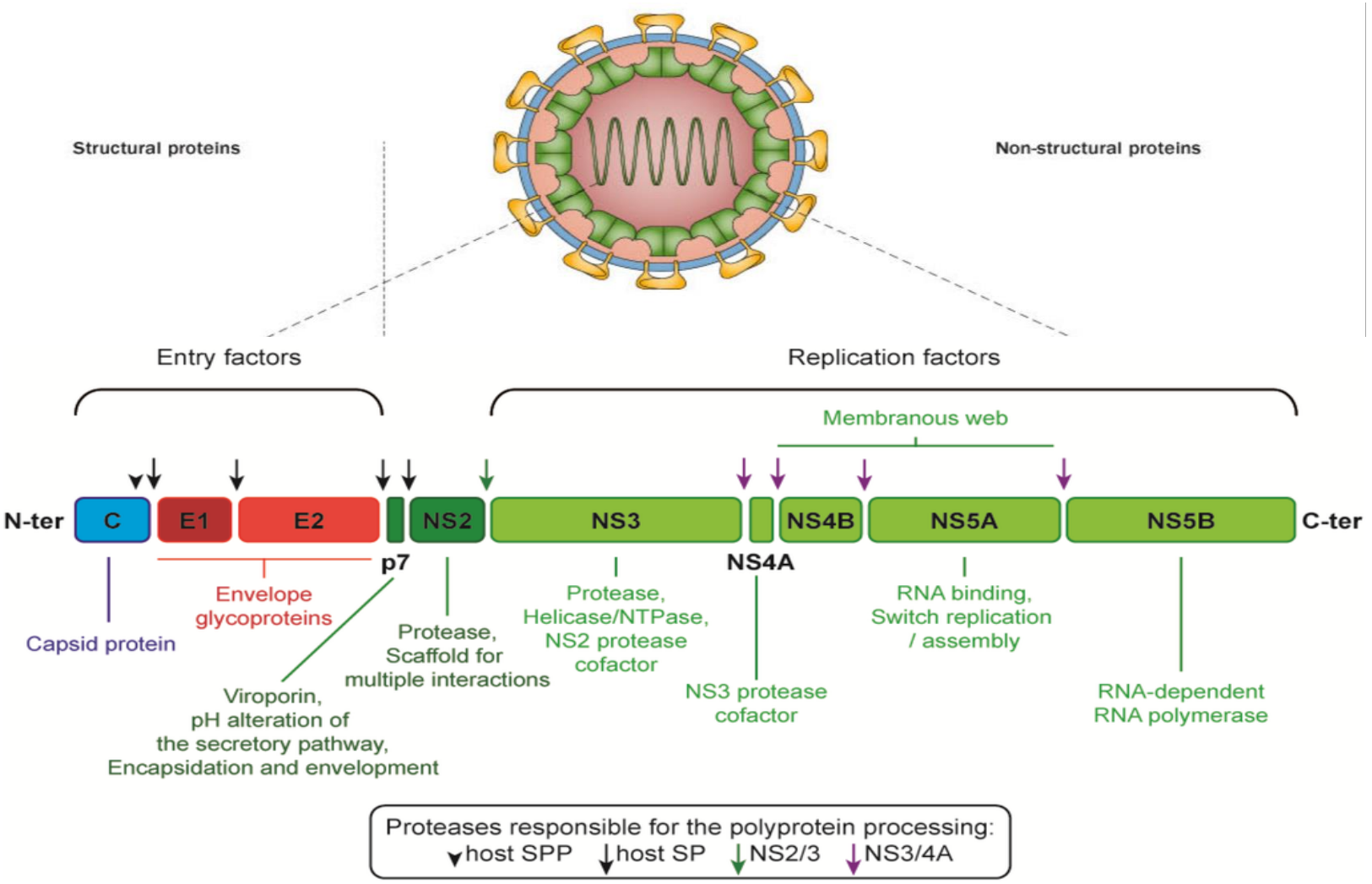
Introduction



Morales et al. Nat Rev Nephrol 2015; 11: 172-82

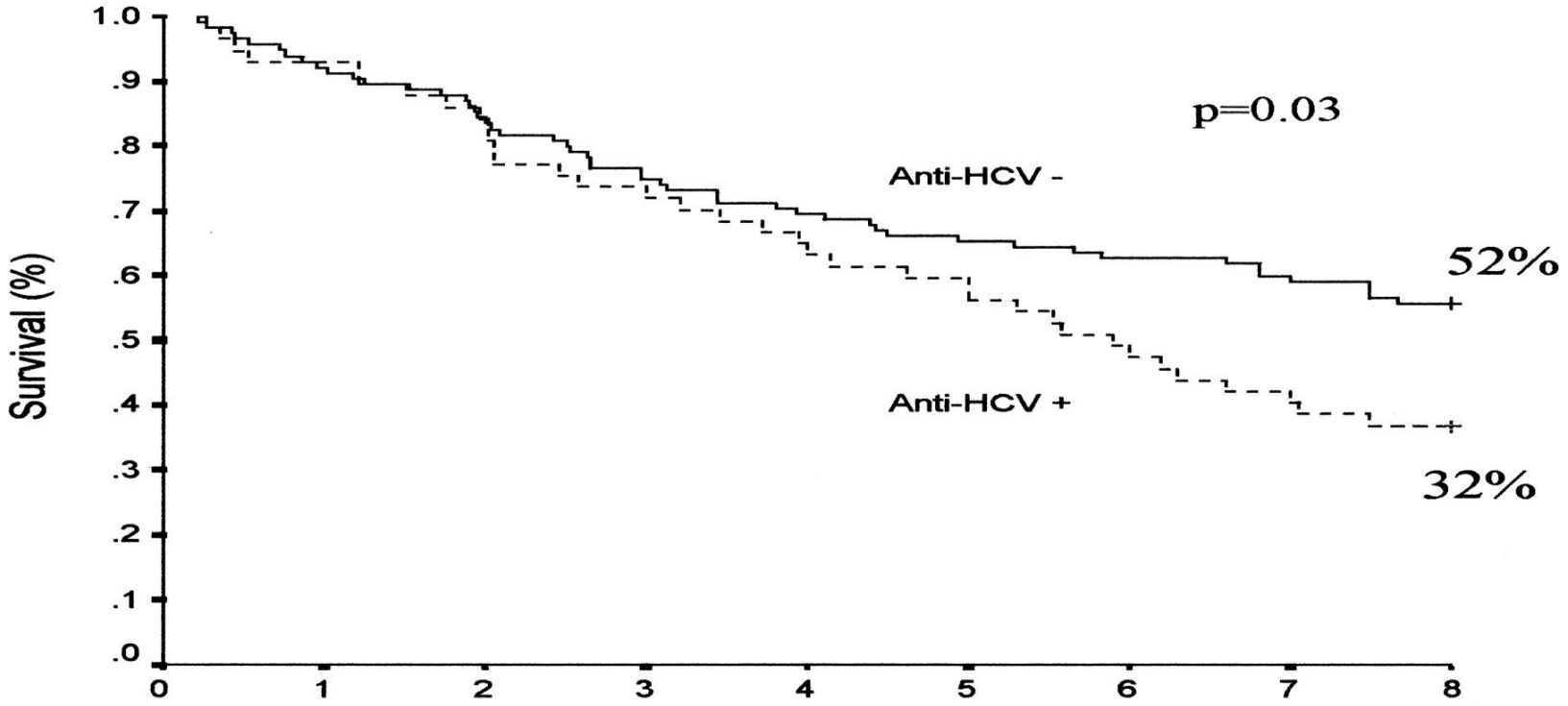
HCV and Solid Organ Transplant

- Patients with ESRD/HD
  - Several outcome studies of HCV infected patients on HD
- Cardiac and Lung Transplant Candidates
  - Natural history data is scanty

HCV and Solid Organ Transplant

Pre – Kidney Transplant

Risk of Death on HD with HCV+



Espinosa M. Nephrol Dial Transplant, 2001

HCV and Solid Organ Transplant

Pre – Kidney Transplant

Risk of Death in HD with HCV

	HCV +	HCV -
Mortality	**33%** (91/276)	**23%** (p<0.01)
Deaths with HCC	**5.5%**	**0%** (p<0.001)
Death from Cirrhosis	**8.8%**	**0.8%** (p<0.01)

HCV positivity Independent risk factor for death: *RR 1.57 (1.23-2.0, p<0.001)*

Consistent globally

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Goodkin DA et al. J Am Soc Nephrol, 2003
Nakayama E et al. J Am Soc Nephrol 2000

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HCV and Solid Organ Transplant

Post – Kidney Transplant

- 834 Renal Tx recipients (128 HCV, 216 HBV, 490 matched controls)
- 10 years follow up

	HCV +	HCV -
5 yr Pt and Graft survival	NS	NS
10 yr Pt and Graft survival	65% 49% (p<0.001)	85% 69% (p<0.01)

* Cirrhosis and Presence of HCV : independent predictors of survival

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Mathurin et al, 1999

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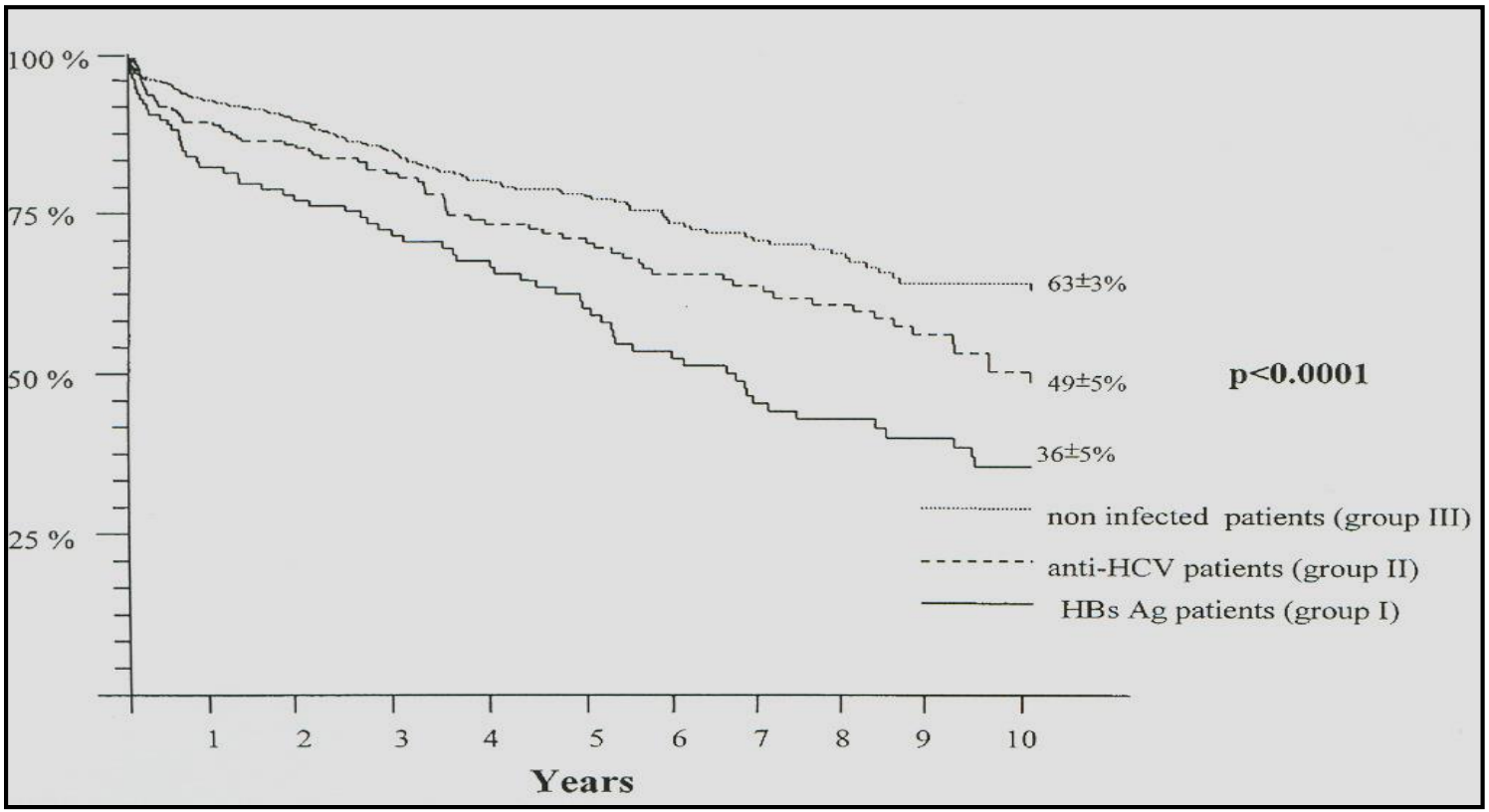
HCV and Solid Organ Transplant

Post – Kidney Transplant



Mathurin et al, 1999

HCV and Solid Organ Transplant

Heart and Lung

SRTR data 1993-2007: 443 HCV+/20,244 HCV-, F/U 5.6 yrs

Adult Heart Recipients	HCV +	HCV -
Mortality	40%	31.5% (p<0.001)

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J Heart Lung Transpl, 2011

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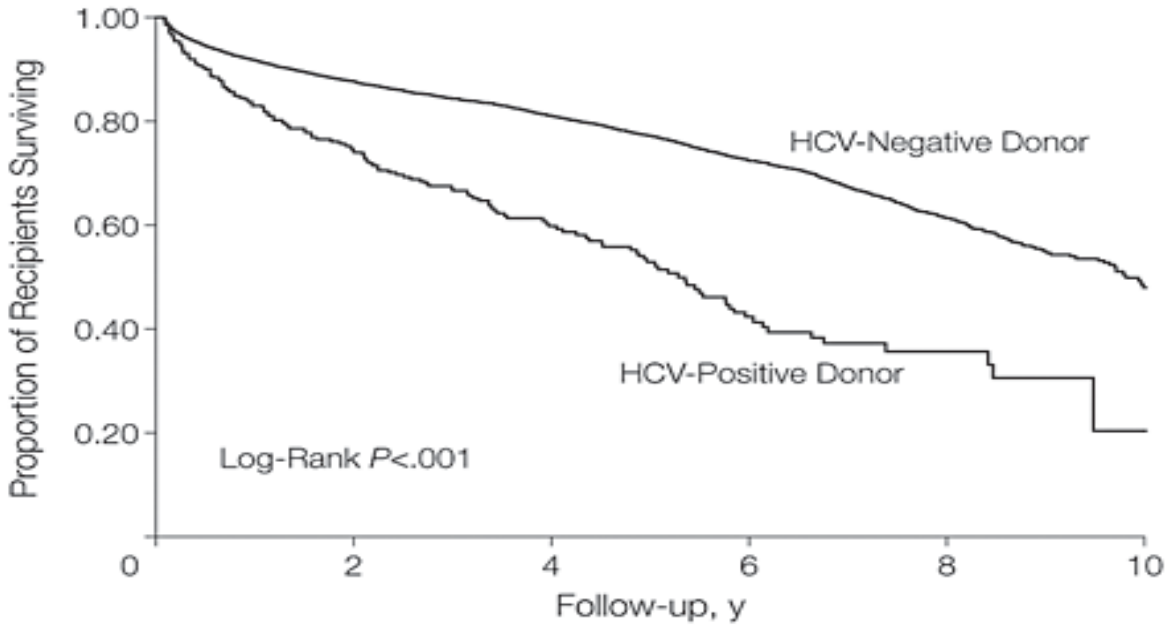
HCV and Solid Organ Transplant

Heart and Lung

Survival of Cardiac Recipients Based on HCV Status



No. at Risk

HCV-Negative Donor	10654	7853	5302	3026	1213	69
HCV-Positive Donor	261	179	117	53	20	1

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SRTR : Gasink LB et al. JAMA 2006:1843-50

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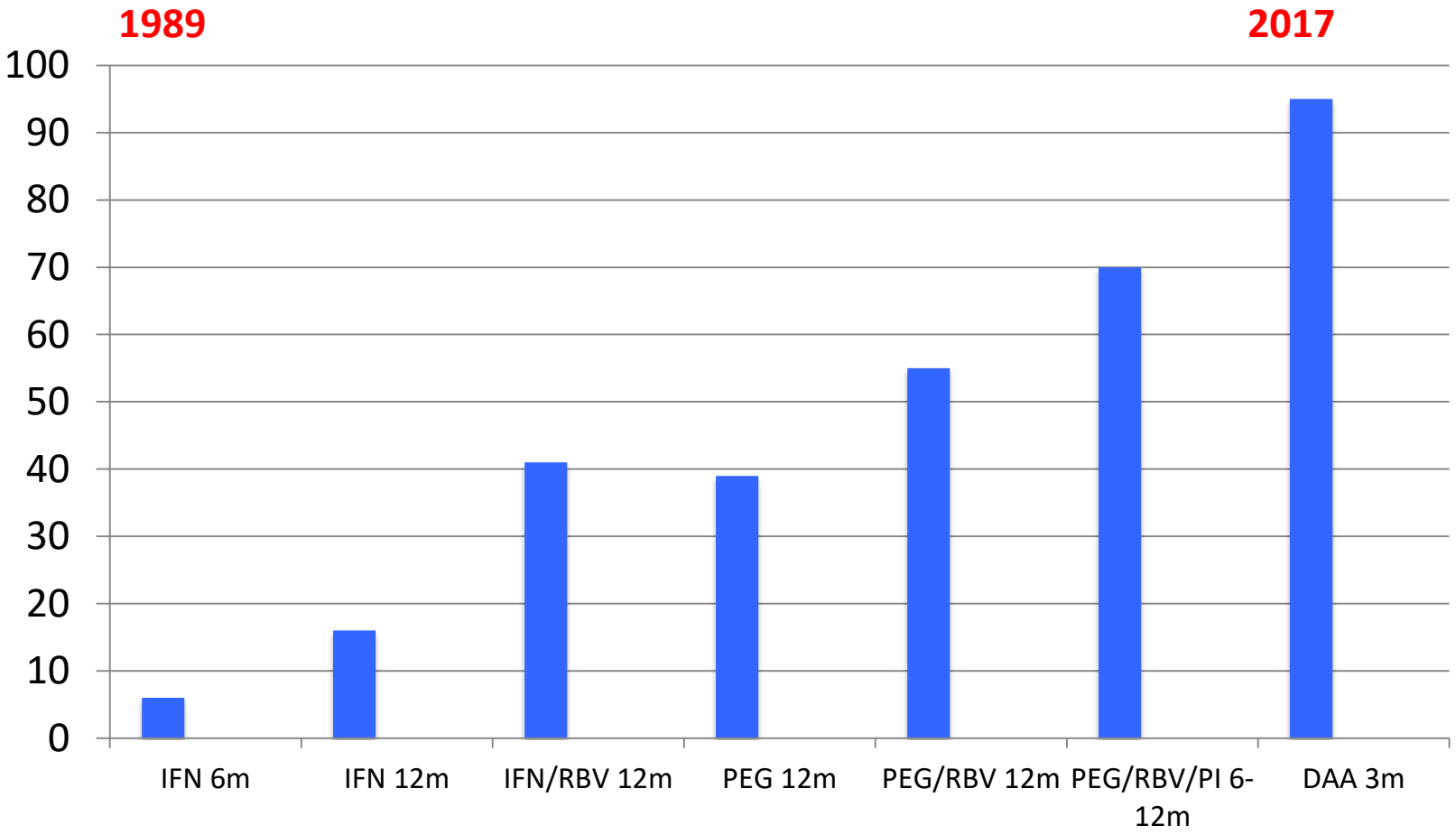
HCV Treatment Evolution



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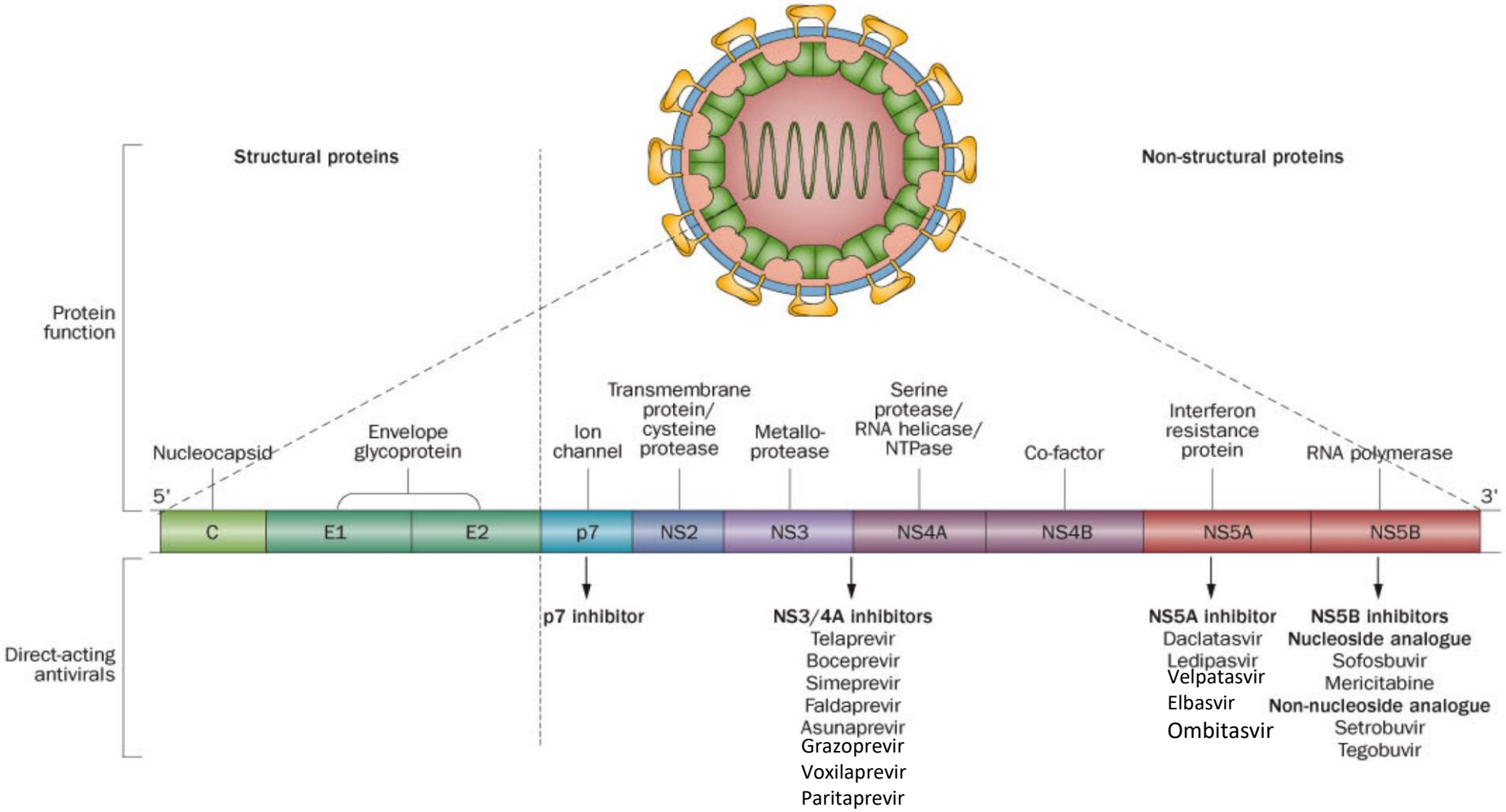

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Morales et al. Nat Rev Nephrol 2015; 11: 172-82

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HCV and Solid Organ Transplant

Treatment	Mild-moderate CKD (eGFR 30-80 ml/min)	Severe CKD (eGFR <30 ml/min)	ESRD/Hemodialysis
Harvoni	Standard dosing	Data not available Avoid use	Data not available Avoid use
Epclusa	Standard dosing	Data not available Avoid use	Data not available Avoid use
Holkira	Standard dosing	Use with caution	Data not available
Zepateir	Standard dosing	Standard dosing	Standard Dosing

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HCV and Solid Organ Transplant 2012

Candidate	HCV Therapy
Renal Treat while awaiting Renal transplant (HD) Treat after Renal transplant	Rarely Not 2013/14, wait IFN free
Cardiac Treat while awaiting Heart transplant Treat after Heart transplant	NO Not Ideal
Lung Treat will awaiting Lung transplant Treat after Lung transplant	Rarely Unknown

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HCV and Solid Organ Transplant 2017

Candidate	HCV Therapy
Renal	
Treat while awaiting Renal transplant (HD)	YES
Treat after Renal transplant	YES
Cardiac	
Treat while awaiting Heart transplant	YES
Treat after Heart transplant	YES
Lung	
Treat will awaiting Lung transplant	YES
Treat after Lung transplant	YES

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HCV and Solid Organ Transplant 2017

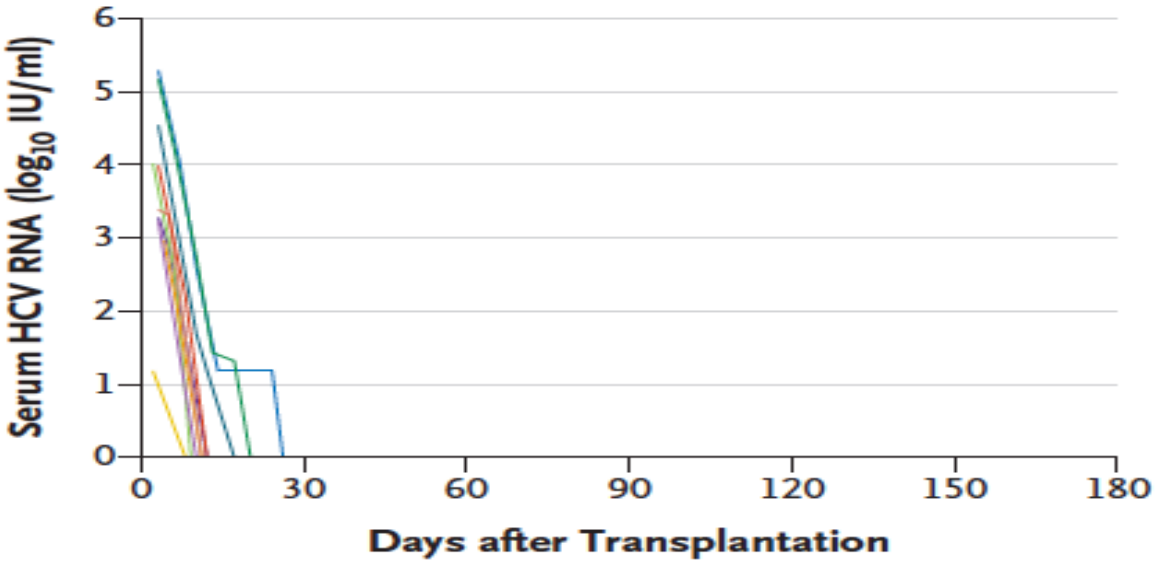
Current Therapies

- Can be used PRE or POST
- Very effective (>95% cure)
- Trivial side effects
- Transplant DDI can be avoided
- Transplant candidates/recipients are NOT special populations for HCV any longer

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients



David S. Goldberg, M.D.

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POLARIS Trials

DAA-Experienced	DAA-Naïve

POLARIS-1

N = 415
NS5A-experienced
± cirrhosis

GT 1 2 3 4 5 6

SOF/VEL/VOX
12 weeks (n=263)

Placebo (n=152)

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Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

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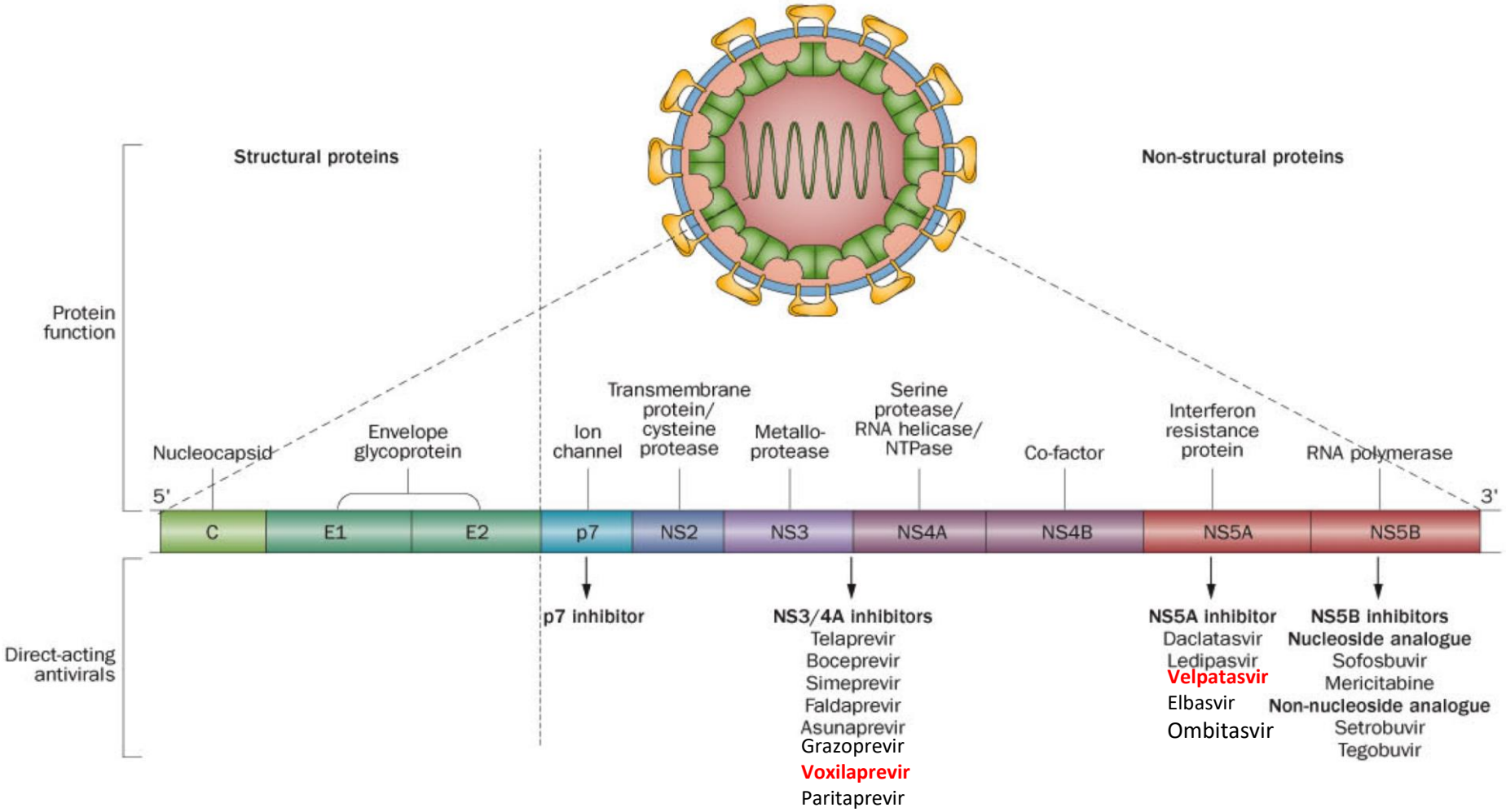

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Morales et al. Nat Rev Nephrol 2015; 11: 172-82

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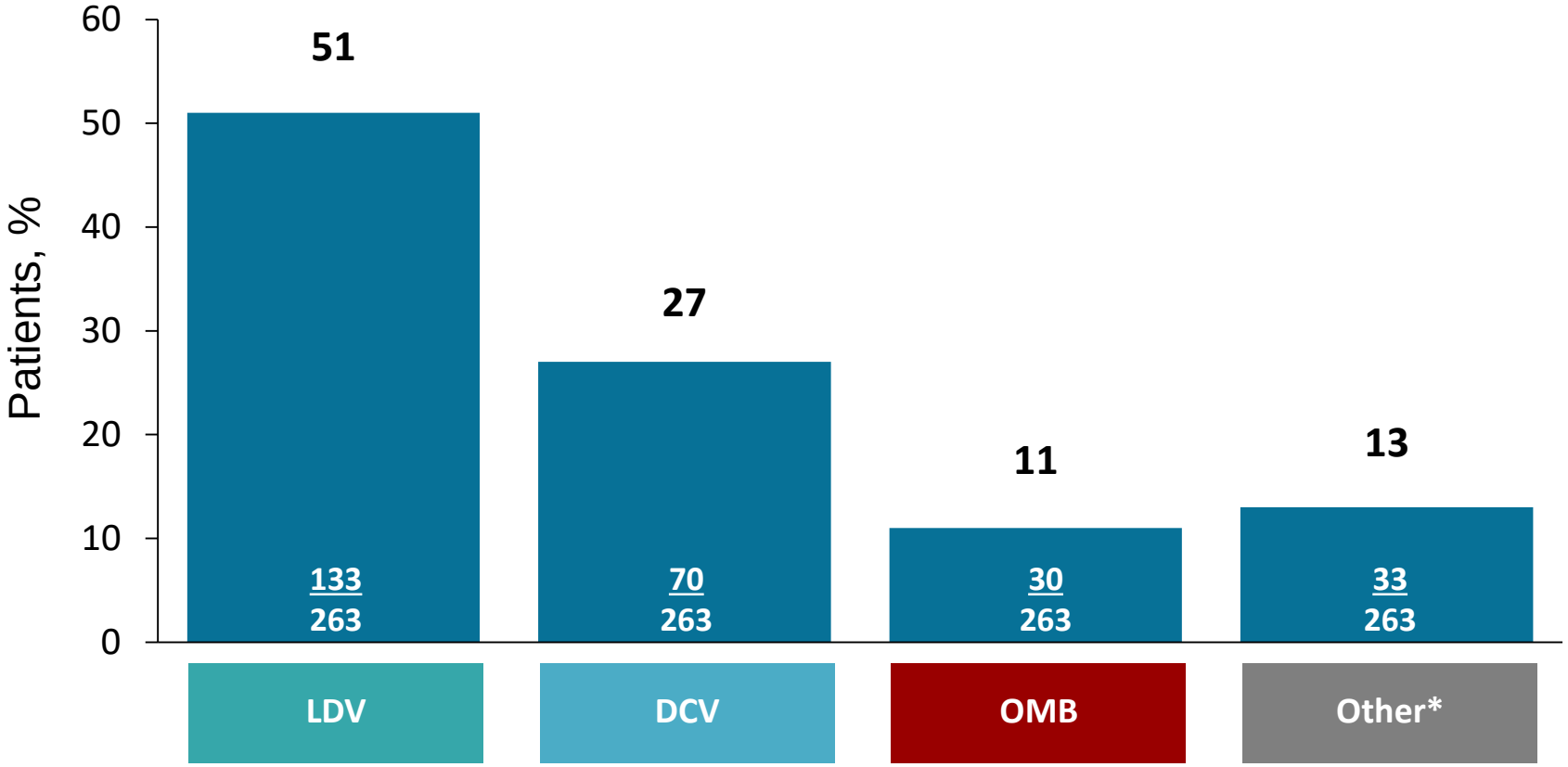
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6



*Other included SOF/VEL experienced, EBR/GZR experienced, and other investigational combinations and/or medications from discontinued programs.

3 patients received both LDV and DCV; DCV, daclatasvir; LDV, ledipasivir; OMB, ombitasvir.

Bourliere M, AASLD 2016, Oral 194

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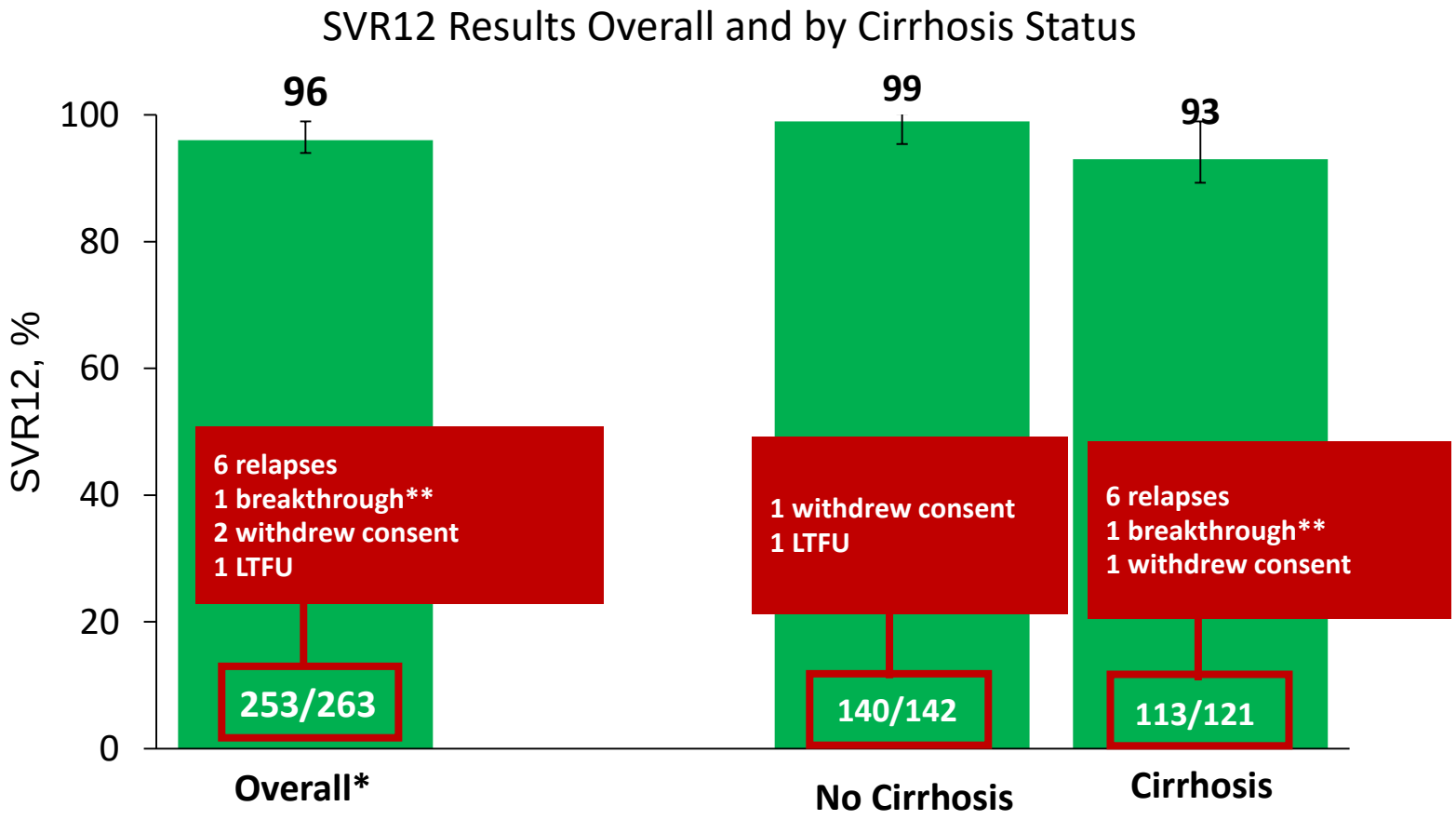
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6



* p <0.001 for superiority compared with prespecified 85% performance goal for SOF/VEL/VOX

** Exposure was consistent with non-adherence

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Bourliere M, AASLD 2016, Oral 194

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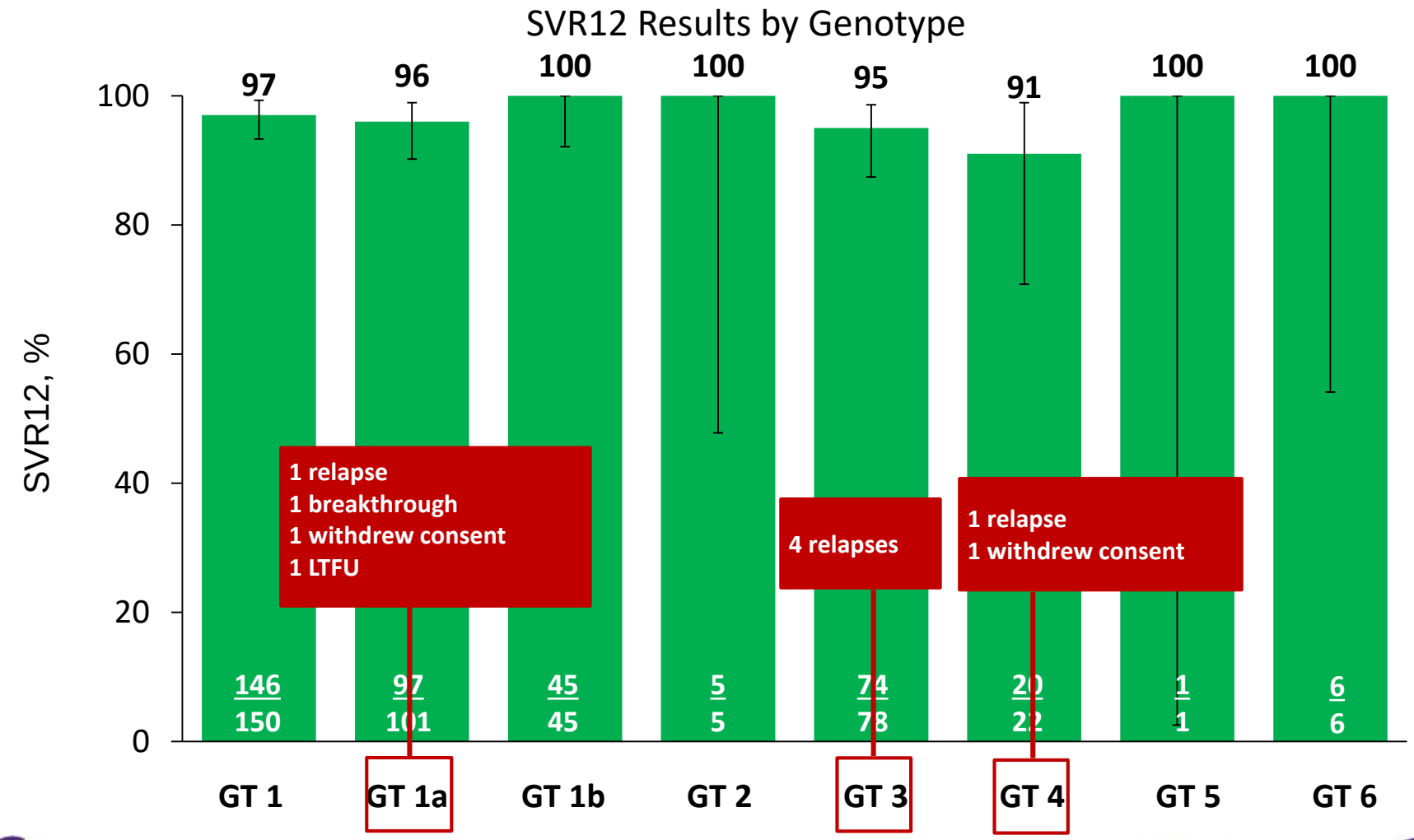
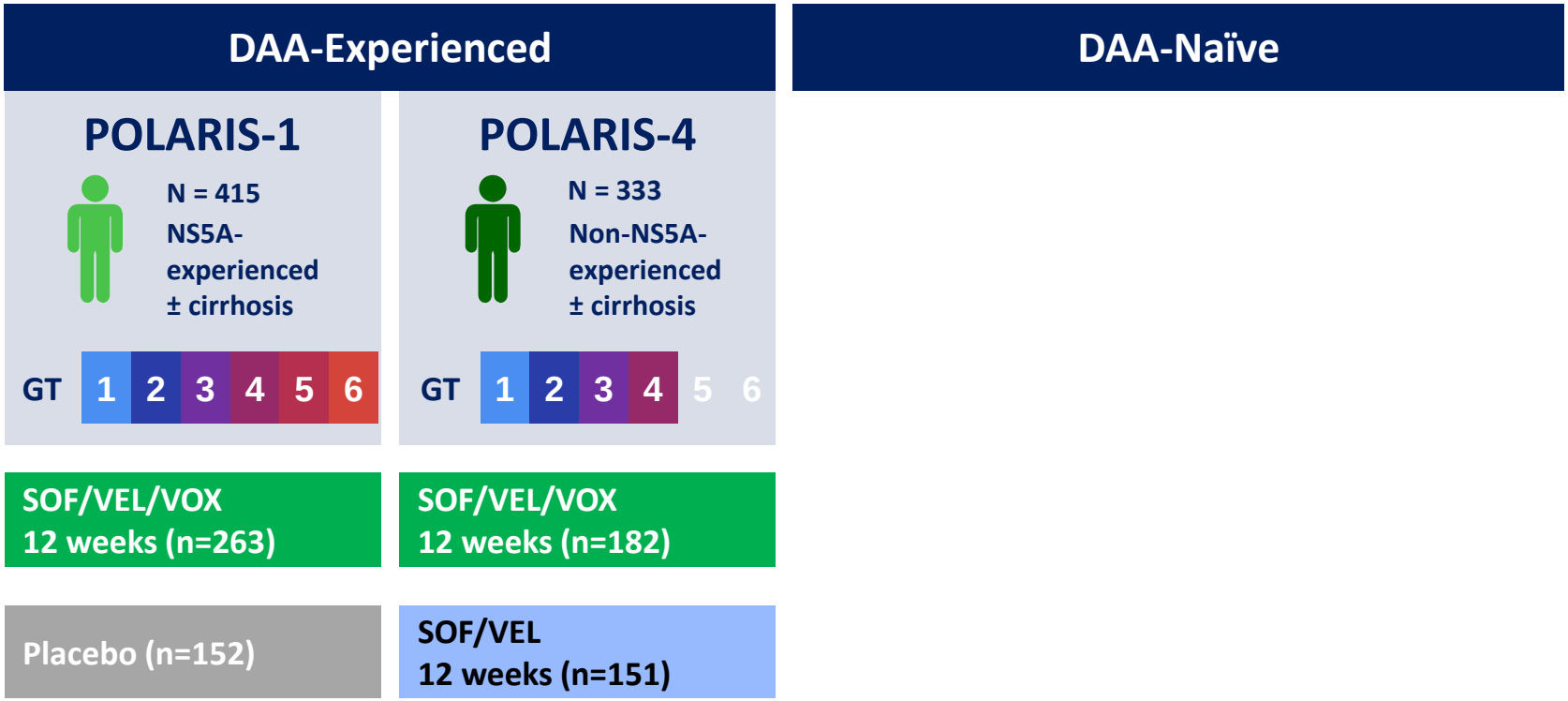
POLARIS-1: SOF/VEL/VOX for 12 Weeks in NS5A Inhibitor-Experienced HCV GT 1–6



Bourliere M, AASLD 2016, Oral 194

POLARIS Trials



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Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

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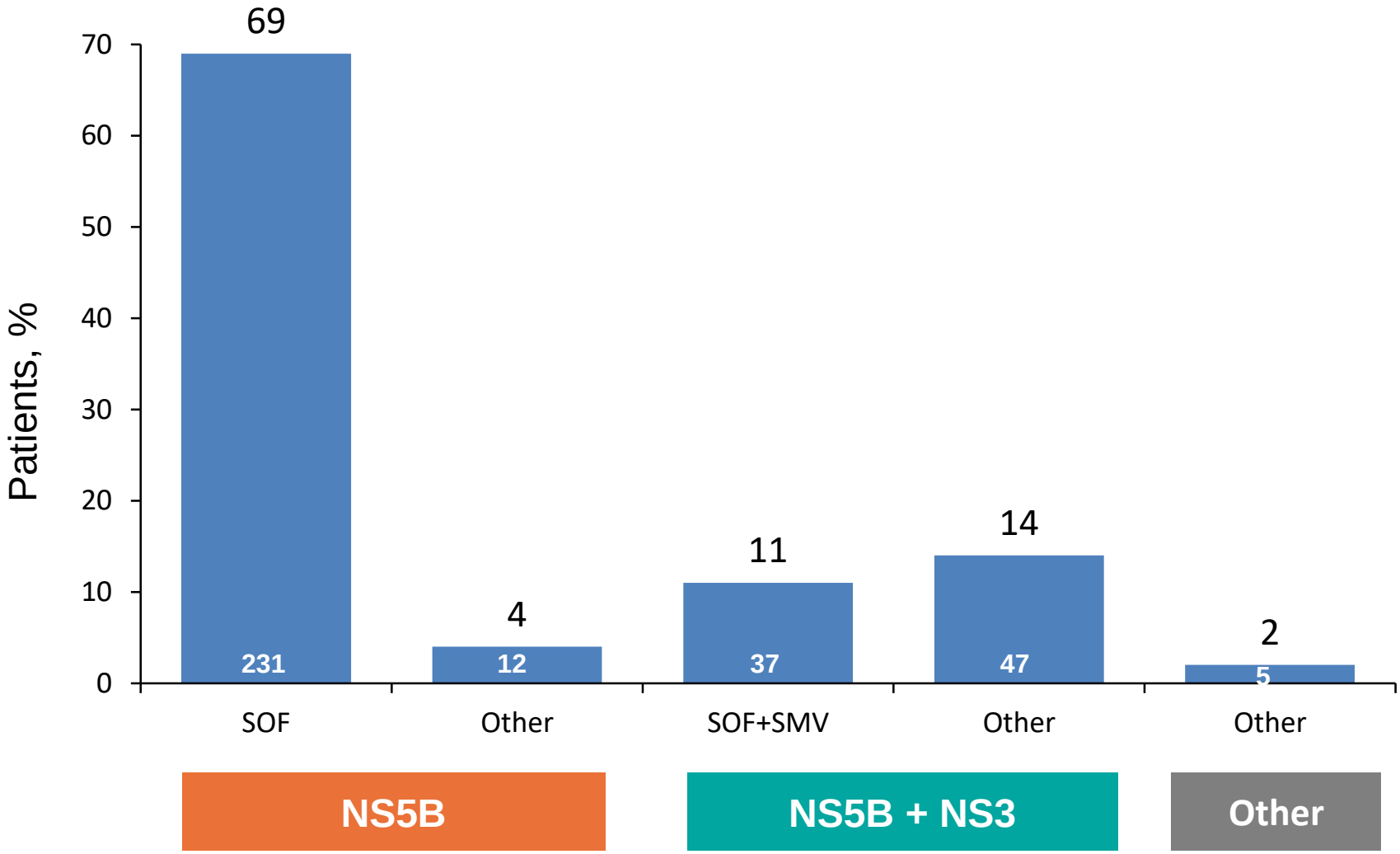
POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4



Other NS5B included mericitabine (n=7); other NS5B+NS3 included deleobuvir+faldaprevir (n=14), mercitabine+danoprevir (n=8), and SOF+telaprevir (n=6); one patient without prior DAA exposure is excluded; SMV, simeprevir; SOF, sofosbuvir.

Zeuzem S, AASLD 2016, Oral 109.

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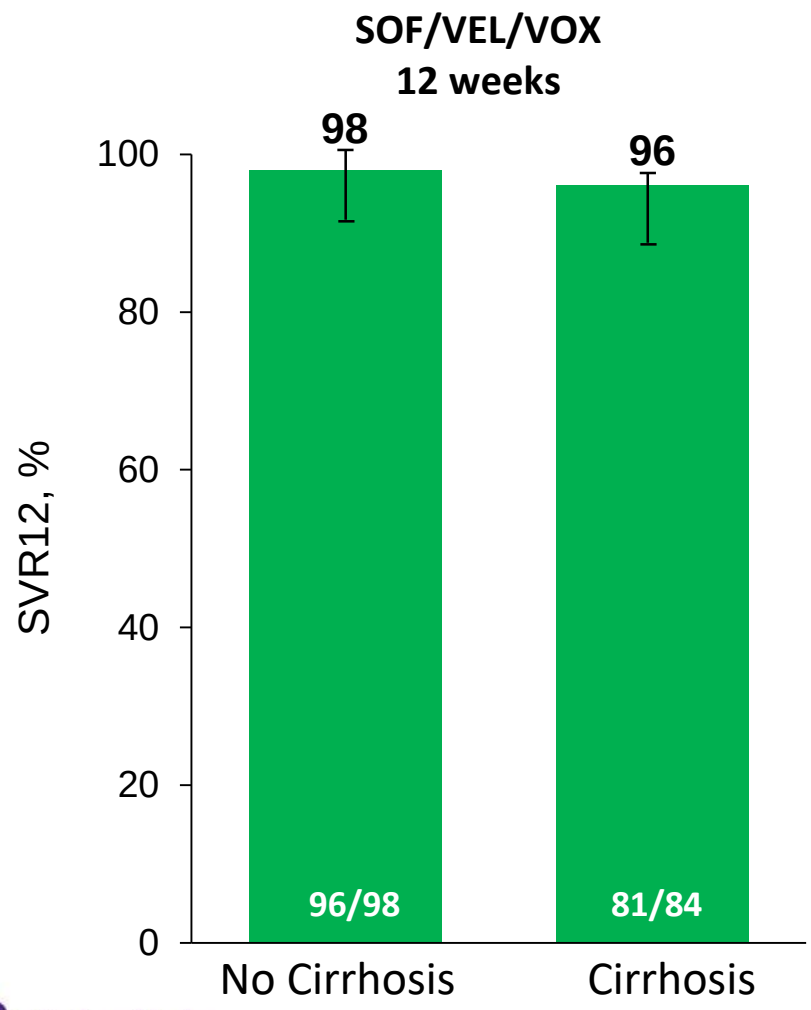
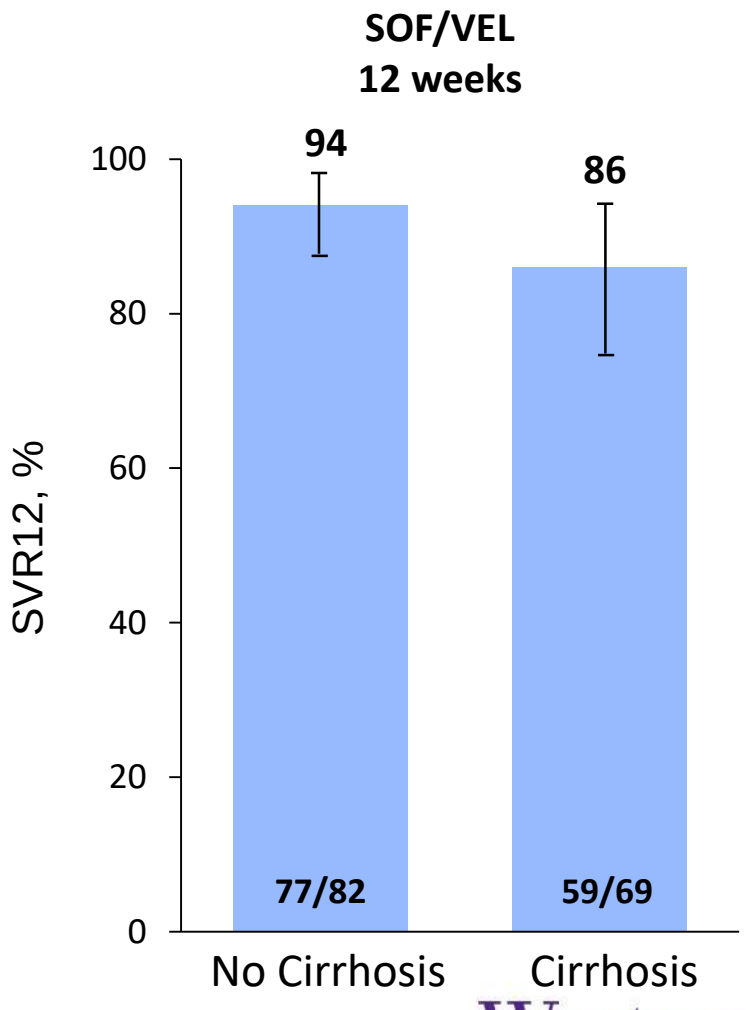
POLARIS-4: SOF/VEL/VOX or SOF/VEL for 12 Weeks in Non-NS5A Inhibitor DAA-Experienced HCV GT 1–4

SVR12 Results by Cirrhosis Status





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Zeuzem S, AASLD 2016, Oral 109

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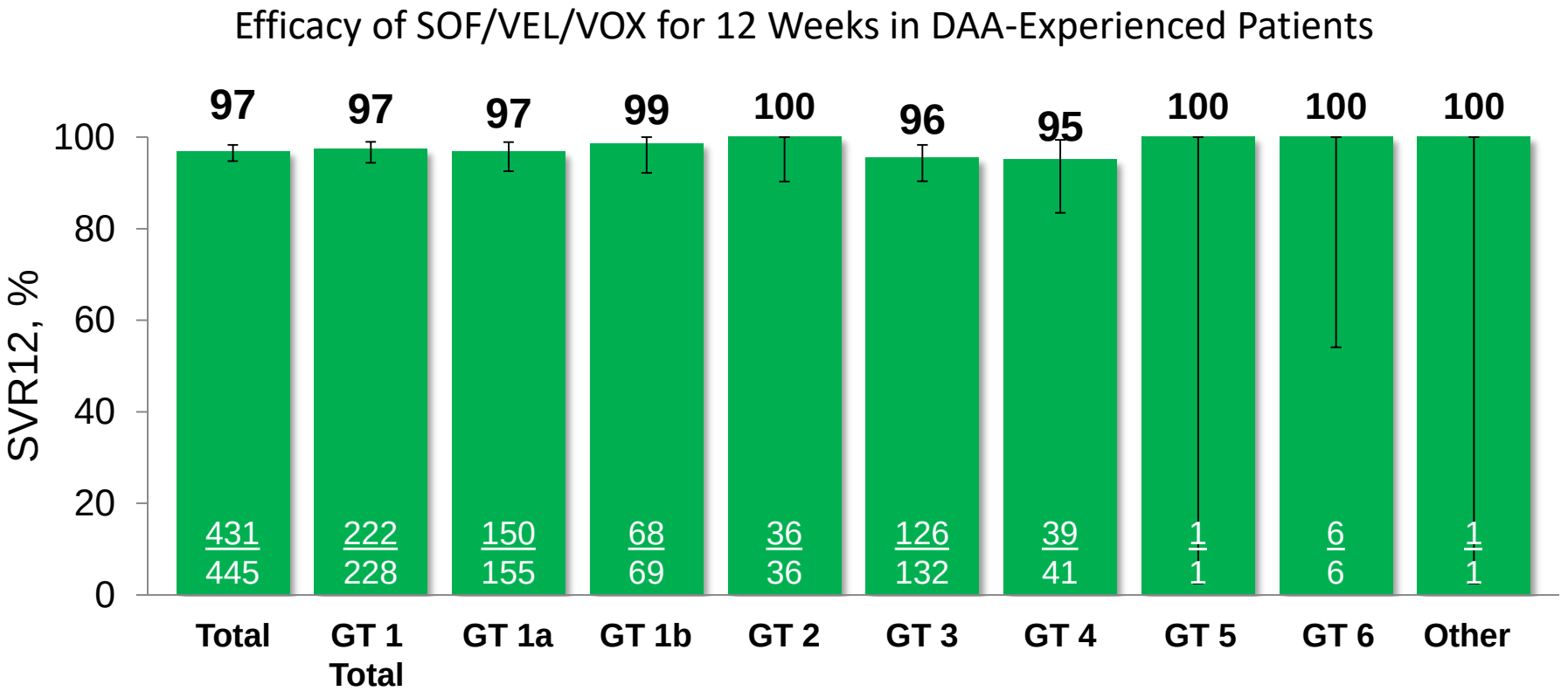
Integrated Efficacy Analysis of POLARIS-1 and -4



Breakthrough	1*	1	1	0	0	0	0	0	0	0
Relapse	7	2	2	0	0	4	1	0	0	0
Other	6	3	2	1	0	2	1	0	0	0

The SVR12 rate was 97% (431/445) in DAA-experienced patients treated with SOF/VEL/VOX for 12 weeks; Rates were similar regardless of genotype

Roberts, EASL 2017, SAT-280

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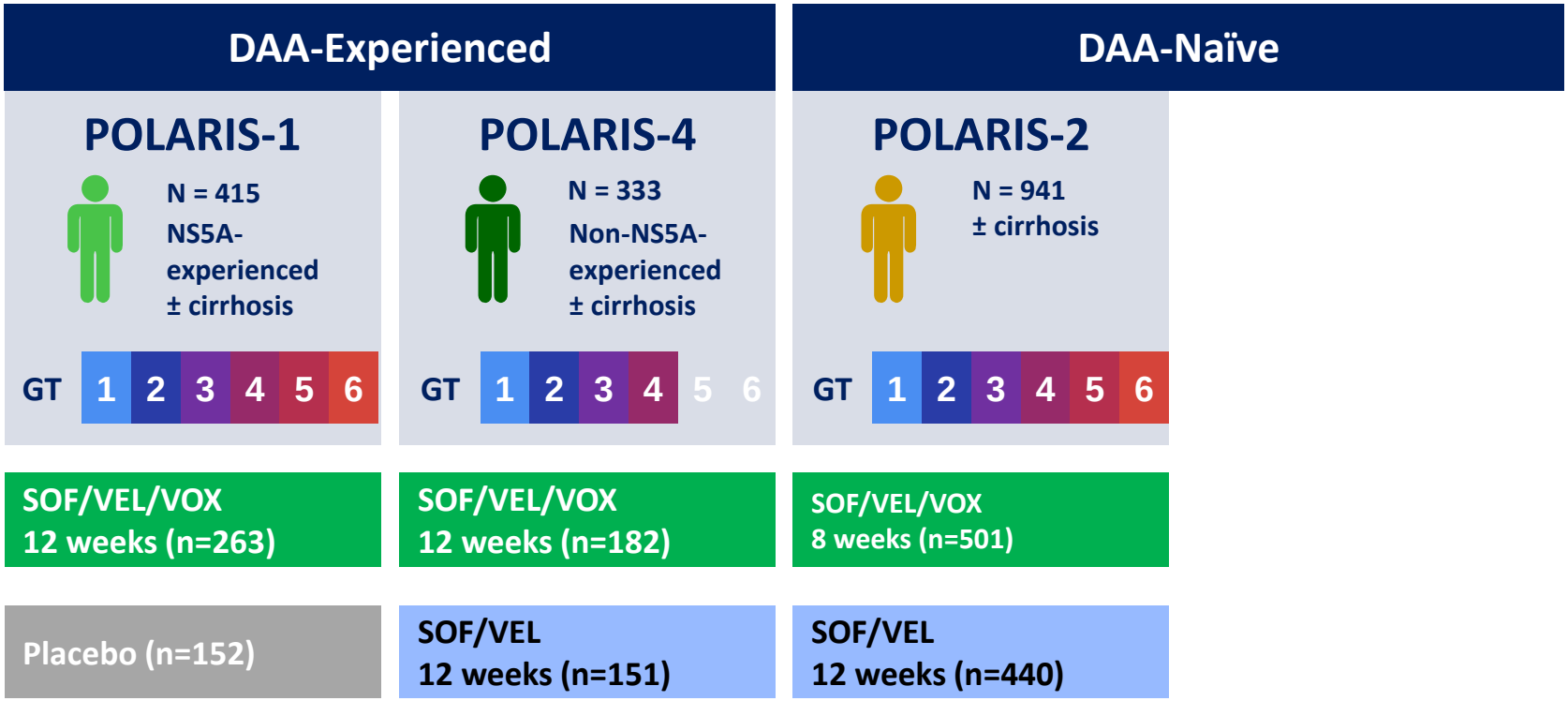
Western

POLARIS Trials



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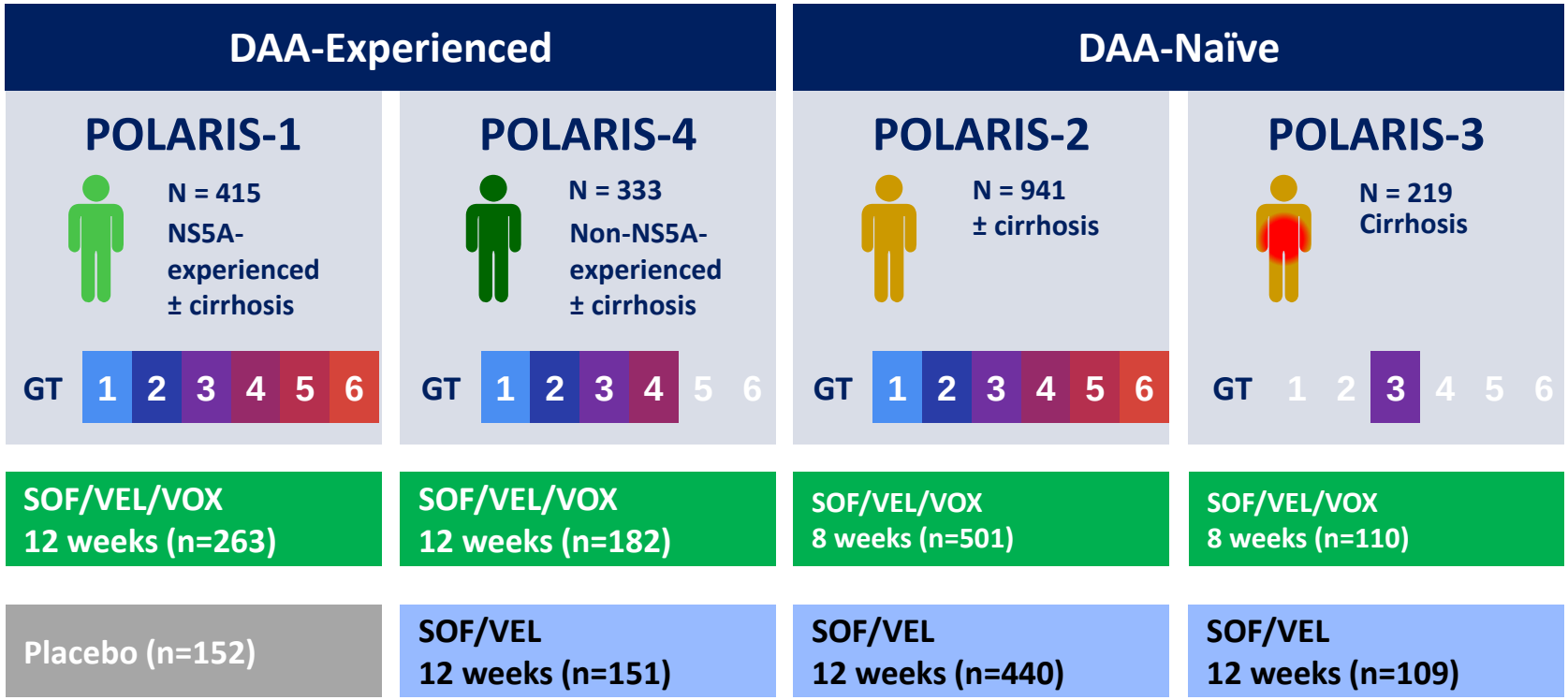
Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

Western

POLARIS Trials



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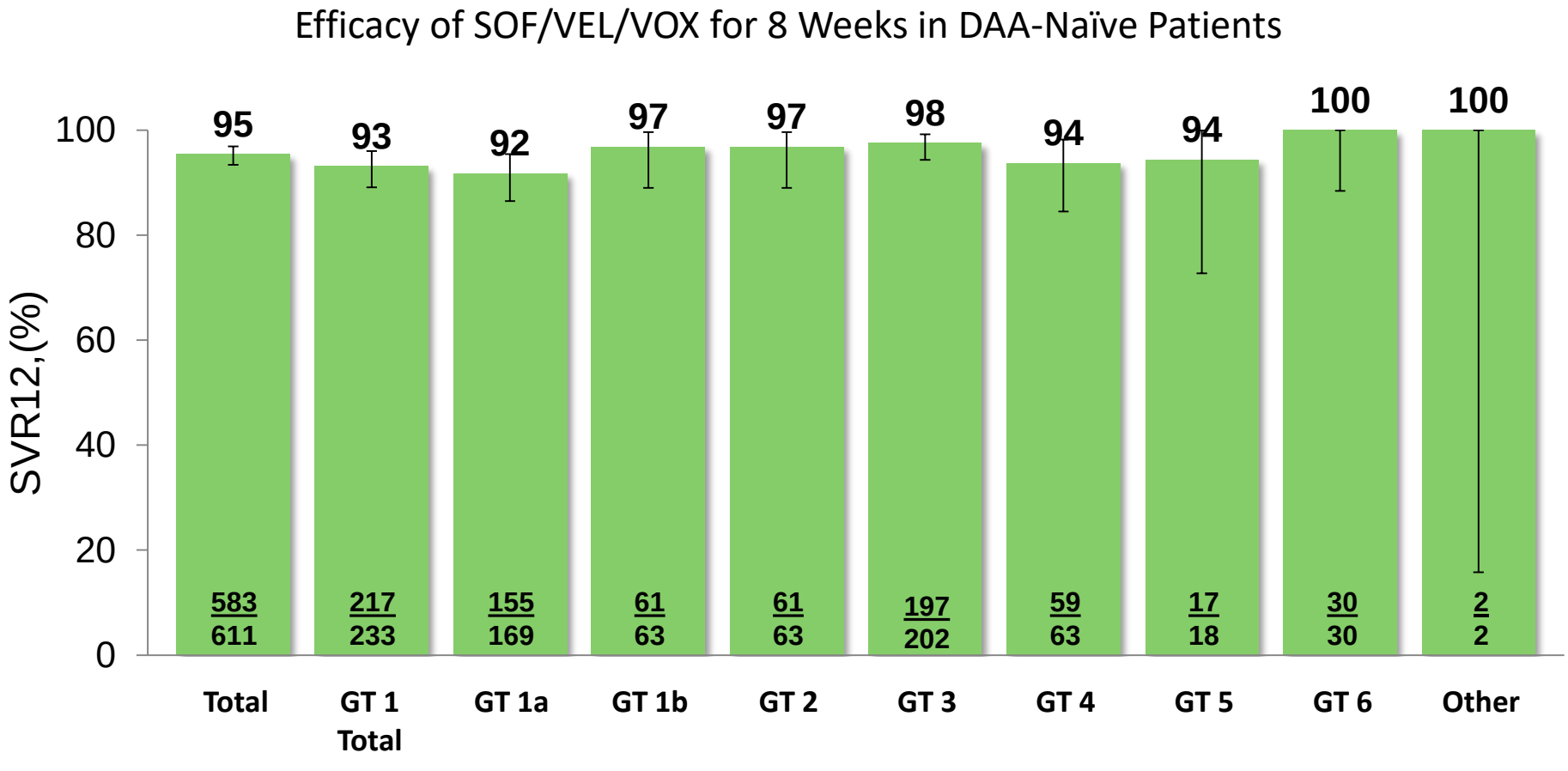
Bourliere M, AASLD 2016, Oral 194. Zeuzem S, AASLD 2016, Oral 109. Jacobson IM, AASLD 2016, Oral LB-12. Foster GR, AASLD 2016, Oral 258

Western

Integrated Efficacy Analysis of POLARIS-2 and 3



	Total	GT 1 Total	GT 1a	GT 1b	GT 2	GT 3	GT 4	GT 5	GT 6	Other
Breakthrough	0	0	0	0	0	0	0	0	0	0
Relapse	23	16	14	2	2	2	2	1	0	0
Other	5	0	0	0	0	3	2	0	0	0

97% SVR (427/441) in DAA-naïve GT 1b, 2–6 patients treated with SOF/VEL/VOX for 8 weeks. Lower SVR in patients with HCV GT 1a infection.

Roberts, EASL 2017, SAT-280

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