HCV Care- Engaging the Infectious Diseases Community

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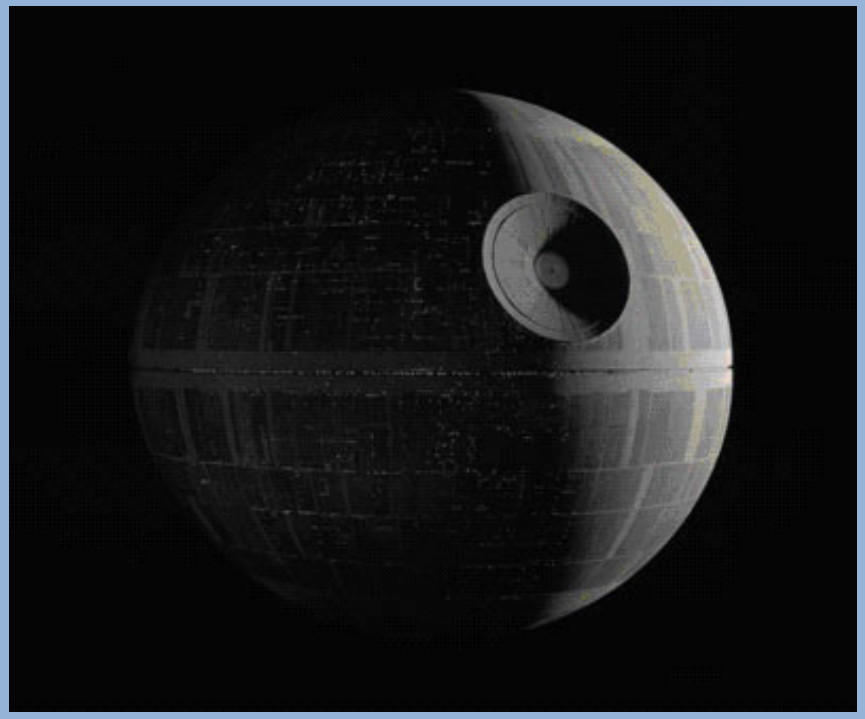
Disclosures

- Industry
  - Investigator: Merck, GS, ABV
  - Consultant/Advisor: Merck, GS, ABV
  - Speaker: Merck, ABV, GS
- Government
  - OHTN
  - CIHR
  - Health Canada
  - Ontario MOH
  - Ministerial Council

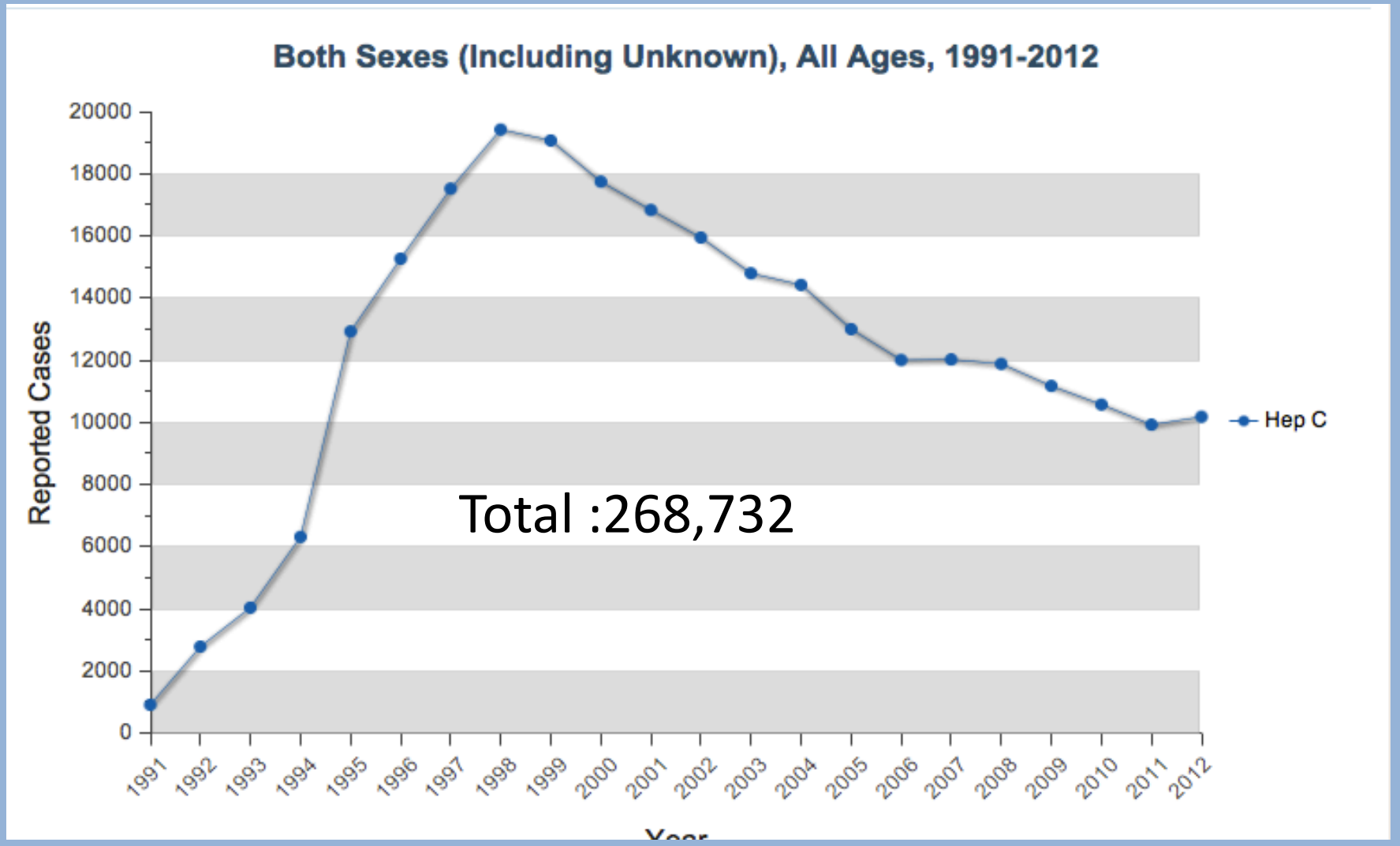


Objectives

- Epidemiology of HCV in Canada
- HCV Treatment Options
- Pediatrics
- Role of Infectious Diseases

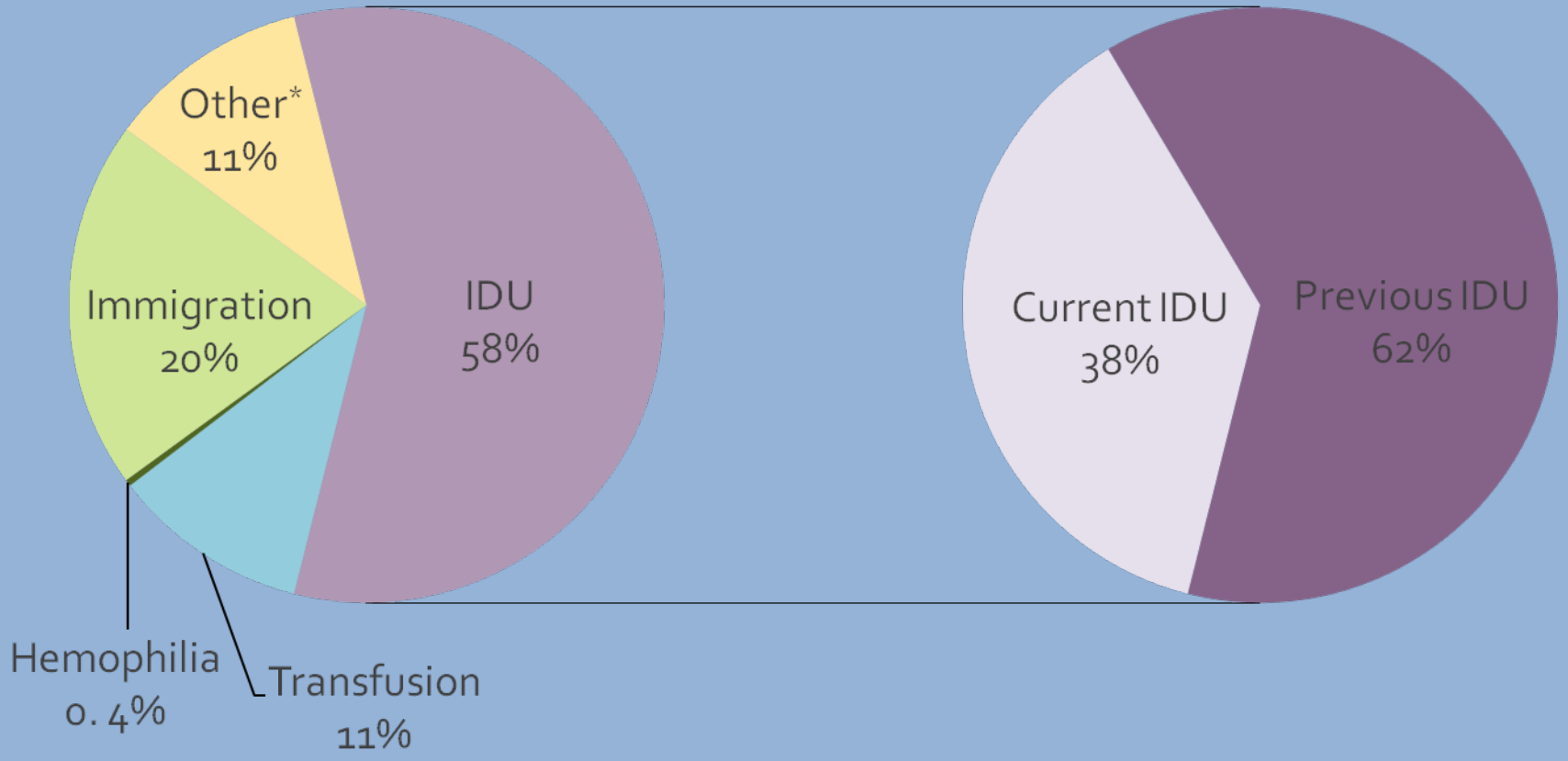
Epidemiology

Cases of HCV in Canada



Source: Public Health Agency of Canada (for details see full publication)

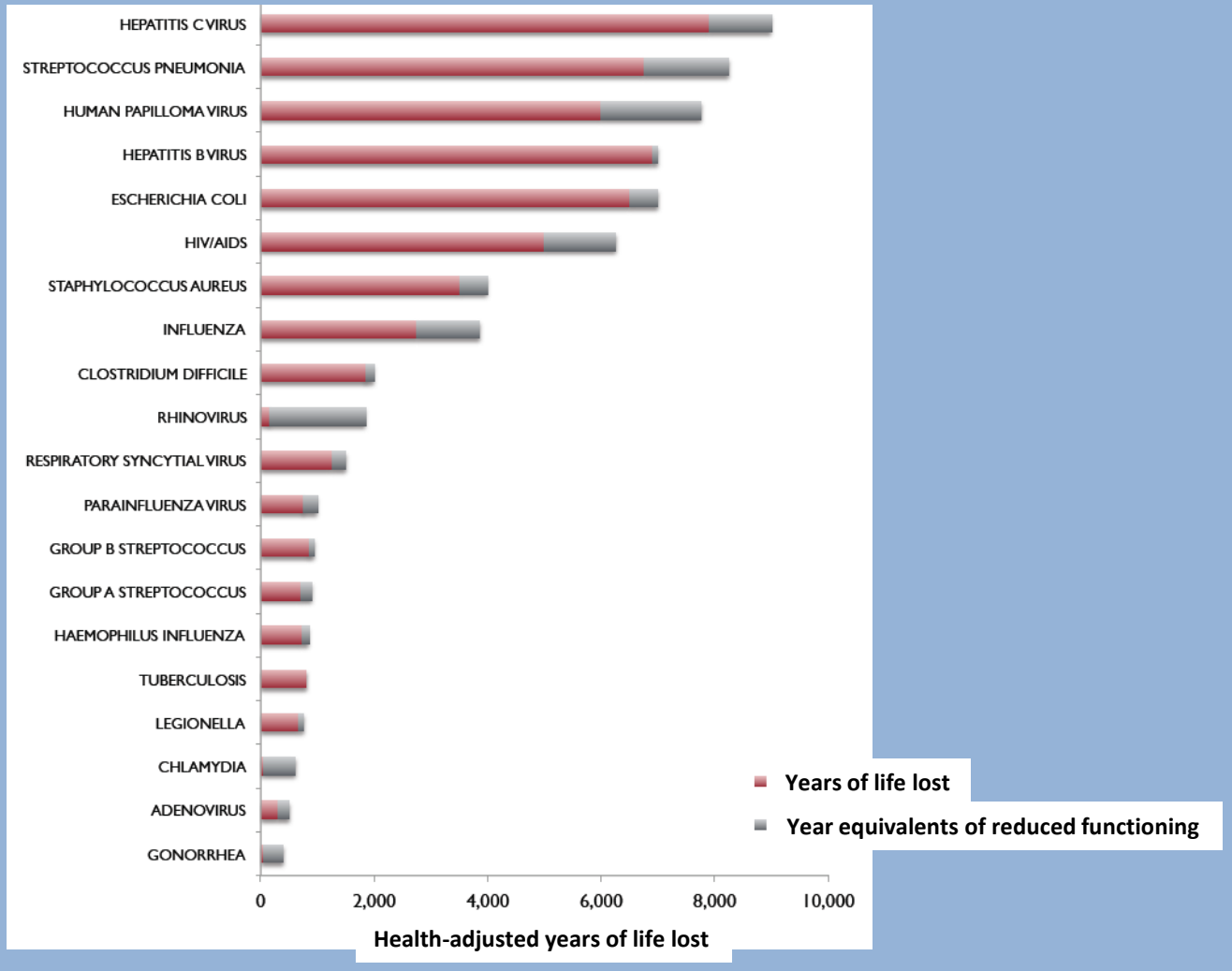
HCV Prevalence in Canada According to Exposure



*Other modes of transmission include sexual, occupational, nosocomial and vertical transmission.
IDU: injection drug use.

1. Remis RS. Final Report. Public Health Agency of Canada. 2007. Available from: http://www.phac-aspc.gc.ca/sti-its-surv-epi/model/pdf/model07-eng.pdf.

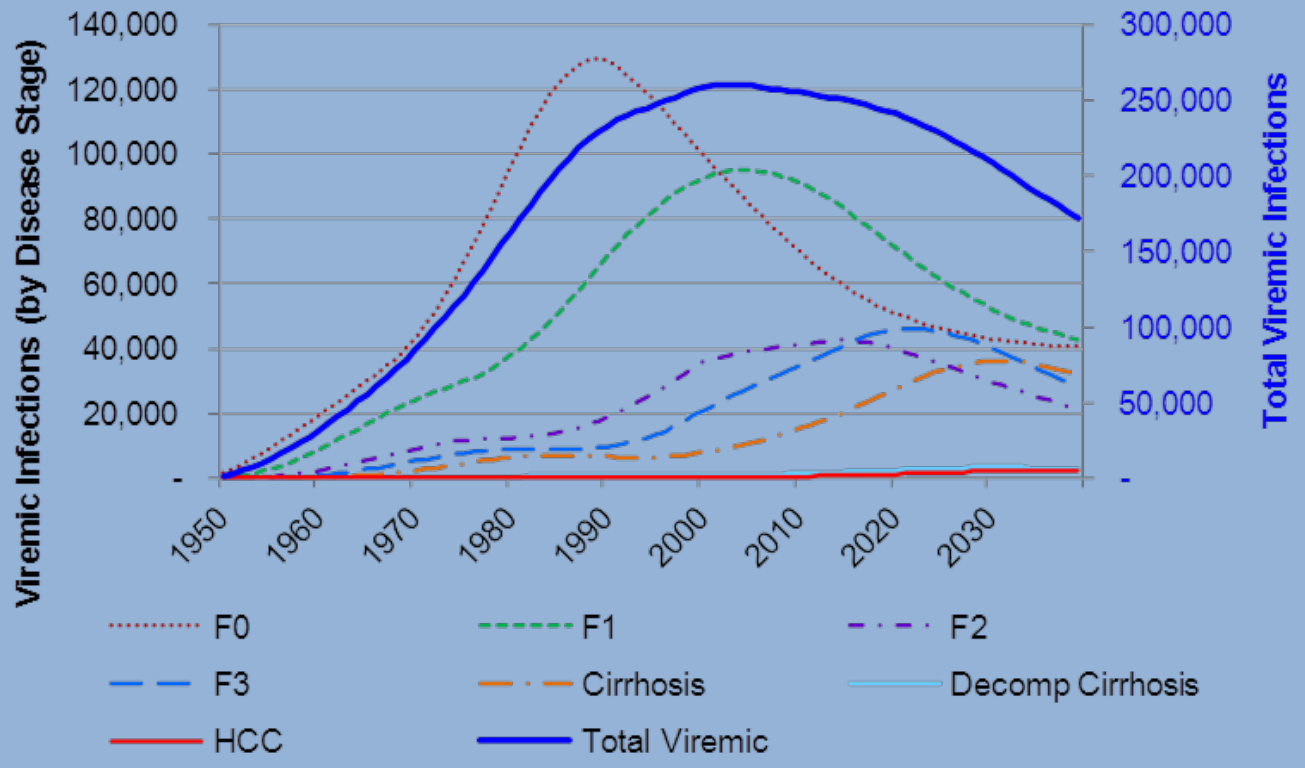
Impact of the top 20 pathogens in health-adjusted life years in Ontario



Source: Kwong et al. Ontario Burden of Infectious Disease Study 2010
http://www.ices.on.ca/file/ONBOIDS_FullReport_intra.pdf

HCV Burden of Disease in Canada:

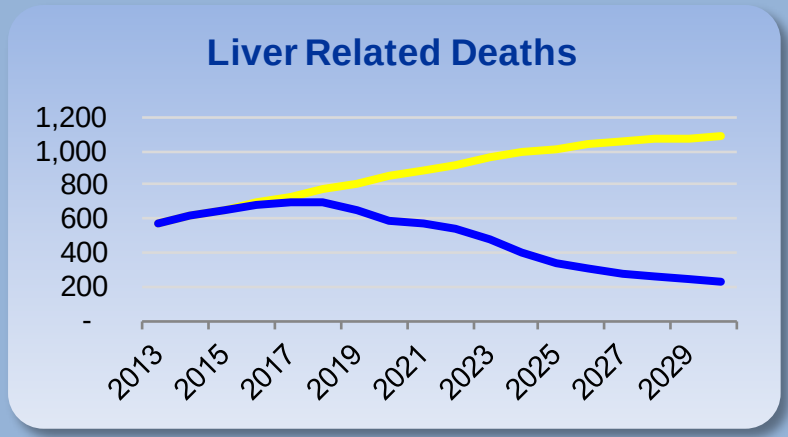
Significant Increase in Medical Burden Due to Continued Progression of Liver Deterioration

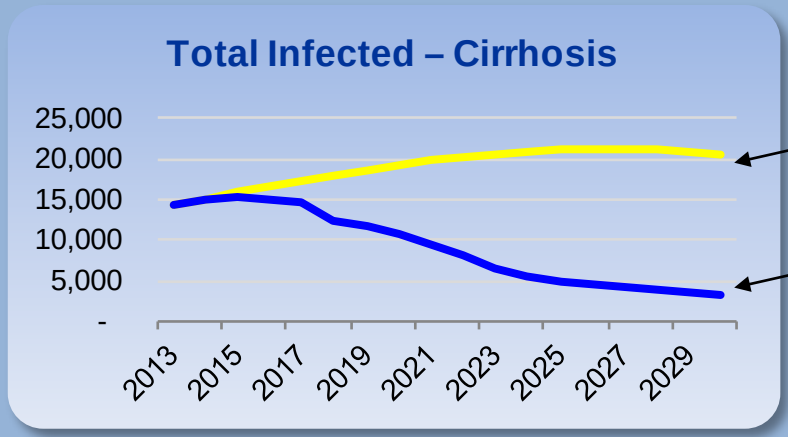


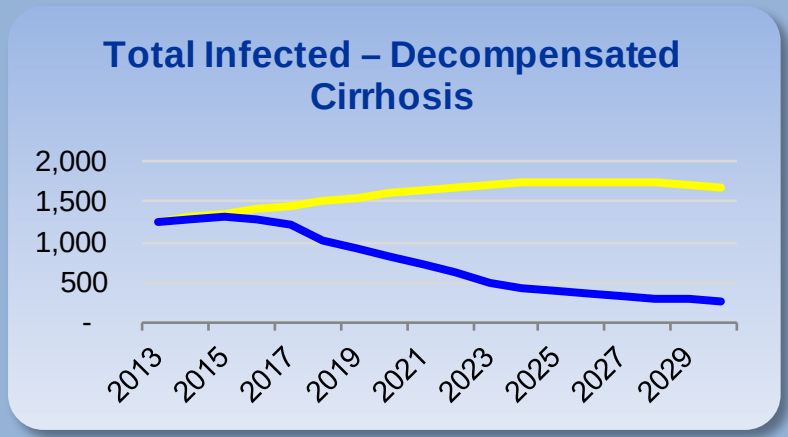
- ***Cirrhosis (+89%)***
- ***Hepatocellular carcinoma (+160%)***
- ***Decompensated Liver Disease (+80%)***
- ***Liver transplantation (+205%)***

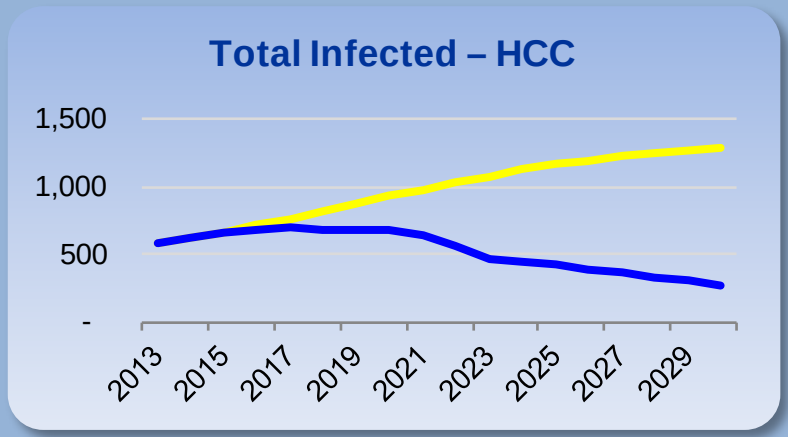
Source of graph data: Robert P. Myers, MD, et al. BURDEN OF DISEASE AND COST OF CHRONIC HEPATITIS C VIRUS INFECTION IN CANADA. Canadian Journal of Gastroenterology May 2014, Volume 28 Issue 5: 243-250.

New therapies can allow us to control the disease burden of HCV



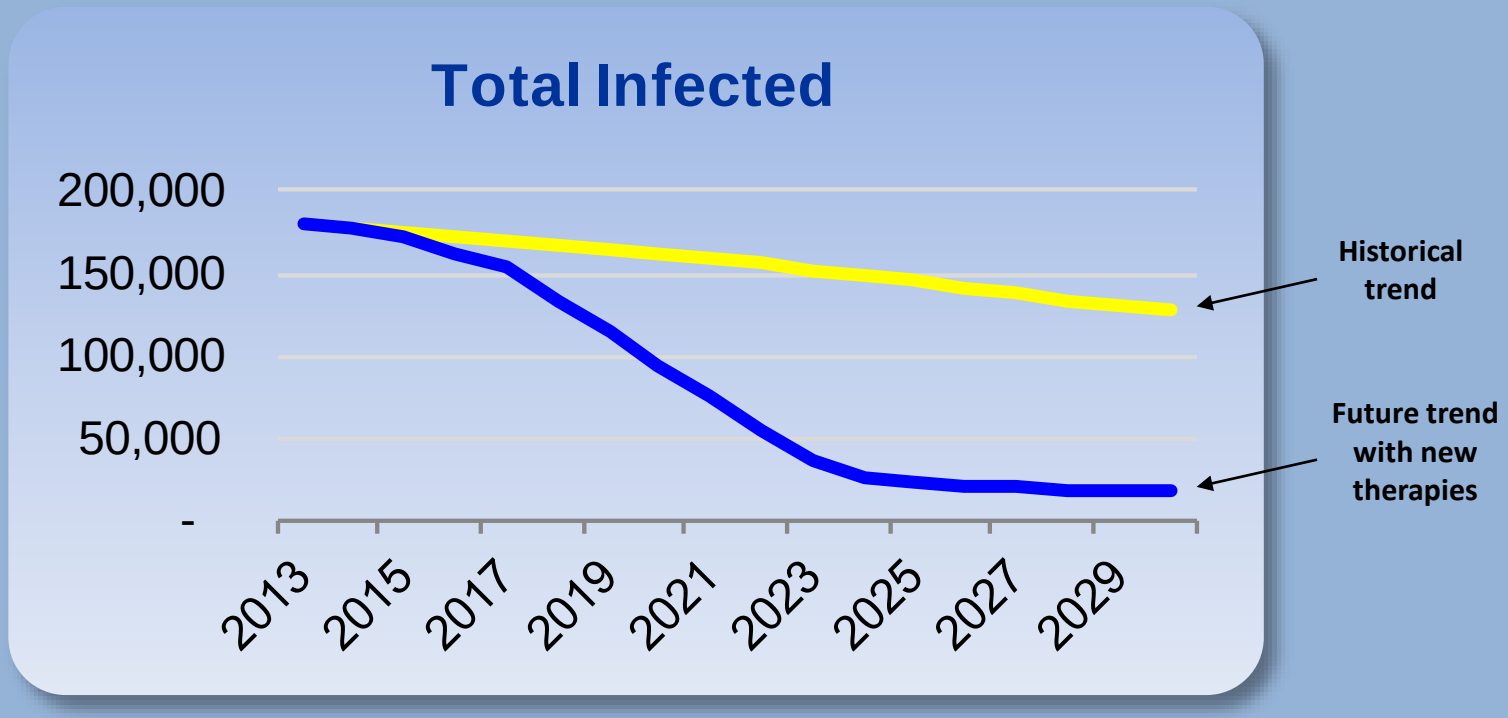






Assumed higher treatment and cure rate (85-90%).

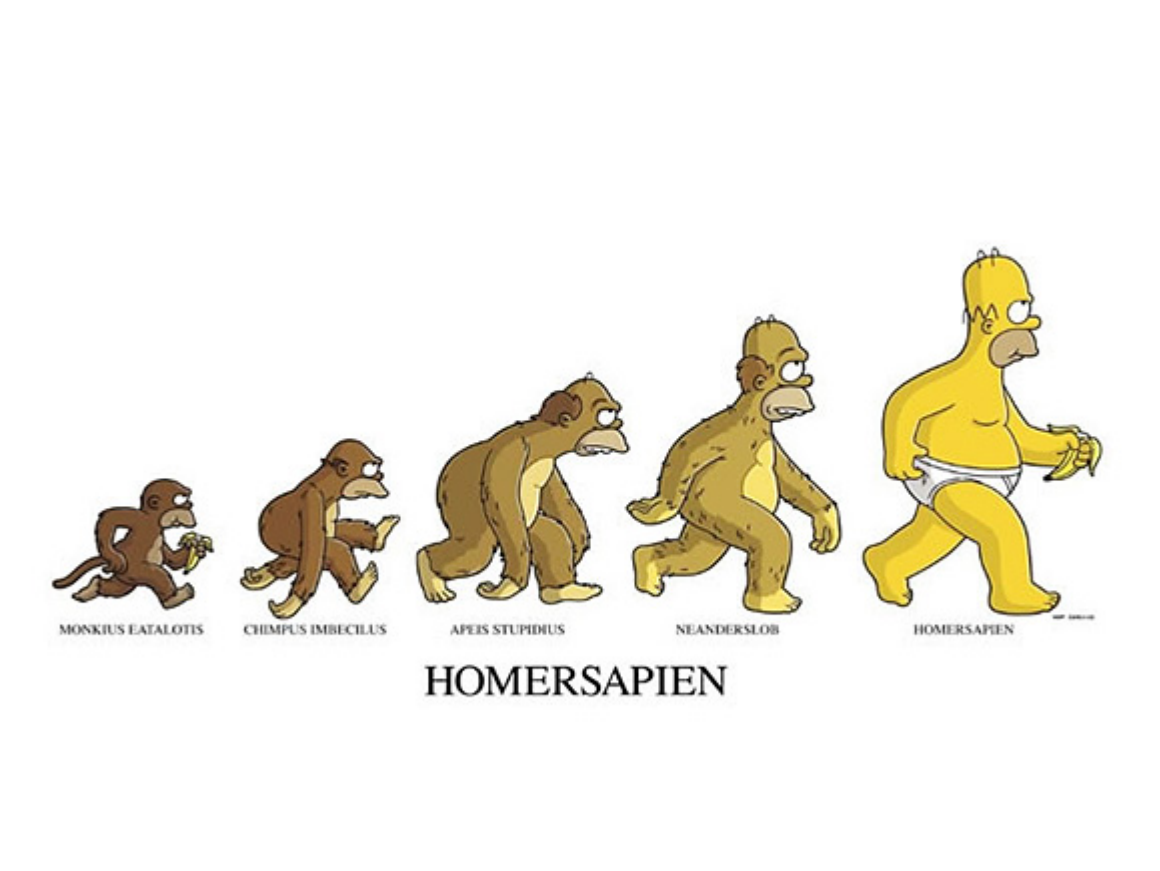
Eliminate HCV infections in Canada by 2025



Canadian Screening Policy

Canadian Task Force on Preventative Health Care

HCV Treatment Options



Reimbursement Criteria

- For treatment naïve or experienced adult patients with CHC infection who meet the following:
  - Tx prescribed by a Hepatologist, GI, or ID Specialist (or other physician experienced in treating patients with CHC)
  - Laboratory confirmed HCV Genotype
  - Two lab confirmed quantitative HCV RNA values taken at least 6 months while the first level may be at the time of the initial dx
  - F2 or greater (METAVIR scale or equivalent) OR <F2 with special criteria

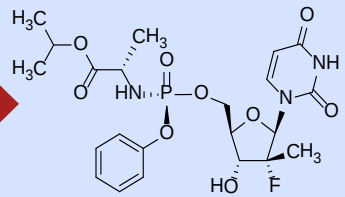
Criteria

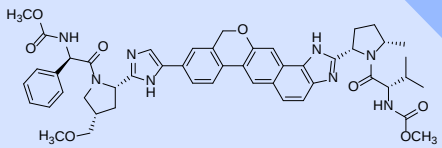
- <F2 and at least one of the following:
  - HIV or HBV co-infection
  - Co-existent liver disease with diagnostic evidence of FLD
  - Post organ transplant (liver or other)
  - Extrahepatic manifestations
  - CKD Stage 3,4,5 as defined by NKFKD outcomes Quality Initiative
  - Diabetes on tx
  - WOCB age planning pregnancy with the next 12 months

Key Direct Acting Antivirals

Sofosbuvir/Velpatasvir

SOF
Nucleotide NS5B polymerase inhibitor





VEL
NS5A inhibitor

SOF

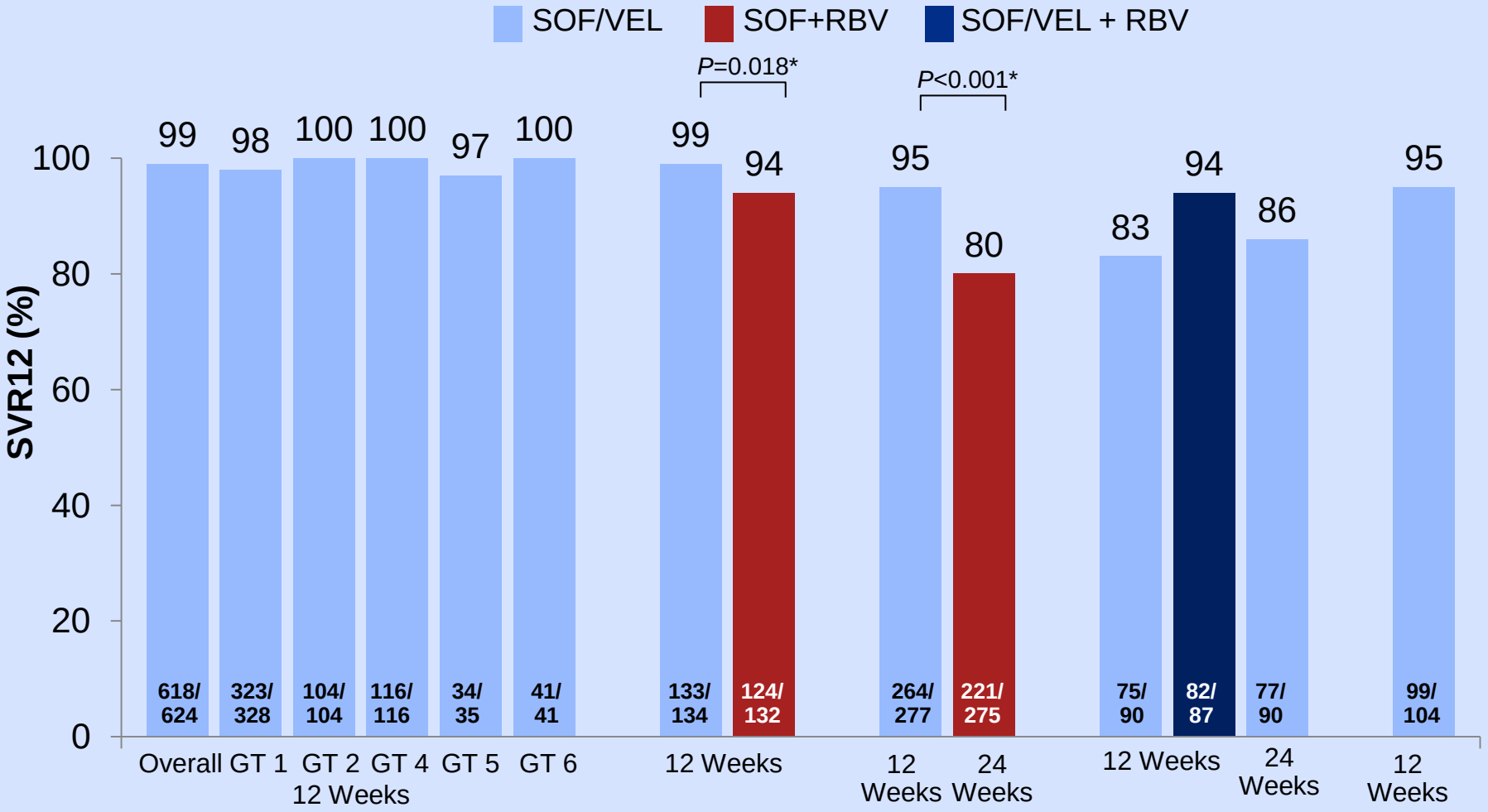
VEL

- **Sofosbuvir (SOF)[1,2]**
  - Potent antiviral activity against HCV GT 1–6
  - Once-daily, oral, 400-mg tablet
- **Velpatasvir (VEL; GS-5816)[3-5]**
  - Picomolar EC_{50} against GT 1–6
  - 2nd-generation NS5A inhibitor with improved resistance profile
  - Long half-life of ~13-23 h supports once-daily dosing
  - No food effect
- **SOF/VEL Single Tablet Regimen (STR)**
  - Once daily, oral, STR (400/100 mg)

MAA, marketing authorization application

1. Jacobson IM, et al. N Engl J Med 2013;368:1867-77; 2. Lawitz E, et al. N Engl J Med 2013;368:1878-87; 3. Cheng G, et al. EASL 2013, poster 1191; 4. German P, et al. EASL 2013, poster 1195; 5. Lawitz E, et al. AASLD 2013, poster 1082.

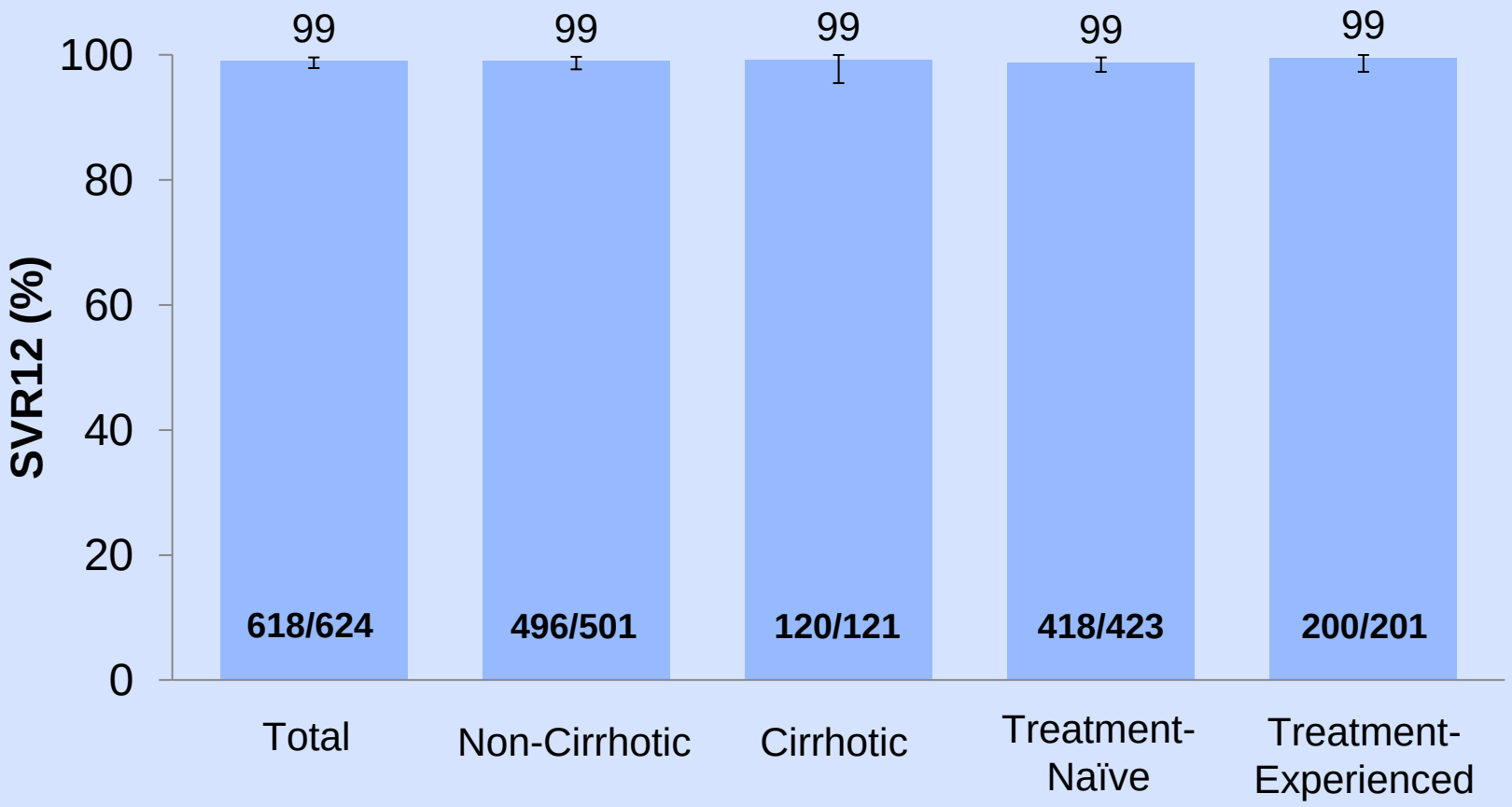
Efficacy Summary (ITT Analysis)



*P-value for superiority of SOF/VEL compared with SOF+RBV.

Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512610; Sulkowski, AASLD, 2015, 205. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612; Mangia, AASLD, 2015, 249; Charlton, AASLD, 2015, LB-13. Curry MP, et al. *New Engl J Med*.2015. DOI: 10.1056/NEJMoa1512614

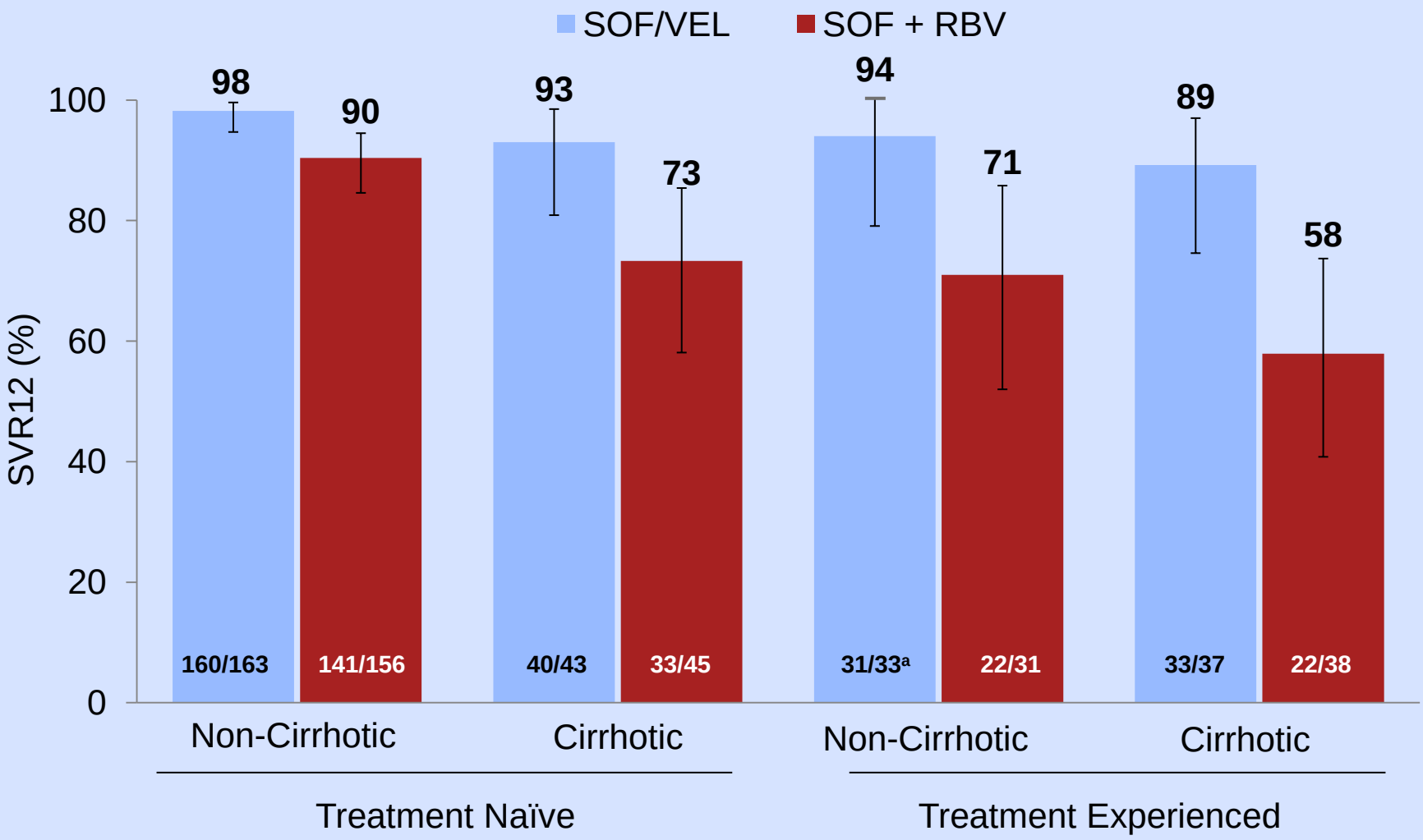
SVR12 by Cirrhosis Status or Treatment History



Error bars represent 95% confidence intervals.

Feld, AASLD, 2015, LB-2. Feld JJ, et al. *N Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512610

SVR12 by Cirrhosis Status and Treatment History

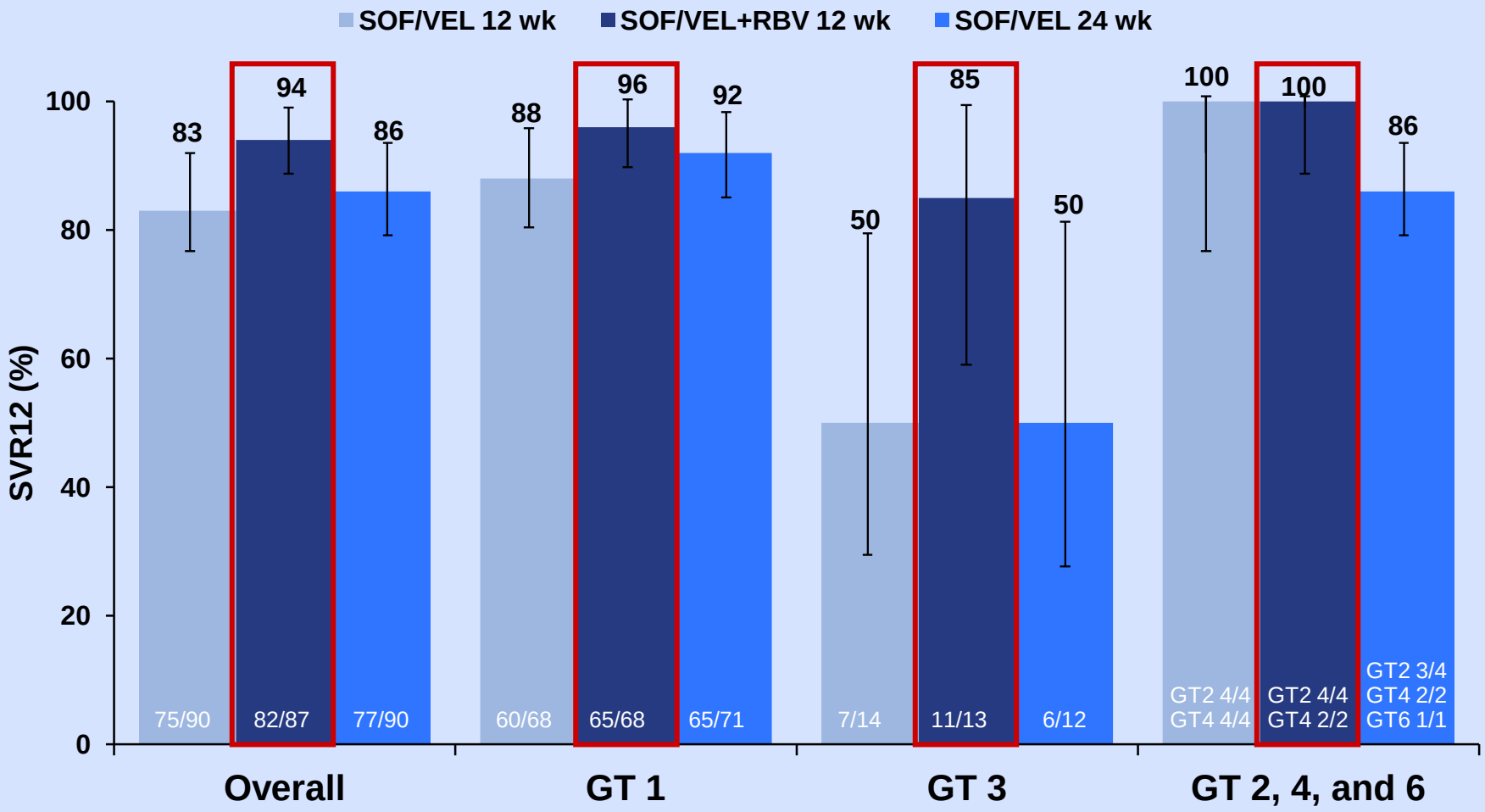


[a] One treatment experienced subject without cirrhosis treated with SOF/VEL had GT1a HCV infection at failure indicating HCV re-infection and is therefore excluded from this analysis

Mangia, AASLD, 2015, 249. Foster GR, et al. *New Engl J Med*. 2015. DOI: 10.1056/NEJMoa1512612; EPCLUSA® Prescribing Information. Gilead Sciences, Inc. June 2016

‡

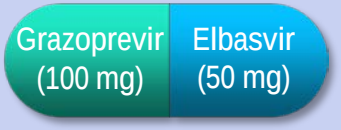
SVR12



SOF/VEL + RBV resulted in highest SVR12 in patients with decompensated liver disease

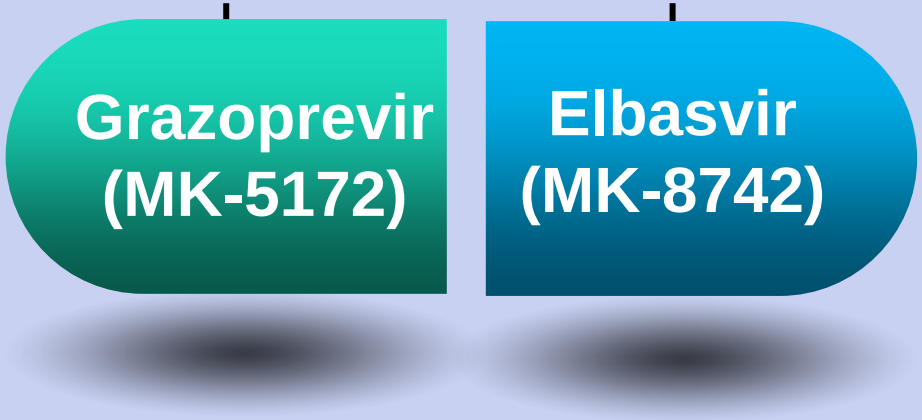
*Patient with nondetectable drug levels at time of virologic failure.

Charlton M, et al., AASLD, 2015, #LB-13



- HCV NS3/4A inhibitor
- 100 mg once-daily, oral

- HCV NS5A inhibitor
- 50 mg, once-daily, oral

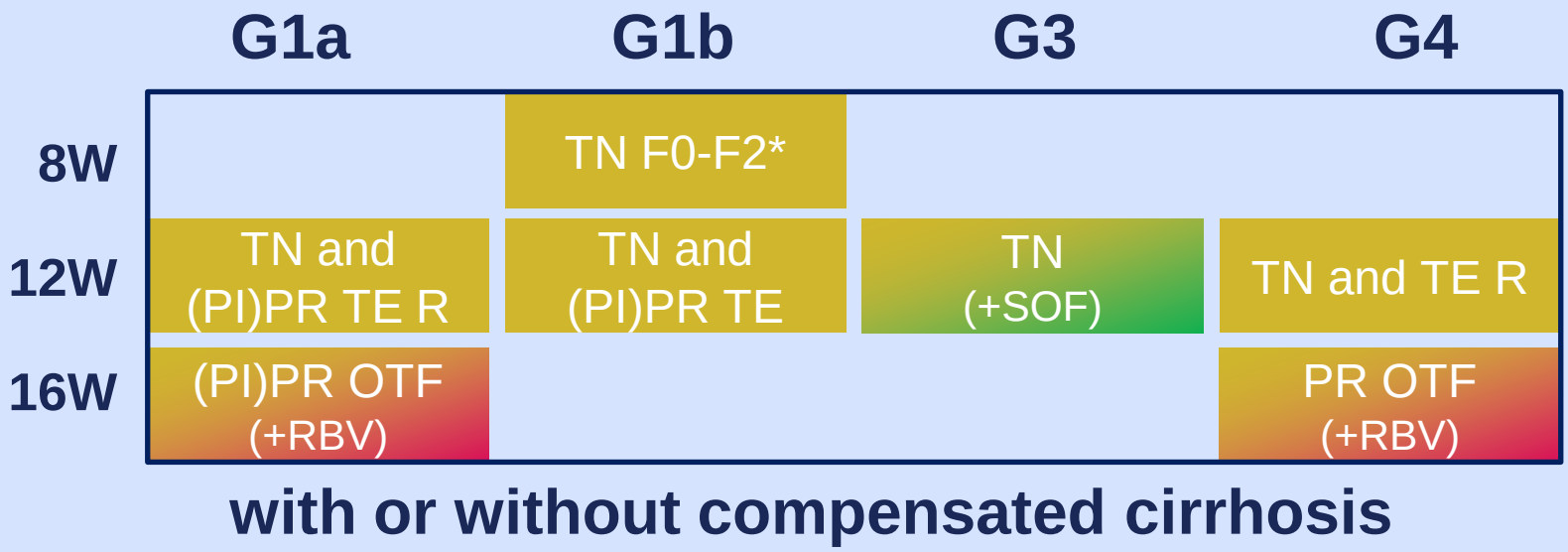


- Fixed-dose combination tablet
- Broad activity against most HCV genotypes *in vitro*[1-3]
- Efficacious in treatment-naive & treatment-experienced cirrhotic and non-cirrhotic patients with HCV, and in HIV/HCV co-infected patients (C-WORTHy)[4,5]

1. Summa V, et al. Antimicrobial Agent Chemother 2012:56;4161-67
2. Coburn CA,, et al. ChemMedChem 2013; 8: 1930–40
3. Harper S, et al. ACS Med Chem Lett. 2012 Mar 2;3(4):332-6.
4. Lawitz et al. Lancet 2015; 385:1075
5. Sulkowski et al. Lancet 2015; 385:1087

EBR/GZR Treatment Algorithm

- Indicated for the treatment of chronic hepatitis C (CHC) genotypes 1, 3, or 4 infection in adults



* 8 weeks may be considered
TN = Treatment Naive
TE = Treatment Experienced
R = Relapser
OTF = On-treatment virologic failure
PR = PegIFN-RBV
PI = 1st generation PI (BOC, TVR, SMV)
RBV = Ribavirin
SOF = Sofosbuvir

MK2 Phase 2b and 3 Program

Study	GT	Sample Size	Cirrhosis	Tx History	Co-Morbidity	Regimen (Weeks)
C-EDGE TN	1, 4, 6	421	± Cirrhosis	TN		12, no RBV
C-EDGE TE	1, 4, 6	420	± Cirrhosis	PR-PTF	±HIV	12 or 16, ±RBV
C-Salvage	1	79	± Cirrhosis	PI/PR-PTF		12, + RBV
C-SURFER	1	237	± Cirrhosis	TN/PR-PTF	CKD 4-5	12, no RBV
C-WORTHY G1	1b	61	No Cirrhosis	TN		8 ±RBV
C-EDGE CO-INFXN	1, 4, 6	218	± Cirrhosis	TN	HIV	12, no RBV
C-SWIFT	3	41	± Cirrhosis	TN		8 or 12 + SOF
C-WORTHY G3	3	41	No Cirrhosis	TN		12 or 18 + RBV
C-EDGE CO-STAR	1, 4, 6	300	± Cirrhosis	TN	OST, ±HIV	12, no RBV
C-EDGE H2H	1	250	± Cirrhosis	TN/PR-PTF	±HIV	12, no RBV
C-EDGE InhBD	1, 4, 6	300	± Cirrhosis	TN/PR-PTF	InhBD	12, no RBV

TN: Treatment Naïve
PR-PTF: Failed Prior Peg-IFN/RBV
InhBD = Inherited Blood Disorders
CKD 4-5: Chronic Kidney Disease Grades 4-5 (incl. Hemodialysis)
OST = Opiate Substitution Therapy

Annals of Internal Medicine

ORIGINAL RESEARCH

Elbasvir–Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy

A Randomized Trial

Gregory J. Dore, MD; Frederick Altice, MD; Alain H. Litwin, MD; Olav Dalgard, MD; Edward J. Gane, MD; Oren Shibolet, MD; Anne Luetkemeyer, MD; Ronald Nahass, MD; Cheng-Yuan Peng, MD; Brian Conway, MD; Jason Grebely, PhD; Anita Y.M. Howe, PhD; Isaias N. Gendrano, MPH; Erluo Chen, MPH; Hsueh-Cheng Huang, PhD; Frank J. Dutko, PhD; David C. Nickle, PhD; Bach-Yen Nguyen, MD; Janice Wahl, MD; Eliav Barr, MD; Michael N. Robertson, MD; and Heather L. Platt, MD; on behalf of the C-EDGE CO-STAR Study Group*

Background: Hepatitis C virus (HCV) infection is common in persons who inject drugs (PWID).

Objective: To evaluate elbasvir–grazoprevir in treating HCV infection in PWID.

Design: Randomized, placebo-controlled, double-blind trial. (ClinicalTrials.gov: NCT02105688)

Setting: Australia, Canada, France, Germany, Israel, the Netherlands, New Zealand, Norway, Spain, Taiwan, the United Kingdom, and the United States.

Patients: 301 treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection who were at least 80% adherent to visits for opioid-agonist therapy (OAT).

Intervention: The immediate-treatment group (ITG) received elbasvir–grazoprevir for 12 weeks; the deferred-treatment group (DTG) received placebo for 12 weeks, no treatment for 4 weeks, then open-label elbasvir–grazoprevir for 12 weeks.

Measurements: The primary outcome was sustained virologic response at 12 weeks (SVR12), evaluated separately in the ITG and DTG. Other outcomes included SVR24, viral recurrence or reinfection, and adverse events.

Results: The SVR12 was 91.5% (95% CI, 86.8 to 95.0) in the ITG and 89.5% (95% CI, 81.5 to 94.8) in the active phase of the DTG. Drug use at baseline and during treatment did not affect SVR12 or adherence to HCV therapy. Among 18 patients with posttreatment viral recurrence through 24-week follow-up, 6 had probable reinfection. If the probable reinfections were assumed to be responses, SVR12 was 94.0% (CI, 89.8 to 96.9) in the ITG. One patient in the ITG (1 of 201) and 1 in the placebo-phase DTG (1 of 100) discontinued treatment because of an adverse event.

Limitation: These findings may not be generalizable to PWID who are not receiving OAT, nor do they apply to persons with genotype 3 infection, a common strain in PWID.

Conclusion: Patients with HCV infection who were receiving OAT and treated with elbasvir–grazoprevir had high rates of SVR12, regardless of ongoing drug use. These results support the removal of drug use as a barrier to interferon-free HCV treatment for patients receiving OAT.

Primary Funding Source: Merck & Co., Inc., Kenilworth, New Jersey, USA.

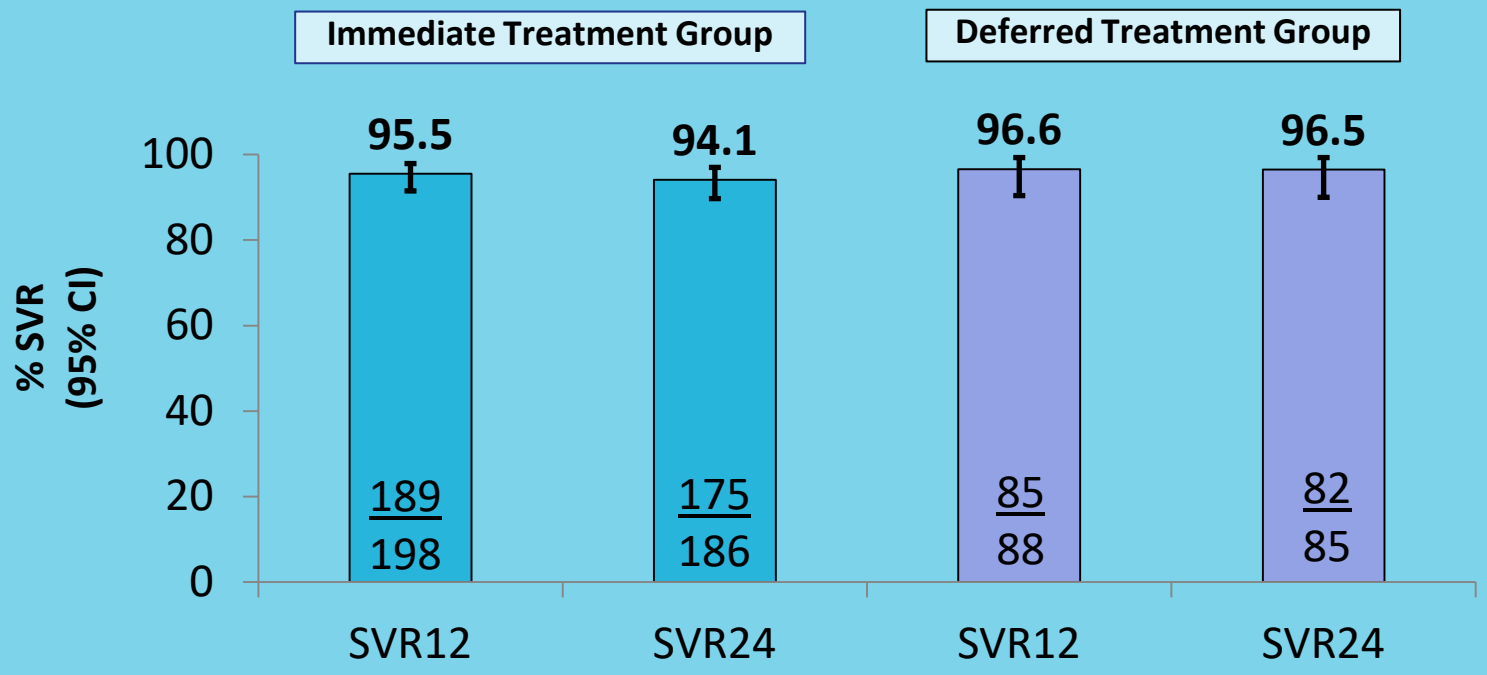
Ann Intern Med. doi:10.7326/M16-0816 www.annals.org

For author affiliations, see end of text.

This article was published at www.annals.org on 9 August 2016.

* For members of the C-EDGE CO-STAR (A Phase III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naive Subjects With Chronic HCV GT1, GT4, and GT6 Infection Who Are on Opioid Substitution Therapy) Study Group, see the Appendix (available at www.annals.org).

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



Reinfection – counted as success				
	5	**5**	**0**	**1**
Failures				
Relapse	**7**	**9**	**1**	**1**
Breakthrough	**0**	**0**	**2**	**2**
Discontinuation	**2**	**2**	**0**	**0**

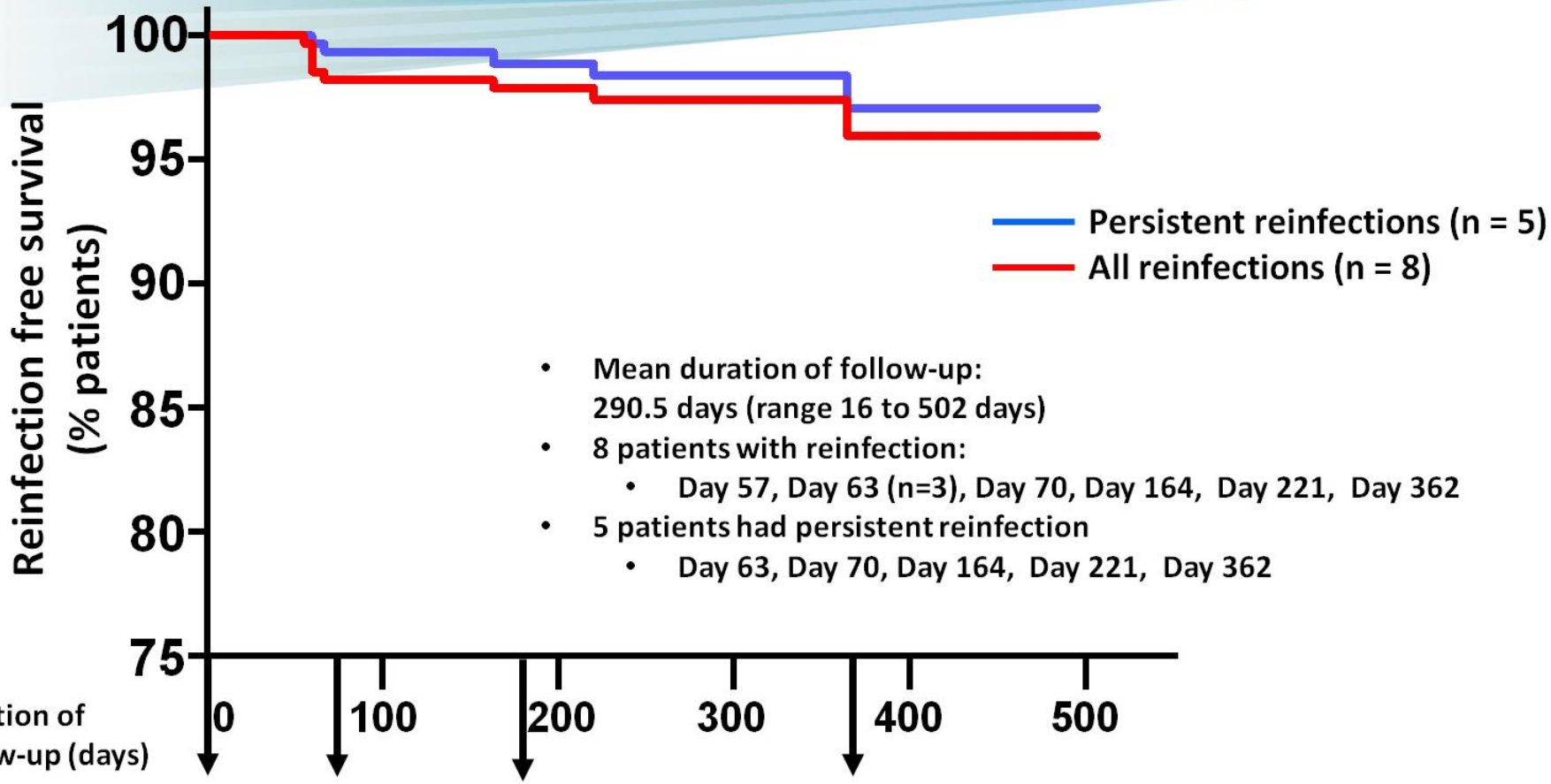
CI, confidence interval.

- In the mFAS, SVR was >94% at FW12 and 24 in both ITG and DTG
- In the FAS (where discontinuations were counted as failures), SVR12 was 91.5% in the ITG and 85.6% in the DTG, SVR24 was 89.5% in the ITG and 85.3% in the DTG.

Dore G.J. et al. EASL 2016. Barcelona, Spain. April 13-17, 2016. SAT-163.

C-EDGE CO-STAR

KAPLAN-MEIER CURVE OF TIME TO HCV REINFECTION



- Mean duration of follow-up: 290.5 days (range 16 to 502 days)
- 8 patients with reinfection:
  - Day 57, Day 63 (n=3), Day 70, Day 164, Day 221, Day 362
- 5 patients had persistent reinfection
  - Day 63, Day 70, Day 164, Day 221, Day 362

Visit	EOT	FW12	FW24	6 month follow-up
Number of subjects at risk	296	292	244	193

C-EDGE CO-STAR

ELBASVIR/GRAZOPREVIR PLUS SOFOSBUVIR ± RIBAVIRIN IN TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS WITH HEPATITIS C VIRUS GENOTYPE 3 INFECTION AND COMPENSATED CIRRHOSIS: THE C-ISLE STUDY

*Graham R. Foster**, *Kosh Agarwal, Matthew Cramp, Sulleman Moreea, Stephen Barclay, Jane Collier, Ashley S. Brown, Stephen D. Ryder, Andrew Ustianowski, Daniel M. Forton, Ray Fox, Fiona Gordon, William M. Rosenberg, David J. Mutimer, Jiejun Du, Christopher L. Gilbert, Ernest Asante-Appiah, Janice Wahl, Eliav Barr, Barbara Haber*

**Queen Mary University, London, United Kingdom*

C·ISLE

PATIENT DEMOGRAPHICS

Sofosbuvir
Elbasvir (MK-8742) Grazoprevir (MK-5172)
HCV Genotype 3

	Cirrhotic GT3-Infected Patients (n = 100)
Male, n (%)	68 (68)
Race, n (%)	
Asian	29 (29)
White	69 (69)
Other	2 (2)
Age, mean (SD)	53.4 (8.7)
BMI ≥30 kg/m^2, n (%)	28 (28)
Cirrhosis diagnosis method	
Liver biopsy, n (%)	16 (16)
FibroScan®, n (%)	84 (84)
Mean FibroScan® score, kPa (SD)	25.4 (12.1)
Prior treatment history, n (%)	
Naive	47 (47)
PR-Experienced	53 (53)
HCV RNA $\log_{10}$ IU/mL mean (SD)	6.2 (0.7)
IL28B CC, n (%)	50 (50)
Albumin, g/dL, mean (SD)	3.6 (1.2)
Total bilirubin, mg/dL, mean (SD)	0.7 (0.4)
Platelets × 10^3 cells/µL, mean (range)	148 (46-396)
Platelet count <100 × 10^3 cells/µL, n (%)	24 (24)

BMI, body mass index;
SD, standard deviation.

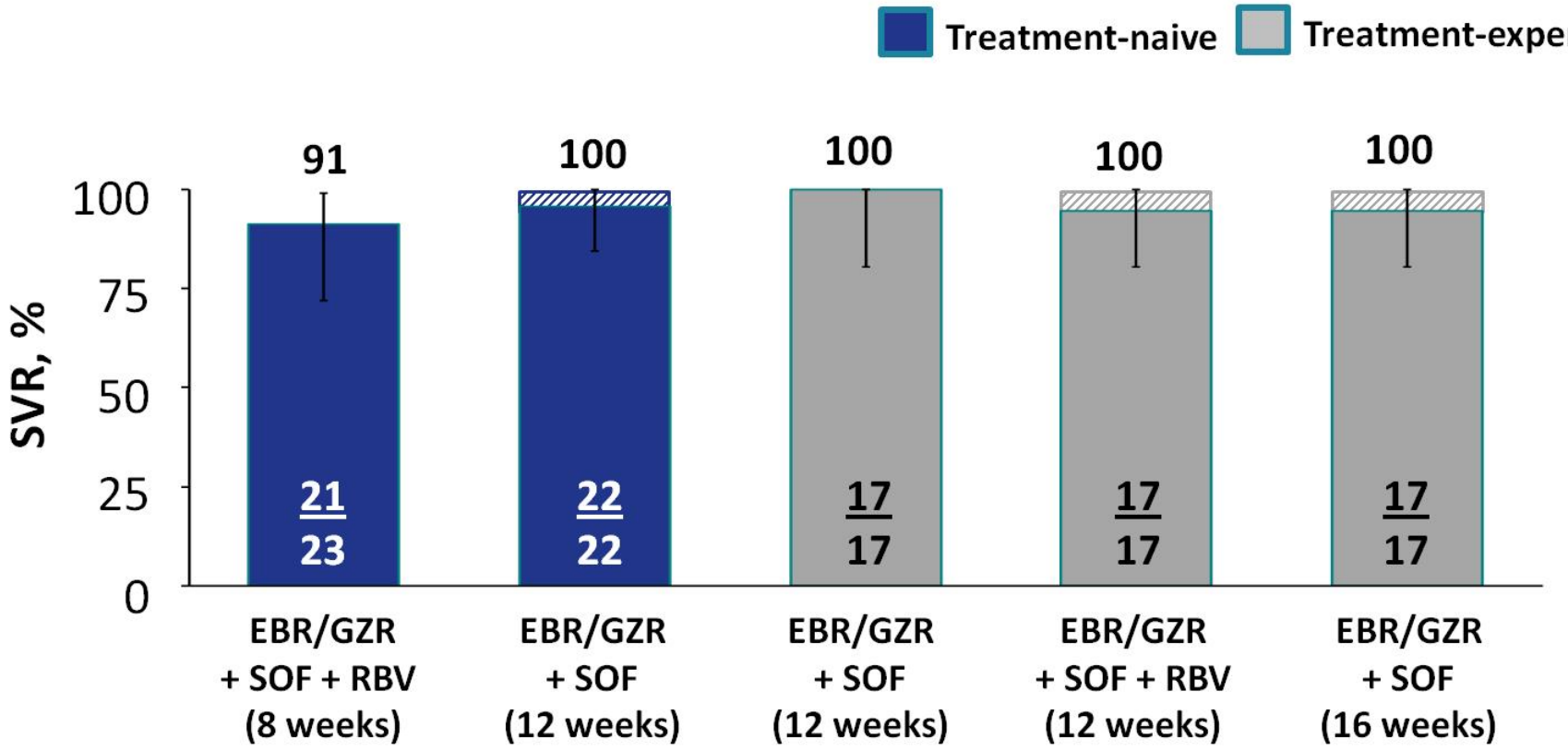
C·ISLE

SVR12 (mFAS)

Sofosbuvir

Elbasvir (MK-8742) Grazoprevir (MK-5172)

HCV Genotype 3



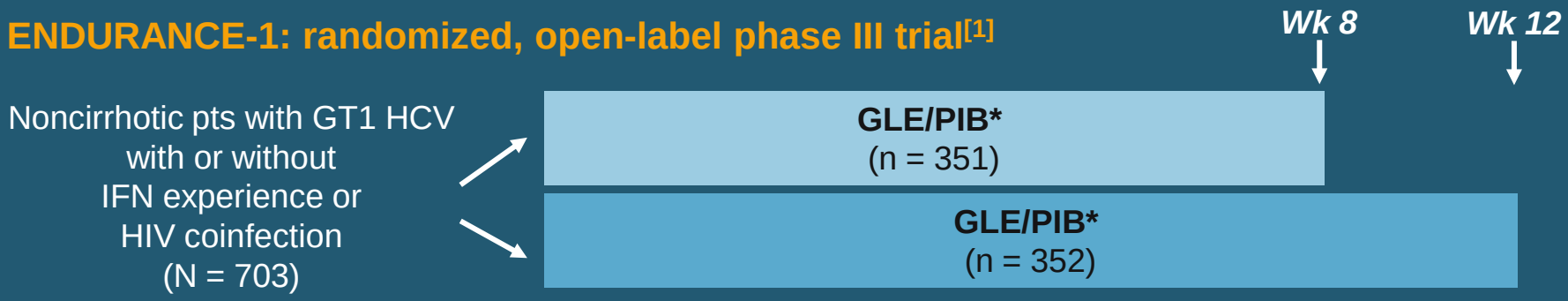
Relapse	2	0	0	0	0

mFAS excluded patients who discontinued treatment for reasons unrelated to study medication.

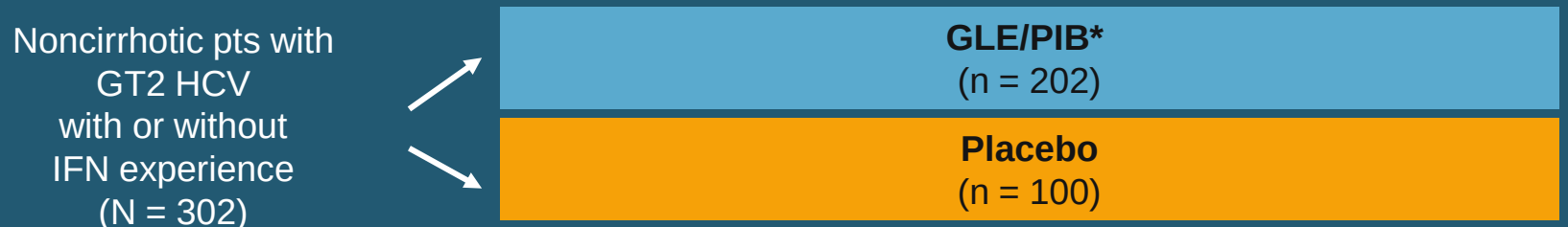
C·ISLE

ENDURANCE-1, 2, 4: GLECAPREVIR / PIBRENTASVIR for Tx GT1, 2, 4, 5, 6

ENDURANCE-1: randomized, open-label phase III trial[1]



ENDURANCE-2: randomized, double-blind, placebo-controlled phase III trial[2]



ENDURANCE-4: open-label, single-arm phase III trial[3]

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

References in slidenotes.

Slide credit: clinicaloptions.com

ENDURANCE Studies: Key Baseline Demographics

Characteristic, %	ENDURANCE-1[1]		ENDURANCE-2[2]		ENDURANCE-4[3]
	GLE/PIB 8 Wks (n = 351)	GLE/PIB 12 Wks (n = 352)	GLE/PIB 12 Wks (n = 202)	PBO 12 Wks (n = 100)	GLE/PIB 12 Wks (N = 121)
Fibrosis stage					
▪ F0-F1	85	85	76	85	86
▪ F2	6	7	9	9	7
▪ F3	9	8	15	6	7
Treatment experienced*	38	38	30	29	32
HIV coinfected	4	5	NA	NA	NA

*Pts could have treatment experience with IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

ENDURANCE Studies: Efficacy of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV

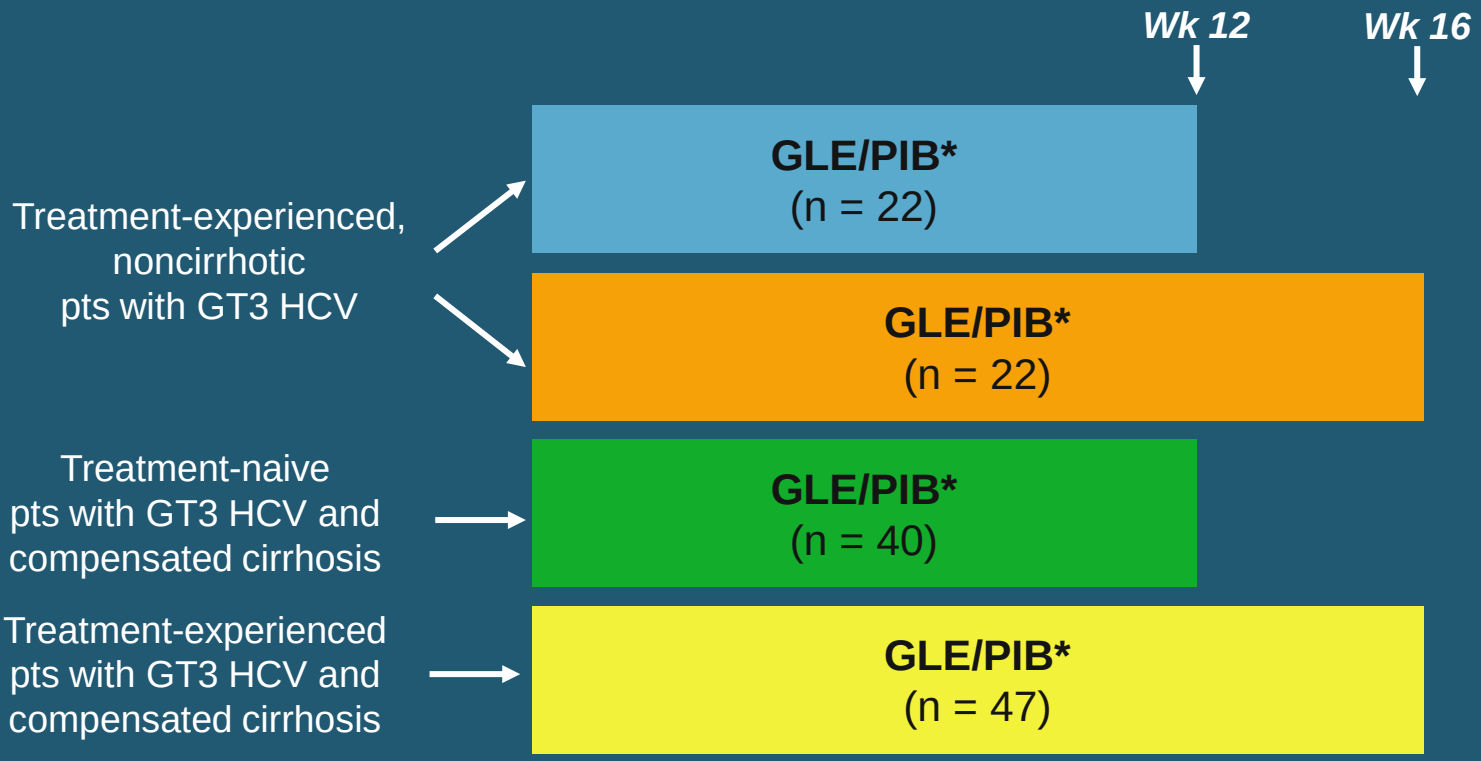
Outcome	ENDURANCE-1[1] (GT1)		ENDURANCE-2[2] (GT2)	ENDURANCE-4[3] (GT4-6)
	GLE/PIB 8 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks	GLE/PIB 12 Wks
SVR12, % (n/N)	99.1* (332/335)	99.7* (331/332)	99† (195/196)	99‡ (120/121)
Relapse/ on-treatment failure, n	1§	0	0	0

*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience. †ITT analysis: excluded pts with SOF experience. ‡ITT analysis. §On-treatment virologic failure at Day 29 in pt with GT1a HCV.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. AASLD 2016. Abstract 114.

SURVEYOR-II, Part 3: GLE/PIB for Pts With GT3 HCV ± Cirrhosis

- Partially randomized, open-label phase II trial (N = 131)



- Prior treatment experience consisted of IFN or pegIFN ± RBV or SOF + RBV ± pegIFN

*Dosing: GLE/PIB given as 3 coformulated 100/40 mg tablets QD for a total dose of 300/120 mg.

Wyles DL, et al. AASLD 2016. Abstract 113.

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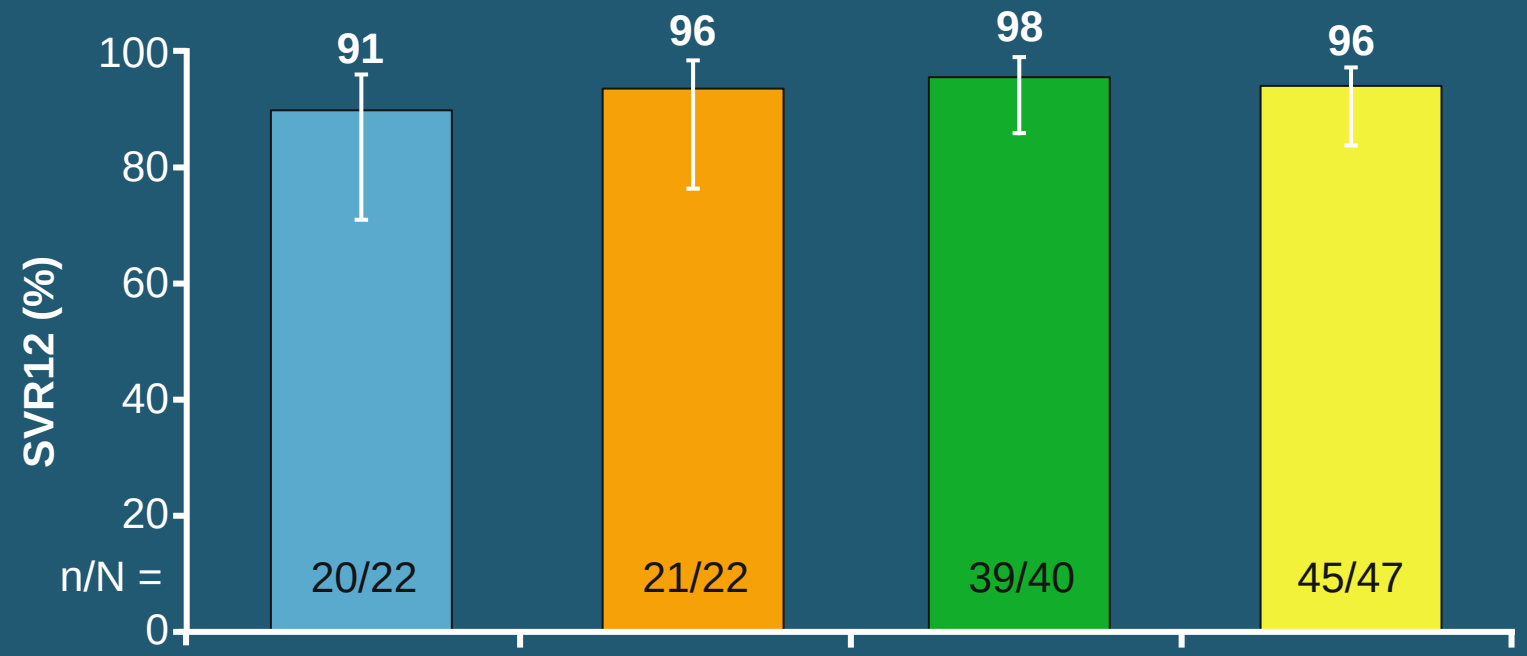
SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis



Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles DL, et al. AASLD 2016. Abstract 113. Reproduced with permission.

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HCV Resistance Testing

- Drug
  - DAA Class
  - Co-Administered DAAs
- Virus
  - Specific Mutation
  - Genotype
  - Resistance Assay Utilized
- Host
  - Concurrent Negative Predictors of DAA Success

- Complexity versus Capacity

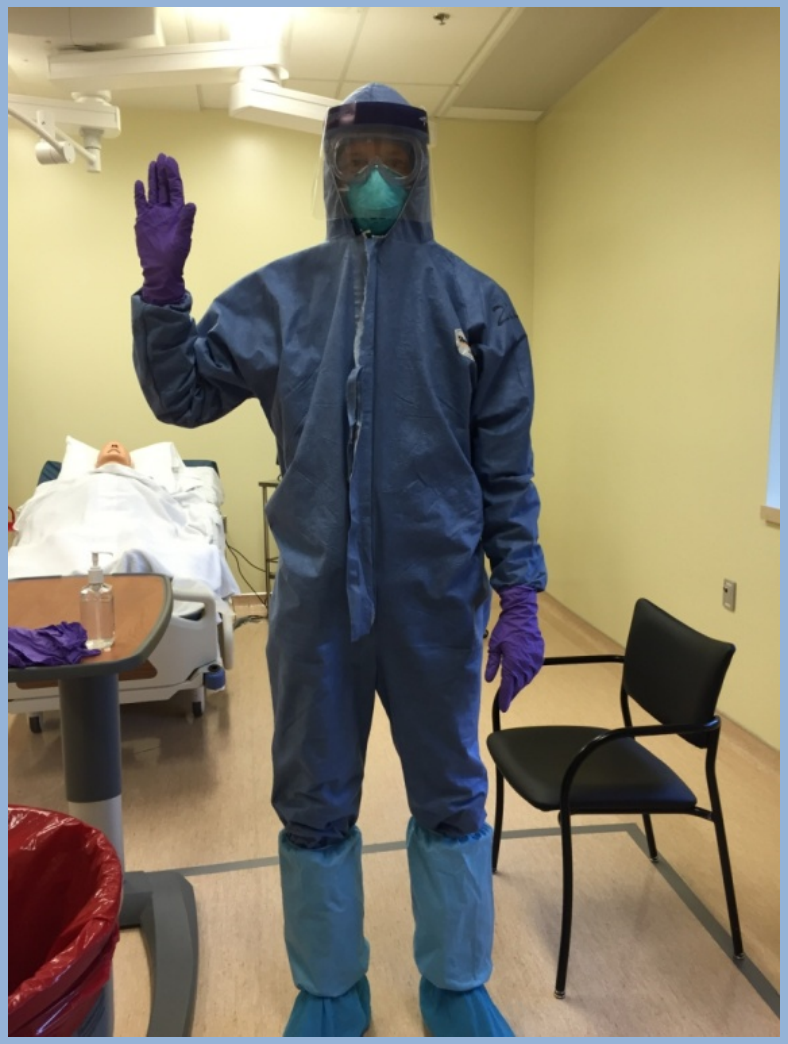
Pediatric HCV

Pediatric HCV

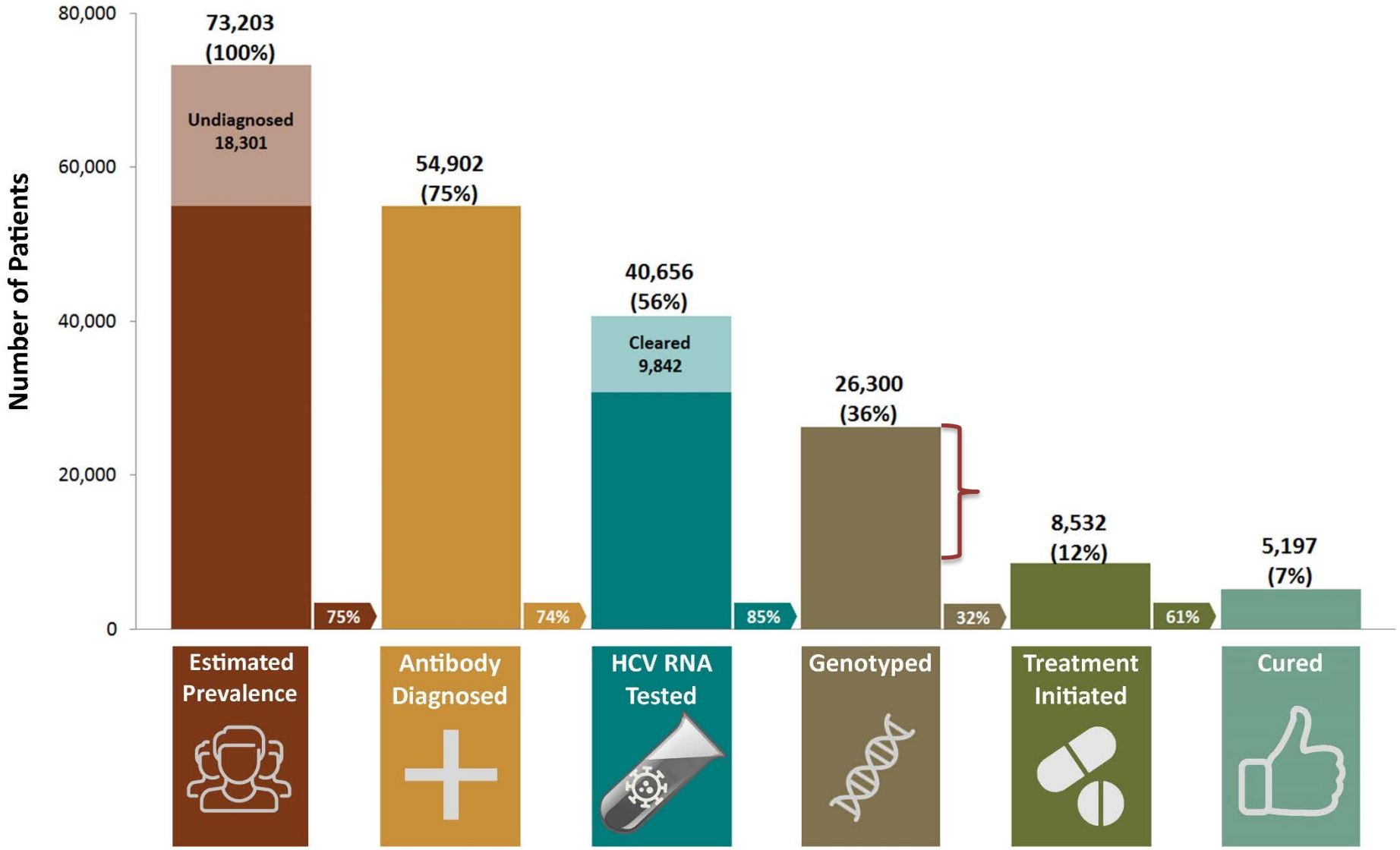
- NHANES3
  - 6-11 yo: 0.17% sero+
  - 12-19 yo: 0.39% sero+
  - 6600 CDN children
- Vertical transmission primary mode of infection
  - 5-7% / pregnancy
- Breast feeding does not promote transmission
- Diagnosis
  - HCV antibodies <18/12
- Spontaneous Resolution- 25-40% (usually by M24)
- Manifestations
- Work-Up
- Treatment
  - FDA: SOF, Harvoni age 12-17

JPGN NASPGHAN Practice Guidelines 2012.

Role of Infectious Diseases



HCV Cascade of Care in BC, 2012



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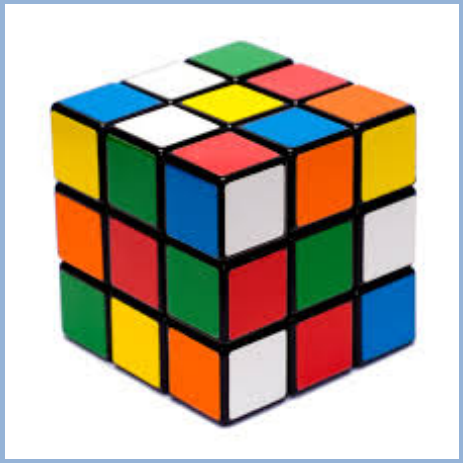
Infectious Disease Expertise

- Virology
- Immunology
- Multisystem Disease
- Polypharmacy
- Side Effect Profile
- DDI

Population

- Concentration of Barriers to Engagement and Treatment Success
  - Diverse populations within the HCV community
  - Socioeconomic
  - Mental Health
  - Substance Abuse
  - Poverty
  - Remoteness
  - Stigma



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