



CLINICAL CARE OPTIONS®
HEPATITIS

Call to Arms: Tools for HCV Treeters to Maximize HCV Cure Rates and Advance Toward HCV Elimination

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Jordan J. Feld, MD, MPH, has disclosed that he has received consulting fees from AbbVie, ContraVir, Gilead Sciences, Janssen, and Merck and funds for research support from Abbott, AbbVie, Gilead Sciences, Janssen, and Merck.

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Outline

- The Path to 100% HCV Elimination
- The Toolkit to Achieve Cure
- Key Targets to Reach 100%
 - Engaging the 50%: Increasing Screening and Diagnosis
 - Treating the 33%: Expanding Therapy to the Previously Excluded
 - Curing the 10%: Evolving Options for DAA-Experienced Patients



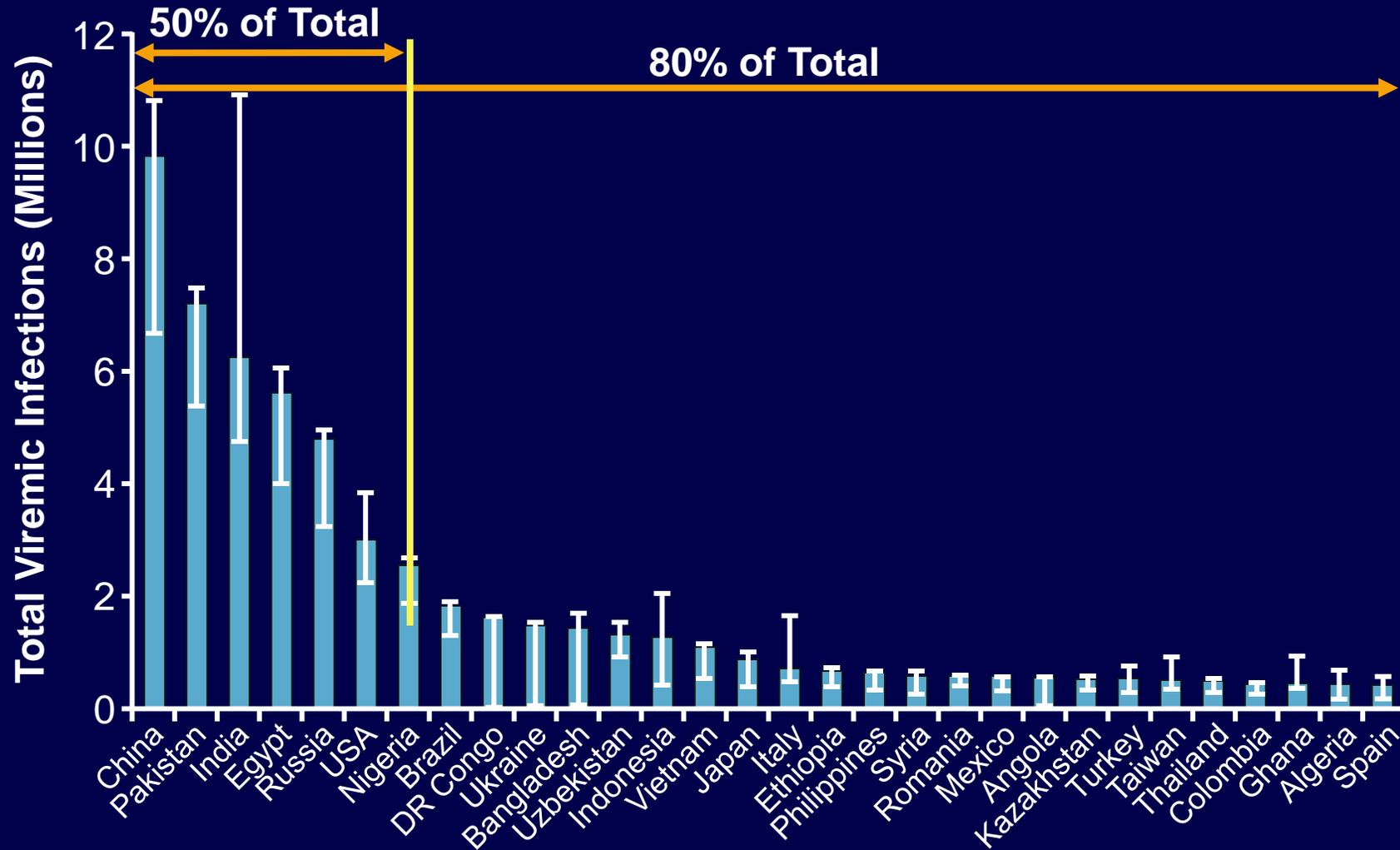
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The Path to 100% HCV Elimination

Norah Terrault, MD, MPH



30 Countries Account for 80% of HCV Infections

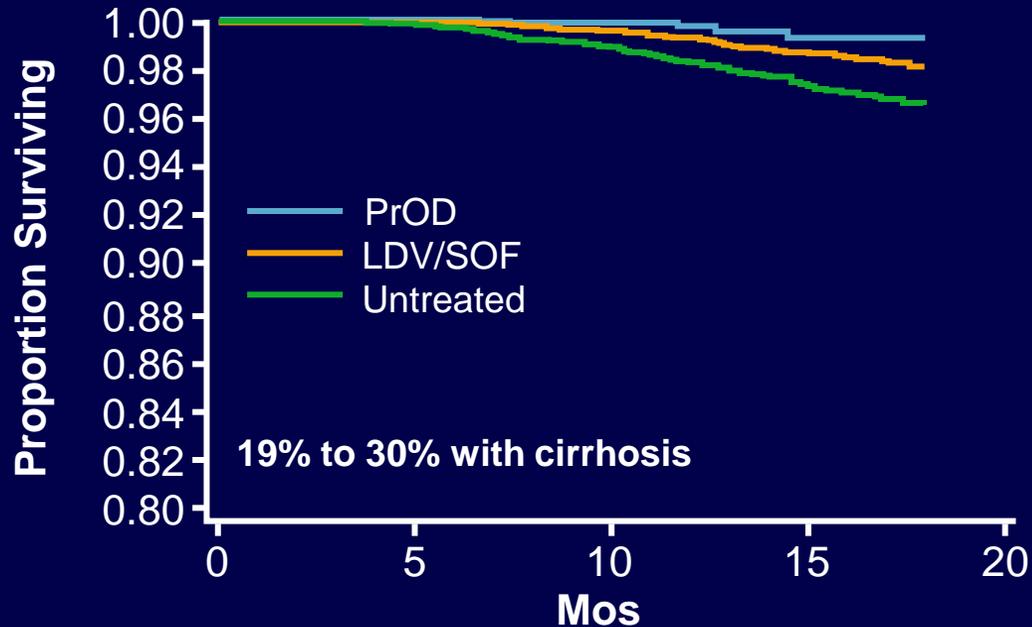


WHO: Global Viral Hepatitis Prevention and Elimination Plans

- HCV and HBV targets for 2030^[1]
 - Incidence
 - 90% reduction in new cases of infection (30% reduction by 2020)
 - Mortality
 - 65% reduction in HCV deaths (10% by 2020)
- Sustainable development goals^[2]
 - Target 3.3: “By 2030, end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases”

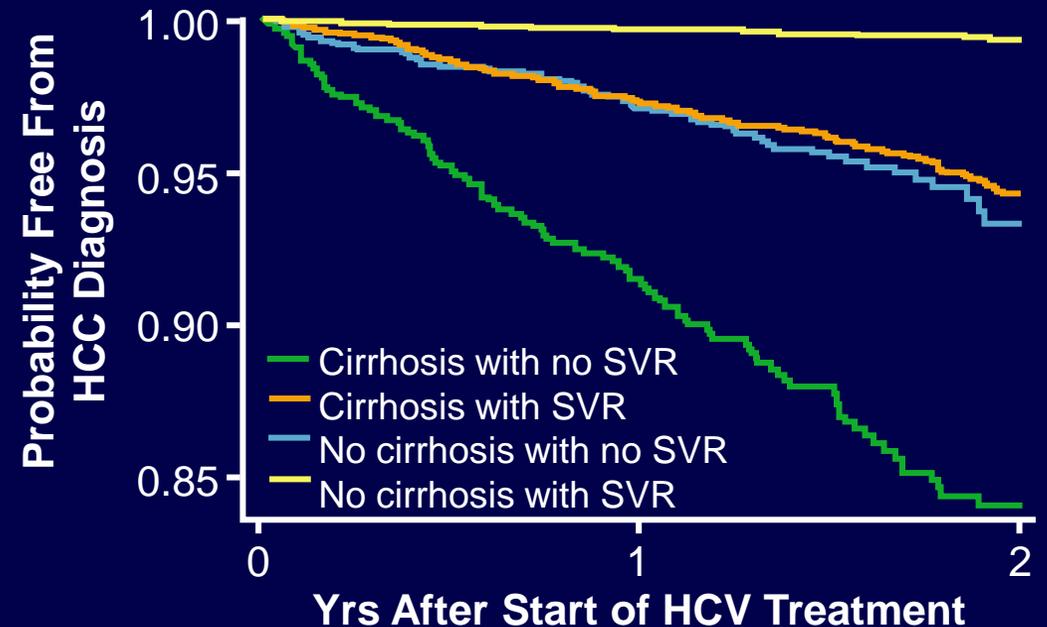
Mortality Reduction Achieved by HCV Cure

Survival in ERCHIVES Veterans (N = 13,940*†)[1]



DAA-induced SVR is associated with a 43% reduction in mortality

HCC Risk in DAA-Treated Veterans (n = 25,424‡)[2]



DAA-induced SVR is associated with a 71% reduction in HCC risk

*For 18 mos of follow-up.

†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.

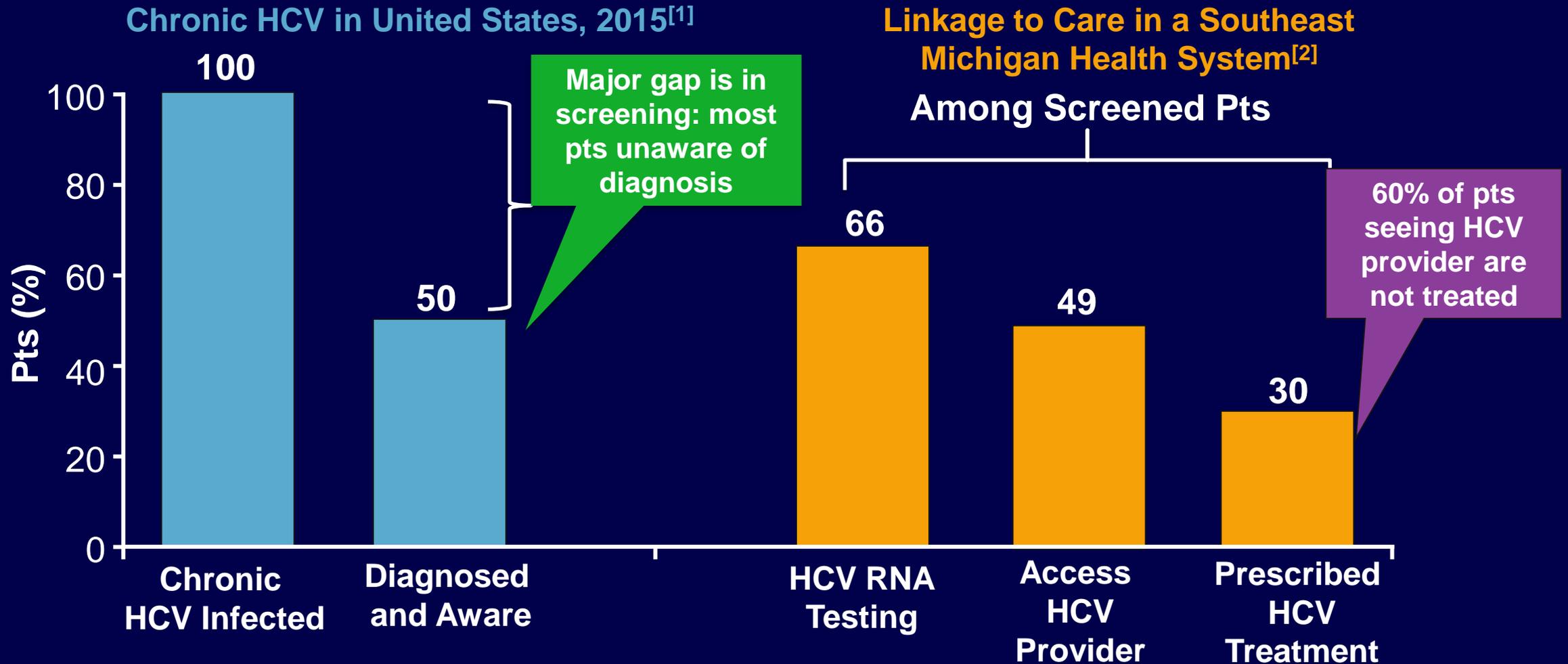
‡For 38,204 pt-yrs of follow-up.

1. Butt AA, et al. Clin Infect Dis. 2017;65:1006-1011.

2. Ioannou GN, et al. J Hepatol. 2017;[Epub ahead of print].

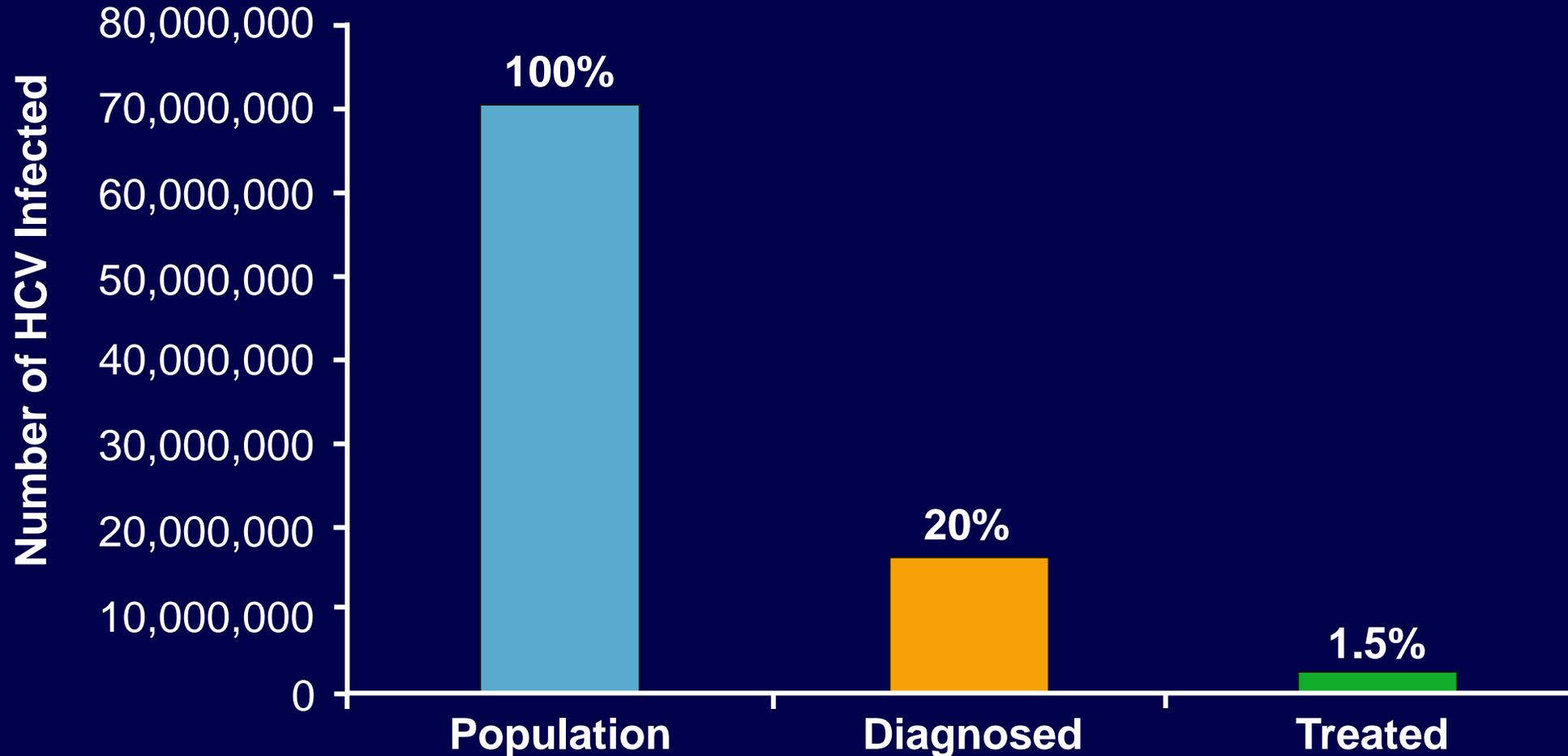


US Estimates of HCV Cascade of Care



1. Bourgi K, et al. PLoS One. 2016;11:e0161241. 2. Yehia BR, et al. PLoS One. 2014;9:e101554.

Estimated Global HCV Cascade of Care



Breakdowns in the HCV Care Cascade

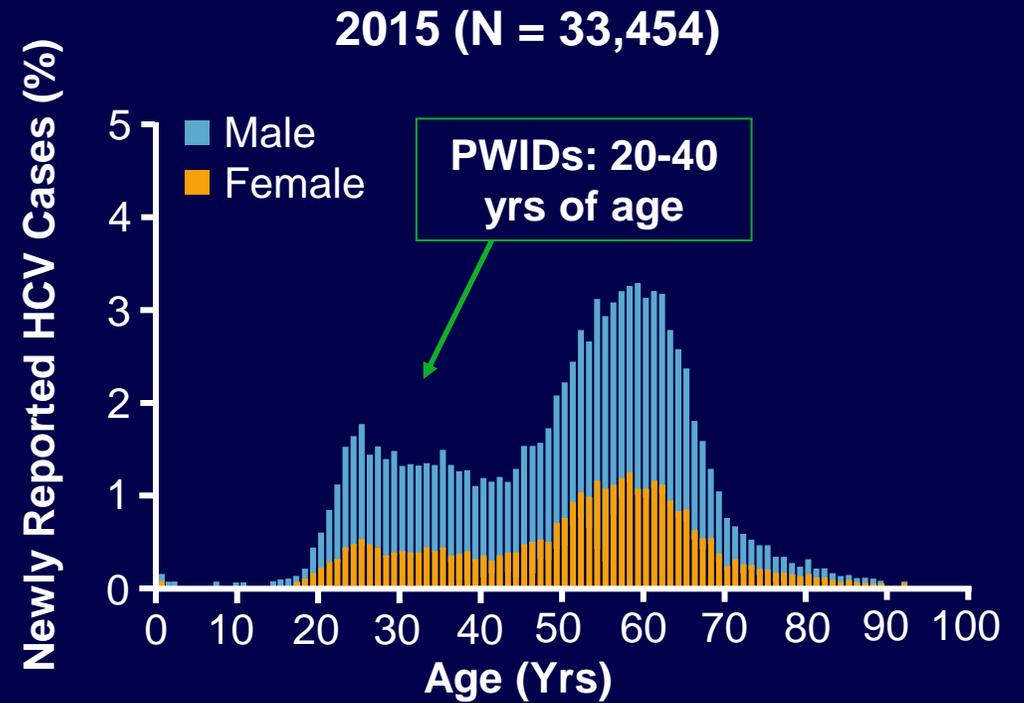
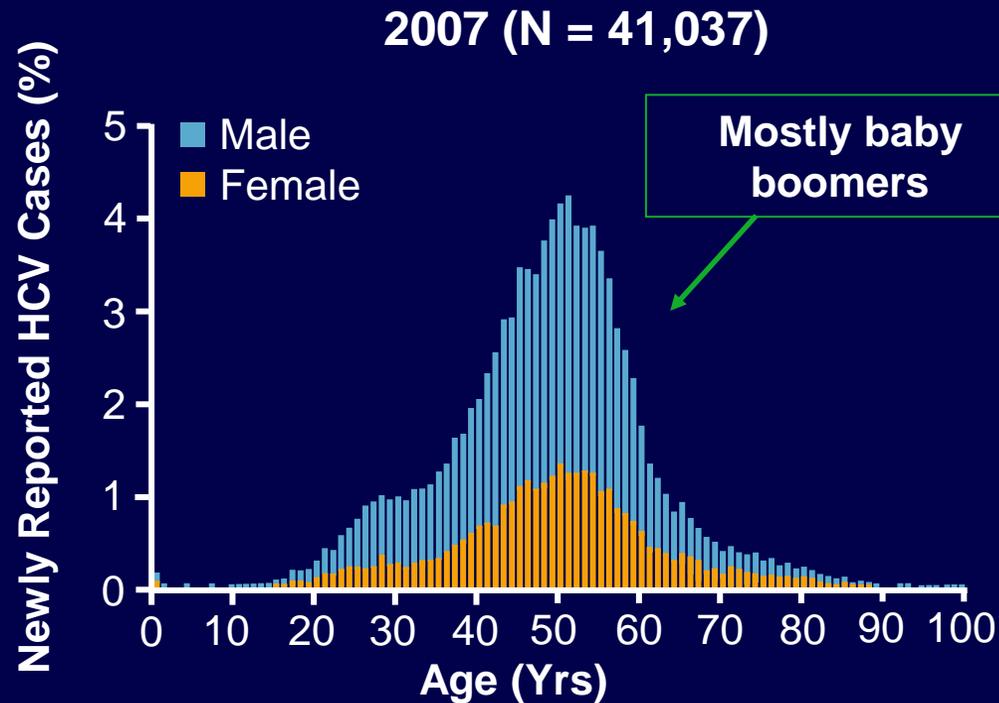
High cost of HCV therapy leads to restrictions based on^[1,2]:

- Stage of disease
- Medical comorbidities
- Abstinence from drugs and alcohol
- Adherence concerns
- Insurance status

Populations with high HCV prevalence and variable access to healthcare^[3]:

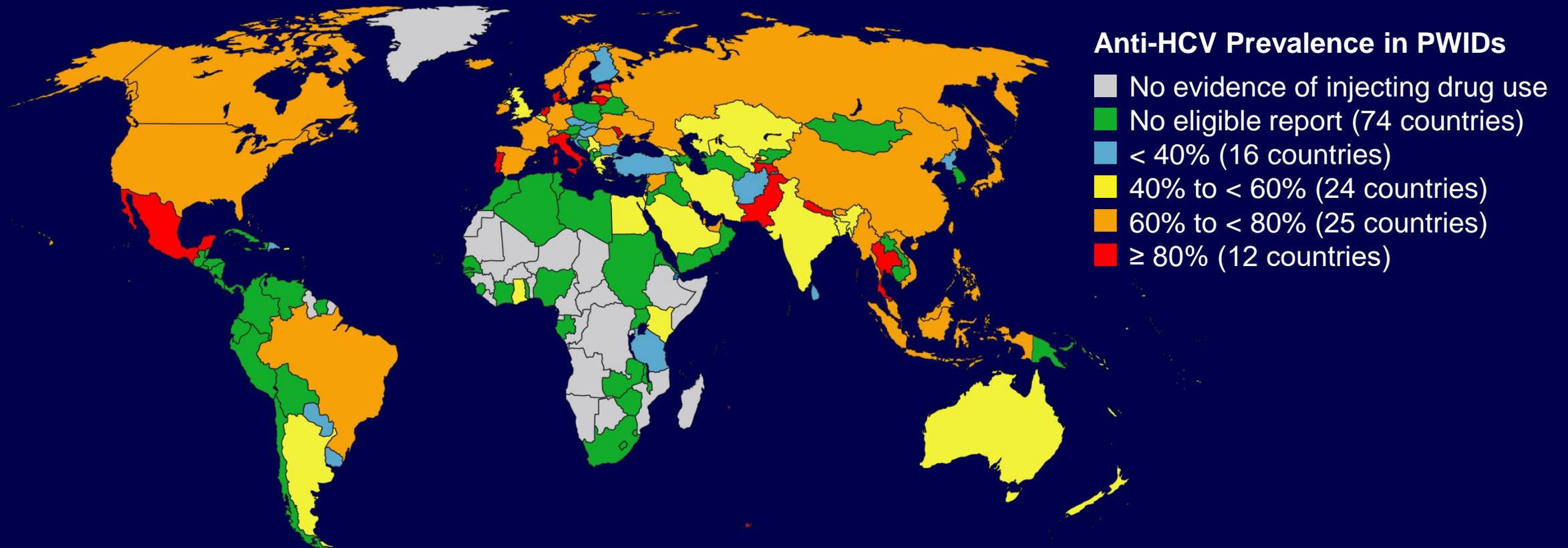
- Prisoners
- People living with HCV/HIV coinfection
- Men who have sex with men
- Migrants
- Persons who use drugs

Changing Epidemiology of HCV in the US



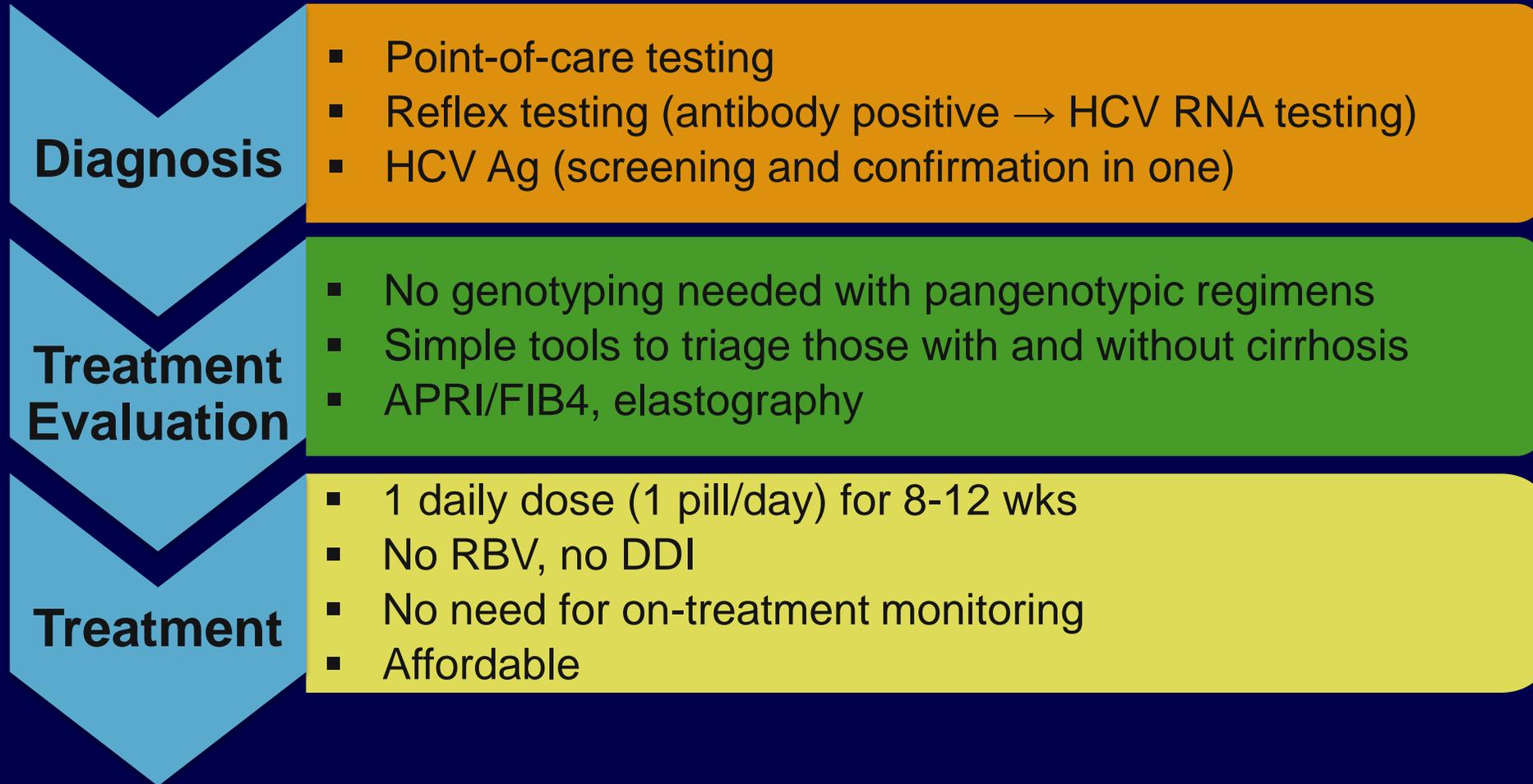
- Screening → linkage to HCV care → DAA treatment cascade must be operative in all those at risk
- Treatment of PWIDs plus harm reduction efforts essential part of elimination efforts

HCV Infection Among Persons Who Inject Drugs



- In most developing countries, injection drug use is primary source of new infections
- HCV treatment must be coupled with harm reduction measures to reduce total infections

HCV Elimination: Simplifying and Streamlining Care





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The Toolkit to Achieve Cure

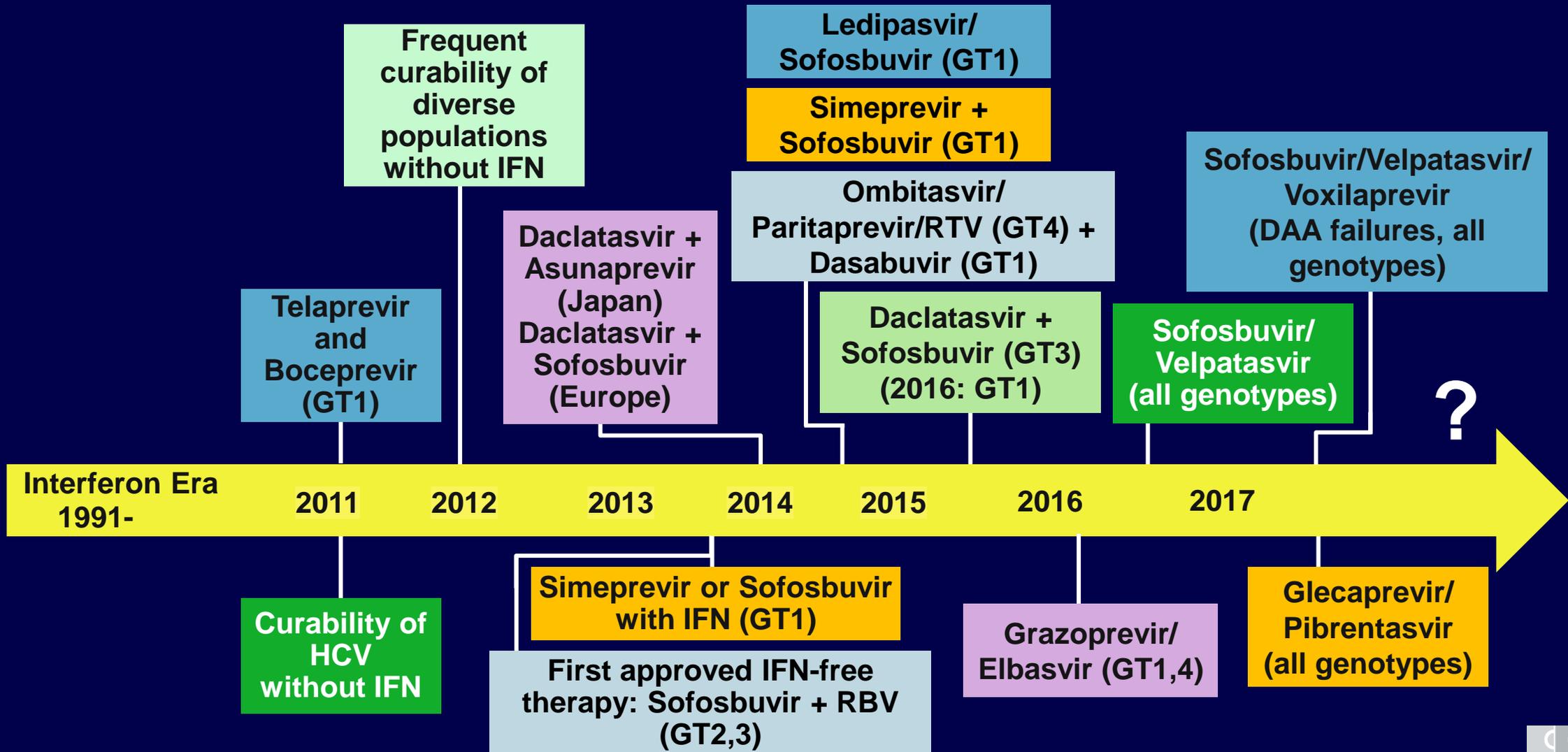
Ira M. Jacobson, MD



What Are the Tools in the Toolkit?



The Evolution of HCV Therapy



Pangenotypic Regimens



Pangenotypic, RBV-Free, Oral HCV Therapy for 8-12 Wks Now an Option for Many Pts

Setting	FDA Indications for Pangenotypic HCV Regimens in Non-DAA Experienced Pts (Except as Noted)	
	SOF/VEL	GLE/PIB
Treatment naive	GT1-6 <ul style="list-style-type: none"> No cirrhosis or compensated cirrhosis: 12 wks 	GT1-6 <ul style="list-style-type: none"> No cirrhosis: 8 wks Compensated cirrhosis: 12 wks
IFN/RBV experienced*	GT1-6 <ul style="list-style-type: none"> No cirrhosis or compensated cirrhosis: 12 wks 	GT1, 2, 4, 5, 6 <ul style="list-style-type: none"> No cirrhosis: 8 wks Compensated cirrhosis: 12 wks GT3 <ul style="list-style-type: none"> No cirrhosis or compensated cirrhosis: 16 wks

*Includes PR ± SOF for GLE/PIB and PR ± BOC, SMV, or TVR for SOF/VEL.

HCV NS5A Inhibitor Activity by HCV Genotype/Subtype

NS5A Inhibitor	Stable/Transient HCV Replicon EC ₅₀ , pM							
	GT1a	GT1b	GT2a	GT2b	GT3a	GT4a	GT5a	GT6a
Ledipasvir ^[1-3]	34	4	21000	NA	35000	110	150	120
Daclatasvir ^[4]	50	9	71	NA	146	12	33	NA
Ombitasvir ^[1]	14	5	12	4	19	2	3	370
Elbasvir ^[1,5]	4	3	3	3000	20	3	NA	NA
Velpatasvir ^[6]	12	15	9	8	12	9	75	6
Pibrentasvir ^[1,7]	2	4	2	2	2	2	1	3

1. Poordad F, et al. AASLD 2015. Abstract 41. 2. Cheng G, et al. EASL 2012. Abstract 1172.
 3. FDA LDV/SOF. 2017. 4. Wang C, et al. Antimicrob Agents Chemother. 2014;58:5155-5163. 5. Liu R, et al. EASL 2012. Abstract 858. 6. Cheng G, et al. EASL 2013. Abstract 1191. 7. Ng TI, et al. Antimicrob Agents Chemother. 2017;61:e02558-16.



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HCV NS3/4A Inhibitor Activity by HCV Genotype/Subtype

NS3/4A Inhibitor	Stable/Transient HCV Replicon EC ₅₀ , nM					
	GT1a	GT1b	GT2a	GT3a	GT4a	GT6a
Simeprevir ^[1,2]	4.0	9.0	15.0	472.0	--	--
Paritaprevir ^[3]	1.0	0.2	5.3*	19.0	0.1	0.7
Grazoprevir ^[3]	0.4	0.9	1.3	36.0	1.2	0.9
Glecaprevir ^[3]	0.8	0.9	2.7*	1.6	2.8	0.9
Voxilaprevir ^[4]	3.9	3.3	3.7	6.1	2.9	1.5

*Study conducted at Southern Research Institute.

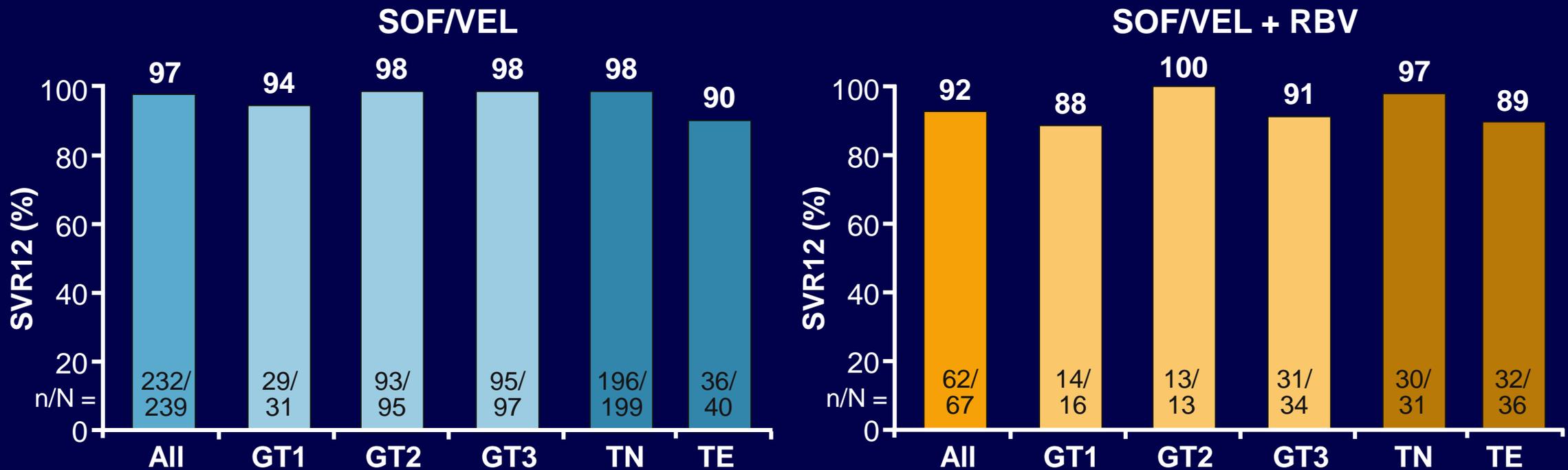
Most Common, Clinically Important RASs to DAAs

DAA	GT1a				GT1b		GT3a
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N	Y93H
Ledipasvir	20x	> 100x	> 100x / > 100x	> 1000x / > 10,000x	> 100x > 50x	> 100x / --	NR
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x / > 10,000x	< 10 x	20x / 50x	NR
Daclatasvir	> 100x	> 1000x	> 100x / > 1000x	> 1000x / > 10,000x	< 10 x	20x / 50x	> 1000x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x / > 1000x	< 10 x	> 100x / --	NR
Velpatasvir	< 10x	< 3x	20x / 50x	> 100x / > 1000x	< 3x	< 3x / --	> 100x
Pibrentasvir	< 3x	< 3x	< 3x	< 10 x	< 3x	< 3x / --	< 3x

■ < 3-fold change
 ■ < 10-fold change
 ■ < 10- to 100-fold change
 ■ > 100-fold change

HCV-TARGET: Real-World Efficacy and Safety of SOF/VEL for GT1-6 HCV

- Pts treated per local standard of care at academic (n = 45) and community medical centers (n = 19) in North America (n = 60) and Europe (n = 4)
 - N = 451 for SOF/VEL; N = 119 for SOF/VEL + RBV



ENDURANCE-1, -2, -4: GLE/PIB for Treatment of GT1, 2, 4, 5, 6 HCV Without Cirrhosis

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



ENDURANCE-2: randomized, double-blind, placebo-controlled phase III trial^[2,3]



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



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

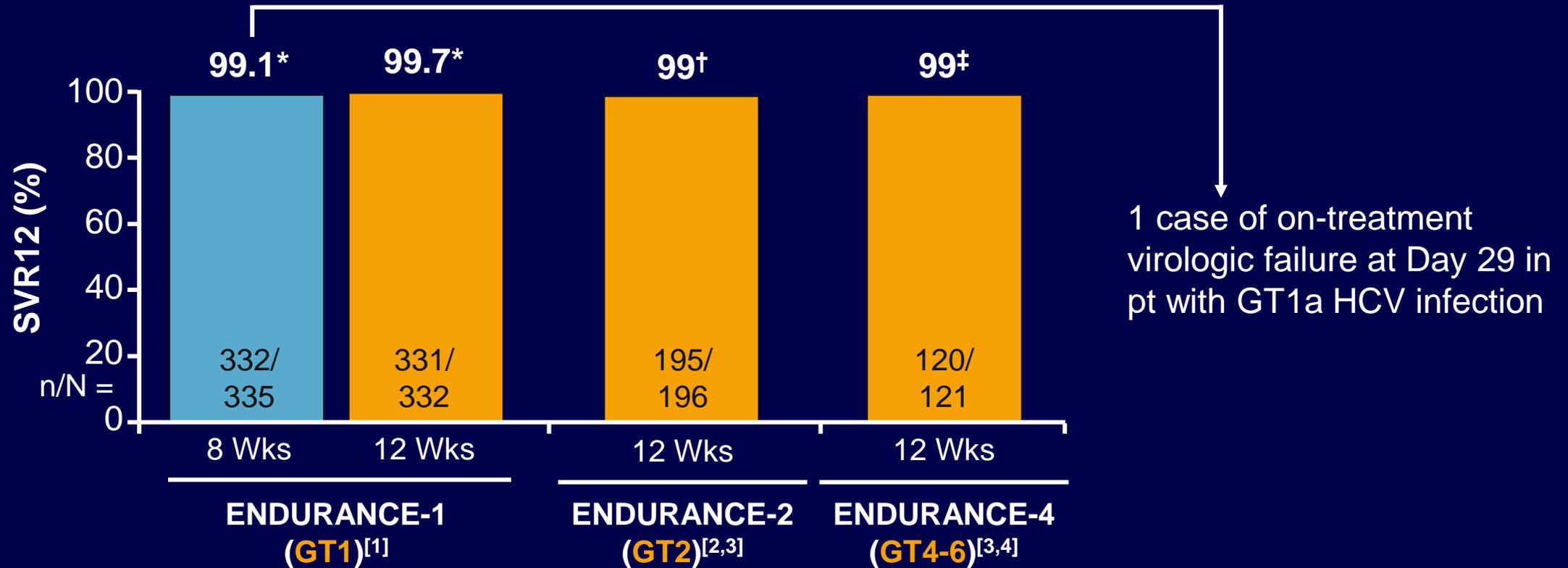
[†]Tx experience permitted: IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.

References in slidenotes.



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ENDURANCE-1, -2, -4 Studies: Efficacy of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV



*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.

1. Zeuzem S, et al. AASLD 2016. Abstract 253.
2. Kowdley KV, et al. AASLD 2016. Abstract 73.
3. Asselah T, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print].
4. Asselah T, et al. AASLD 2016. Abstract 114.



ENDURANCE-1, -2, -4 Studies: Safety of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV

Outcome, %	ENDURANCE-1 (GT1) ^[1]		ENDURANCE-2 (GT2) ^[2,3]		ENDURANCE-4 (GT4-6) ^[3,4]
	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)
Any AE	62	66	65	58	69
D/c for AE	0	< 1	0	0	2
Serious AE	1	1	1	1	< 1
Death	0	< 1	0	0	0
AE in ≥ 10% of pts					
▪ Fatigue	9	12	11	10	17
▪ Headache	19	18	12	12	21
AST grade ≥ 3*	0	< 1	1	1	0
ALT grade ≥ 3*	0	0	< 1	2	0
Tot. bilirubin grade 3 [†]	< 1	< 1	< 1	0	0

* > 5 times ULN. † 3-10 times ULN.

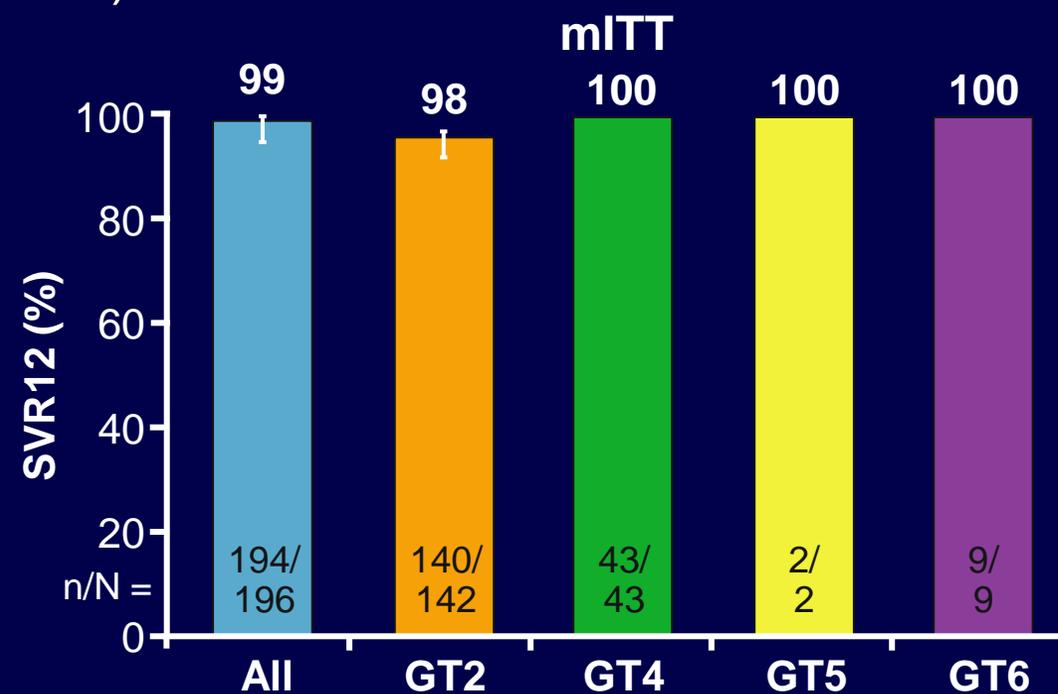
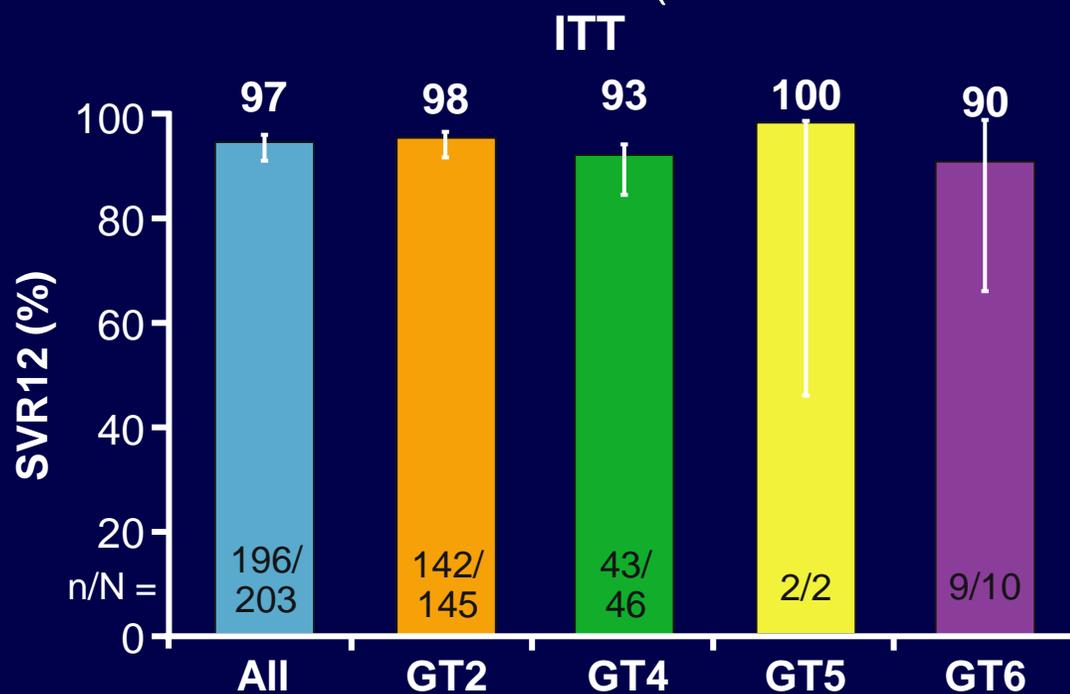
1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print]. 4. Asselah T, et al. AASLD 2016. Abstract 114.



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SURVEYOR 2, Part 4: 8-Wk GLE/PIB for Pts With GT2, 4, 5, 6 HCV Without Cirrhosis

- 99% SVR12 rate with 8-wk regimen in DAA-naive pts with GT2 HCV—noninferior to 95% historical control (SOF + RBV for 12 wks)

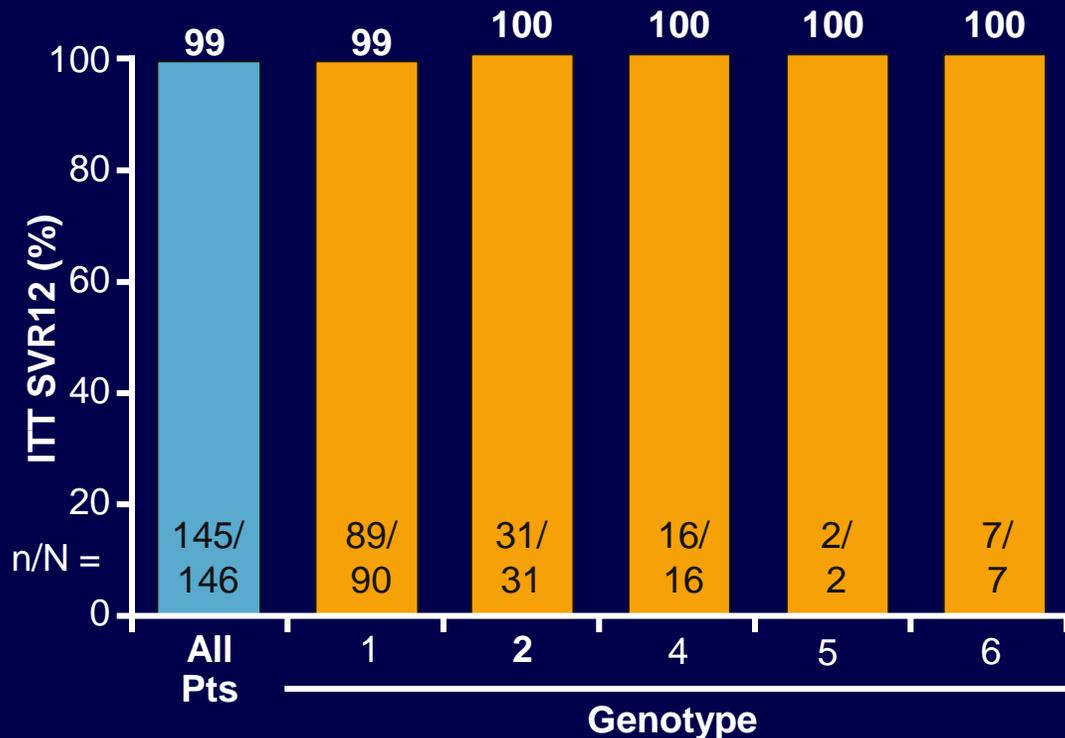


Relapse	2	2	0	0	0
D/c	2	1	1	0	0
No SVR12 data	3	0	2	0	1



EXPEDITION-1: Glecaprevir/Pibrentasvir in GT1, 2, 4, 5, or 6 HCV and Compensated Cirrhosis

- Tx-naive and tx-exp'd pts enrolled
 - 1 relapse in pt with GT1a HCV with new NS5A mutations (Q30R, H58D)



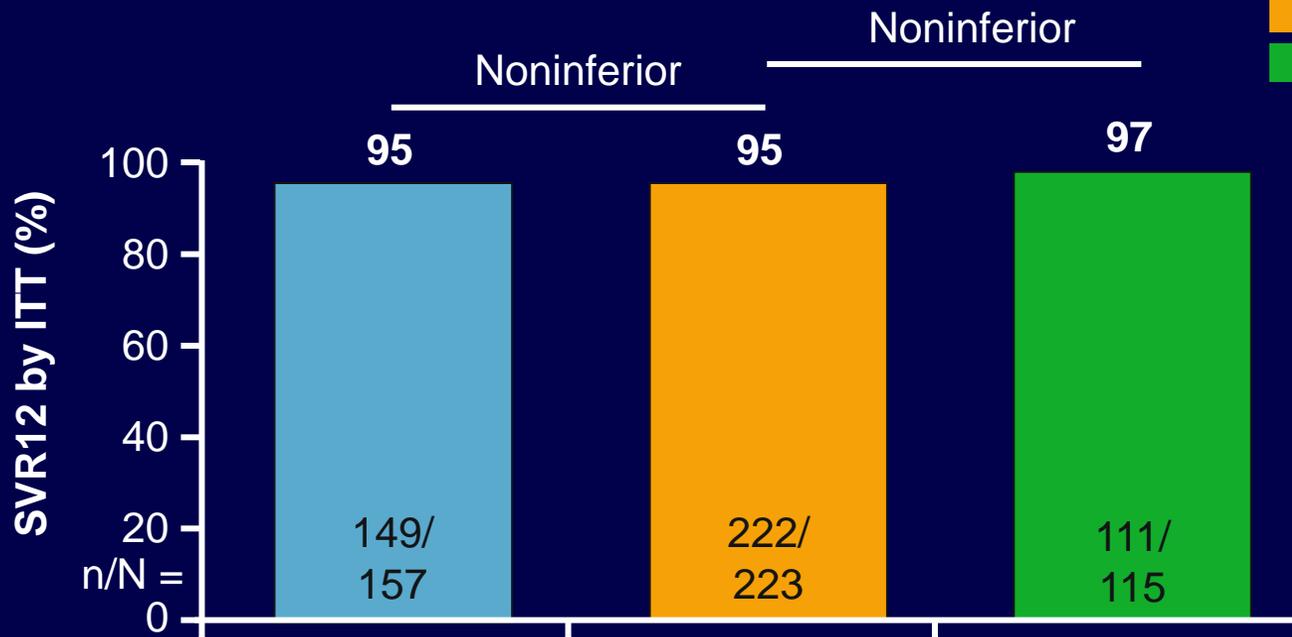
- No AE-related discontinuations or DAA-related serious AEs
 - 1 death deemed unrelated to study drug
- Rare grade 3 laboratory abnormalities

AE, n (%)	Pts (N = 146)
Any AE	101 (69)
Any serious AE	11 (8)
AEs occurring in ≥ 10% of pts	
▪ Fatigue	28 (19)
▪ Headache	20 (14)
▪ Pruritus	14 (10)
HCC	2 (1)



ENDURANCE-3: Glecaprevir/Pibrentasvir in GT3 HCV Without Cirrhosis

- Majority of pts had history of IDU (63% to 66%)



Failure, n (%)	8-wk GLE/PIB	12-wk GLE/PIB	12-wk DCV + SOF
Breakthrough	1 (1)	1 (< 1)	0
Relapse	5 (3)	3 (1)	1 (1)
AE-related d/c	0	1 (< 1)	1 (1)
LTFU	2 (1)	4 (2)*	2 (2)

*2 other failures due to consent withdrawal and noncompliance.

Foster GR, et al. EASL 2017. Abstract GS-007.

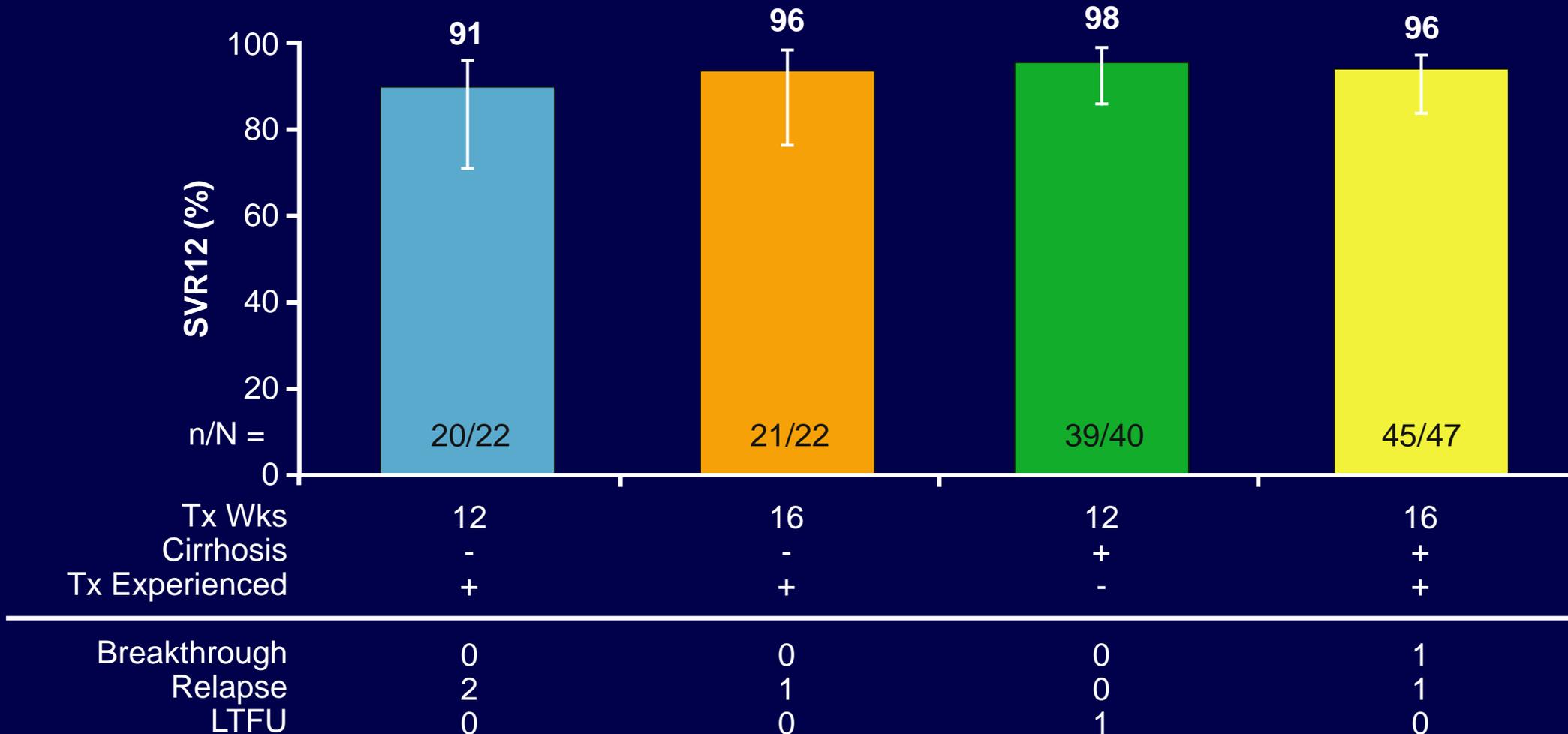
- 8-wk GLE/PIB
- 12-wk GLE/PIB
- 12-wk DCV + SOF

- No serious AEs deemed related to study drug
- No clinically relevant ALT increases, 1 isolated bilirubin increase (GLE/PIB 8 wks), 1 isolated neutrophil count decrease (GLE/PIB 12 wks)



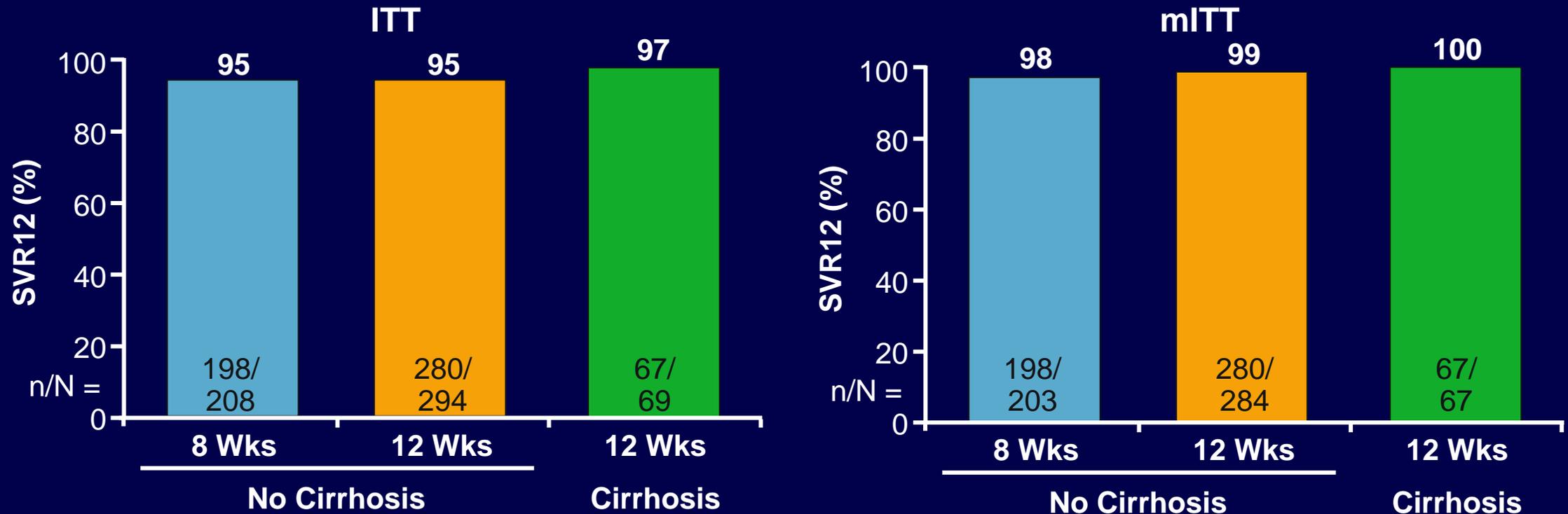
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SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis



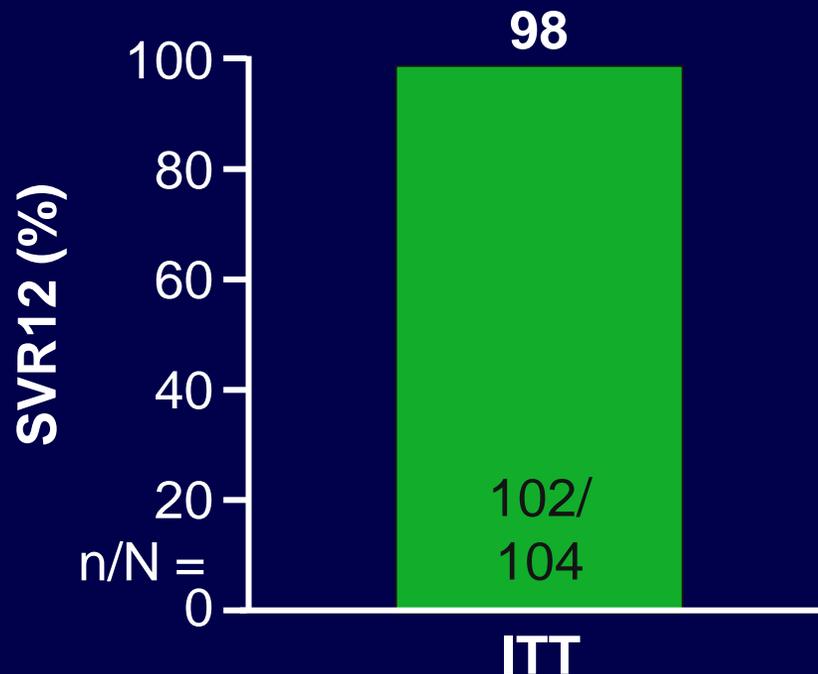
GLE/PIB for 8 or 12 Wks in Treatment-Naive GT3 HCV: Integrated Analysis of Phase II/III Data

- Pooled data from treatment-naive pts with GT3 HCV infection, without cirrhosis or with compensated cirrhosis, across 7 phase II and III studies of 8 or 12 wks
GLE/PIB QD: N = 571 (22% had BL NS5A polymorphisms; 66% had IDU history)



EXPEDITION-4: Glecaprevir/Pibrentasvir in Pts With GT1-6 HCV and Renal Impairment

- Pts with GT1-6 HCV and stage 4 or 5 CKD, with or without compensated cirrhosis, and with or without treatment experience (N = 104)
 - All treated with GLE/PIB for 12 wks



mITT SVR12 = 100%
(no virologic failure or relapse)

AASLD/IDSA HCV Guidance: Genotype 1



Recommended for GT1 Treatment-Naive or IFN-Experienced Pts, ± Compensated Cirrhosis

Treatment Experience	Recommended Regimens for GT1
Treatment naive	<ul style="list-style-type: none"> ▪ EBR/GZR* 12 wks ▪ GLE/PIB 8 wks if no cirrhosis, 12 wks if compensated cirrhosis ▪ LDV/SOF 12 wks ▪ LDV/SOF 8 wks if no cirrhosis, nonblack, no HIV, HCV RNA < 6 million IU/mL ▪ SOF/VEL 12 wks
PegIFN/RBV experienced	<ul style="list-style-type: none"> ▪ EBR/GZR* 12 wks ▪ GLE/PIB 8 wks (only if no cirrhosis) ▪ LDV/SOF 12 wks (only if no cirrhosis) ▪ SOF/VEL 12 wks ▪ GLE/PIB 12 wks (compensated cirrhosis)

*For GT1a, only if no baseline NS5A elbasvir RASs detected.

AASLD/IDSA HCV Guidance: Genotype 3



Recommended for Treatment-Naive or PegIFN/RBV-Experienced Pts With GT3 HCV

Population	Cirrhosis?	Recommended Regimens for GT3
Treatment naive	No	<ul style="list-style-type: none"> GLE/PIB 8 wks SOF/VEL 12 wks
	Yes	<ul style="list-style-type: none"> GLE/PIB 12 wks SOF/VEL 12 wks*
PegIFN/RBV Experienced	No	<ul style="list-style-type: none"> SOF/VEL 12 wks[†]
	Yes	<ul style="list-style-type: none"> EBR/GZR + SOF 12 wks SOF/VEL/VOX 12 wks

*NS5A RAS testing recommended if considering this regimen in treatment-naive pts with cirrhosis; if Y93H present, add RBV.

[†]NS5A RAS testing recommended; if Y93H present, use SOF/VEL/VOX 12 wks or add RBV to SOF/VEL 12 wks.

AASLD/IDSA HCV Guidance: Genotypes 2, 4, 5, 6



Recommended Regimens for Treatment-Naive or PegIFN/RBV-Experienced Pts With GT2 HCV

No Cirrhosis

- GLE/PIB 8 wks
- SOF/VEL 12 wks

Compensated Cirrhosis

- SOF/VEL 12 wks
- GLE/PIB 12 wks

Recommended Regimens for Treatment-Naive Pts With GT4, 5, 6 HCV

HCV GT	No Cirrhosis	Compensated Cirrhosis
4	<ul style="list-style-type: none"> GLE/PIB 8 wks SOF/VEL 12 wks EBR/GZR 12 wks LDV/SOF 12 wks 	<ul style="list-style-type: none"> SOF/VEL 12 wks GLE/PIB 12 wks EBR/GZR 12 wks LDV/SOF 12 wks
5 or 6	<ul style="list-style-type: none"> GLE/PIB 8 wks SOF/VEL 12 wks LDV/SOF 12 wks 	<ul style="list-style-type: none"> GLE/PIB 12 wks SOF/VEL 12 wks LDV/SOF 12 wks

Recommended Regimens for PegIFN/RBV-Experienced Pts With GT 4, 5, 6 HCV

HCV GT	No Cirrhosis	Compensated Cirrhosis
4	<ul style="list-style-type: none"> ▪ SOF/VEL 12 wks ▪ GLE/PIB 8 wks ▪ EBR/GZR* 12 wks ▪ LDV/SOF 12 wks 	<ul style="list-style-type: none"> ▪ SOF/VEL 12 wks ▪ EBR/GZR* 12 wks ▪ GLE/PIB 12 wks
5 or 6	<ul style="list-style-type: none"> ▪ GLE/PIB 8 wks ▪ LDV/SOF 12 wks ▪ SOF/VEL 12 wks 	<ul style="list-style-type: none"> ▪ GLE/PIB 12 wks ▪ LDV/SOF 12 wks ▪ SOF/VEL 12 wks

*Previous relapse only; pts with previous virologic failure or breakthrough should be treated for 16 wks with addition of RBV.

Considerations for Careful Use of the Tools



AASLD/IDSA HCV Guidance for Stage 4 or 5 Chronic Kidney Disease

- Stage 4 (severe) CKD: eGFR 15-29 mL/min
- Stage 5 (end-stage) CKD: eGFR <15 mL/min

HCV GT	Recommended Regimens for Stage 4 or 5 CKD
1a, 1b, 4	▪ EBR/GZR 12 wks
1, 2, 3, 4, 5, 6	▪ GLE/PIB 8-16 wks*

*Use durations recommended for pts without CKD - based on cirrhosis, previous treatment experience.

DDIs Between Recommended DAAs and Selected Medications

Concomitant Medication	DCV	LDV	SOF	EBR/GZR	GLE/PIB	SOF/VEL	SOF/VEL/VOX
Acid-reducing agents*		X				X	X
Amiodarone	X	X	X			X	X
Anticonvulsants*	X	X	X	X	X	X	X
Azole antifungals*	X†			X			
Calcineurin inhibitors,* cisapride, PDE inhibitors,* other antiarrhythmics* or sedatives*				X			
Calcium channel blockers*	X			X			
Cyclosporine					X		
Digoxin	X	X		X	X		X
Ethinyl estradiol–containing products					X		
Glucocorticoids*	X			X			
Herbals, St John’s wort, milk thistle	X	X	X	X	X	X	X
Statins*	X	X		X	X		X
Macrolide antimicrobials*	X†			X			
Rifamycin antimicrobials*	X	X	X	X	X	X	X

*Some DDIs not class specific; see prescribing information for specific drugs within a class. †Requires DCV dose adjustment.



HCC Occurrence or Recurrence Equivalent in Pts With SVR to DAAs vs IFN

- Meta-analysis and meta-regression analysis of 41 studies (N = 13,875)
 - HCC occurrence in cirrhotic pts who achieved SVR with DAAs or IFN
 - HCC recurrence in pts who had had curative treatment for liver cancer

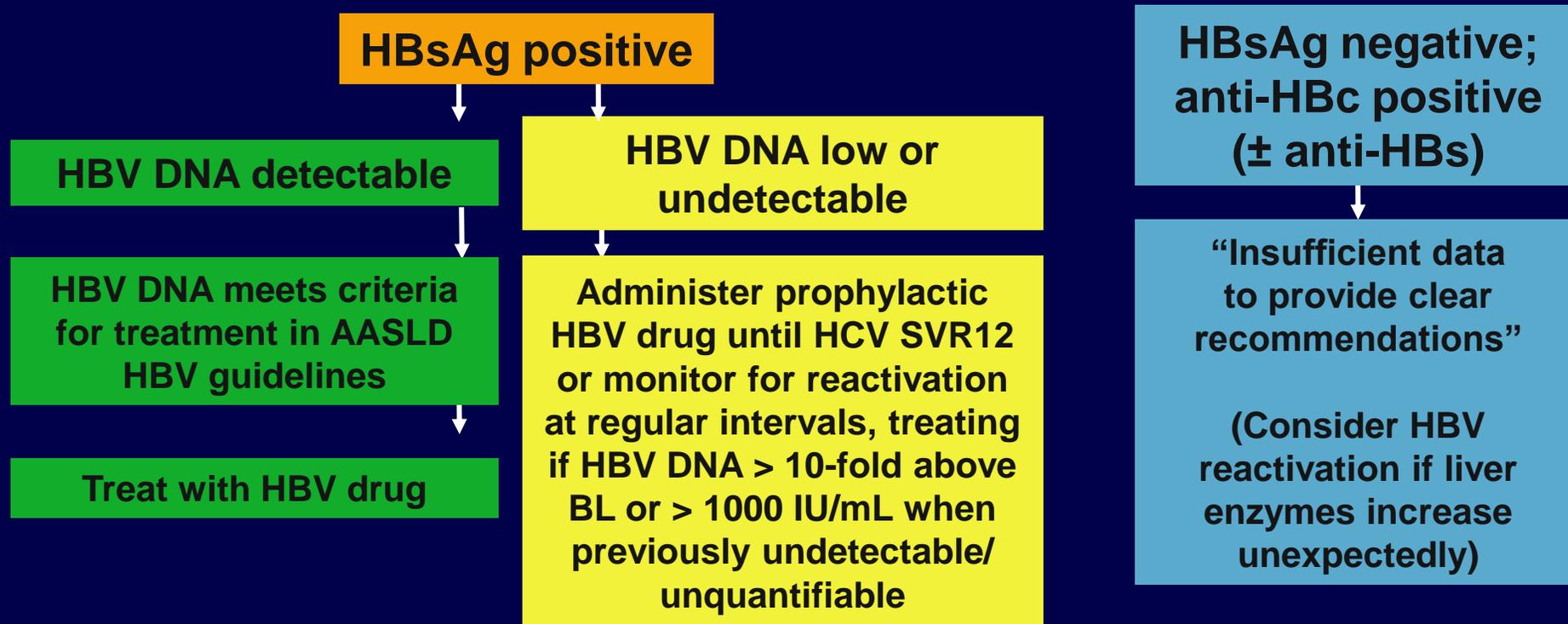
HCC and Risk Factor	Adjusted RR (95% CI)	P Value
HCC occurrence		
▪ Average follow-up	0.77 (0.62-0.97)	.03
▪ Average age	1.06 (0.99-1.14)	.08
▪ Treatment (DAA vs IFN)	0.75 (0.22-2.52)	.62
HCC recurrence		
▪ Average follow-up	0.79 (0.55-1.15)	.19
▪ Average age	1.11 (0.96-1.27)	.14
▪ Treatment (DAA vs IFN)	0.62 (0.11-3.45)	.56

HBV Reactivation in Pts Receiving HCV DAAs

- Case reports of HBV reactivation in pts treated with SMV + SOF ± RBV,^[1,2] DCV + ASV,^[3,4] and LDV/SOF^[5]
 - Possibly due to loss of host immune response to HBV^[6]
- 29 confirmed cases of HBV reactivation in HCV DAA recipients in ~ 3 yrs (most from Japan, November 2013 to October 2016)^[7]
 - Most cases occurred within 4-8 wks of HCV DAA initiation
 - 2 deaths, 1 liver transplant
 - 3 reactivations in pts with anti-HBc alone (one receiving rituximab)
- October 2016 FDA issued boxed warning^[8]

HBV Testing/Monitoring During HCV DAA Therapy

- Test all pts initiating HCV therapy for HBsAg, anti-HBc, and anti-HBs
 - Vaccinate if no HBV markers; follow flow chart below if HBV markers present



Conclusions

- Multiple current regimens highly effective and safe across genotypes
 - 8-12 wks without RBV for vast majority of pts
- SOF/VEL and GLE/PIB provide 12-wk or 8-wk pangenotypic regimens for DAA-naive noncirrhotic pts; other regimens remain first-line for specific genotypes, especially GT1
- No convincing evidence of increased risk of de novo HCC after DAA-induced SVR
 - Controversy persists regarding potential increased risk for HCC recurrence after SVR with DAAs
- HBV reactivation very rare in anti-HBc–positive pts; precautions in HBsAg-positive pts especially with HBV viremia





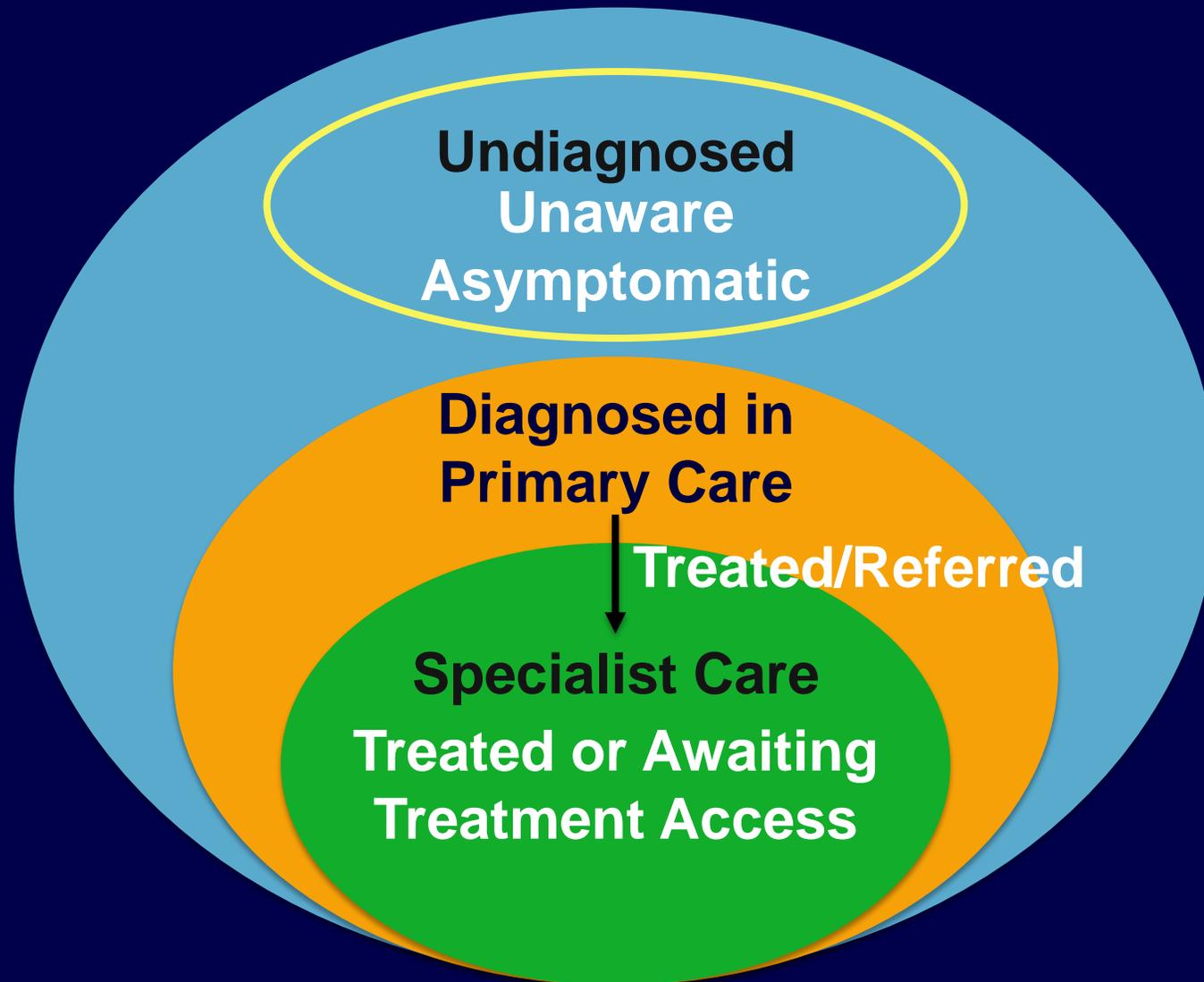
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Engaging the 50%: Increasing Screening and Diagnosis

Jordan J. Feld, MD, MPH

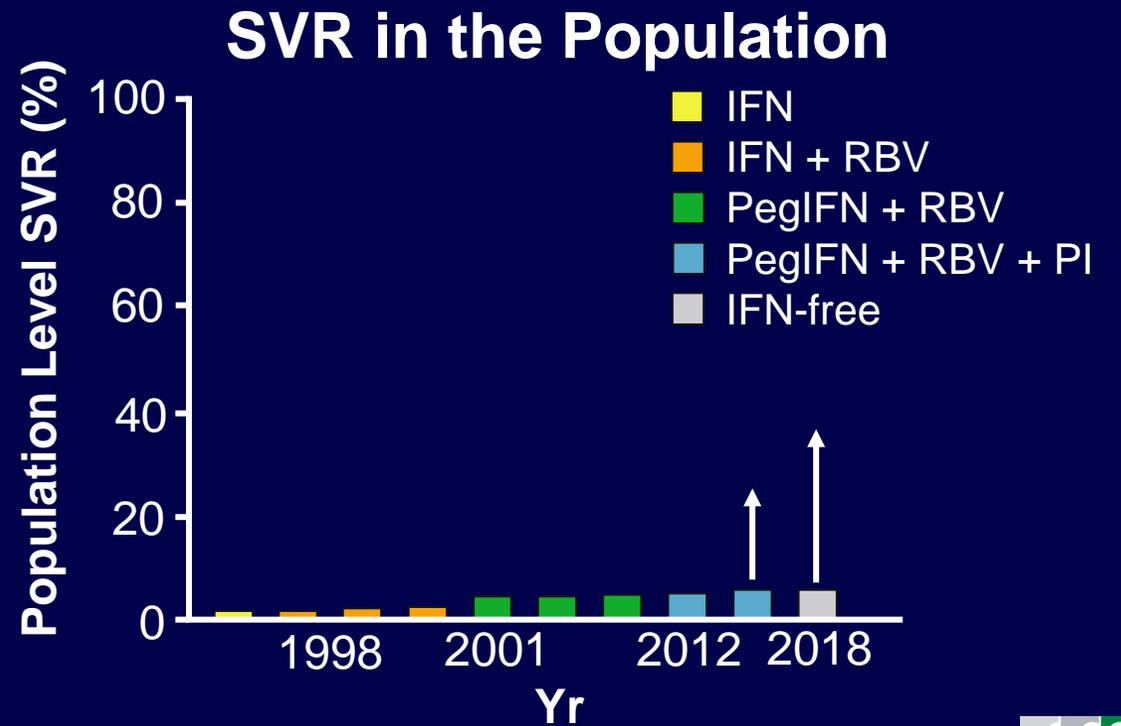
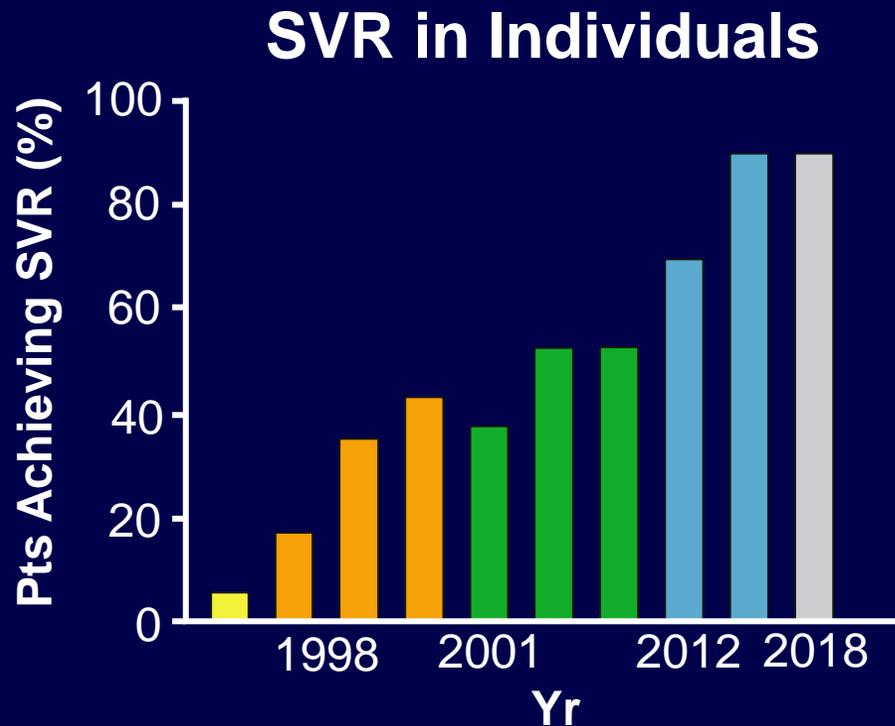


HCV Population

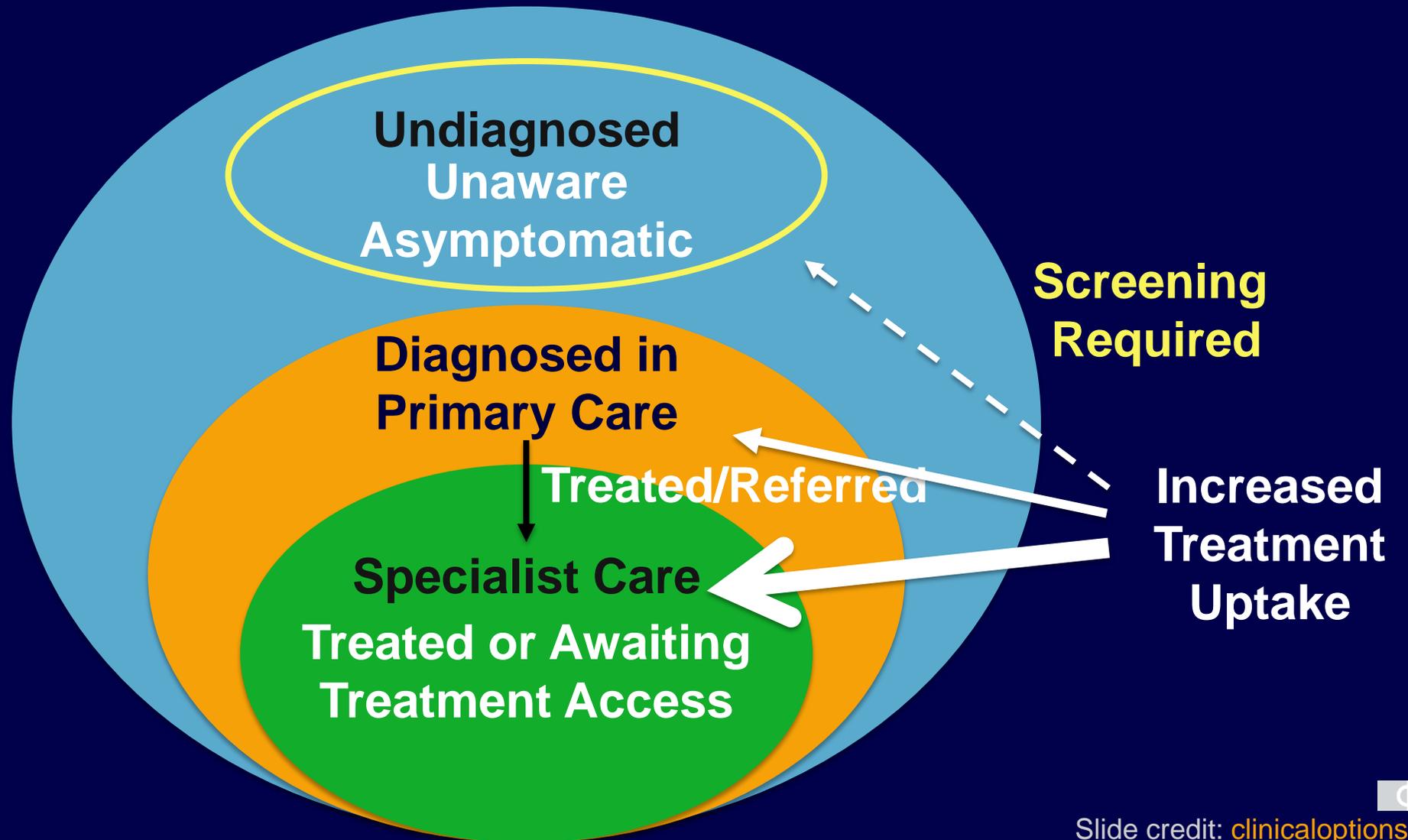


We Need More Than Great Drugs

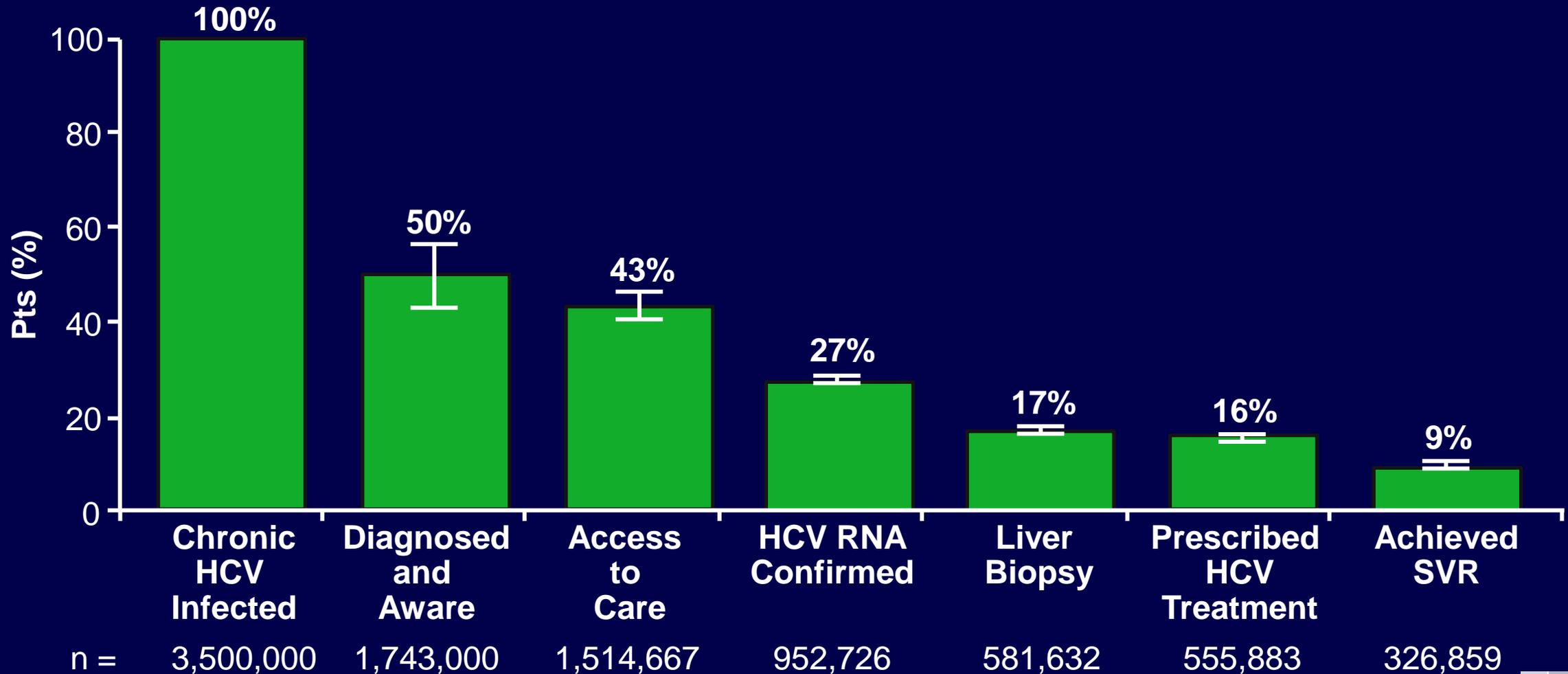
- Curing the individual is now easy
- Curing the population will take a lot more work . . .



HCV Population

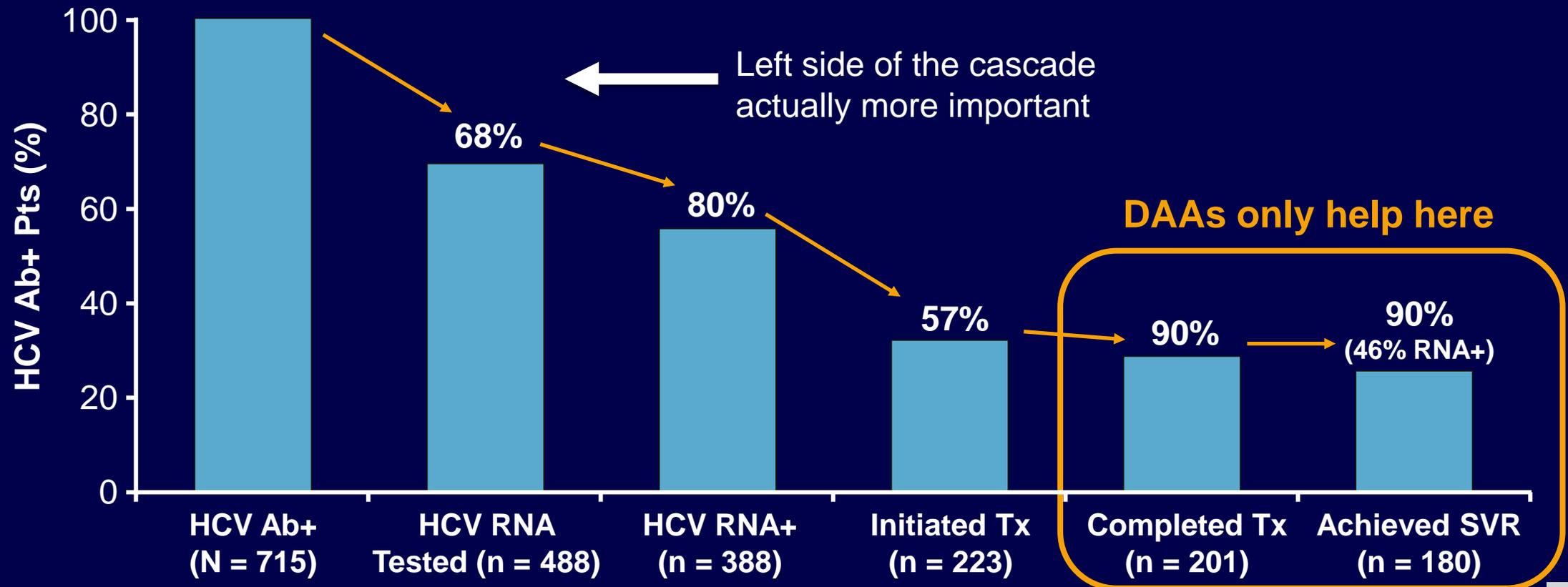


Hepatitis C Virus in the US: Gaps in Current Practice



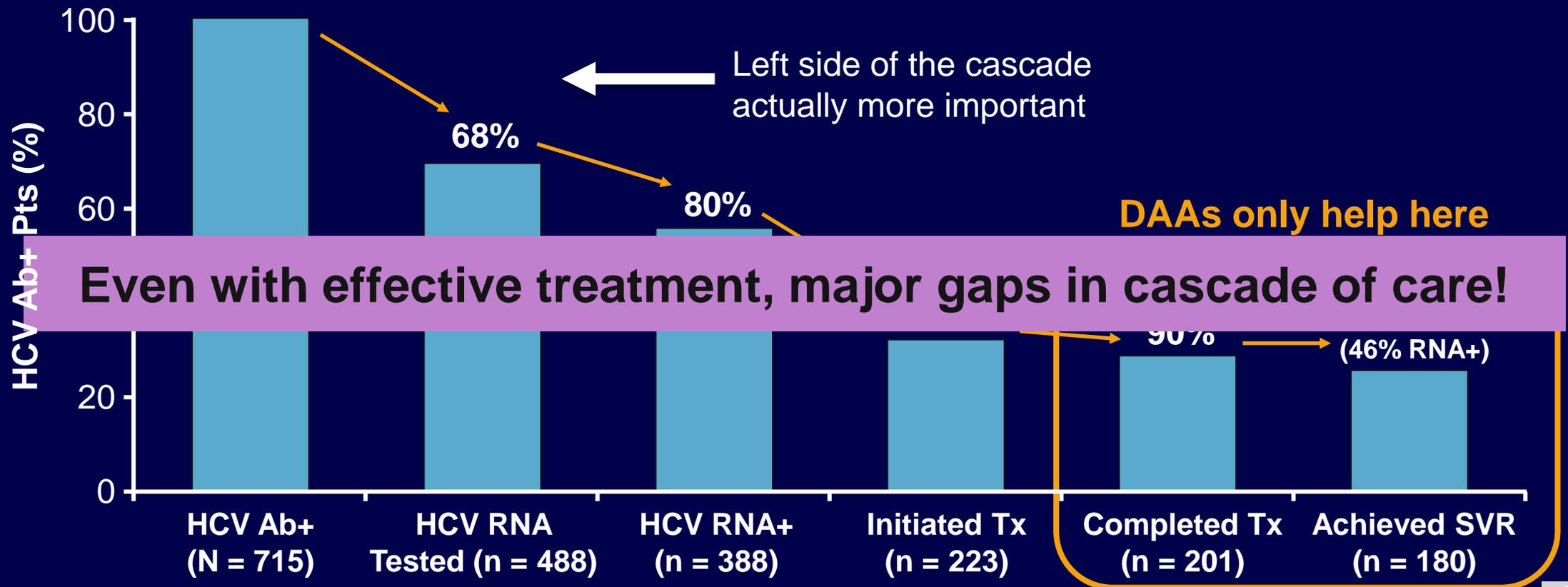
An HCV Elimination Strategy: Cascade of HCV Care—Cherokee Nation, Oct 2012 - July 2015

- Oct 2012: HCV testing reminder added to CNHS EHR → 92,012 visits from October 2012 to July 2015 → 16,772 (18.2%) pts tested → 715 Ab positive (4.3%)



An HCV Elimination Strategy: Cascade of HCV Care—Cherokee Nation, Oct 2012 - July 2015

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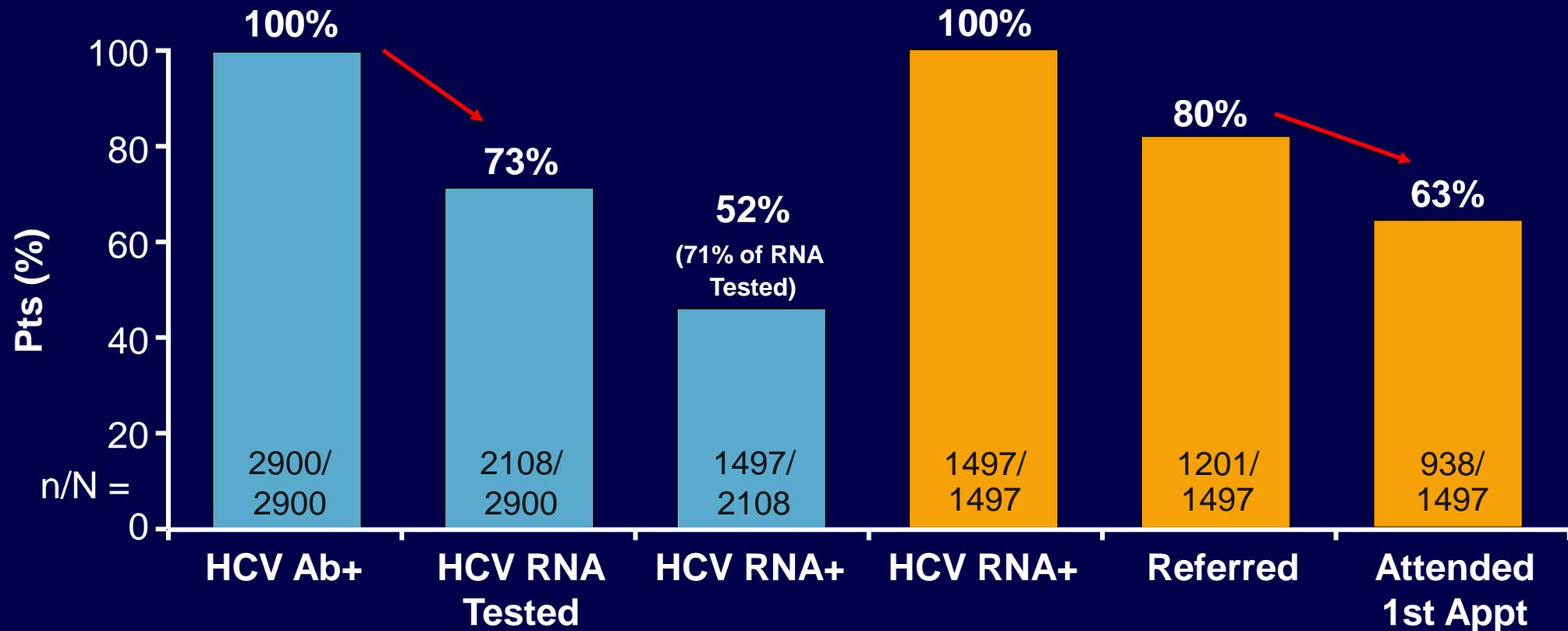
HCV Screening

The Where	The How	The Who
<ul style="list-style-type: none">▪ PCP office—birth cohort▪ Hospital—ED/inpatient▪ Prenatal▪ OST▪ Outreach—homeless shelters, supervised injection sites	<ul style="list-style-type: none">▪ Current—Ab then RNA▪ Point-of-care—Ab+ then RNA▪ Dried blood spot—Ab with reflex RNA▪ Rapid diagnostic test—RNA	<ul style="list-style-type: none">▪ PCP—GP/RN▪ ED staff▪ Peer workers

All interrelated—the *how* will depend on the *who* and the *where*

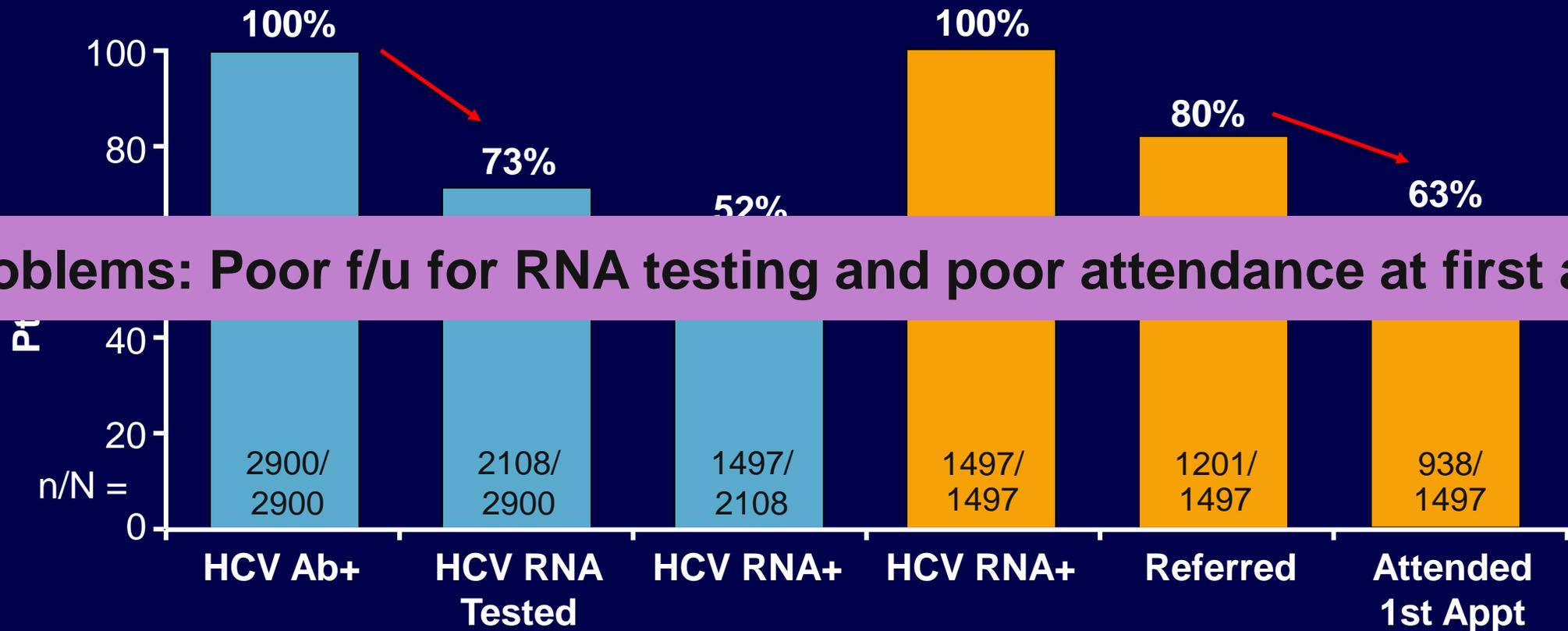
Is Boomer Screening Working?

24,966 boomers tested in urban healthcare settings → 11.6% HCV Ab+!



Is Boomer Screening Working?

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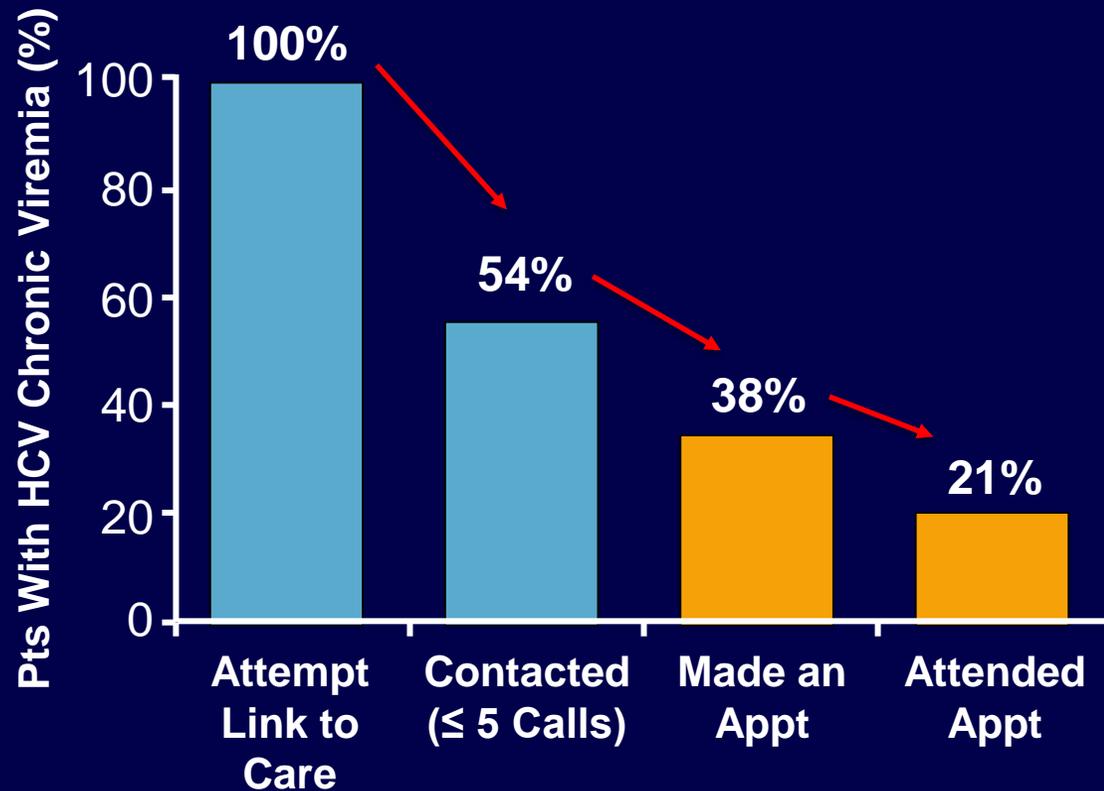


Problems: Poor f/u for RNA testing and poor attendance at first appt



Other Settings: The Emergency Department

2325 boomers tested → 87.3% agreed → 11.1% (170/1529) HCV Ab+!



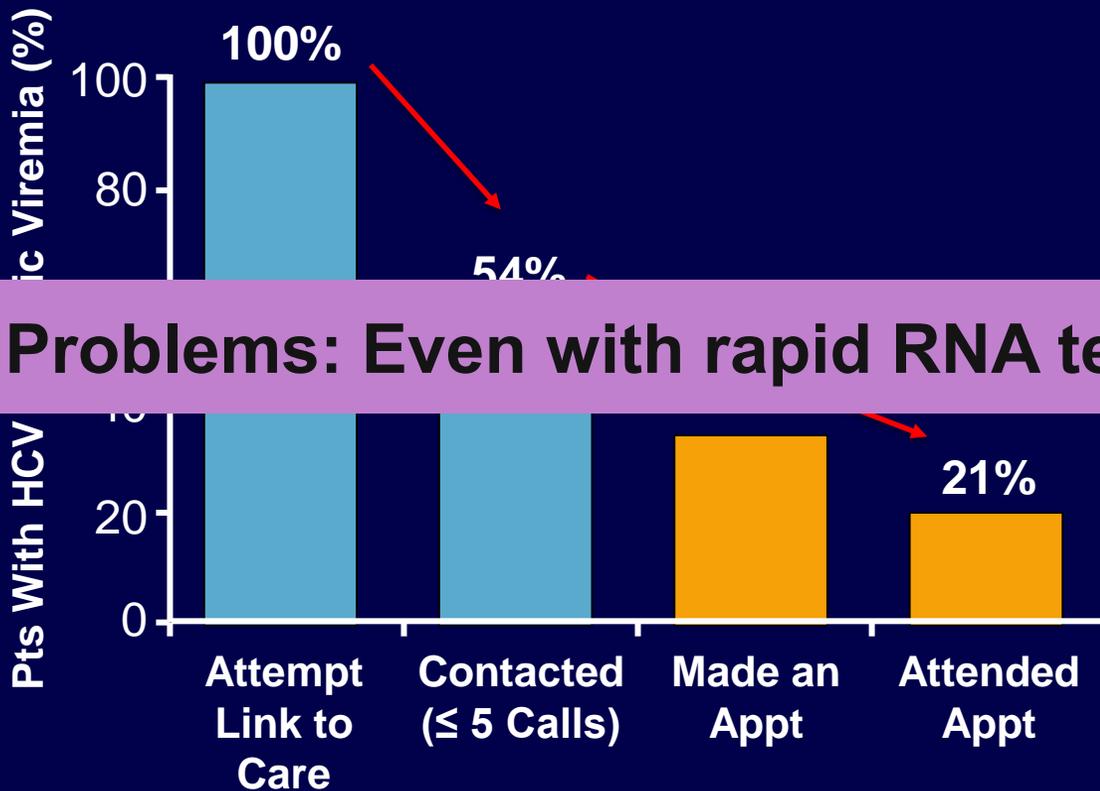
- Of 170 HCV Ab+ → 150 (88%) RNA tested → 102 (68%) RNA+

Characteristic	HCV-Reactive Pts, n (% of Total Screened)
Pts	170 (11.1)
Sex	
▪ Female	57 (7.4)
▪ Male	111 (14.7)
Race	
▪ Black	104 (13.3)
▪ White	63 (8.8)
Insurance	
▪ Private	19 (5.0)
▪ Public/Medicaid	48 (16.8)
▪ Uninsured	55 (16.9)



Other Settings: The Emergency Department

2325 boomers tested → 87.3% agreed → 11.1% (170/1529) HCV Ab+!



- Of 170 HCV Ab+ → 150 (88%) RNA tested → 102 (68%) RNA+

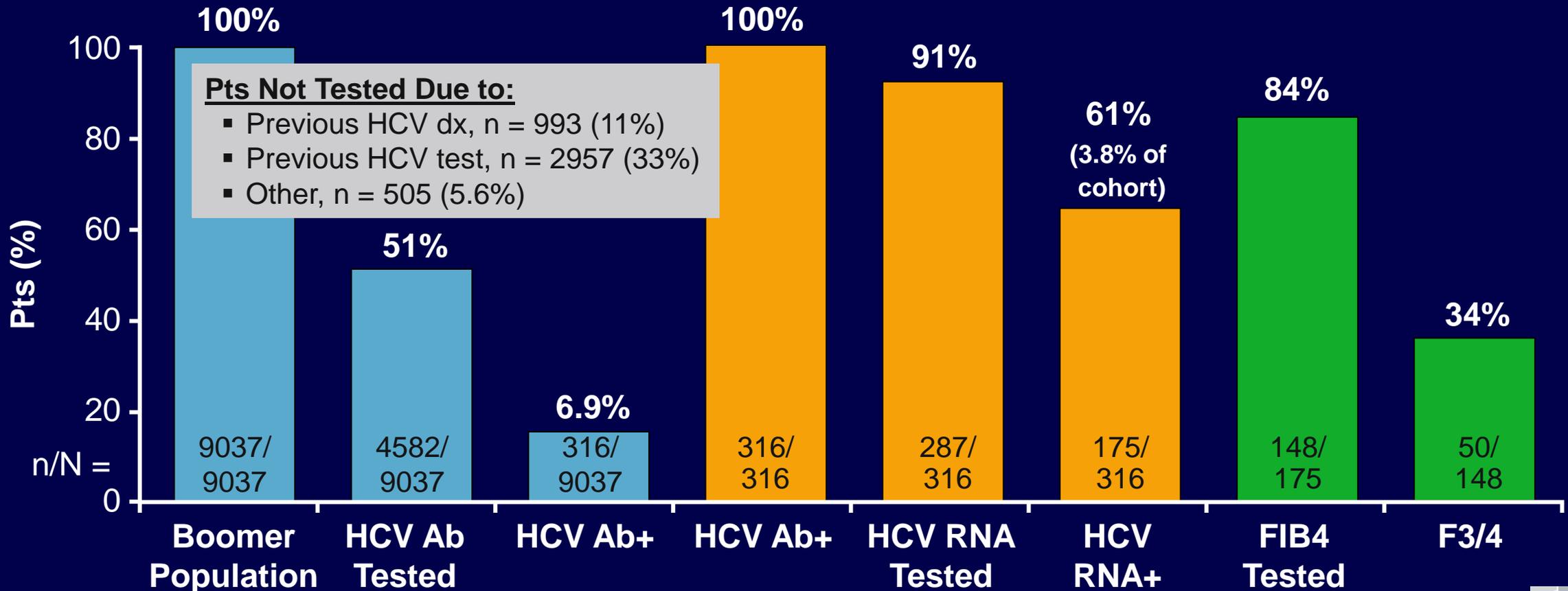
Problems: Even with rapid RNA testing...follow-up a MAJOR problem

Characteristic	HCV-Reactive Pts, n (% of Total Screened)
Total	170 (11.1%)
Sex	
▪ Male	111 (14.7%)
Race	
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Insurance	
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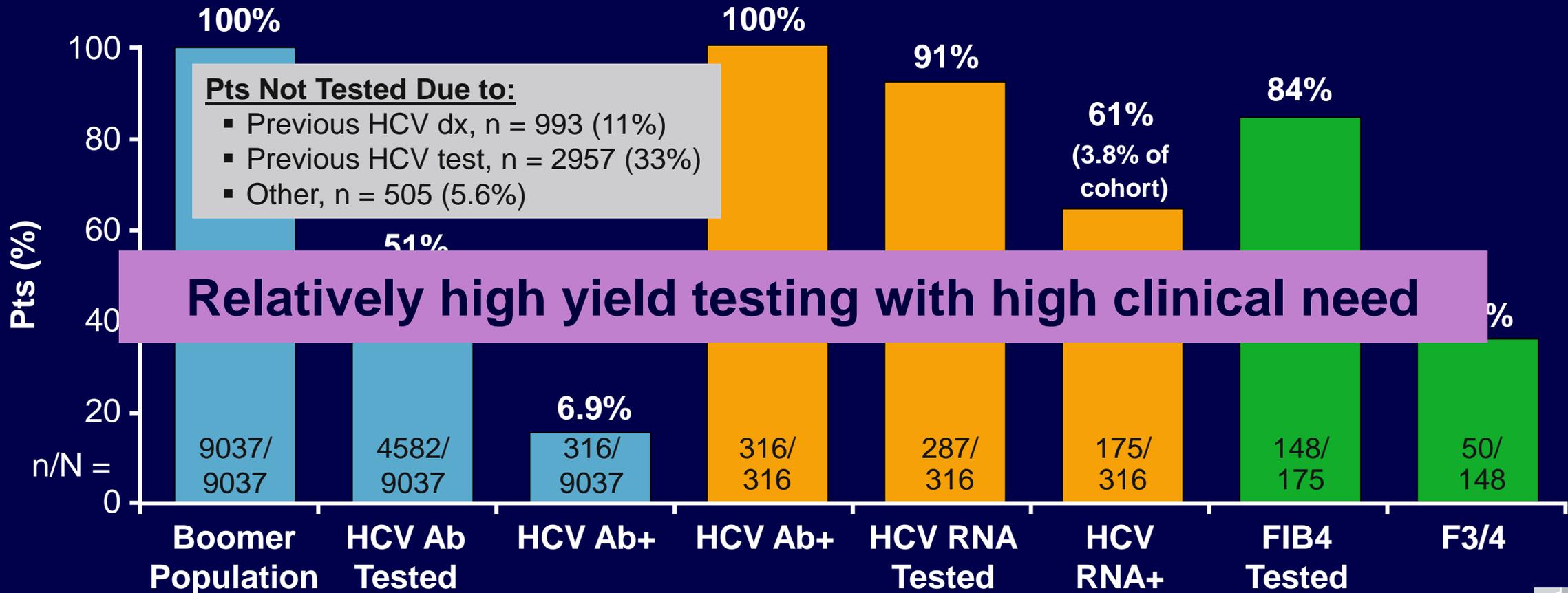
Other Settings: Hospitalized Pts

Safety net hospital—all baby boomers offered testing over 21-mo period



Other Settings: Hospitalized Pts

Safety net hospital—all baby boomers offered testing over 21-mo period



Recurrent Themes

- Urban clinics → high yield HCV Ab+
 - Most have identifiable risk factors but not all
- Drop-off for RNA testing
 - Improved with rapid turn-around or in-hospital testing
- *Major drop-off for linkage to care*
- Treatment access likely an issue for many
- Treatment rates very low

RDTs vs PoCT

- **Rapid diagnostic test:** rapid but requires special equipment ± trained personnel
 - Antibody (blood, serum, or saliva)
 - RNA (blood, serum)
- **Point-of-care test:** rapid and no special equipment or electricity required, easier to perform, no cold chain required
 - Antibody (blood, saliva)
 - RNA (blood)
- **Dried blood spot test**
 - Pros: no blood draw (screening drives, PWID), peer testing—key in certain populations, easy storage → mail to lab, no need for second visit for confirmatory RNA test
 - Cons: smaller volume, no immediate result—need follow-up

RDTs vs PoCT

- **Rapid diagnostic test:** rapid but requires special equipment ± trained personnel
 - Antibody (blood, serum, or saliva)
 - RNA (blood, **Not all tests are created equal!**)
- **Point-of-care test:** no special equipment or electricity required, easier to perform, no cold chain required
 - Antibody (blood, saliva)
 - RNA (blood)
- **Dried blood spot test**
 - Pros: no blood draw (screening drives, PWID), peer testing—key in certain populations, easy storage → mail to lab, no need for second visit for **Not all tests are created equal!** test
 - Cons: time, no immediate result—need follow-up

**More Difficult Than Screening . . . What to Do
With a Positive Test → Linkage to Care!**

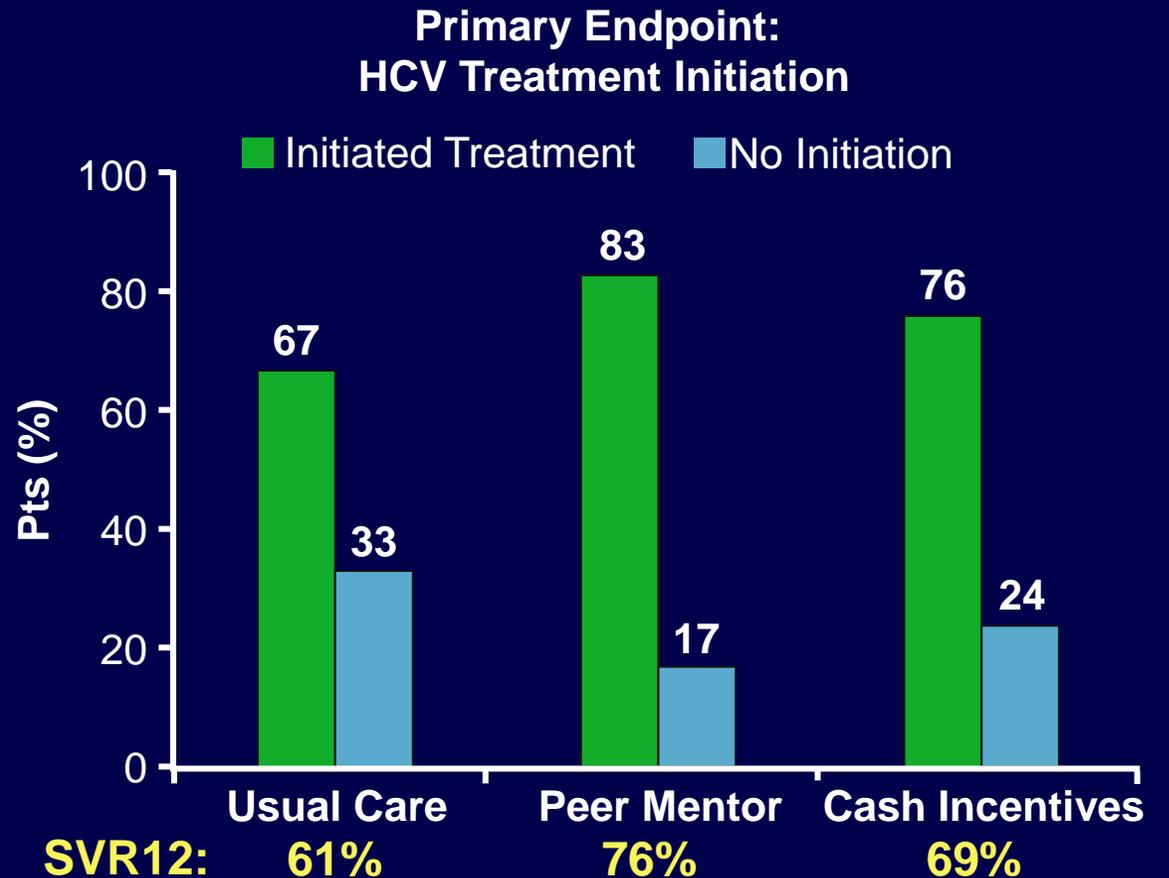


After a Positive Test

- Preferred option
 - Immediate linkage
 - Screening in a setting where care is provided (OST clinic, PCP)
- Second option
 - Facilitated linkage
 - Peer navigators
- Third option (the most common)
 - Referral to a specialist . . .

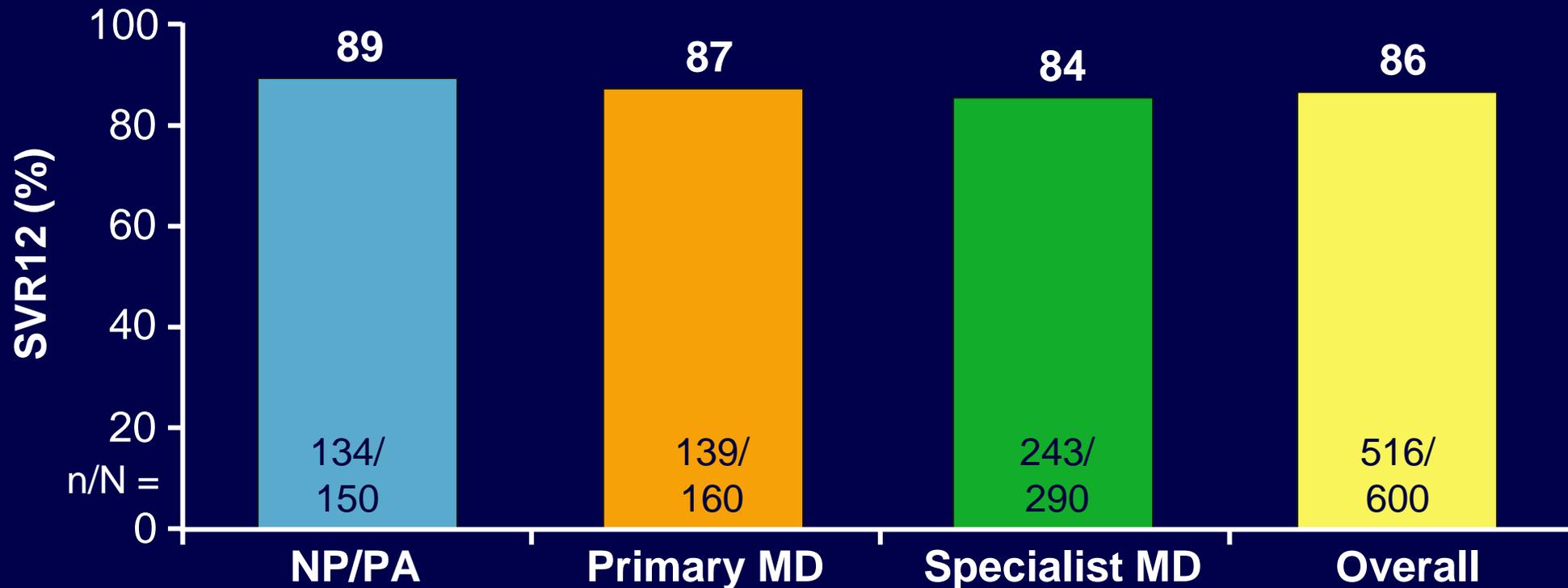
CHAMPS: Impact of Incentives on HCV Treatment Uptake, Cure Among HIV+ PWID

- Novel interventions offered for HIV/HCV GT1-coinfected pts from Johns Hopkins HIV clinic receiving no previous HCV treatment (N = 144)
- Pts randomized 1:2:2 for 8-12 wks of pre-tx intervention followed by 12 wks LDV/SOF
 - **Usual care:** standard HIV care with nursing, pharmacy support, adherence support using Stop Light Protocol
 - **Peer mentor:** Persons with HIV were trained as peer mentors following HCV cure and had in-person contact and dedicated cell phone before, during, after treatment
 - **Cash incentives:** Participants paid on ascending scale contingent on attendance at visits; Max compensation of \$220 US
- 61% male, 93% black, 85% unemployed, 46% urine + for cocaine/heroin, 97% on ART



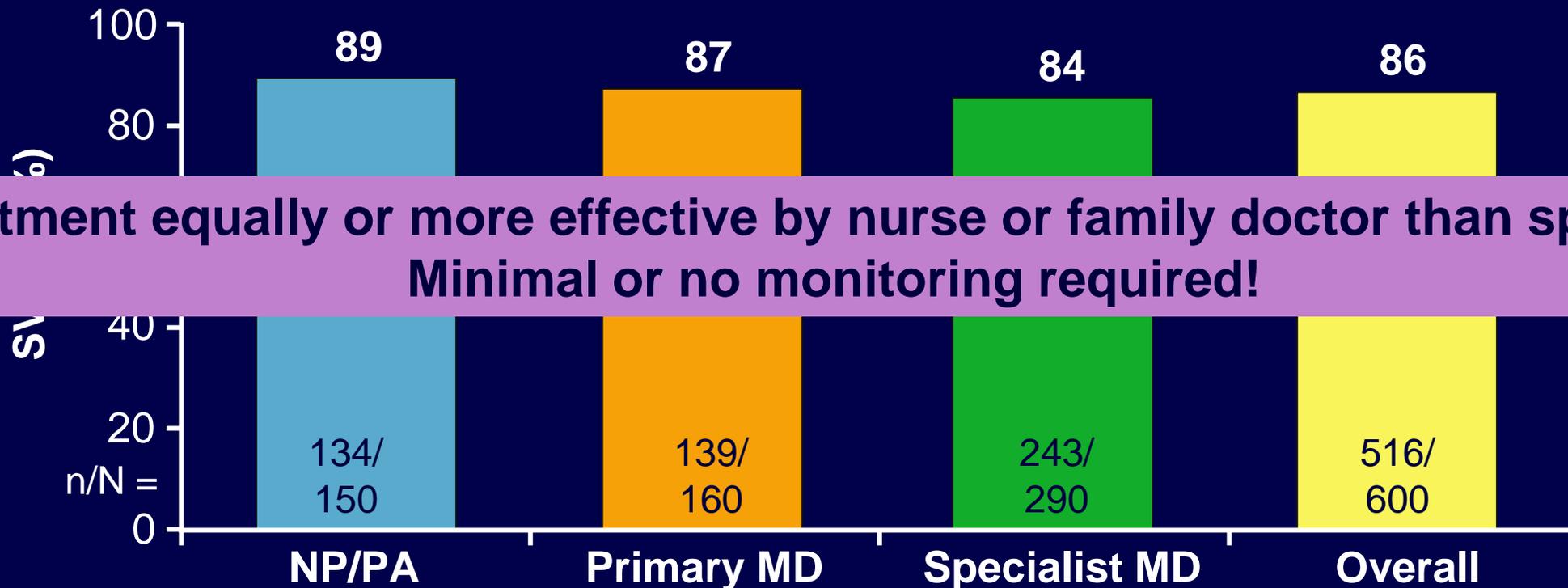
ASCEND: Nonrandomized Phase IV Trial of HCV Treatment Outcomes by DAA Prescriber Type

- Pts (N = 600) from 13 urban, FQHCs in DC, all treated with LDV/SOF per FDA prescribing info; all providers given 3-hr training in AASLD/IDSA HCV guidance



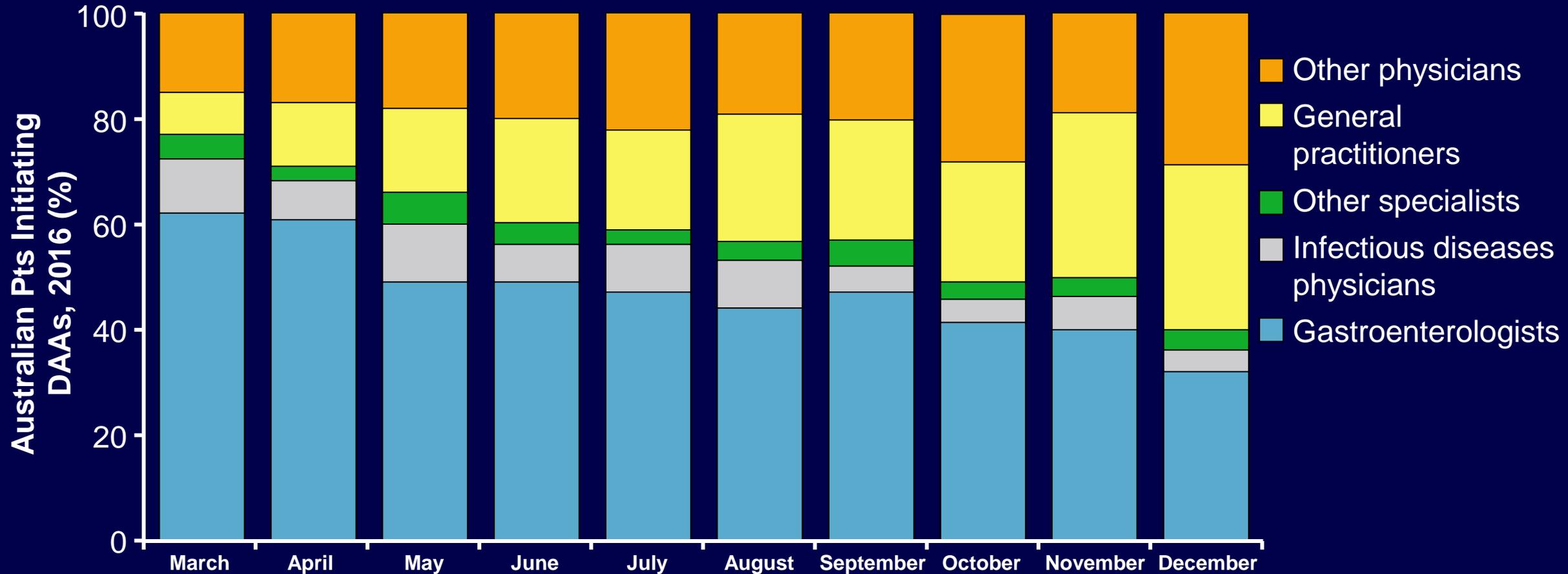
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Treatment equally or more effective by nurse or family doctor than specialist.
Minimal or no monitoring required!

Nonspecialists Can Effectively Treat HCV



Project ECHO: A Key to Linkage to Care

- Linking PCPs to specialists
- Program is expanding rapidly
- Expert care does not require MD
- Enables new treaters
- Knowledge translation
- Facilitates linkage to care
- Allows people to be treated by people and in settings they know and trust

Many HCV treatment support options available

Viral Hepatitis Care Network (VIRCAN)



- Uses a “**hub and spoke**” model to diagnose and treat pts “**where they are**”
- Local screening and local treatment
- PoC Ab test with reflex RNA (DBS)
- Linkage to care simultaneous with screening—pts seen at time of Ab+
 - In ED/walk-in clinic
 - In addiction center
 - In community health center

Coupling HCV Screening With Addiction Services

- **Addiction services**

- Needle syringe program
- Opioid substitution therapy
- Harm reduction outreach
- Supportive housing
- Daily drop-in center

- **VIRCAN HCV Program**

- Peer counselors but *no trained medical staff*
- Peer HCV screening and counseling using PoC or DBS



Geography Can Be a Major Challenge

- High burden of HCV in Canadian First Nations/aboriginal population
 - Remote communities → no road access
 - Very limited resources
- HCV screening
 - Community leaders (chief and council) support
 - Peer screeners → dried blood spot screening
 - Peer and RN counseling
- Linkage to care
 - Local MD/RN—treatment by ECHO model
 - OST clinics
- 2 yrs of planning; finally paying dividends

Role of the PCP

- **Screening! Screening! Screening!**
- Treatment or linkage to care
 - Not all will treat, but for those who do, it eliminates loss between positive screening test and linkage to care
 - Have to have an interest—addiction specialists/OST, inner city, prison, immigrant population, rural (?)
 - Need some training/mentoring
 - If not treating, must establish strong system for efficient linkage to specialist
- Follow-up
 - Post SVR—monitor for reinfection (if needed)
 - HCC surveillance

Role of Specialist (ID/GI)

- **Champion HCV elimination!**
- Education
 - CME for PCPs and luminal GI
 - Preceptorships
- Mentoring
 - Project ECHO
 - Telementoring
- Develop screening programs
 - ED, inpatient, other settings



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Treating the 33%: Expanding Therapy to the Previously Excluded

Christian B. Ramers, MD, MPH



Who Has Been Left Behind?

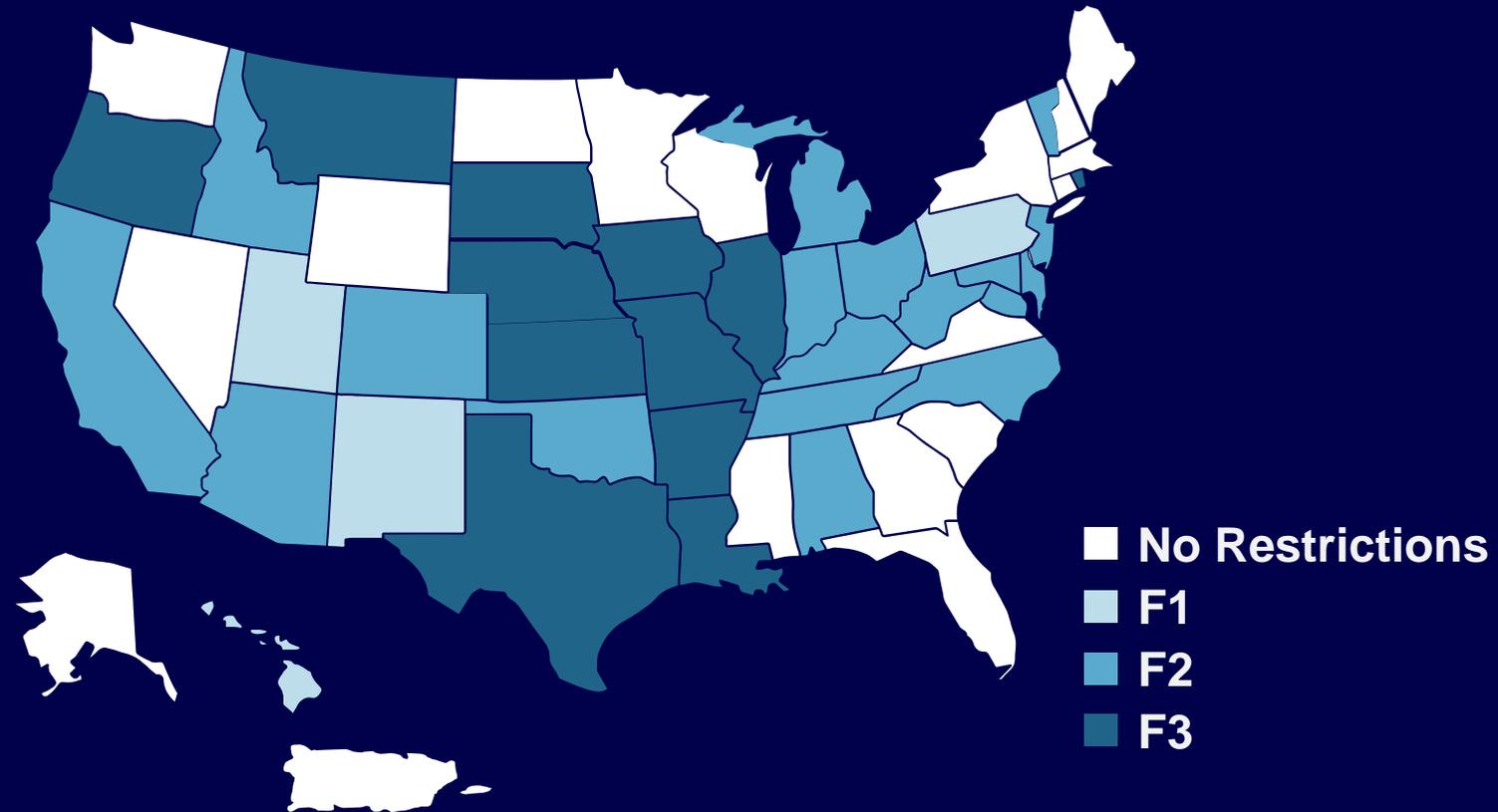


Historical Exclusions for HCV Therapy

- Active PWID
- Homelessness
- EtOH use
- Adherence concerns
- Mild liver disease
- Advanced liver disease
- Mental health diagnoses (IFN)
- Autoimmune disease (IFN)
- Complex cardiopulmonary disease (RBV)

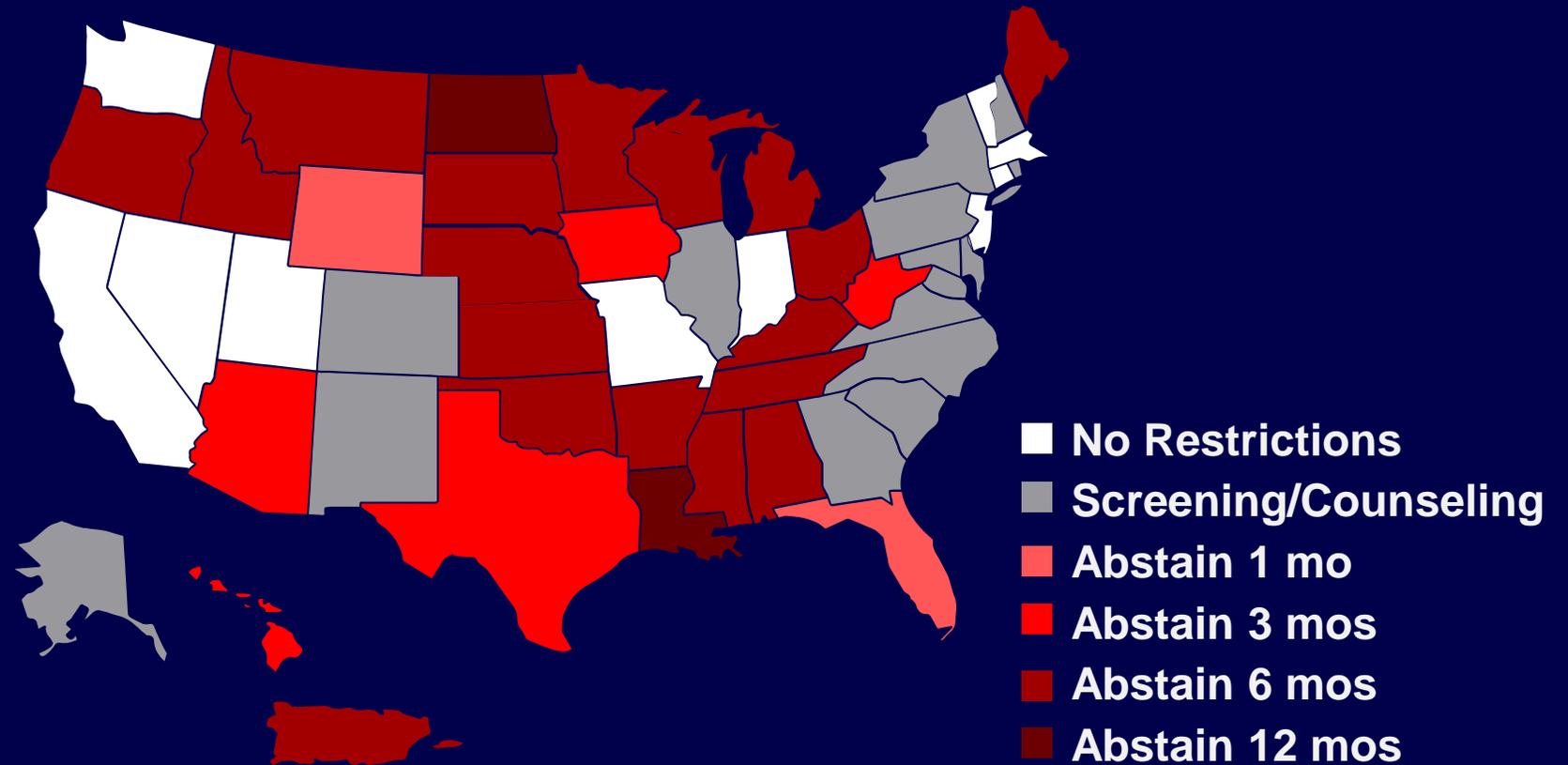
2017 NVHR Update: Reduced Treatment Access in Many Settings for Pts With Mild Liver Disease

2017 Medicaid FFS Liver Damage Restrictions for HCV Treatment



2017 NVHR Update: Drug/Alcohol Use Leads to Reduced Treatment Access in Some Settings

2017 Medicaid FFS Sobriety Restrictions for HCV Treatment



Are There Issues in Treating All With HCV?

- Prescriber concerns
 - Perceived lack of value in treating certain pts
 - Maladherence
 - Medical contraindications
- Payer restrictions
- Patient factors
 - Competing priorities
 - Challenge of screening asymptomatic pts

HCV Treatment as Prevention

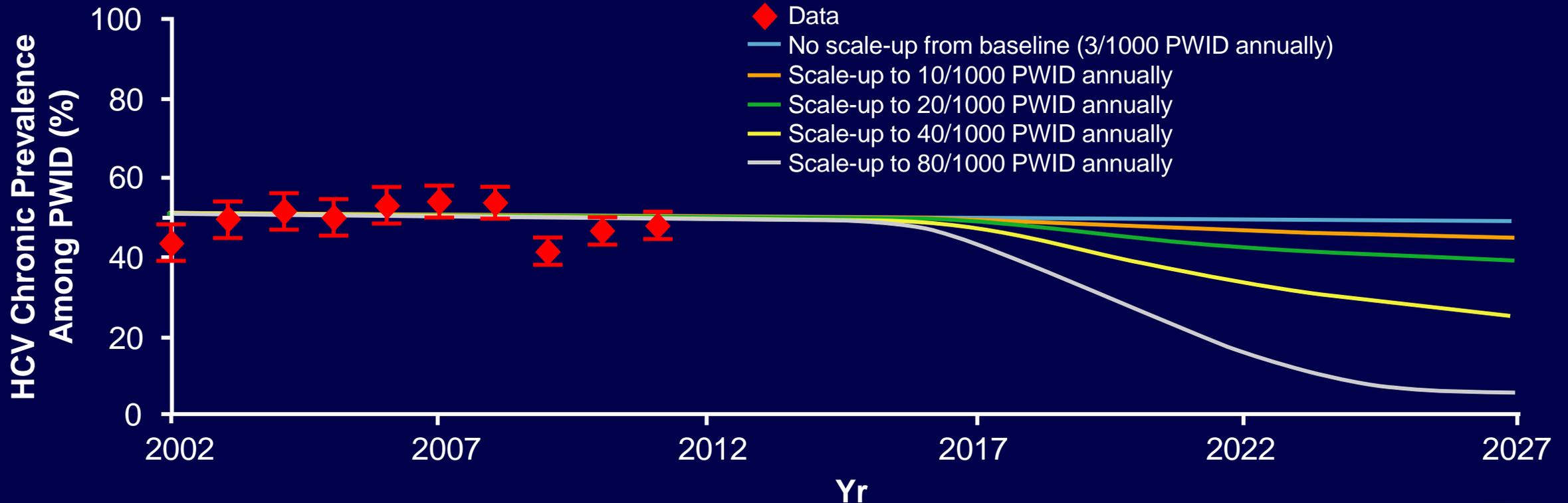


AASLD/IDSA HCV Treatment Guidelines: PWID

- “Recent or active IDU should not be seen as an absolute contraindication to HCV therapy”
- “Scaling up HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the US and globally”

HCV Treatment Can Prevent Onward Transmission

- Observed and modeled HCV chronic prevalence among PWID in Melbourne, Australia



Global Call for HCV Elimination

- Vision: “A world where viral hepatitis transmission is stopped and everyone has access to safe, affordable, and effective treatment and care”
 - 2020 target: 3 million HCV infections treated
- **Feasible** by scaling up **6 key interventions** to high coverage:
 - Hepatitis B vaccination (including birth dose)
 - **Safe injection practices and safe blood**
 - **Harm reduction for injecting drug users**
 - **Safer sex (including condom promotion)**
 - Hepatitis B treatment
 - **Hepatitis C cure**

2030 Targets

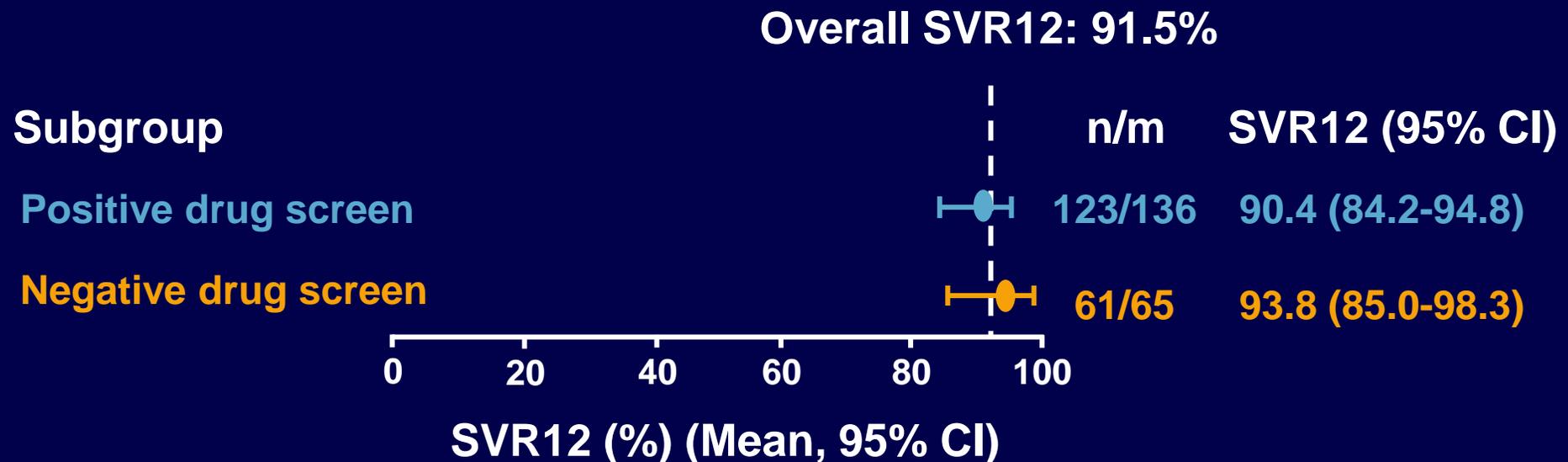
90% Diagnosed

80% Treated

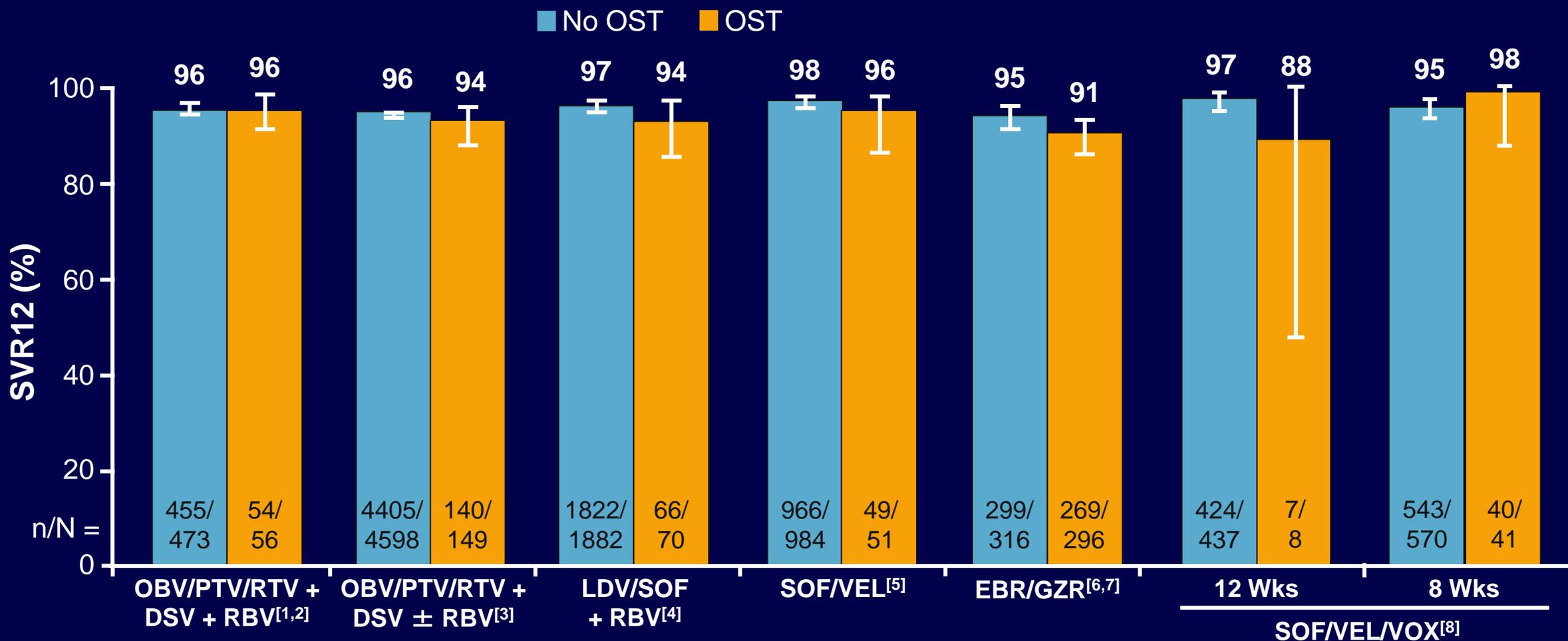
65% Reduced Mortality

C-EDGE CO-STAR: Impact of Baseline Drug Use on SVR

- Treatment-naive F0-4 PWID with GT1/4/6 HCV who were on OST were treated with grazoprevir/elbasvir (N = 301)
 - > 40% had injection drug use during therapy (excluding cannabinoids)



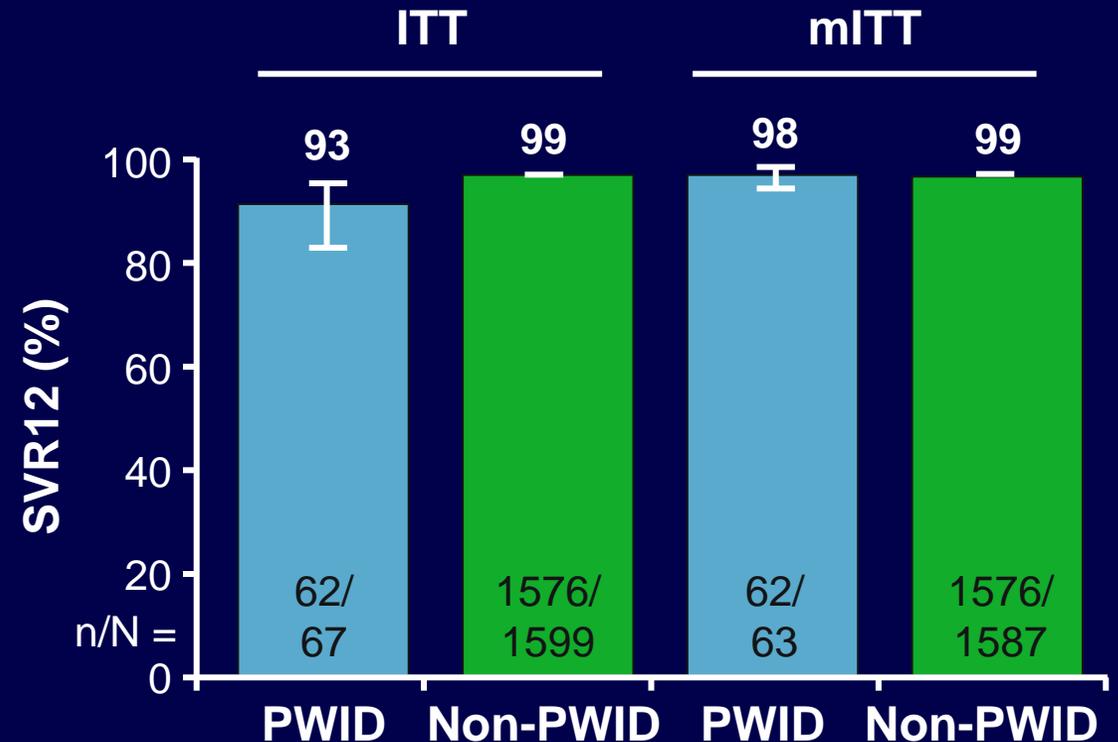
IFN-Free DAA Therapy: Opioid Substitution Therapy vs No Opioid Substitution Therapy



GLE/PIB in Pts With GT1-6 HCV and Recent Drug Use

- Pooled analysis from 6 phase III trials of GLE/PIB for 8 or 12 wks to evaluate outcomes in pts with recent IDU (self reported ≤ 12 mos before screening and/or positive urine drug screen)
 - Non-PWID: n = 1599; PWID: n = 67
 - $\geq 90\%$ adherence: 98% in PWIDs

SVR12 by GT (mITT), %	PWID	Non-PWID
GT1	100	99
GT2	100	99
GT3	97	98
GT4-6	100	99



SIMPLIFY: SOF/VEL for 12 Wks in Recent IDU

- International, open-label, single-arm phase IV trial of pts with GT1-6 HCV infection and recent (previous 6 mos) IDU: N = 103
 - Cirrhosis 9%; GT1: 35%; GT2: 5%; GT3: 58%; GT4: 2%
 - At screening: 57% on OST, 74% injected in past mo
- 96% completed 12 wks of SOF/VEL
- **SVR12: 94% (96/102)**
 - No VF and 1 relapse/reinfection (sequence analysis ongoing)

Treatment Options for Opioid Use Disorder

- **Methadone**, long-acting PO opioid agonist
 - Must be delivered in methadone treatment center
- **Buprenorphine**, short-acting SL/TD partial agonist
 - Prescribed by primary care clinician (MD, NP, PA) with SAMHSA-approved waiver
- **LA-naltrexone**, long-acting IM opioid antagonist
 - No restrictions, may be court mandated
- **Detox → abstinence**

C-SCOPE: Perceived Barriers to HCV Care Among Physicians Providing OAT

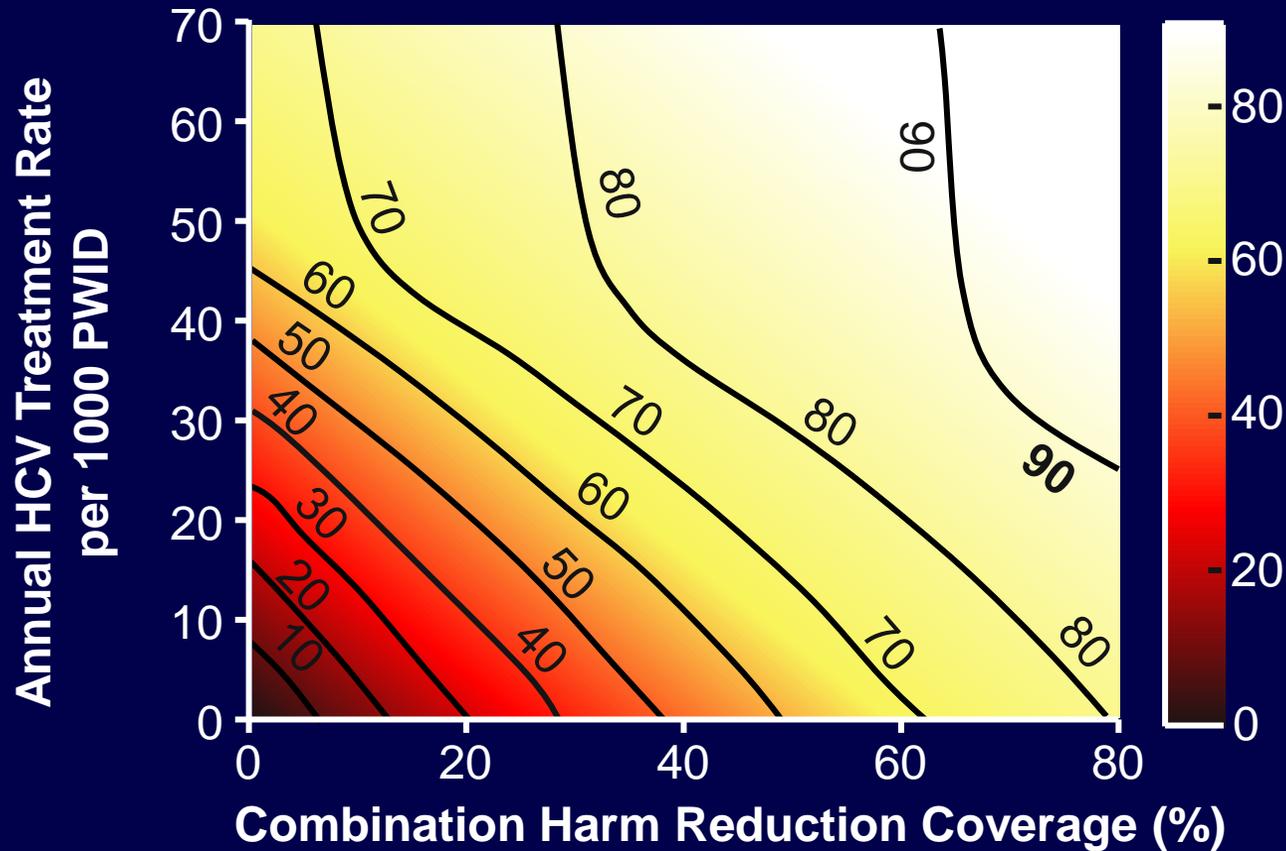
- Self-administered survey of physicians at clinics providing OAT April-May 2017: N = 203
- 85% perceived HCV testing and 82% perceived HCV treatment of PWIDs as important

Perceived Barriers to HCV Testing, Evaluation, Treatment	Mean Likert Scale Score* (N = 203)
Lack of funding for noninvasive liver disease testing	2.78
Lack of funding for new DAA therapies	2.76
Reimbursement restrictions based on drug and/or alcohol use	2.73
Long wait times for pts to see HCV specialist	2.71
Lack of case managers or link-to-care coordinators	2.35
Need for off-site referral for liver disease assessment/treatment	2.31
Lack of peer-support programs	2.27
Nonattendance for referral appointments	3.05
Pts having difficulty navigating the health system	3.01

*5-point Likert scale: 1 = not a barrier, 3 = moderate barrier, 5 = extreme barrier.

Modeling: HCV Elimination Possible in PWIDs With Treatment + Harm Reduction

10-Yr Impact on Incidence
Assuming 40% HCV Prevalence Among PWIDs



White region of graph: > 90% incidence reduction within 10 yrs

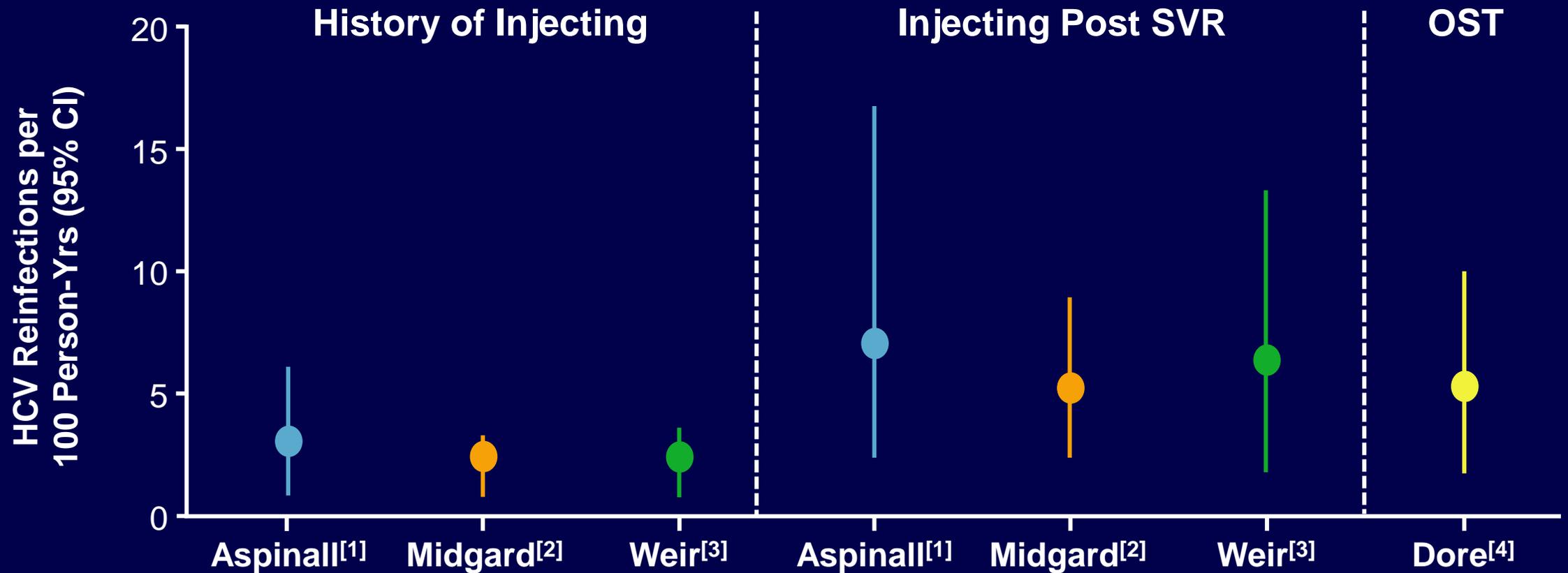
HCV Treatment-as-Prevention (TAP) Study

- Goal to determine if treating HCV among PWID in Melbourne reduces transmission within the community and decreases prevalence
- Community-based program using “treatment vans” to recruit and treat with nurse-led model of HCV care
- 3 HCV treatment groups
 - All participants treated at end of project only
 - Immediate treatment for primary participants only; secondary participants treated at end of project
 - Immediate treatment for primary and secondary participants - “bring your friends” approach

HCV Reinfection



HCV Reinfection by Study Population



1. Aspinall EJ, et al. Clin Infect Dis. 2013;57(suppl 2):S80-S89. 2. Midgard H, et al. J Hepatol. 2016;64:1020-1026. 3. Weir A, et al. Drug Alcohol Depend. 2016;165:53-60. 4. Dore GJ, et al. Ann Intern Med. 2016; 2016;165:625-634.



Slide credit: clinicaloptions.com

Co-STAR Part B: HCV Reinfection Rate Among Pts on OAT Treated With EBR/GZR

- Co-STAR **Part A**: phase III trial of EBR/GZR for 12 wks in pts on OAT (N = 296); reinfection rate: 3.4/100 PY (n/N = 6/296) through FW24
- Co-STAR **Part B**: 3-yr observational study of participants who received at least 1 dose of EBR/GZR in Part A; 199/296 Part A participants enrolled in Part B
- Positive urine drug screening rates stable at 59% to 62% throughout Parts A and B
- 4 more HCV recurrences in Part B (in addition to 6 in Part A)
 - Spontaneous clearance occurred in 3 of 5 reinfections detected through FW12 and 0 of 5 reinfections detected after FW12

Reinfection Rate From EOT Through Part B	Rate/100 PY	95% CI
Overall	2.3	1.1-4.3
If including only persistent infections	1.6	0.7-3.4

Specific Issues on HCV Reinfection for PWID

- **Acknowledgement:** There will be cases of HCV reinfection; if there are no cases, it is not a current PWID population
- **Harm reduction optimization (NSP, OST access):** HCV reinfection incidence will reflect HCV incidence in the setting
- **Rapid scale-up:** A slow scale-up will create HCV “susceptible” PWID without reduction in viremic pool
- **Individual-level strategies:** Treatment of injecting partners crucial
- **Access to retreatment:** Without stigma and discrimination
- **Community engagement and partnership:** Use of peer workers

Key Take-home Points

- Guidelines recommend treatment for all, notwithstanding potential barriers
- Challenging populations can achieve comparable SVR12 rates to other populations
- HCV treaters should offer appropriate referrals and be familiar with harm reduction strategies
- HCV Treatment as Prevention has potential to decrease ongoing transmission
- HCV elimination only possible with engagement, linkage, and treatment of more challenging populations



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Curing the 10%: Evolving Options for DAA- Experienced Patients

Paul Y. Kwo, MD



Overview of DAA Failure in GT1 and 3: General Principles



GT1 HCV: Low VF Rate With DAA Regimens in Clinical Trials, but Not 0%

IFN-Free Regimens for GT1*	Duration, Wks	Trials (Pre-2017)
Ledipasvir/sofosbuvir	12	ION-1, ^[1] ION-2, ^[2] ION-3 ^[3]
Sofosbuvir/velpatasvir	12	ASTRAL-1 ^[4]
Elbasvir/grazoprevir 1a (± NS5A RAS) and 1b	12	C-EDGE ^[5]
Ombitasvir/ritonavir/paritaprevir + dasabuvir 1b	12	PEARL-III, ^[6] TURQUOISE-III ^[7]
Ombitasvir/ritonavir/paritaprevir + dasabuvir + RBV 1a	24	PEARL-IV, ^[6] TUROQUOISE-II ^[8]
Simeprevir + sofosbuvir ± RBV	12-24	OPTIMIST-1, ^[9] COSMOS ^[10]
Daclatasvir + sofosbuvir	12	ALLY-2 (HIV coinfectd) ^[11]

*Includes treatment-naive and treatment-experienced pts ± cirrhosis. Does not include nonresponders to SOF + RBV.

No SVR: 3%

SVR: 97%
(n/N = 1980/2040)

Response



GT3 HCV: VF Rate With DAA Regimens in Clinical Trials Slightly Higher Than for GT 1

IFN-Free Regimens for GT 3*	Duration, Wks	Trials (Pre-2017)
DCV + SOF	12	ALLY-3 ^[1]
SOF/VEL or SOF + RBV	12-24	ASTRAL-3 ^[2]

*Included treatment-naive and treatment-experienced patients ± cirrhosis

GT1 and 3 remain the most challenging when it comes to retreatment after DAA failure

No SVR: 12%

SVR: 88%
(n/N =
620/704)

Response

1. Nelson DR, et al. Hepatology. 2015;61:1127-1135.
2. Foster GR, et al. N Engl J Med. 2015;373:2608-2617.



DAA Drug Classes Are Important in Planning Retreatment Strategies

Inhibitor Class	Reminder	Examples
Targeting HCV Protein Processing		
NS3/4A protease	PREVIR	▪ Glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir
Targeting HCV Replication		
NS5B polymerase	BUVIR	▪ Nucleos(t)ide: sofosbuvir ▪ Non-nucleos(t)ide: dasabuvir
NS5A	ASVIR	▪ Daclatasvir, elbasvir, ledipasvir, ombitasvir, pibrentasvir, velpatasvir

- **Resistance is shared within classes**
 - New-generation drugs may overcome single-site polymorphisms associated with in-class resistance
- **Resistance mutants are sensitive to drugs from other classes**
 - Basis for combination DAA therapies

Most Common, Clinically Important RASs to DAAs

DAA	GT1a				GT 1b		GT 3a
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N	Y93H
Ledipasvir	20x	> 100x	> 100x / > 100x	> 1000x / > 10,000x	> 100x > 50x	> 100x / --	NR
Ombitasvir	> 1000x	> 100x	< 3x > 100x	> 10,000x / > 10,000x	< 10 x	20x / 50x	NR
Daclatasvir	> 100x	> 1000x	> 100x / > 1000x	> 1000x / > 10,000x	< 10 x	20x / 50x	> 1000x
Elbasvir	20x	> 100x	> 10x > 100x	> 1000x / > 1000x	< 10 x	> 100x / --	NR
Velpatasvir	< 10x	< 3x	20x / 50x	> 100x / > 1000x	< 3x	< 3x / --	> 100x
Pibrentasvir	< 3x	< 3x	< 3x	< 10 x	< 3x	< 3x / --	< 3x

■ < 3-fold change

■ < 10-fold change

■ < 10- to 100-fold change

■ > 100-fold change

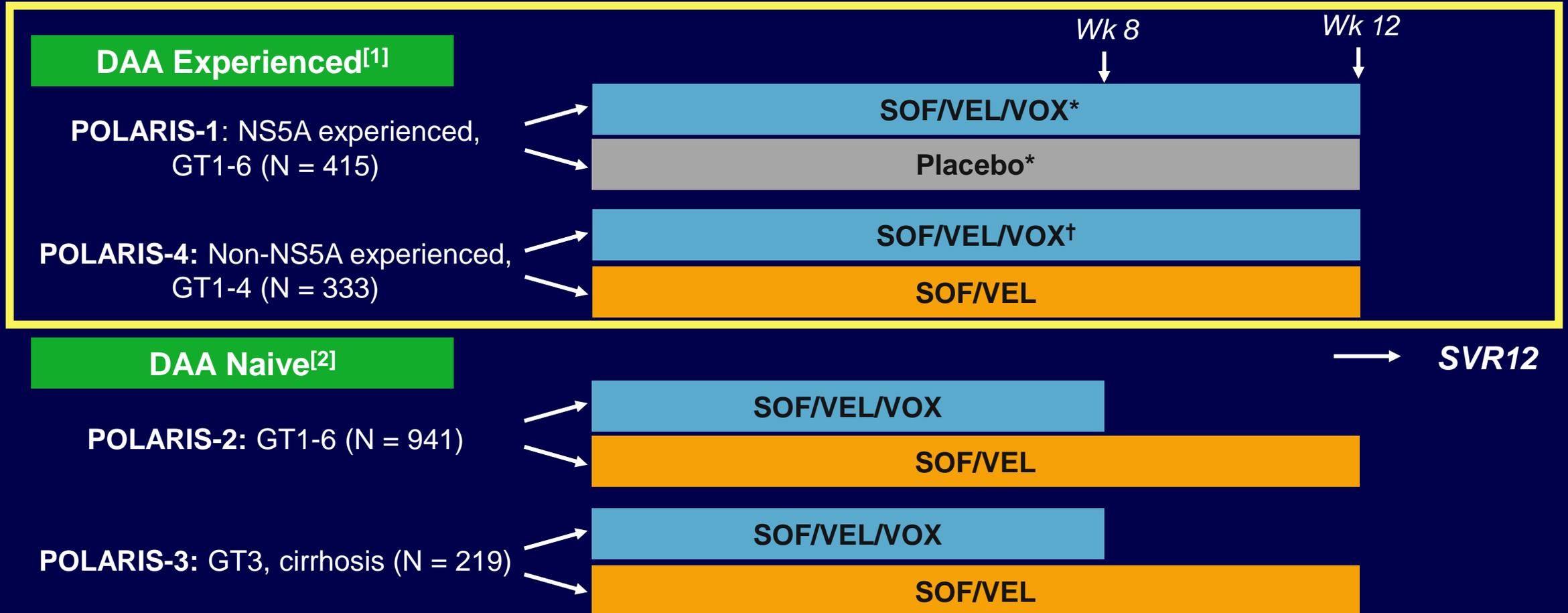
New Options for Retreating DAA Failure



Sofosbuvir/Velpatasvir/Voxilaprevir

- SOF: potent pangenotypic nucleoside polymerase inhibitor
- VEL: potent pangenotypic NS5A inhibitor
- VOX: potent pangenotypic NS3/4A protease inhibitor
- **SOF/VEL/VOX:** once daily, oral, fixed-dose combination (400/100/100 mg) for GTs 1-6

POLARIS Phase III: 4 Trials of SOF/VEL/VOX



*Only pts with GT1 infection randomized to SOF/VEL/VOX vs placebo. All others received SOF/VEL/VOX.

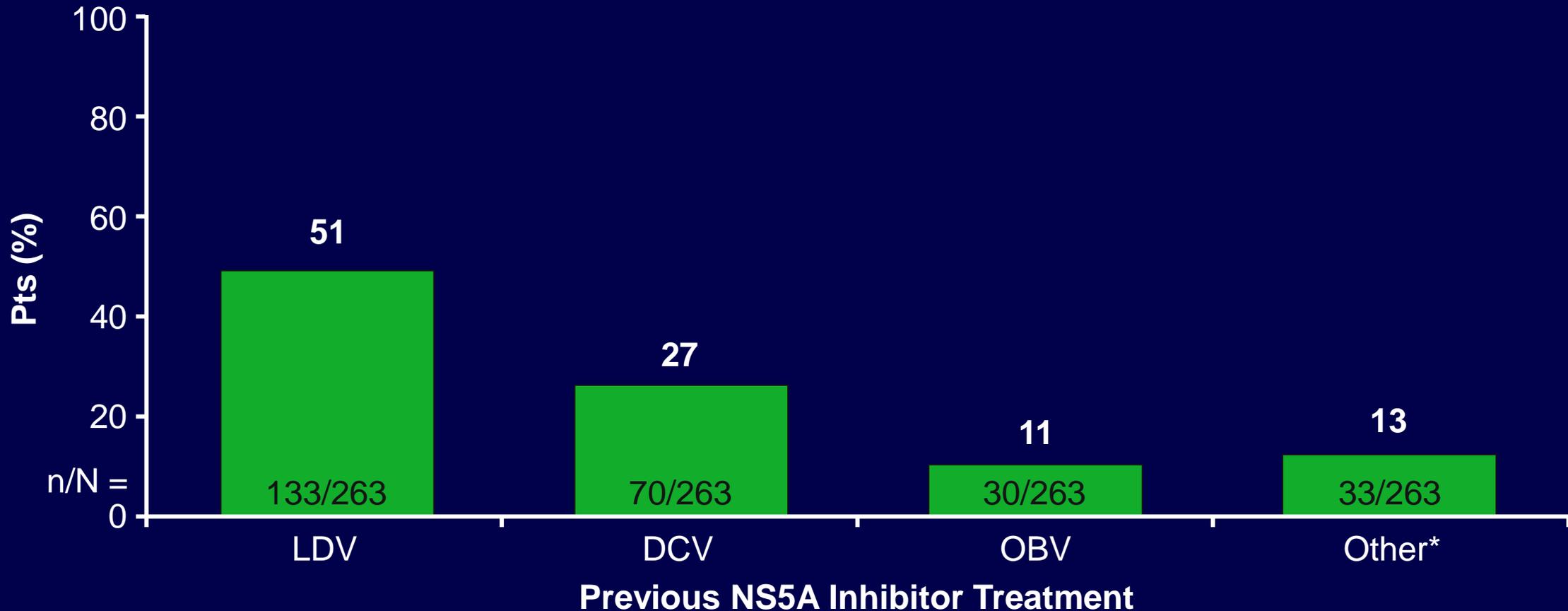
[†]All pts with GT4 infection received SOF/VEL/VOX.

1. Bourlière M, et al. N Engl J Med. 2017;376:2134-2146.

2. Jacobson IM, et al. Gastroenterology. 2017;153:113-122.



POLARIS-1: SOF/VEL/VOX for 12 Wks in NS5A Inhibitor-Experienced GT1-6 HCV

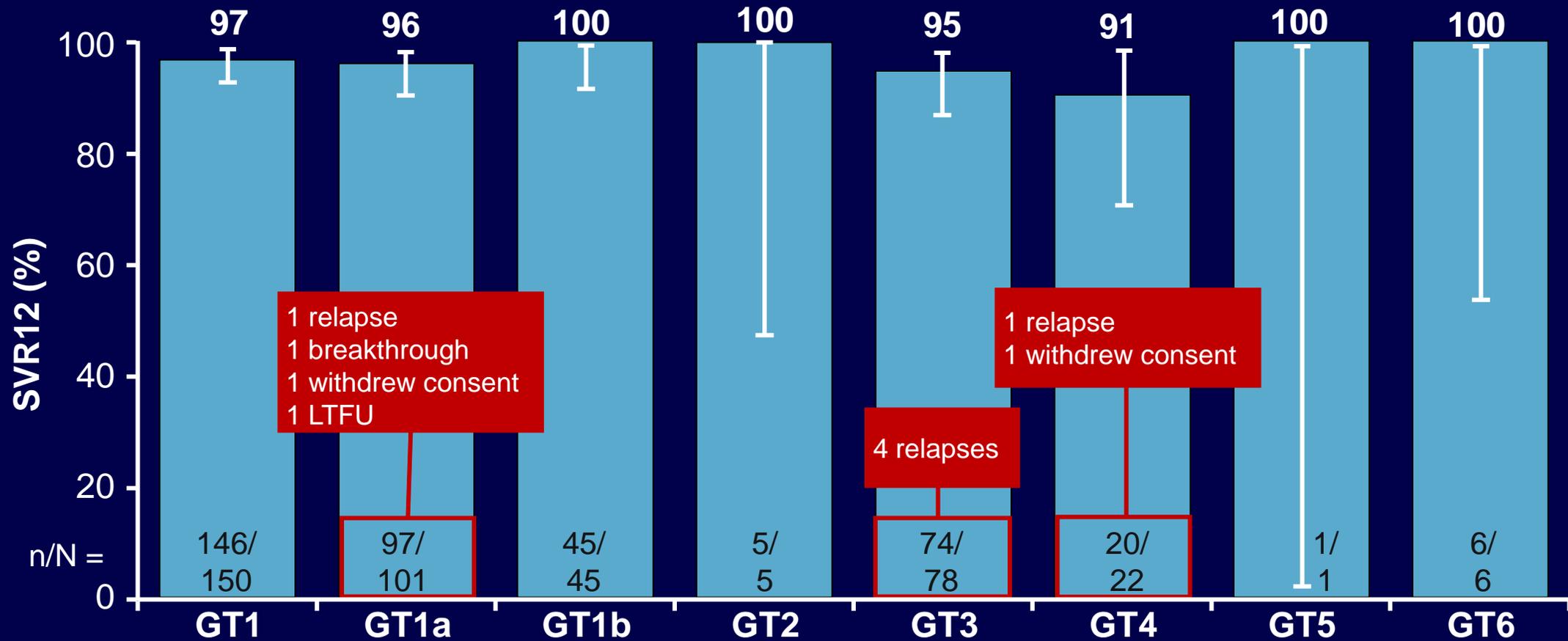


*Included SOF/VEL, EBR/GZR, and other investigational combinations and/or medications from discontinued programs.
Three pts received both LDV and DCV.

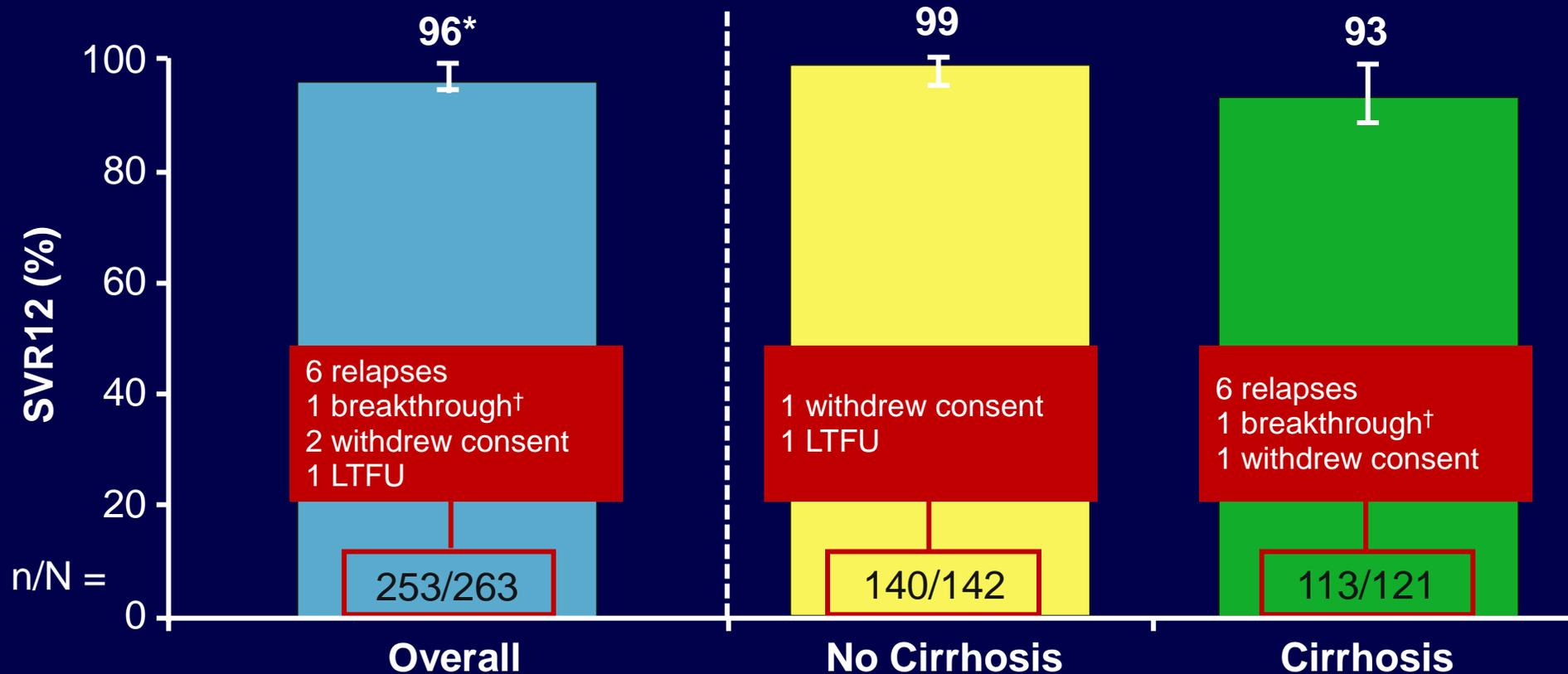


POLARIS-1: SVR12 by Genotype With 12-Wk SOF/VEL/VOX in NS5A Inhibitor–Experienced Pts

- Only 1 GT4 pt developed a treatment-emergent RAS (NS5A Y93H)



POLARIS-1: SVR12 With SOF/VEL/VOX for 12 Wks Overall and by Cirrhosis Status

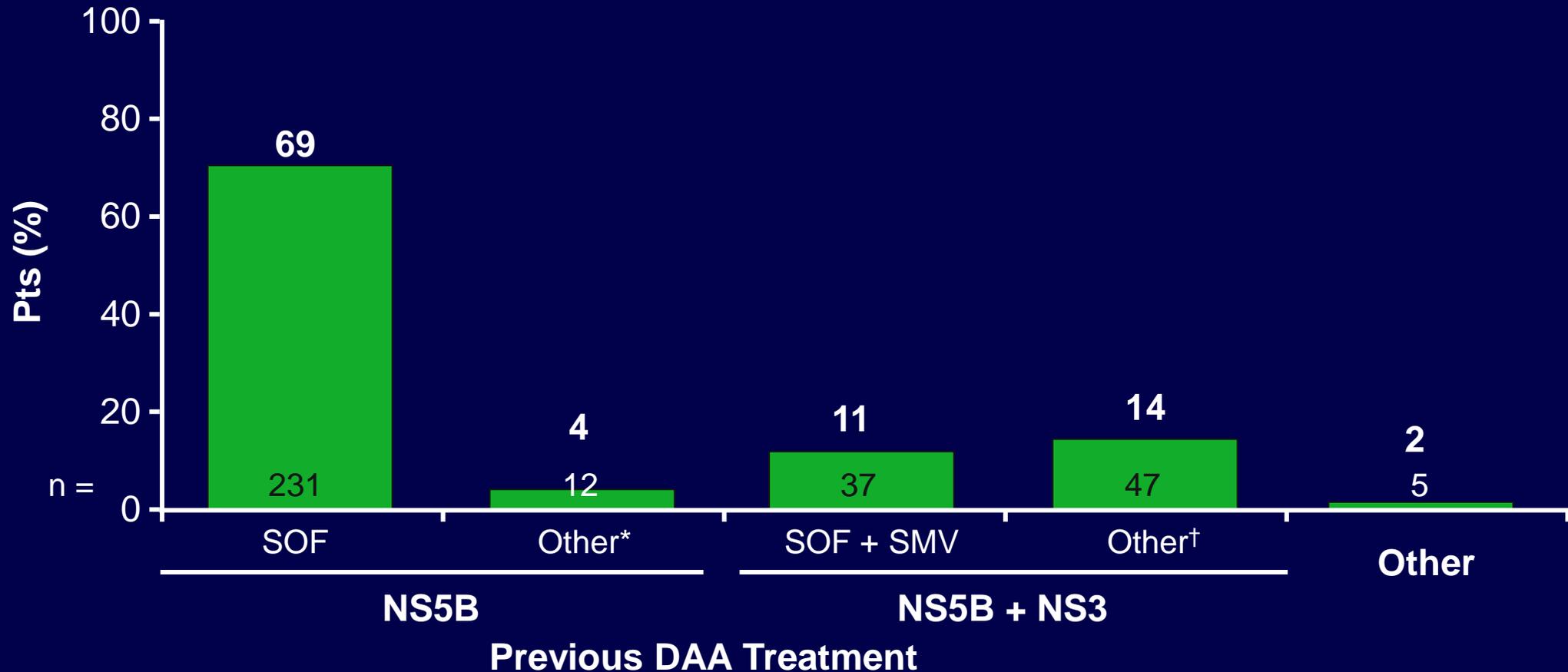


* $P < .001$ for superiority vs prespecified 85% performance goal for SOF/VEL/VOX.

[†]Exposure was consistent with nonadherence.



POLARIS-4: SOF/VEL/VOX for 12 Wks in Non-NS5A Inhibitor, DAA-Experienced GT1-4 HCV



*Other NS5B included mericitabine (n = 7).

†Other NS5B + NS3 included deleobuvir + faldaprevir (n = 14), mericitabine + danoprevir (n = 8), and SOF + telaprevir (n = 6).

One pt without previous DAA exposure excluded.

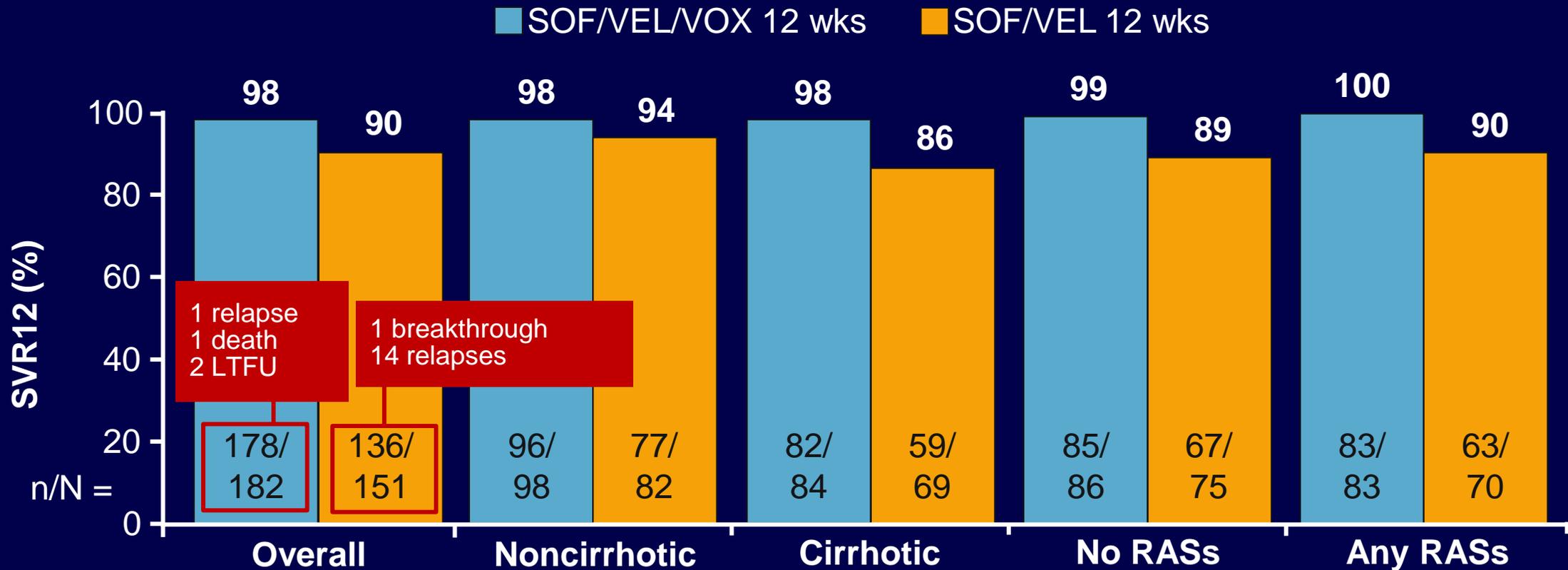
Zeuzem S, et al. AASLD 2016. Abstract 109.



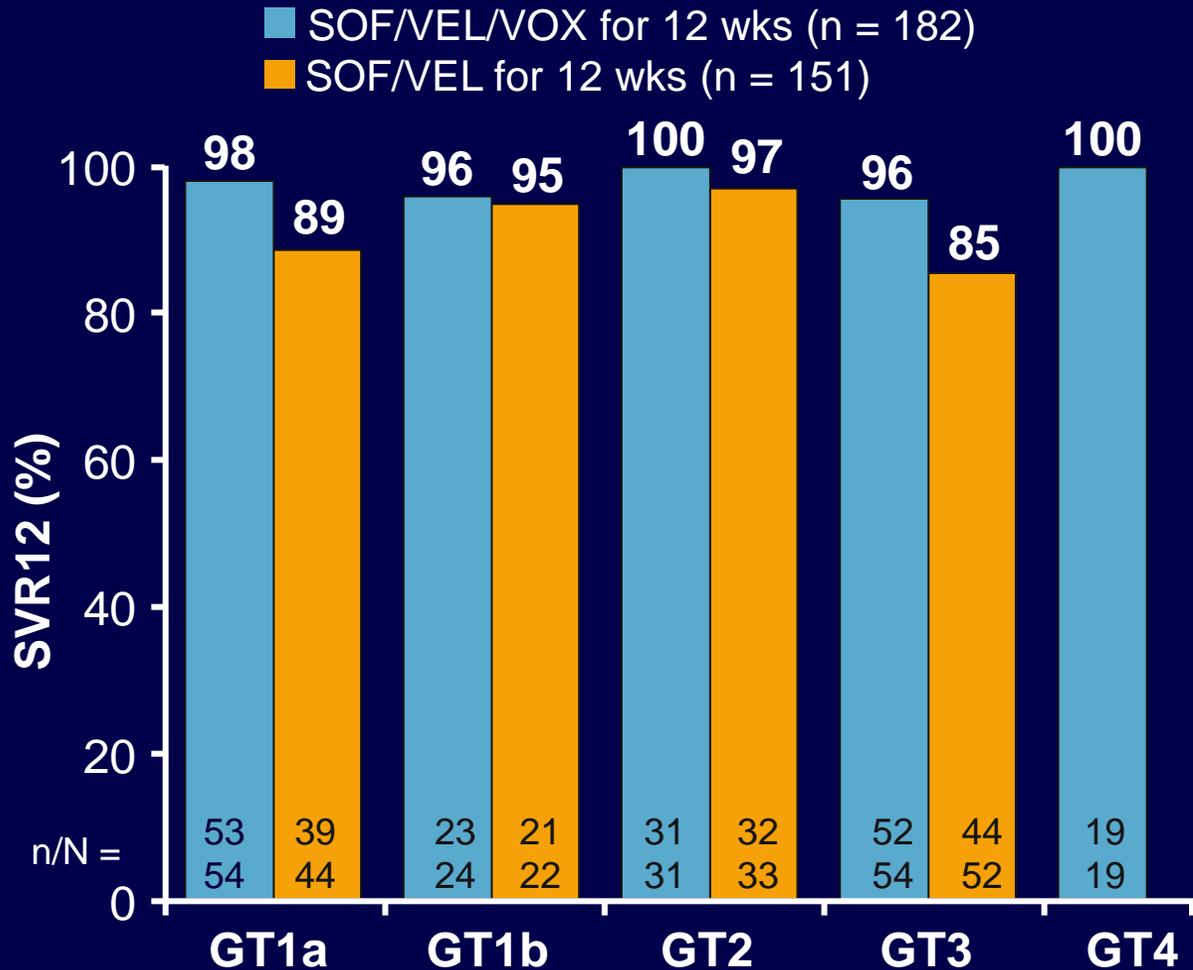
Slide credit: clinicaloptions.com

POLARIS-4: SVR12 With SOF/VEL/VOX for 12 Wks in Non-NS5A Inhibitor, DAA-Exp'd Pts

- SOV/VEL/VOX: $P < .001$ for superiority vs prespecified 85% goal; SOV/VEL: $P = .09$



POLARIS-4: SVR12 by Genotype and Other Outcomes

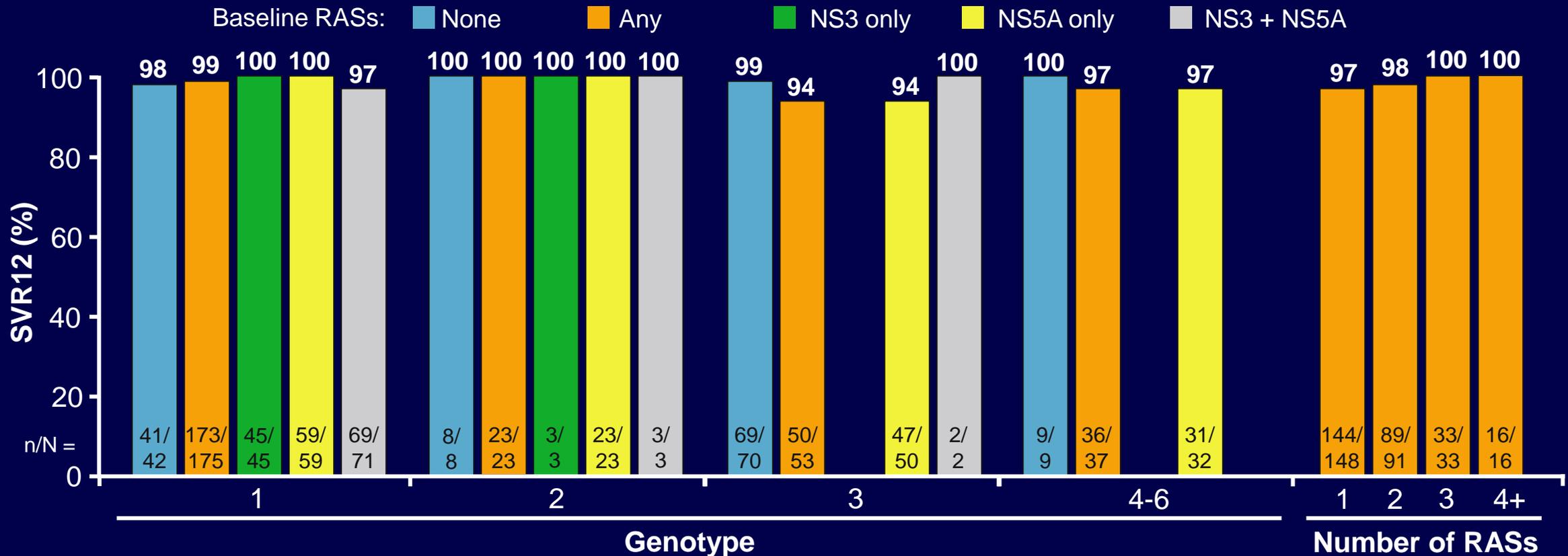


- Treatment emergent RASs
 - SOF/VEL/VOX: none
 - SOF/VEL: 11 of 15 with Y93H
- 4 serious AEs in each arm; no discontinuation for AE with SOF/VEL/VOX
- VOX associated with increase in diarrhea (20%) vs SOF/VEL alone (5%) and trend toward more nausea
 - All mild and no discontinuations



POLARIS-1 and -4: Impact of Baseline RASs on 12-Wk SOF/VEL/VOX in DAA-Experienced Pts

- Integrated analysis of data from SOF/VEL/VOX arms of 2 phase III trials of DAA-experienced pts with (n = 263) and without (n = 182) previous NS5A inhibitors, 46% with cirrhosis

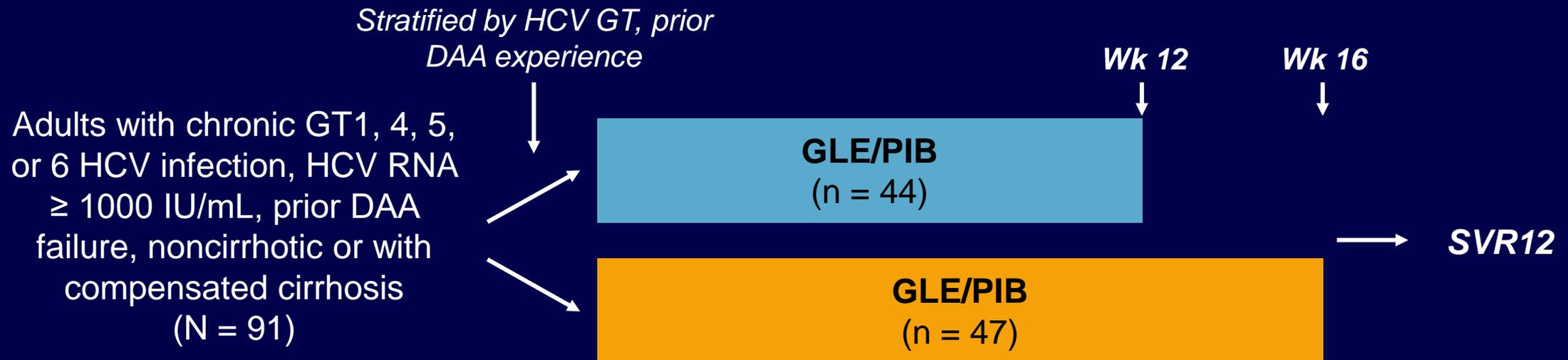


Glecaprevir/Pibrentasvir

- GLE: potent pangenotypic NS3/4A protease inhibitor
- PIB: potent pangenotypic NS5A inhibitor
- **GLE/PIB**: once daily (taken as 3 tablets with food), oral, fixed-dose combination (100/40 mg) for GT1-6

MAGELLAN-1, Pt 2: GLE/PIB for 12 or 16 Wks in DAA-Experienced Pts With GT1 or 4 HCV

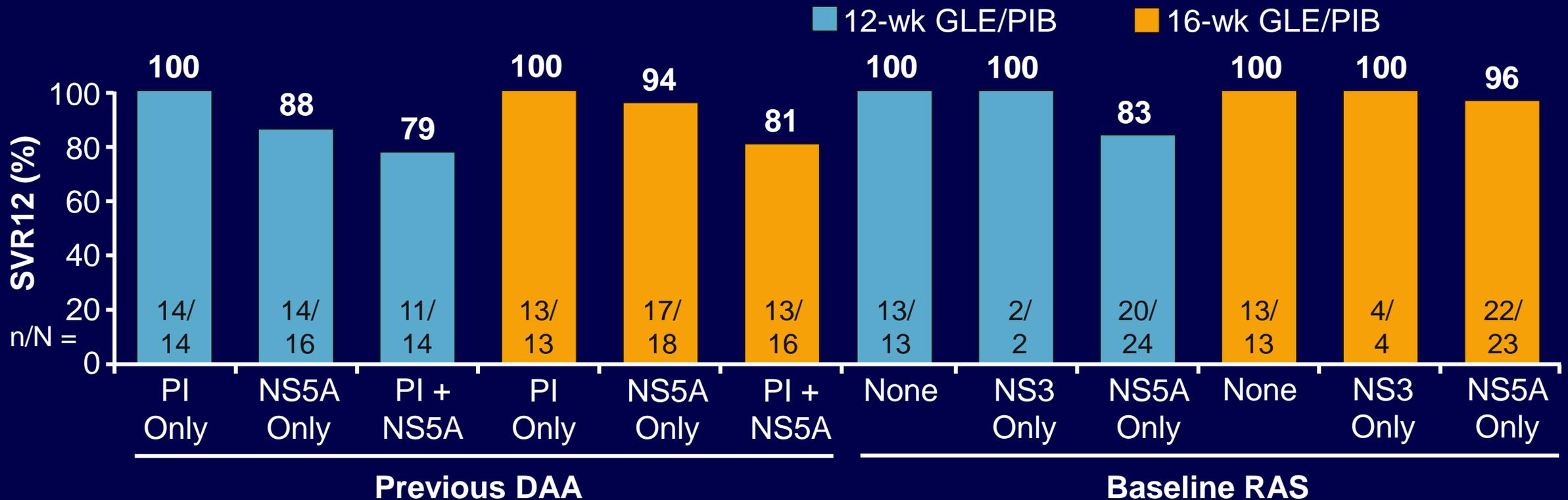
- Randomized, open-label study



- BL characteristics of 12-wk vs 16-wk arms well balanced by sex, race, BMI, previous DAA regimen and response, RASs
 - GT1a, 80% vs 71%; compensated cirrhosis, 34% vs 26%

MAGELLAN-1, Pt 2: SVR12 With GLE/PIB in GT1 or 4 HCV With Previous DAA Failure

- Of pts with NS3 & NS5A RASs, 9/9 had previous failure with PI + NS5A, 5/9 had SVR12 on GLE/PIB
- Rare grade 3 lab abnormalities, no d/c for AEs, no DAA-related serious AEs



AASLD/IDSA Recommended Retreatment Regimens for DAA-Experienced **GT1** HCV

- **SOF experienced**, but no previous NS5A inhibitor, ± compensated cirrhosis
 - **SOF/VEL/VOX for 12 wks (GT1a)**
 - **SOF/VEL for 12 wks (GT1b)**
 - **GLE/PIB for 12 wks (GT1a or 1b)**
- **NS5A inhibitor experienced** (regardless of NS3 inhibitor experience) ± compensated cirrhosis:
 - **SOF/VEL/VOX for 12 wks**

FDA indications include GLE/PIB for 8 wks if no cirrhosis

FDA indications include GLE/PIB for 16 wks if NS5A (without NS3) experienced

AASLD/IDSA Recommended Retreatment Regimens for DAA-Experienced **GT3** HCV

- **DAA experienced** (including NS5A inhibitors) ± compensated cirrhosis
 - **SOF/VEL/VOX for 12 wks**
 - Add RBV if previous NS5A inhibitor failure + compensated cirrhosis

Key Take-home Points for Retreatment of DAA-Experienced GT1 or 3 HCV Infection

- GLE/PIB approved for GT1 with NS5A *or* NS3 inhibitor experience only, not both^[1]
 - AASLD/IDSA only recommends for GT1 with SOF experience without NS5A inhibitor experience^[2]
- SOF/VEL/VOX approved for GT1, 2, 3, 4, 5, or 6 with NS5A inhibitor experience (regardless of NS3 experience) and GT1a or GT3 with SOF experience without NS5A inhibitor experience (regardless of NS3 experience)^[3]

SOF/VEL/VOX is now the go-to regimen for dual NS5A and NS3 inhibitor–experienced pts with GT1 or 3

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