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HEPATITIS

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

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# Faculty Disclosures

**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.

**Ira M. Jacobson, MD,** has disclosed that he has received consulting fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Intercept, Merck, and Trek; fees for non-CME/CE services from AbbVie, Gilead Sciences, Intercept, and Merck; and funds for research support from Genfit, Gilead Sciences, and Merck.

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**Christian B. Ramers, MD, MPH,** has disclosed that he has received consulting fees from Bristol-Myers Squibb, Gilead Sciences, and Janssen; fees for non-CME/CE services from AbbVie, Gilead Sciences, Janssen, and Merck; and funds for research support from Gilead Sciences.

**Norah Terrault, MD, MPH,** has disclosed that she has received consulting fees from Gilead Sciences and Merck and funds for research support from AbbVie, Gilead Sciences, and Merck.

# 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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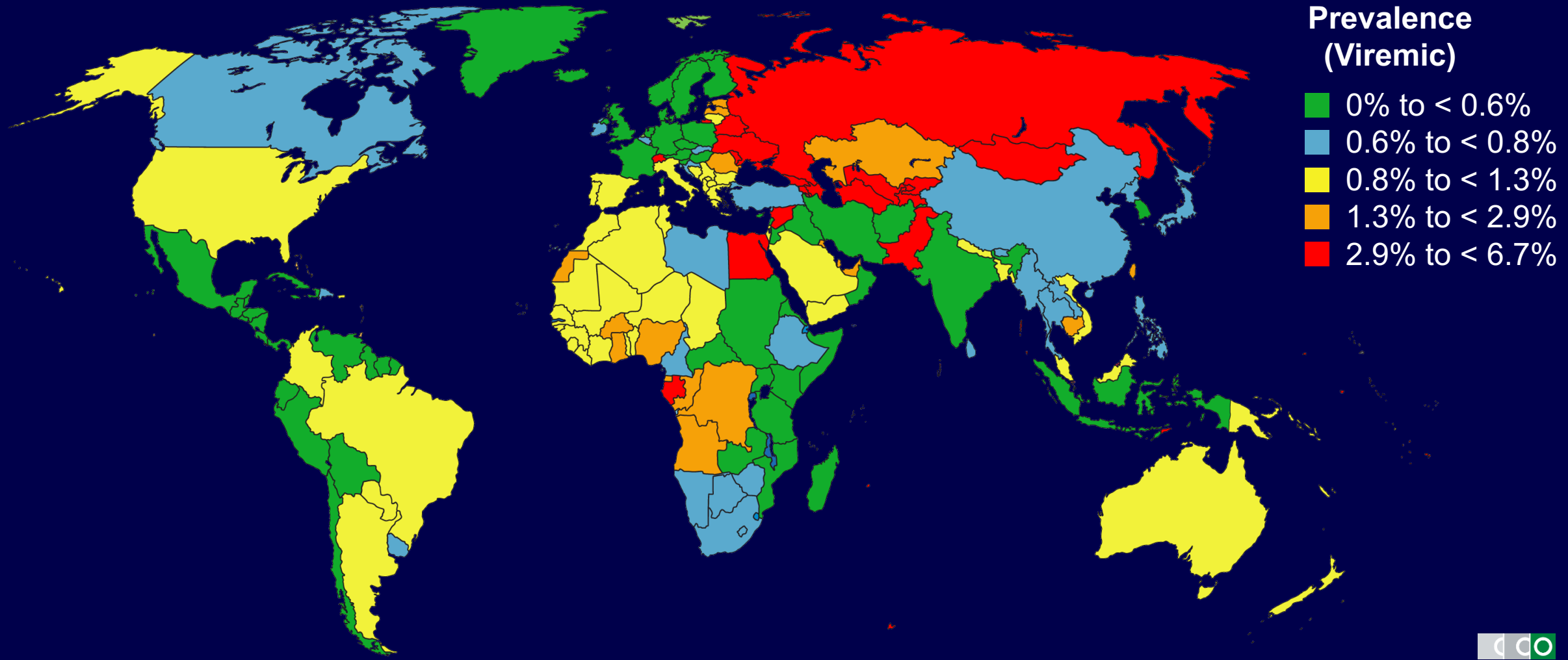
# The Path to 100% HCV Elimination

Norah Terrault, MD, MPH

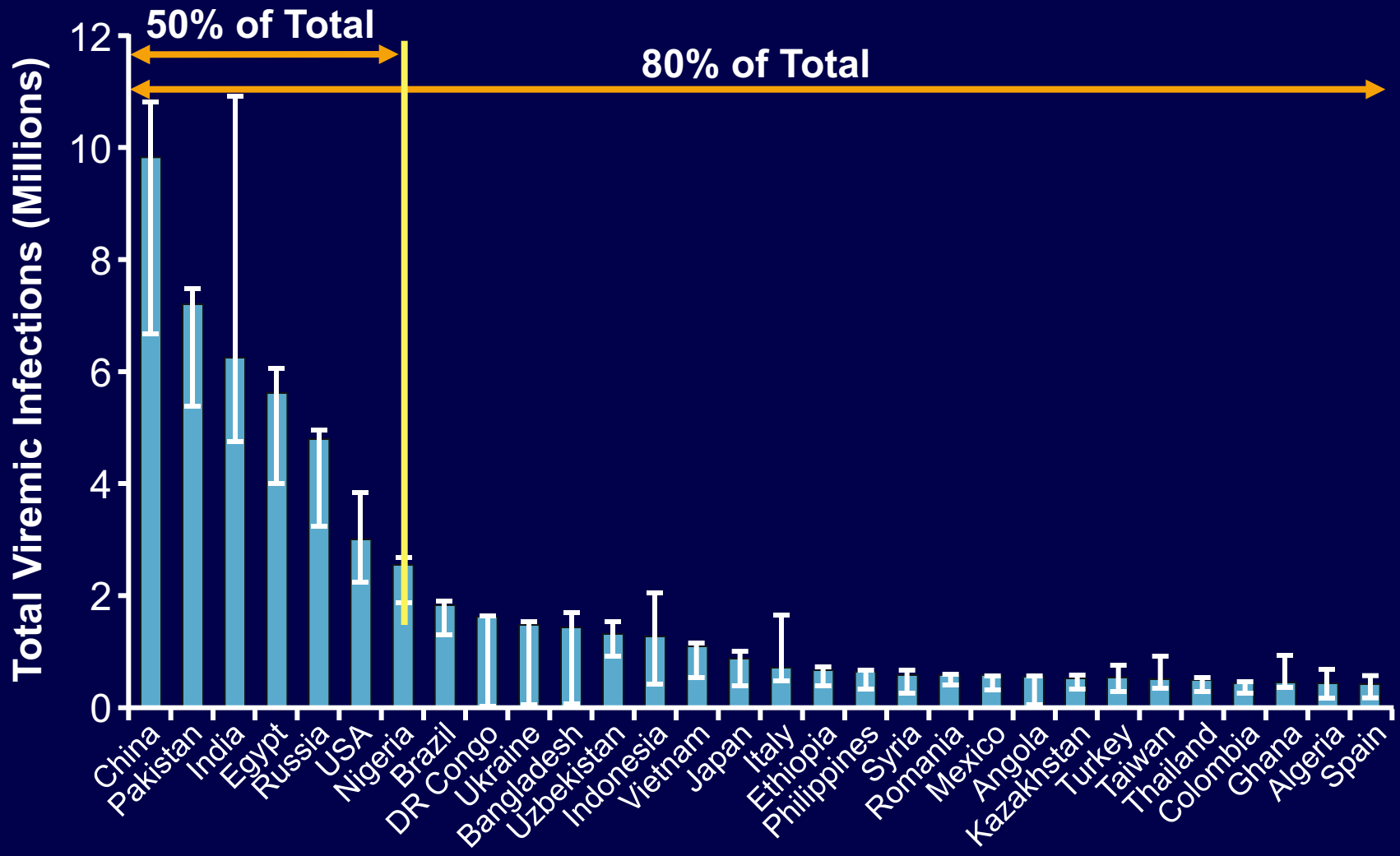
# Estimated 70 Million Persons Living With HCV




Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2:161-176.

Slide credit: clinicaloptions.com

# 30 Countries Account for 80% of HCV Infections




Polaris Observatory HCV Collaborators. Lancet Gastroenterol Hepatol. 2017;2:161-176.
Blach S, et al. AASLD 2016. Abstract 753.

Slide credit: clinicaloptions.com

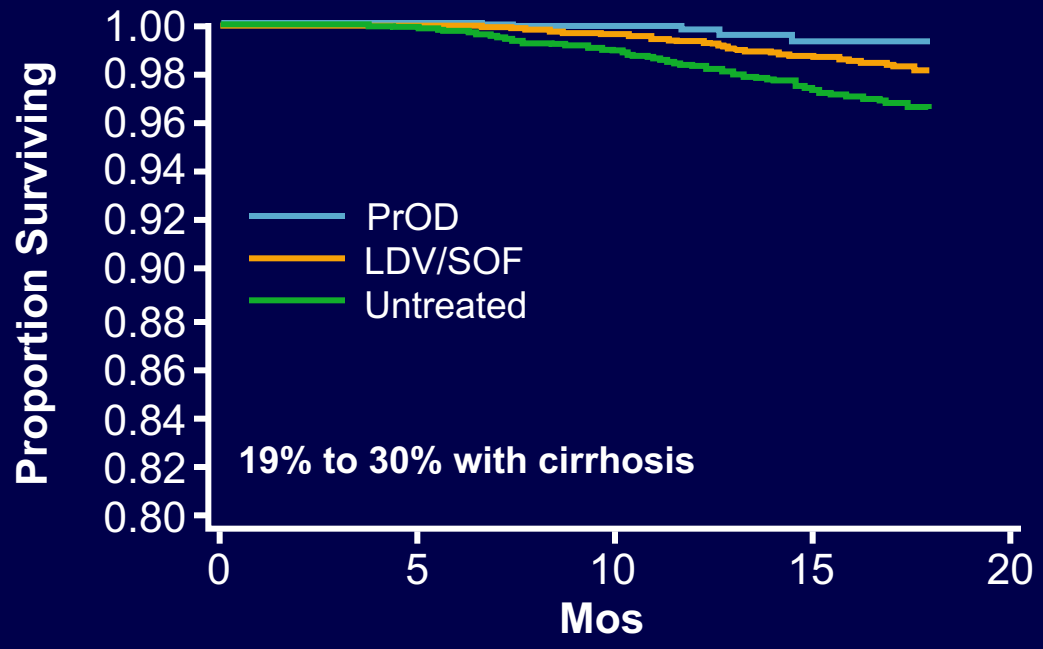
# WHO: Global Viral Hepatitis Prevention and Elimination Plans

- 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”

1. WHO. Global health sector strategy on viral hepatitis 2016-2021. June 2016. 2. WHO. SDG 3: Ensure healthy lives and promote wellbeing for all at all ages. Available at: http://www.who.int/sdg/targets/en/.

# Mortality Reduction Achieved by HCV Cure

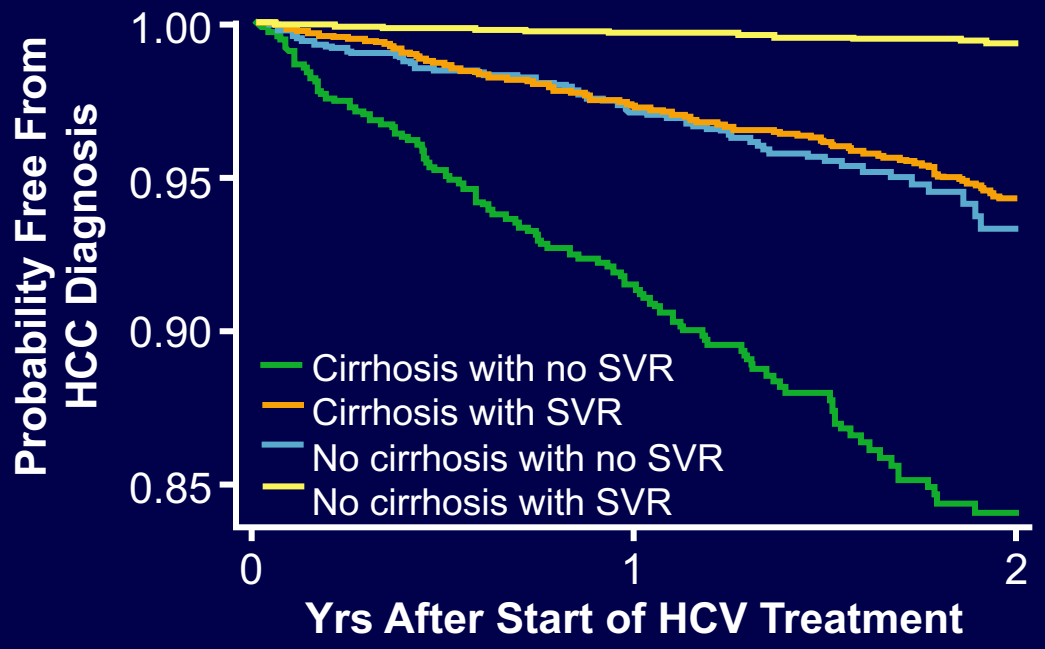
## Survival in ERCHIVES Veterans (N = 13,940*†)[1]




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

*For 18 mos of follow-up.
†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.

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



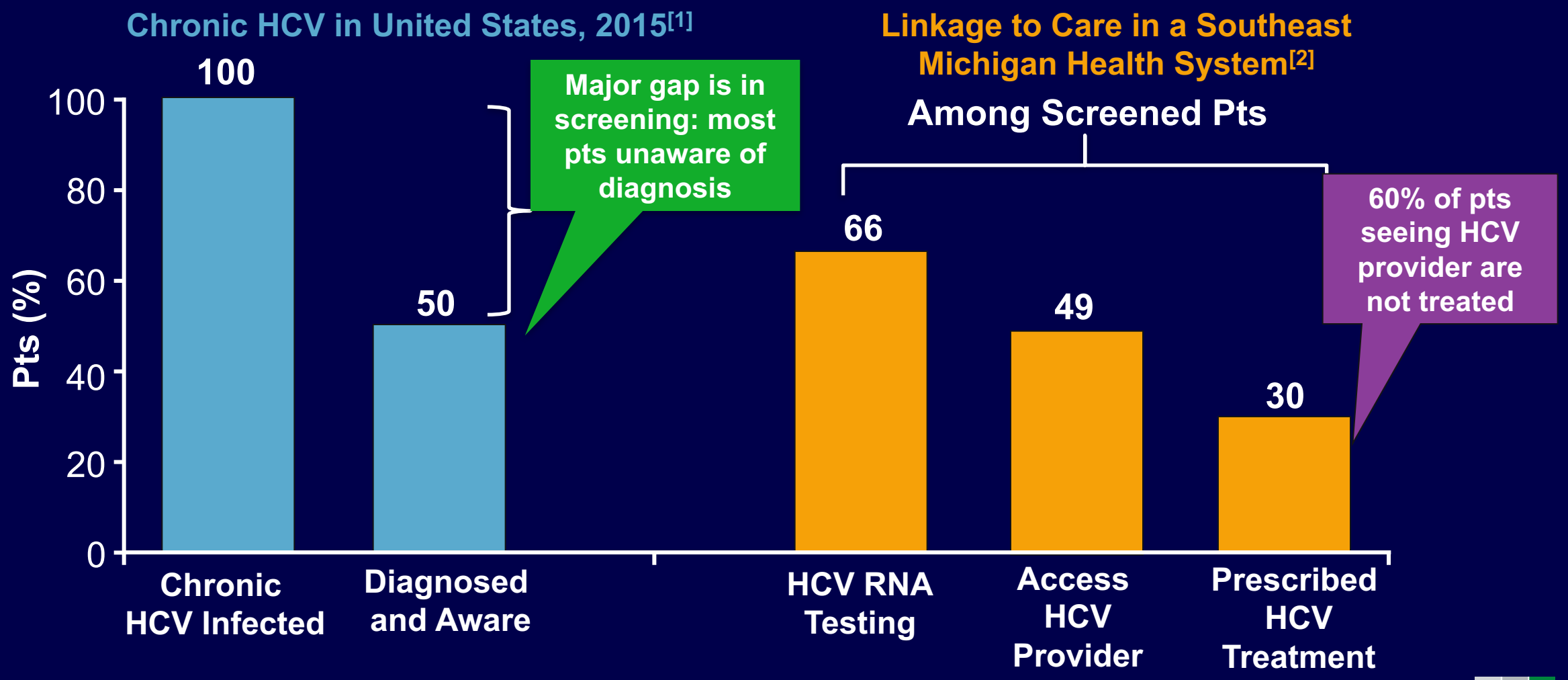

**DAA-induced SVR is associated with a 71% reduction in HCC risk**

‡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].


Slide credit: clinicaloptions.com

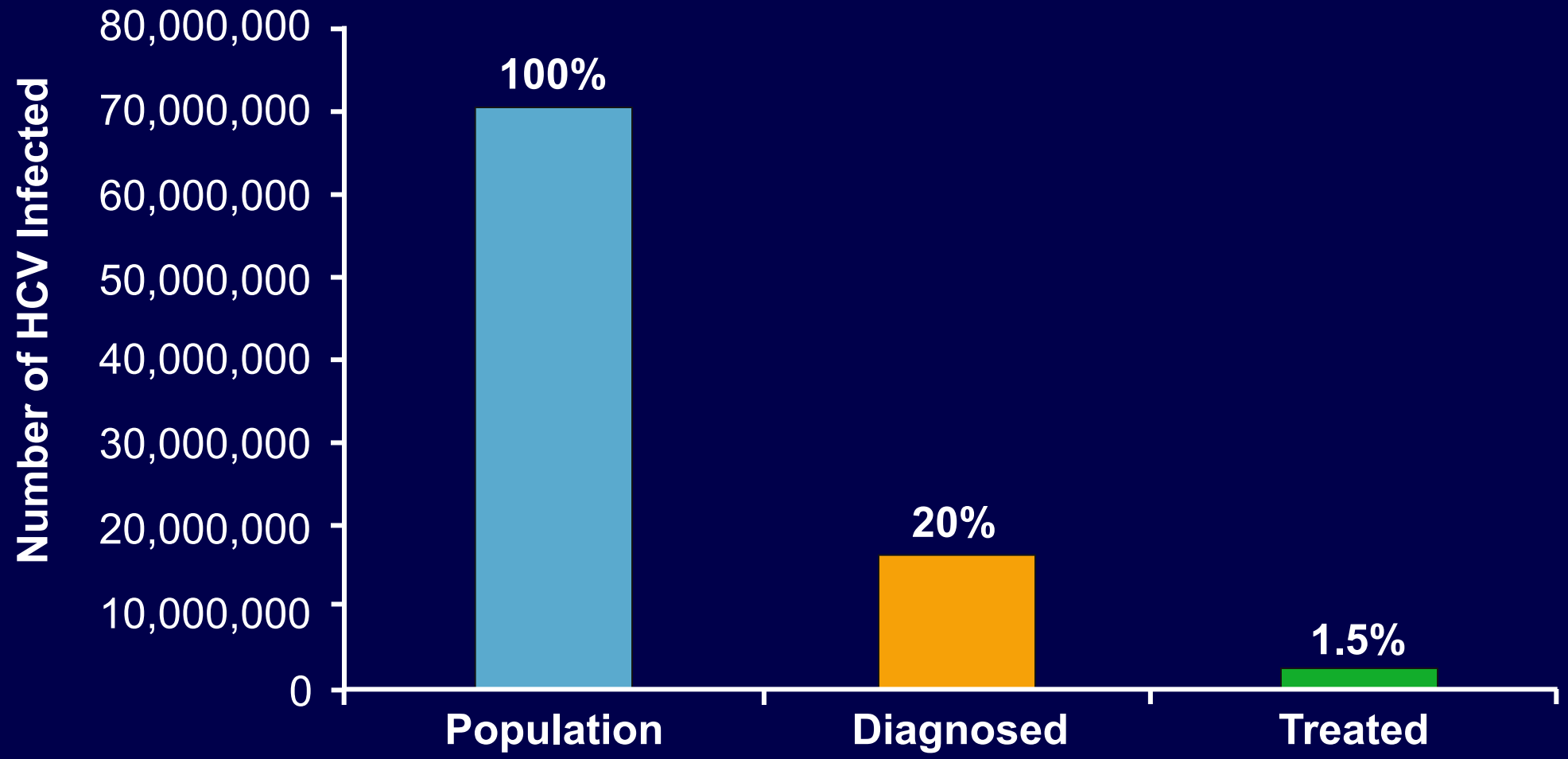
# US Estimates of HCV Cascade of Care




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

Slide credit: clinicaloptions.com

# Estimated Global HCV Cascade of Care




WHO 2015. http://www.who.int/mediacentre/factsheets/fs164/en/

Slide credit: clinicaloptions.com

# Breakdowns in the HCV Care Cascade

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

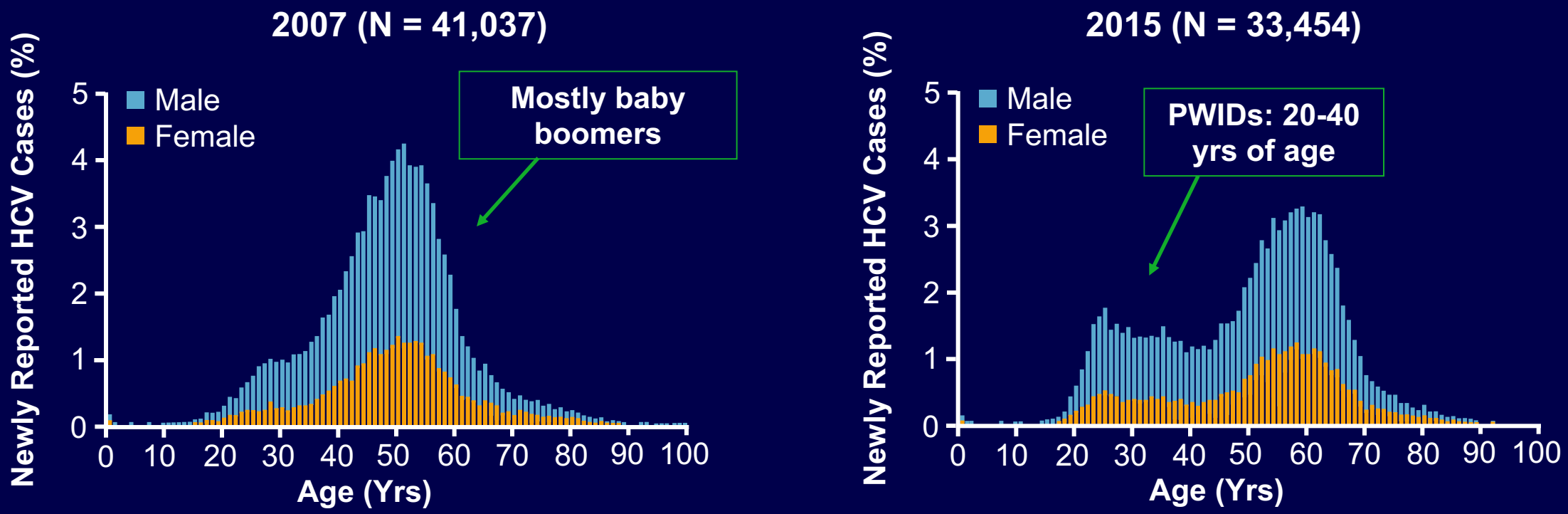
- Stage of disease
- Medical comorbidities
- Abstinence from drugs and alcohol
- Adherence concerns
- Insurance status

**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

1. Yehia BR, et al. PLoS One. 2014;9:e101554. 2. Lynch SM, et al. J Clin Transl Hepatol. 2016;4:310-319. 3. Midgard H, et al. J Hepatol. 2016;65(1 suppl):S33-S45.

# Changing Epidemiology of HCV in the US

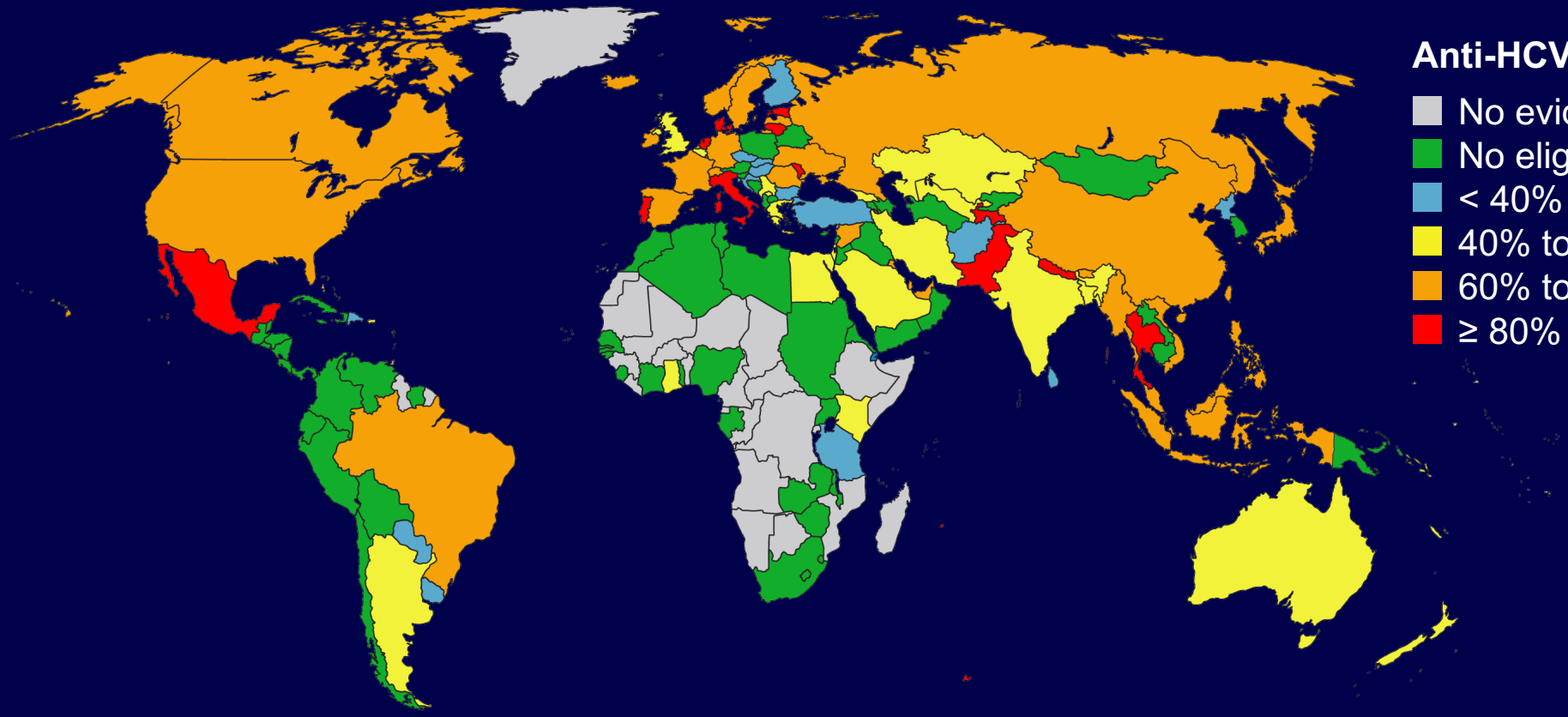



- Screening → linkage to HCV care → DAA treatment cascade must be operative in all those at risk
- Treatment of PWIDs plus harm reduction efforts essential part of elimination efforts

California Department of Public Health. Chronic hepatitis C infections in California: cases newly reported through 2015. June 2017.

Slide credit: clinicaloptions.com

# HCV Infection Among Persons Who Inject Drugs

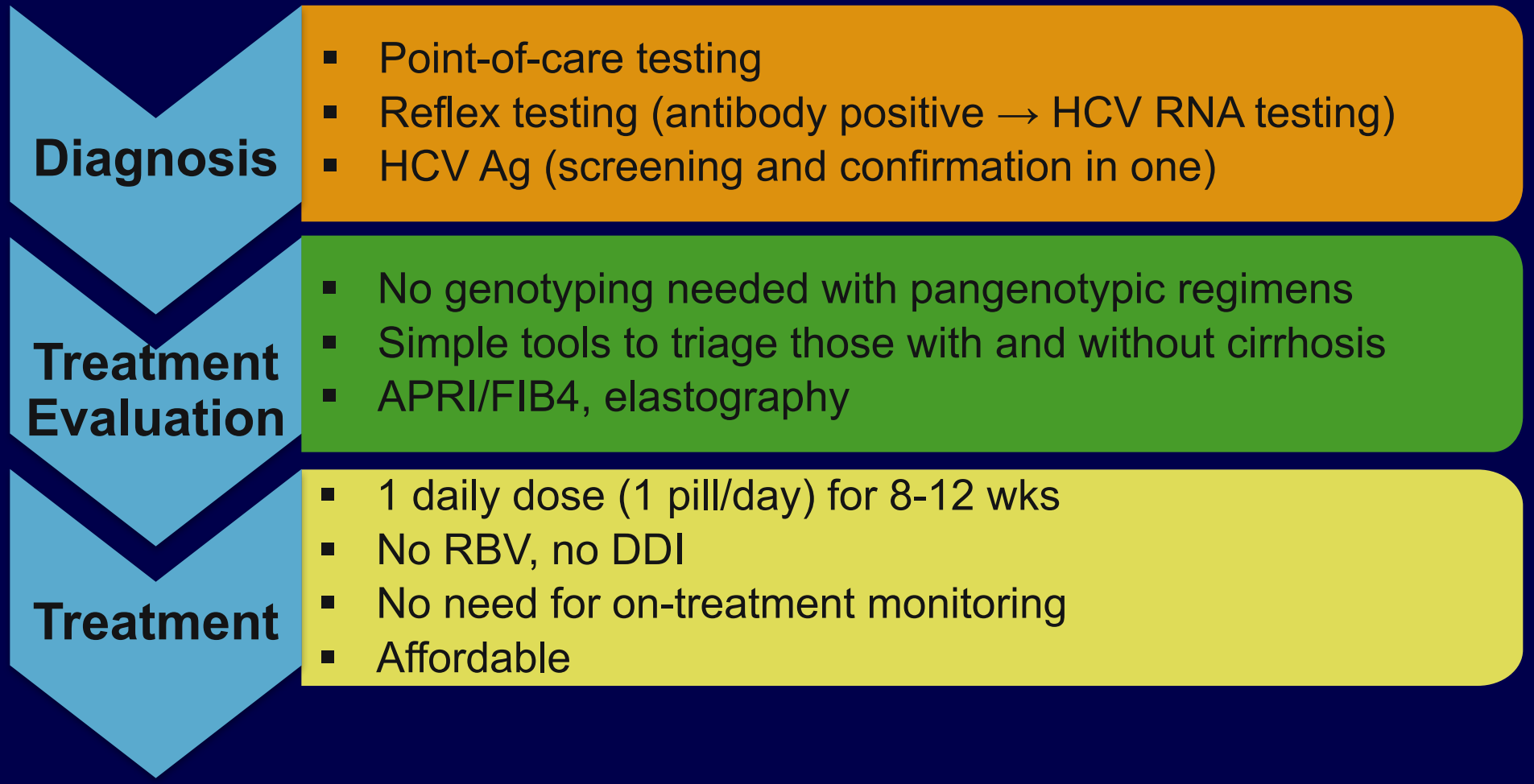



- In most developing countries, injection drug use is primary source of new infections
- HCV treatment must be coupled with harm reduction measures to reduce total infections

Nelson P, et al. Lancet. 2011;378:571-583.

Slide credit: clinicaloptions.com

# HCV Elimination: Simplifying and Streamlining Care

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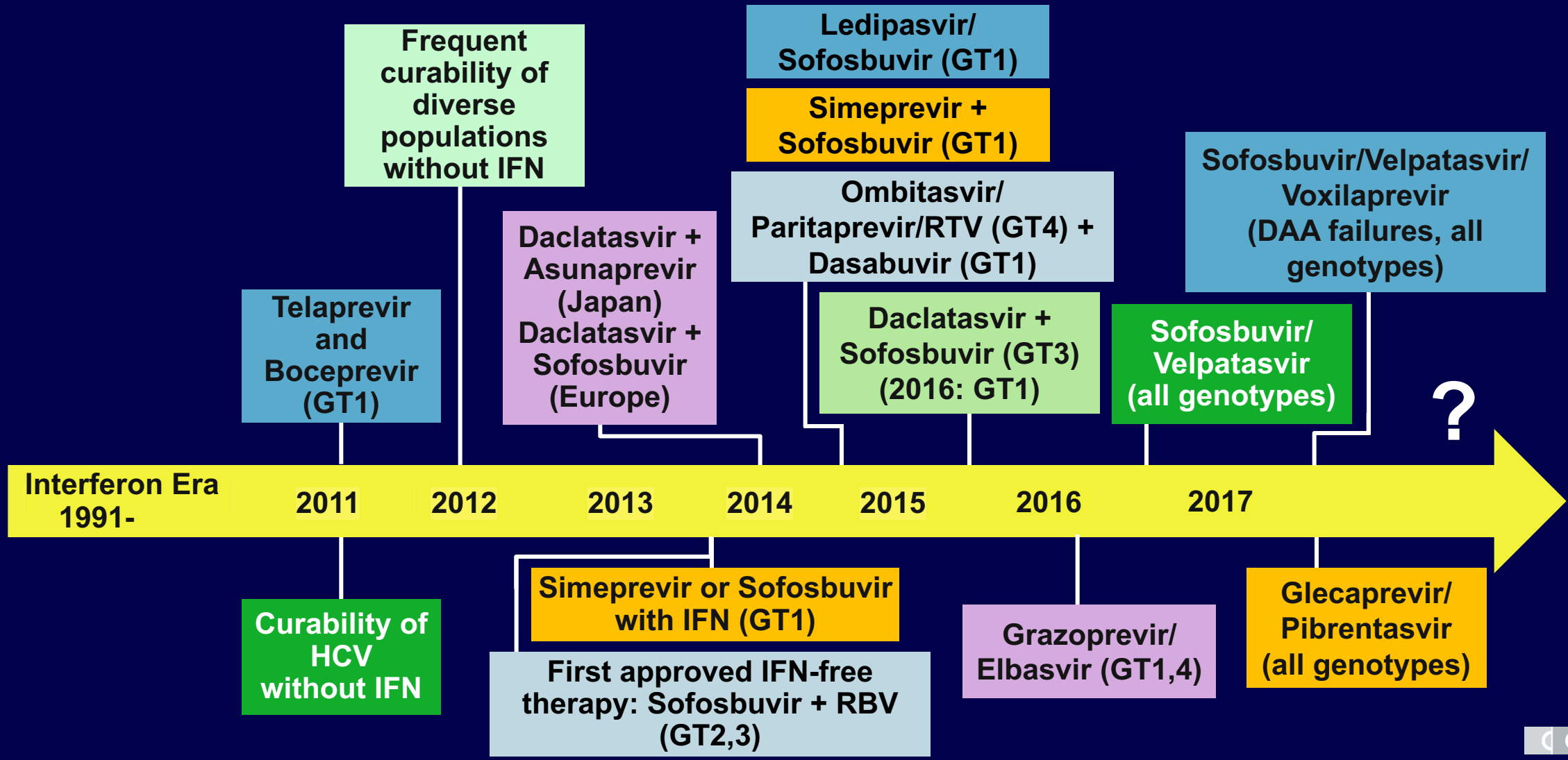
# The Toolkit to Achieve Cure

Ira M. Jacobson, MD

# What Are the Tools in the Toolkit?

# The Evolution of HCV Therapy




References in slidenotes.

Slide credit: clinicaloptions.com

# 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<br>▪ No cirrhosis or compensated cirrhosis: 12 wks | GT1-6<br>▪ No cirrhosis: 8 wks<br>▪ Compensated cirrhosis: 12 wks |
| IFN/RBV experienced* | GT1-6<br>▪ No cirrhosis or compensated cirrhosis: 12 wks | GT1, 2, 4, 5, 6<br>▪ No cirrhosis: 8 wks<br>▪ Compensated cirrhosis: 12 wks<br>GT3<br>▪ No cirrhosis or compensated cirrhosis: 16 wks |

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

FDA GLE/PIB 2017. FDA SOF/VEL 2017.

Slide credit: clinicaloptions.com

# 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.

# 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.

1. FDA Simeprevir. 2017. 2. Chase R, et al. IAPAC 2013. Abstract OA25.
3. Poordad F, et al. AASLD 2015. Abstract 41. 4. Taylor JG, et al. EASL 2015. Abstract P0899.

# 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<br>> 50x | > 100x / -- | NR |
| Ombitasvir | > 1000x | > 100x | < 3x<br>> 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<br>> 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 |

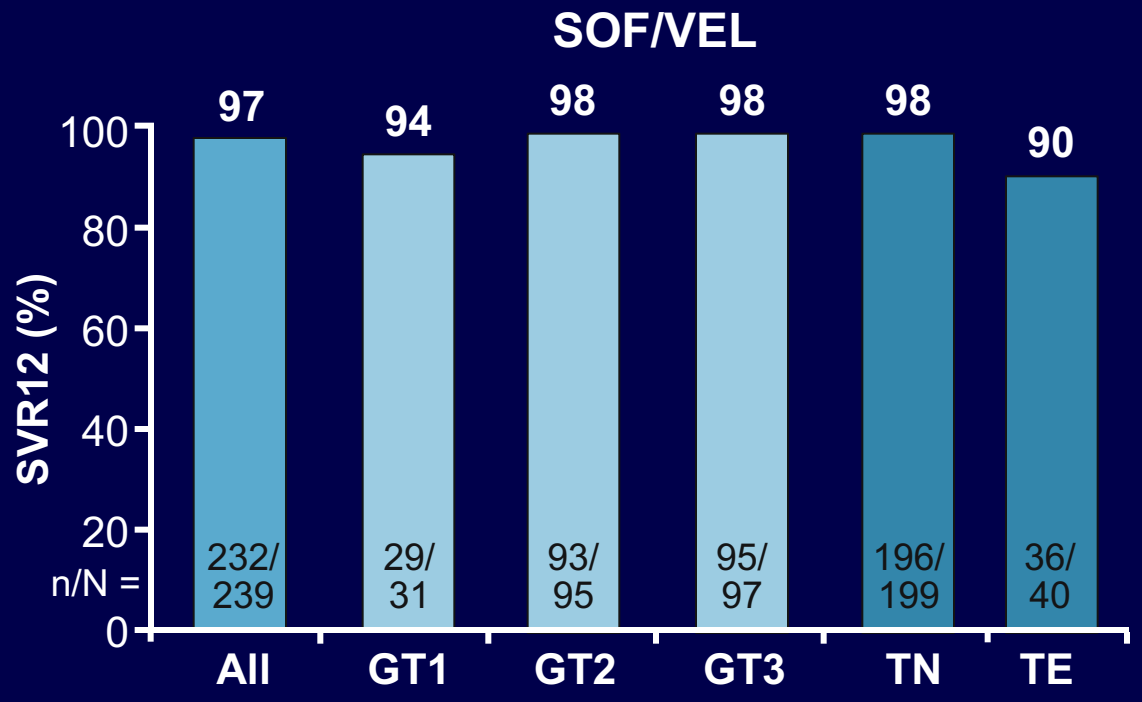
< 3-fold change  < 10-fold change  < 10- to 100-fold change  > 100-fold change

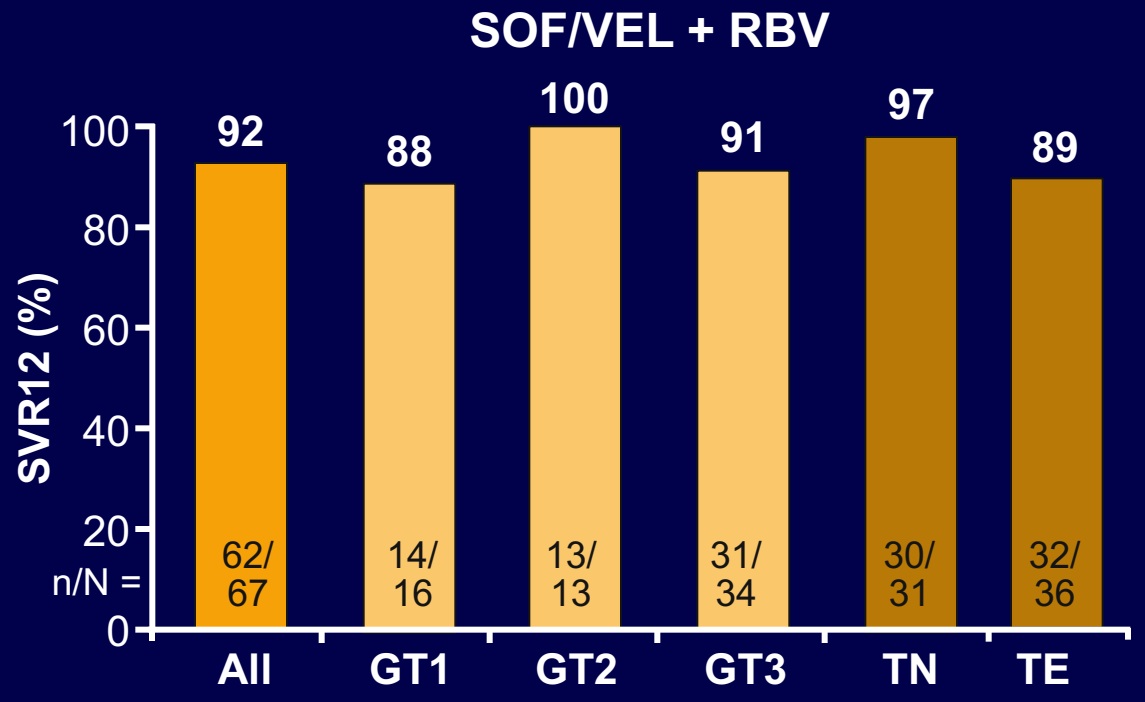
AASLD/IDSA. HCV guidance. September 2017. Ng TI, et al. Antimicrob Agents Chemother. 2017;61:e02558-16. FDA Sofosbuvir/velpatasvir. FDA Daclatasvir.

Slide credit: clinicaloptions.com

# 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

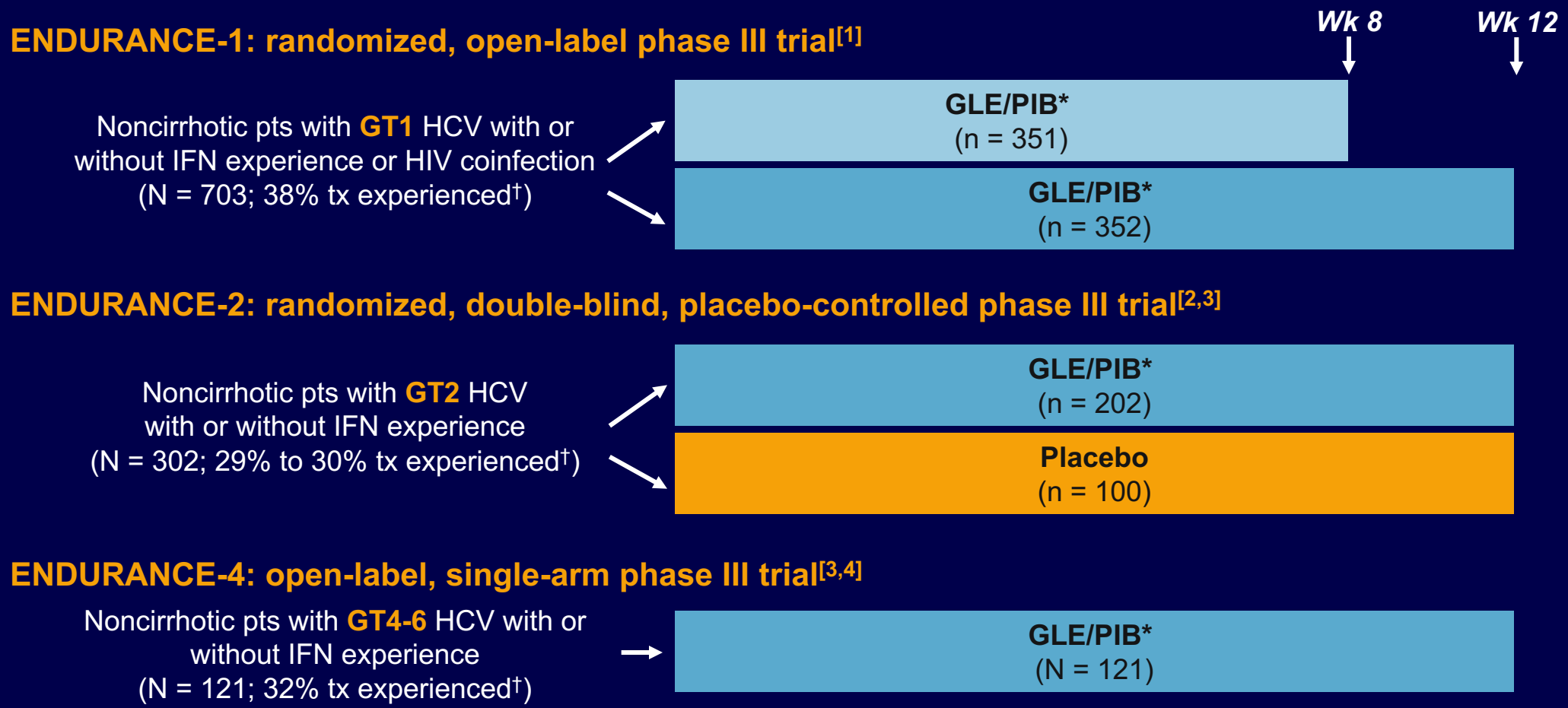



Landis CS, et al. AASLD 2017. Abstract 1096.

Slide credit: clinicaloptions.com

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

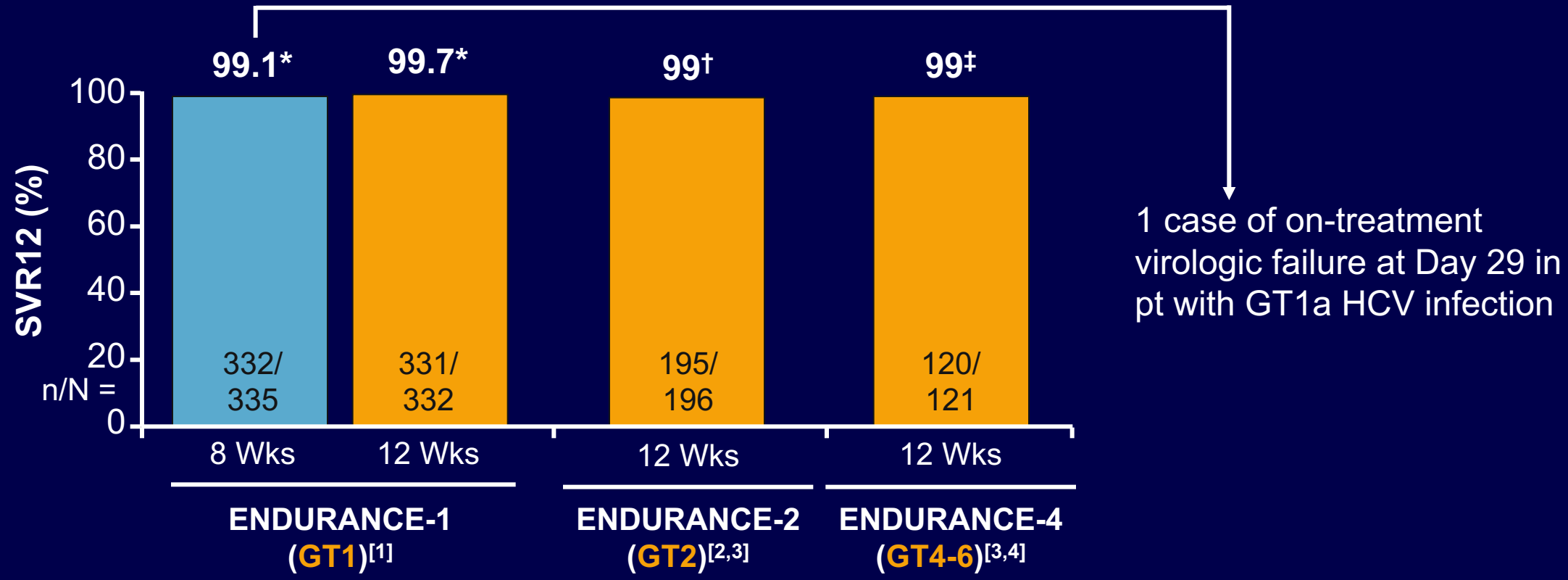



*Dosing: GLE/PIB given as 3 coformulated 100/40-mg tablets QD for a total dose of 300/120 mg.
†Tx experience permitted: IFN or pegIFN ± RBV or SOF + RBV ± pegIFN.

References in slidenotes.

Slide credit: clinicaloptions.com

# 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

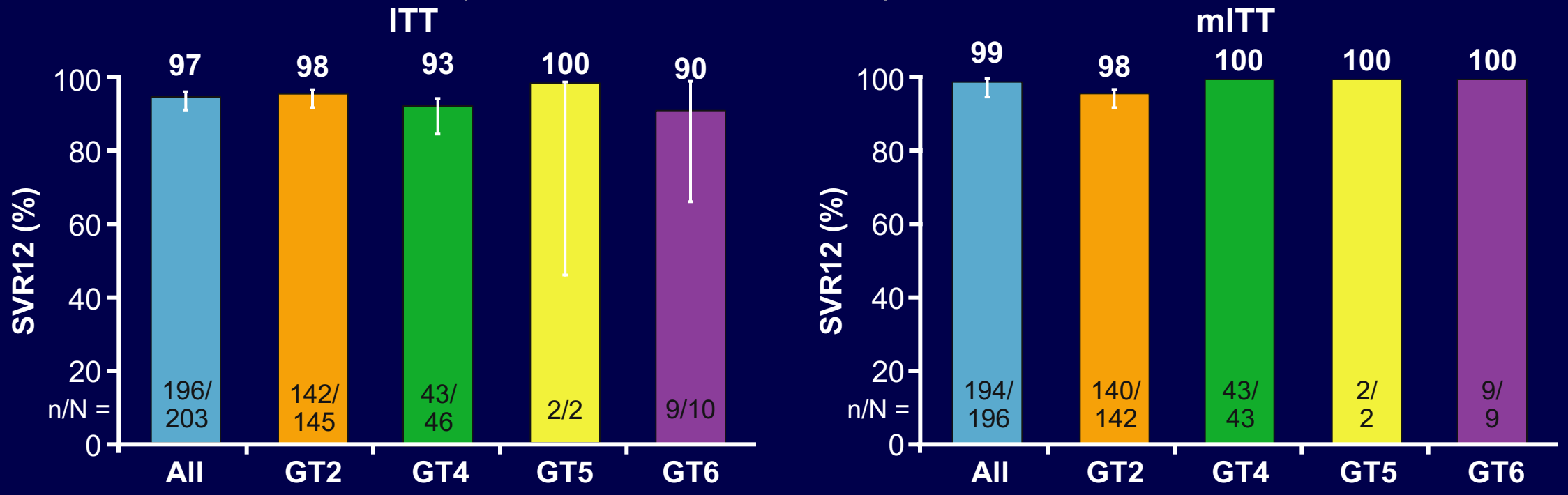
| Outcome, % | ENDURANCE-1 (GT1)[1] | | ENDURANCE-2 (GT2)[2,3] | | ENDURANCE-4 (GT4-6)[3,4] |
|---|---|---|---|---|---|
| | GLE/PIB 8 Wks (n = 351) | GLE/PIB 12 Wks (n = 352) | GLE/PIB 12 Wks (n = 202) | PBO 12 Wks (n = 100) | GLE/PIB 12 Wks (n = 121) |
| Any AE | 62 | 66 | 65 | 58 | 69 |
| D/c for AE | 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.

# 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)



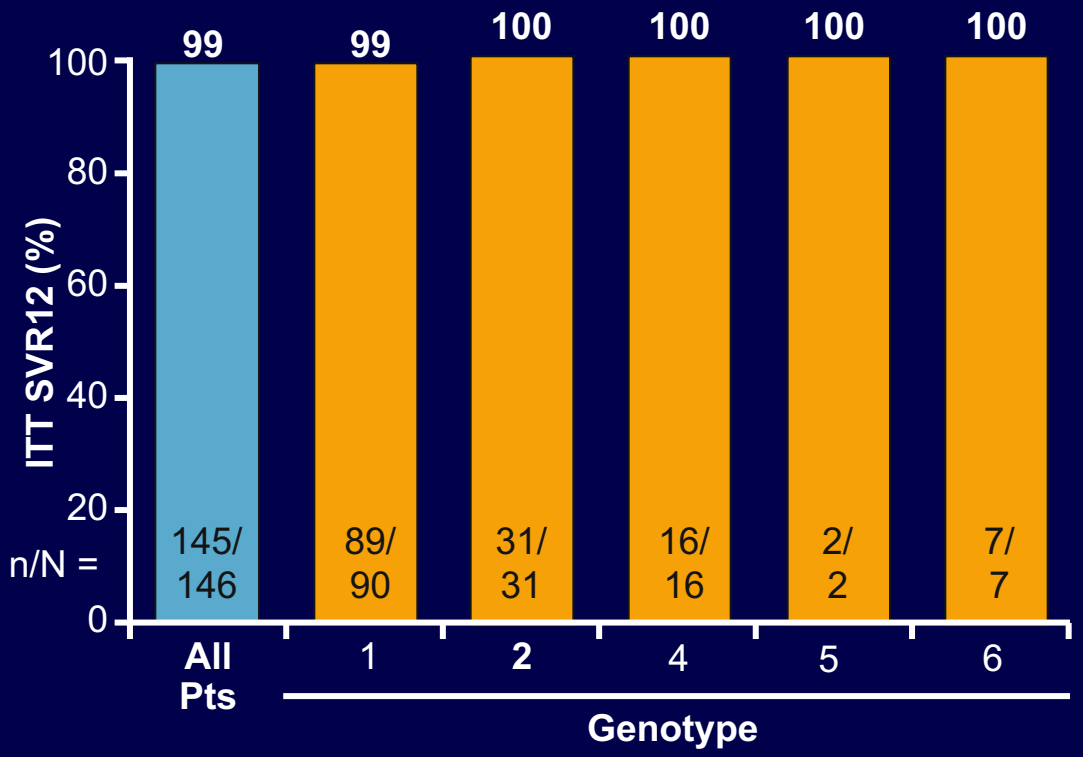

| | All | GT2 | GT4 | GT5 | GT6 |
|---|---|---|---|---|---|
| Relapse | 2 | 2 | 0 | 0 | 0 |
| D/c | 2 | 1 | 1 | 0 | 0 |
| No SVR12 data | 3 | 0 | 2 | 0 | 1 |

Hassanein TI, et al. AASLD 2016. Abstract LB-15. Kwo PY, et al. J Hepatology 2017;67:263-271.

Slide credit: clinicaloptions.com

# 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

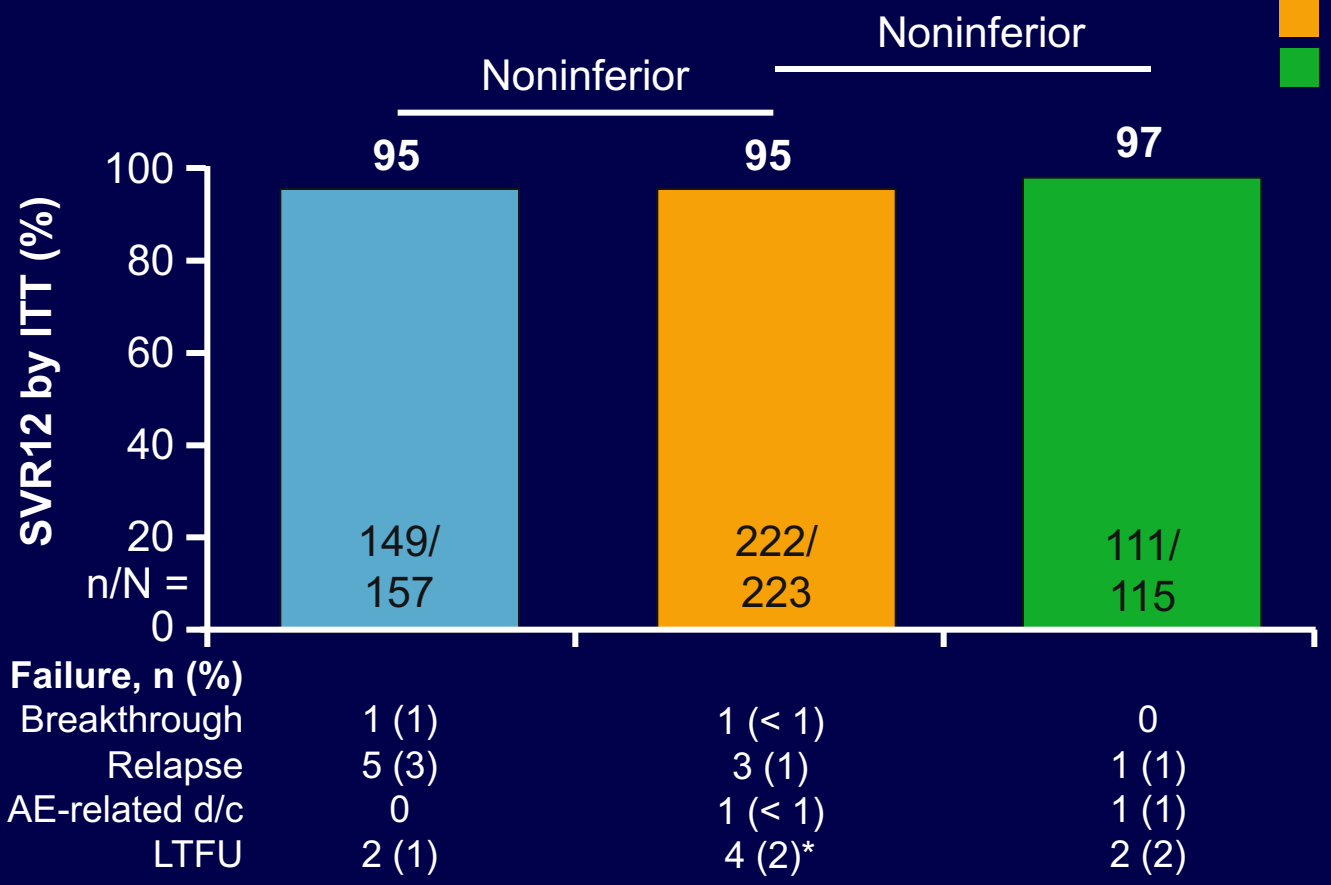
| AE, n (%) | Pts (N = 146) |
|---|---|
| Any AE | 101 (69) |
| Any serious AE | 11 (8) |
| AEs occurring in ≥ 10% of pts | |
| ▪Fatigue | 28 (19) |
| ▪Headache | 20 (14) |
| ▪Pruritus | 14 (10) |
| HCC | 2 (1) |

Forns X, et al. Lancet Infect Dis. 2017;17:1062-1068.

Slide credit: clinicaloptions.com

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

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




| Failure, n (%) | | | |
|---|---|---|---|
| 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) |

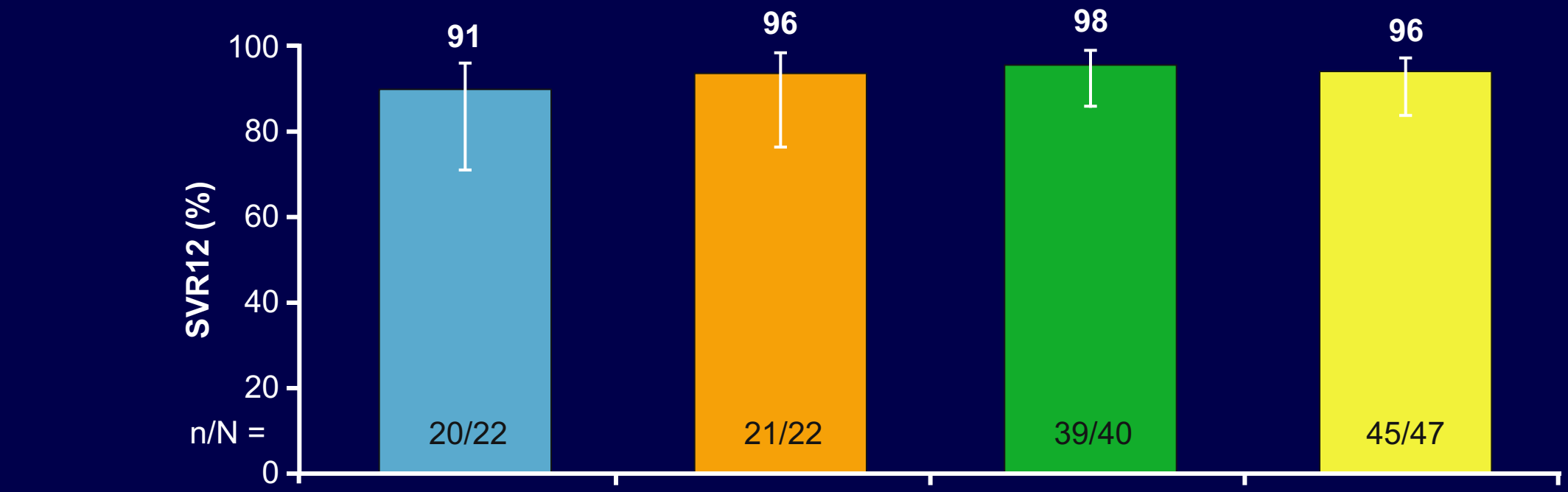
*2 other failures due to consent withdrawal and noncompliance.

- 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)

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

Slide credit: clinicaloptions.com

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



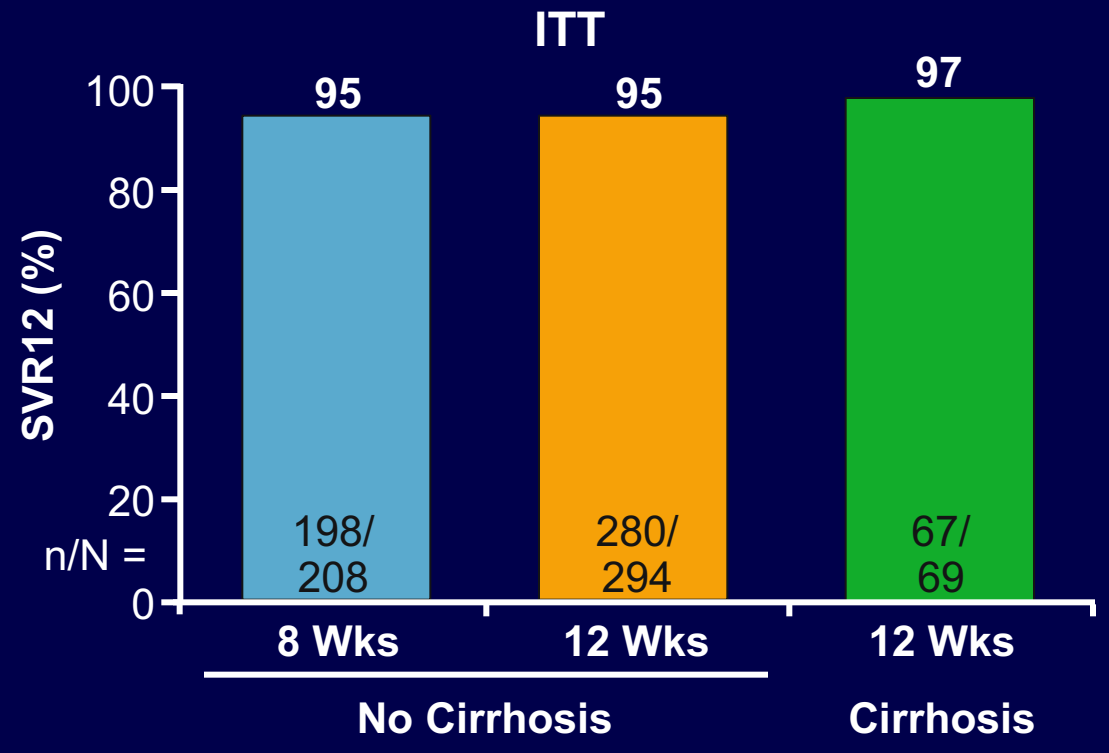

| | | | | |
|---|---|---|---|---|
| Tx Wks | 12 | 16 | 12 | 16 |
| Cirrhosis | - | - | + | + |
| Tx Experienced | + | + | - | + |
| Breakthrough | 0 | 0 | 0 | 1 |
| Relapse | 2 | 1 | 0 | 1 |
| LTFU | 0 | 0 | 1 | 0 |

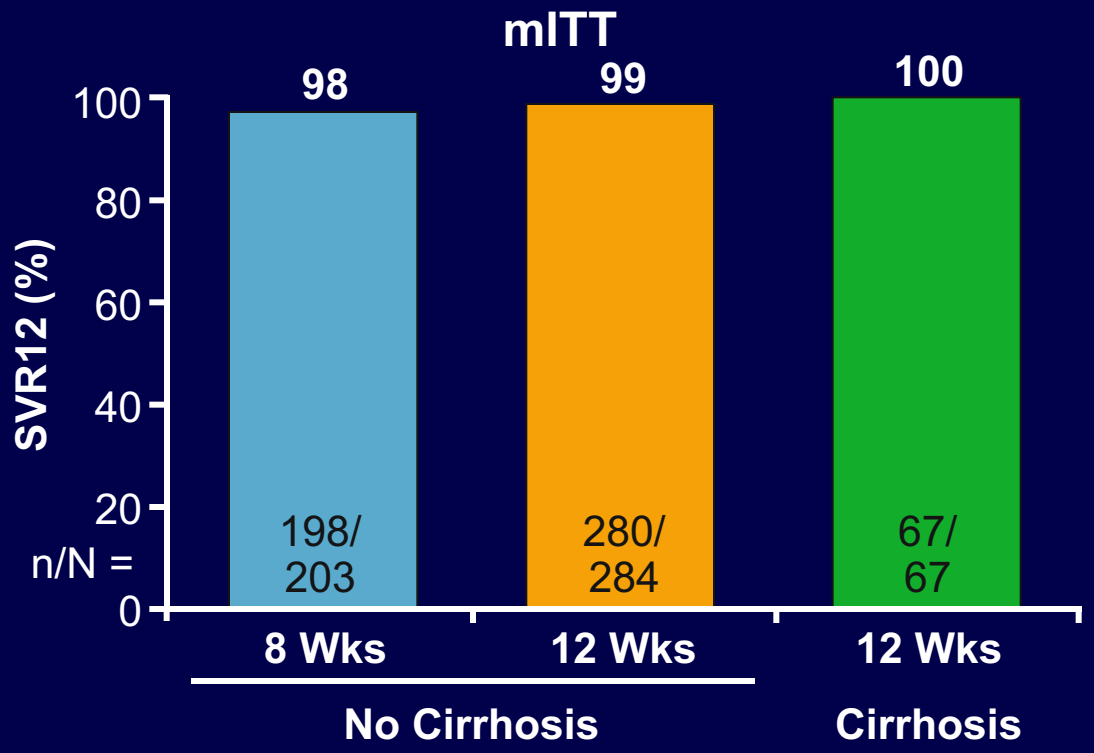
Wyles DL, et al. Hepatology. 2017;[Epub ahead of print].

Slide credit: clinicaloptions.com

# 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)



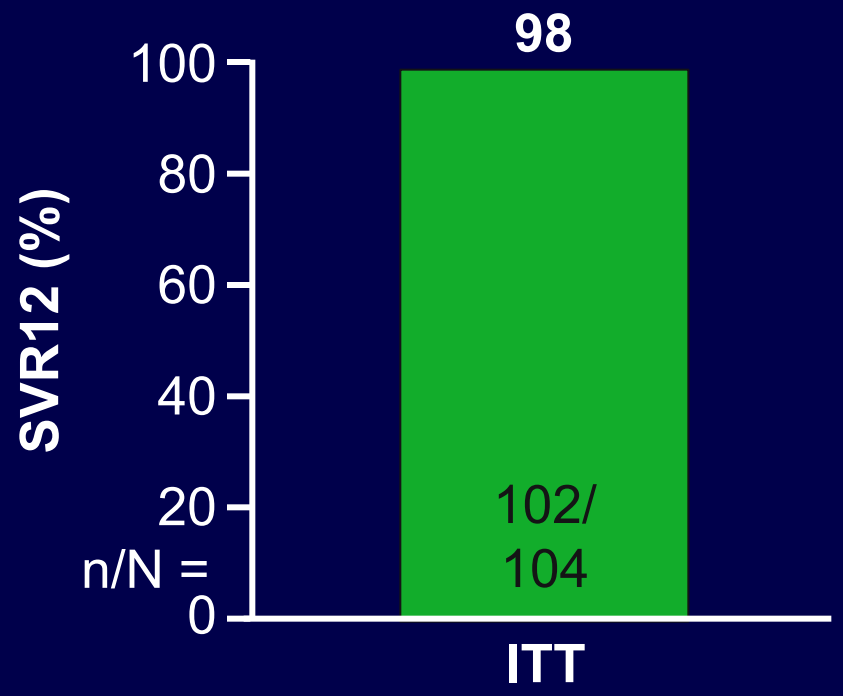




Flamm SL, et al. AASLD 2017. Abstract 62.

Slide credit: clinicaloptions.com

# 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)**

Gane EJ, et al. N Engl J Med. 2017;377:1448-1455.

# 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 | ▪ EBR/GZR* 12 wks<br>▪ GLE/PIB ***8 wks*** *if no cirrhosis,* ***12 wks*** *if compensated cirrhosis*<br>▪ LDV/SOF 12 wks<br>▪ LDV/SOF ***8 wks*** *if no cirrhosis, nonblack, no HIV, HCV RNA < 6 million IU/mL*<br>▪ SOF/VEL 12 wks |
| PegIFN/RBV experienced | ▪ EBR/GZR* 12 wks<br>▪ GLE/PIB ***8 wks*** *(****only*** *if no cirrhosis)*<br>▪ LDV/SOF 12 wks *(****only*** *if no cirrhosis*)<br>▪ SOF/VEL 12 wks<br>▪ GLE/PIB ***12 wks*** *(compensated cirrhosis)* |

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

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

# 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 | ▪ GLE/PIB 8 wks<br>▪ SOF/VEL 12 wks |
| | Yes | ▪ GLE/PIB 12 wks<br>▪ SOF/VEL 12 wks* |
| PegIFN/RBV Experienced | No | ▪ SOF/VEL 12 wks† |
| | Yes | ▪ EBR/GZR + SOF 12 wks<br>▪ 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. September 2017.

Slide credit: clinicaloptions.com

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

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

| No Cirrhosis | Compensated Cirrhosis |
| --- | --- |
| ▪ GLE/PIB **8 wks**<br>▪ SOF/VEL 12 wks | ▪ SOF/VEL 12 wks<br>▪ GLE/PIB 12 wks |

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

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

| HCV GT | No Cirrhosis | Compensated Cirrhosis |
|---|---|---|
| 4 | ▪ GLE/PIB **8 wks**<br>▪ SOF/VEL 12 wks<br>▪ EBR/GZR 12 wks<br>▪ LDV/SOF 12 wks | ▪ SOF/VEL 12 wks<br>▪ GLE/PIB 12 wks<br>▪ EBR/GZR 12 wks<br>▪ LDV/SOF 12 wks |
| 5 or 6 | ▪ GLE/PIB **8 wks**<br>▪ SOF/VEL 12 wks<br>▪ LDV/SOF 12 wks | ▪ GLE/PIB 12 wks<br>▪ SOF/VEL 12 wks<br>▪ LDV/SOF 12 wks |

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

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

| HCV GT | No Cirrhosis | Compensated Cirrhosis |
|---|---|---|
| 4 | ▪ SOF/VEL 12 wks<br>▪ GLE/PIB **8 wks**<br>▪ EBR/GZR* 12 wks<br>▪ LDV/SOF 12 wks | ▪ SOF/VEL 12 wks<br>▪ EBR/GZR* 12 wks<br>▪ GLE/PIB 12 wks |
| 5 or 6 | ▪ GLE/PIB **8 wks**<br>▪ LDV/SOF 12 wks<br>▪ SOF/VEL 12 wks | ▪ GLE/PIB 12 wks<br>▪ LDV/SOF 12 wks<br>▪ SOF/VEL 12 wks |

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

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

# 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.

AASLD/IDSA. HCV guidance. September 2017.

# 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.

AASLD/IDSA. HCV guidance. September 2017. FDA GLE/PIB. FDA SOF/VEL/VOX.

Slide credit: clinicaloptions.com

# 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 |

Dore G, et al. EASL 2017. Abstract PS-160.

Slide credit: clinicaloptions.com

# HBV Reactivation in Pts Receiving HCV DAAs

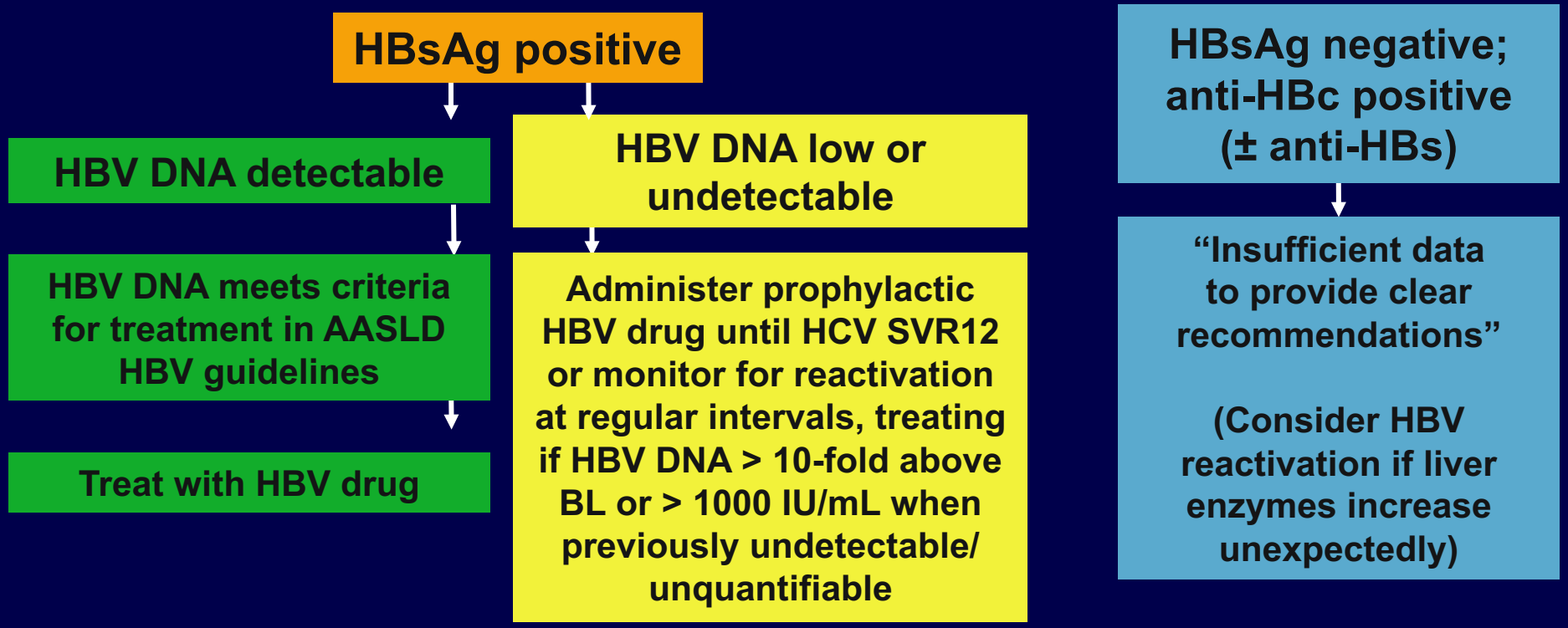
- Case reports of HBV reactivation in pts treated with SMV + SOF ± RBV,[1,2] DCV + ASV,[3,4] and LDV/SOF[5]
  - Possibly due to loss of host immune response to HBV[6]
- 29 confirmed cases of HBV reactivation in HCV DAA recipients in ~ 3 yrs (most from Japan, November 2013 to October 2016)[7]
  - Most 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]

References in slidenotes.

Slide credit: clinicaloptions.com

# 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




AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

# Conclusions

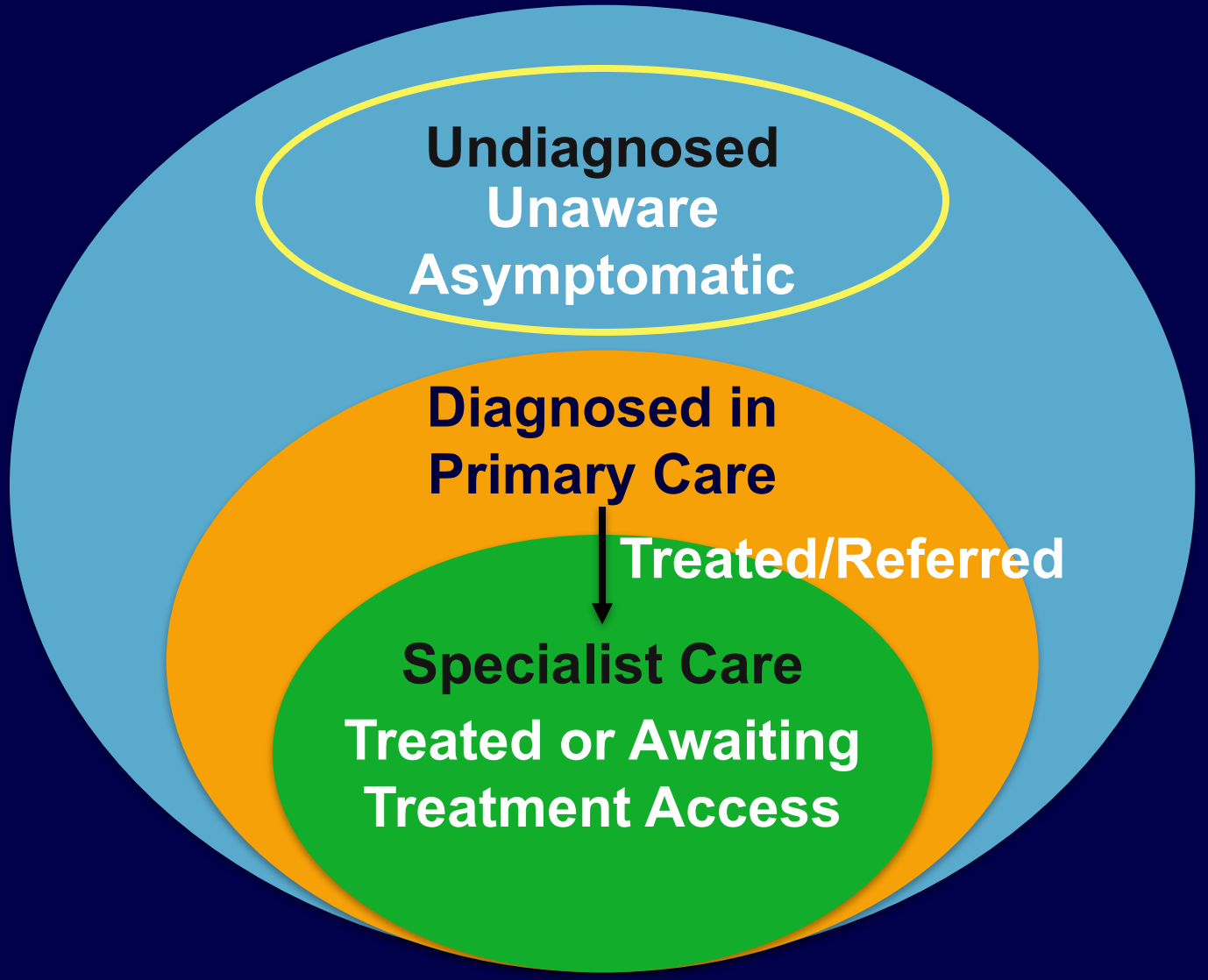
- Multiple current regimens highly effective and safe across genotypes
  - 8-12 wks without RBV for vast majority of pts
- SOF/VEL and GLE/PIB provide 12-wk or 8-wk pangenotypic regimens for DAA-naive noncirrhotic pts; other regimens remain first-line for specific genotypes, especially GT1
- No convincing 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

CLINICAL CARE OPTIONS®
HEPATITIS

# Engaging the 50%: Increasing Screening and Diagnosis

Jordan J. Feld, MD, MPH

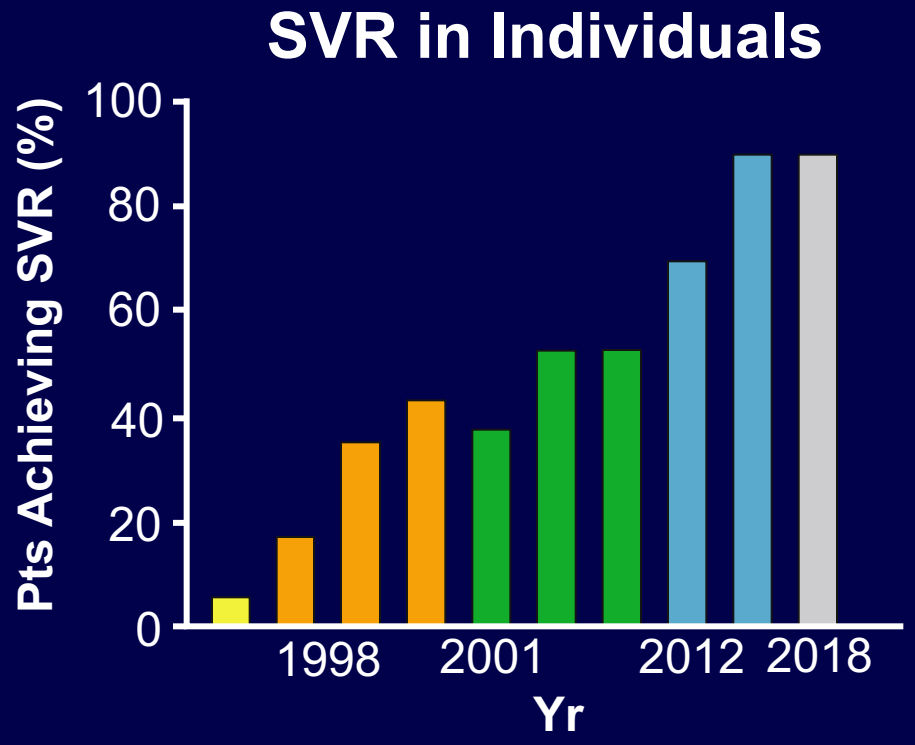
# HCV Population

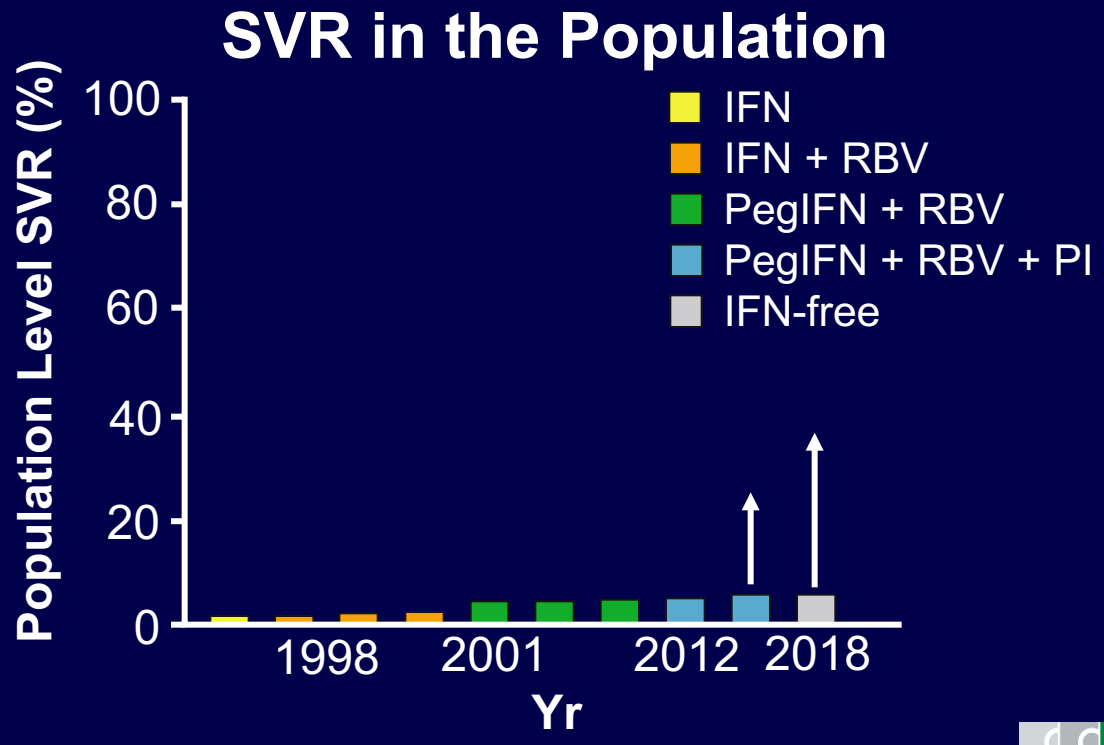



Slide credit: clinicaloptions.com

# We Need More Than Great Drugs

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

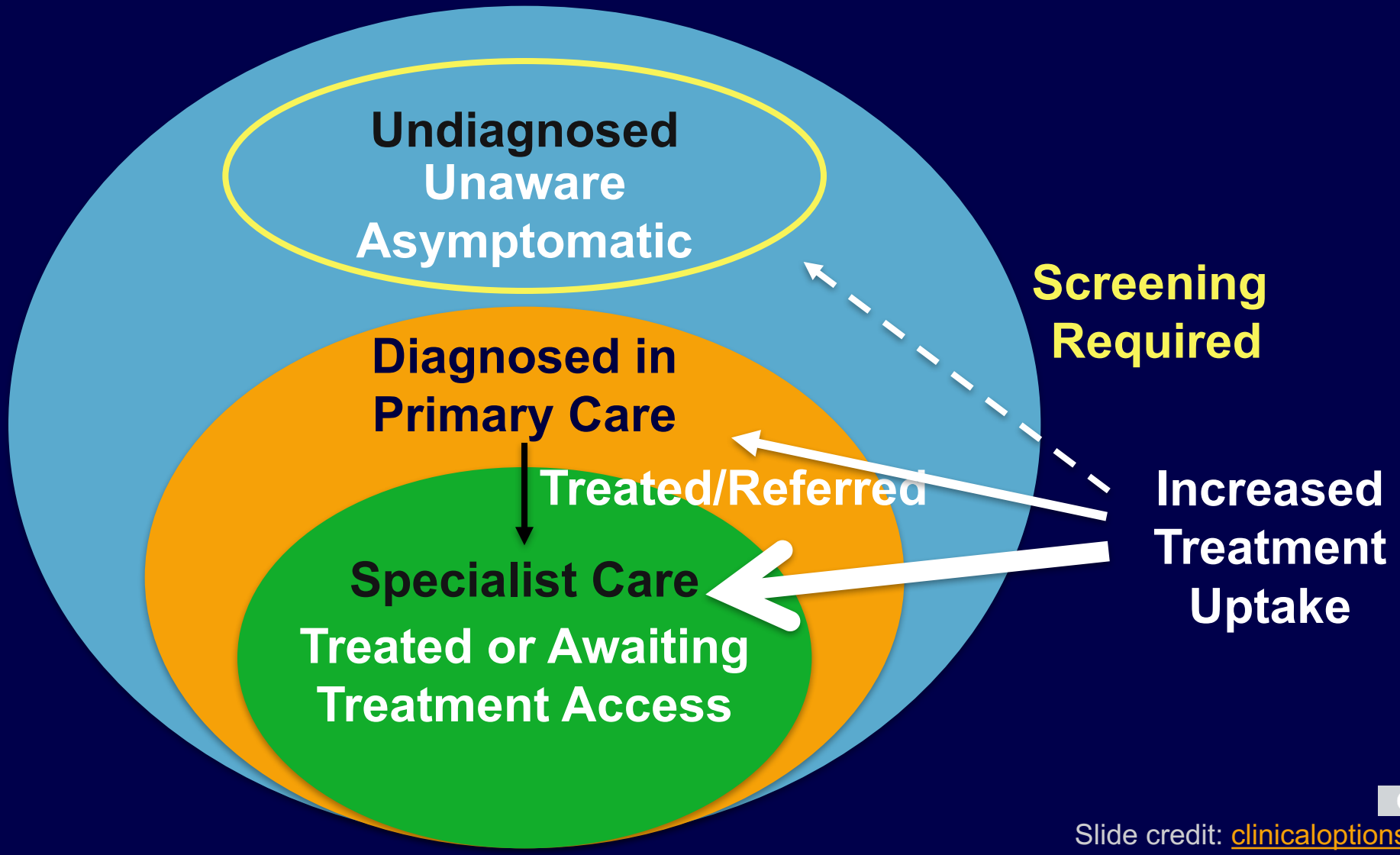



Thomas DL, et al. Antivir Ther. 2012;17:1183-1188.

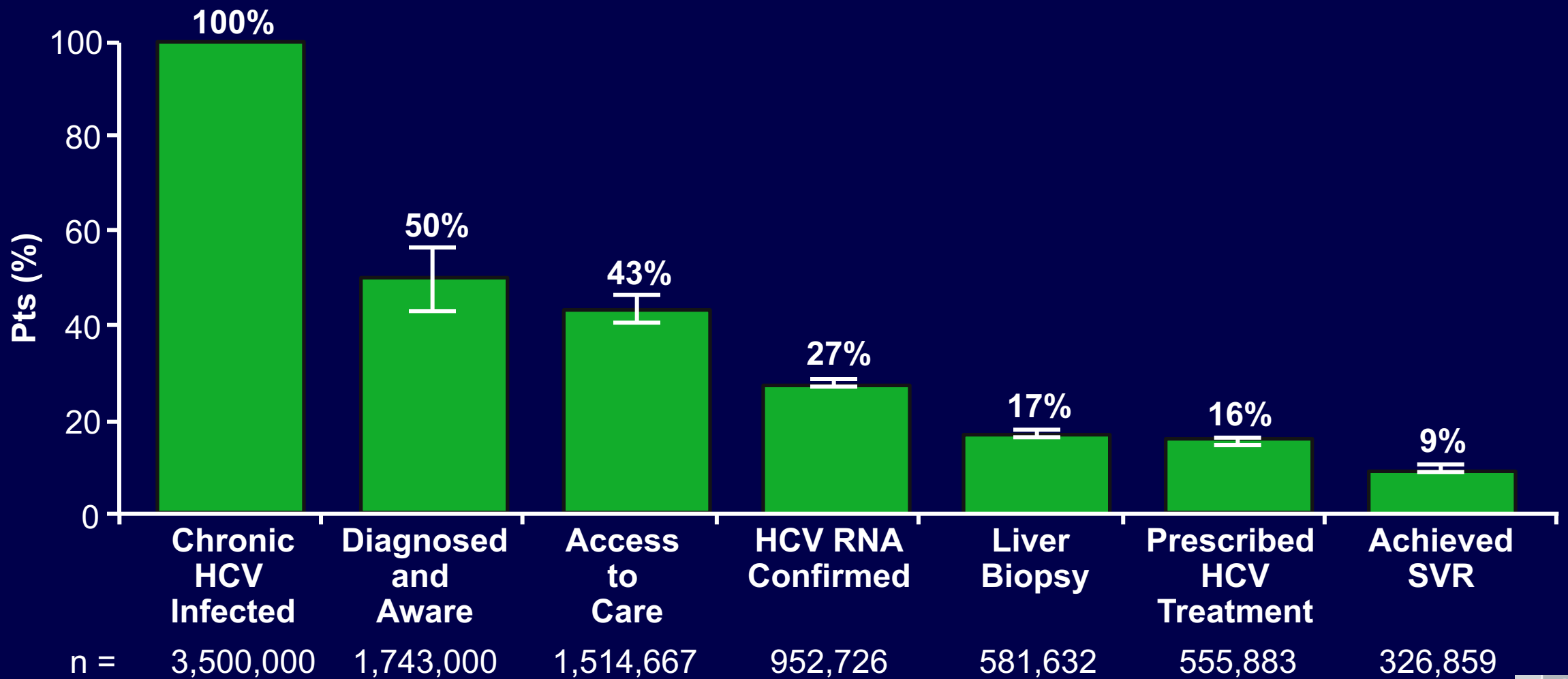
Slide credit: clinicaloptions.com

# HCV Population




Slide credit: clinicaloptions.com

# Hepatitis C Virus in the US: Gaps in Current Practice

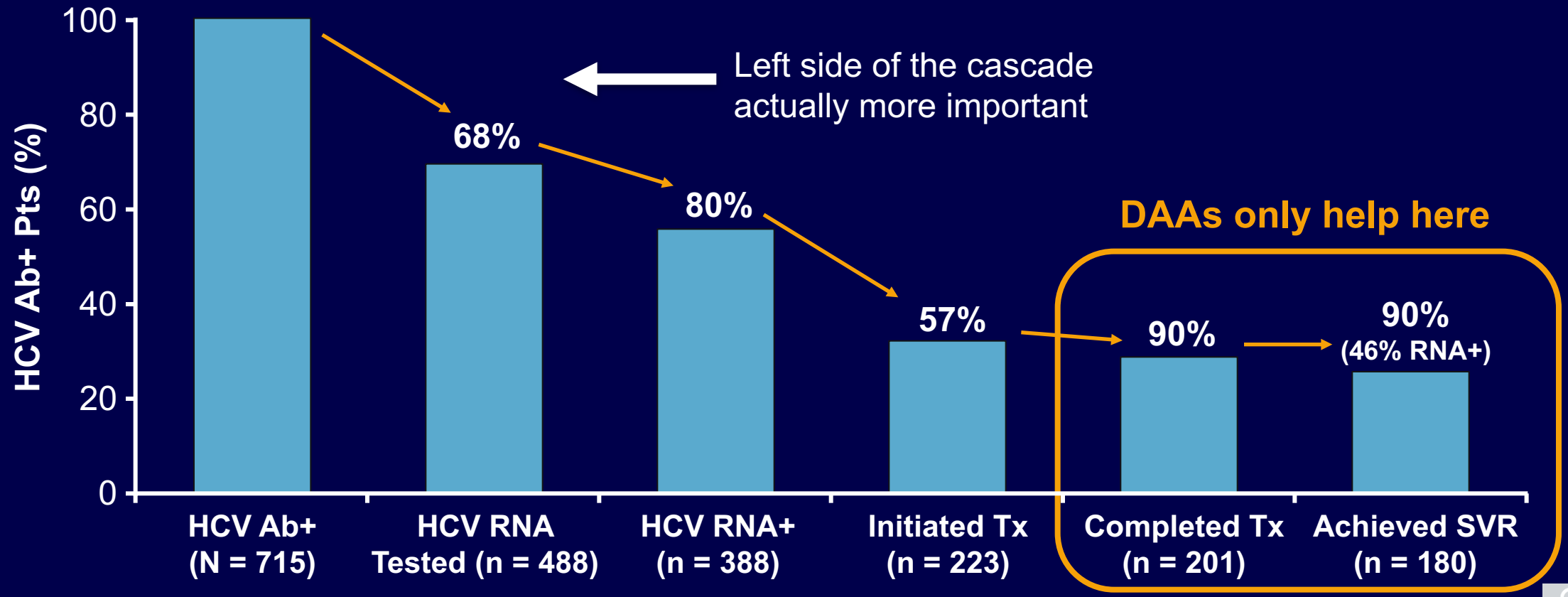



Yehia BR, et al. PLoS One. 2014;9:e101554.

Slide credit: clinicaloptions.com

# 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%)




Mera J, et al. MMWR Morb Mortal Wkly Rep. 2016;65:461-466.

Slide credit: clinicaloptions.com

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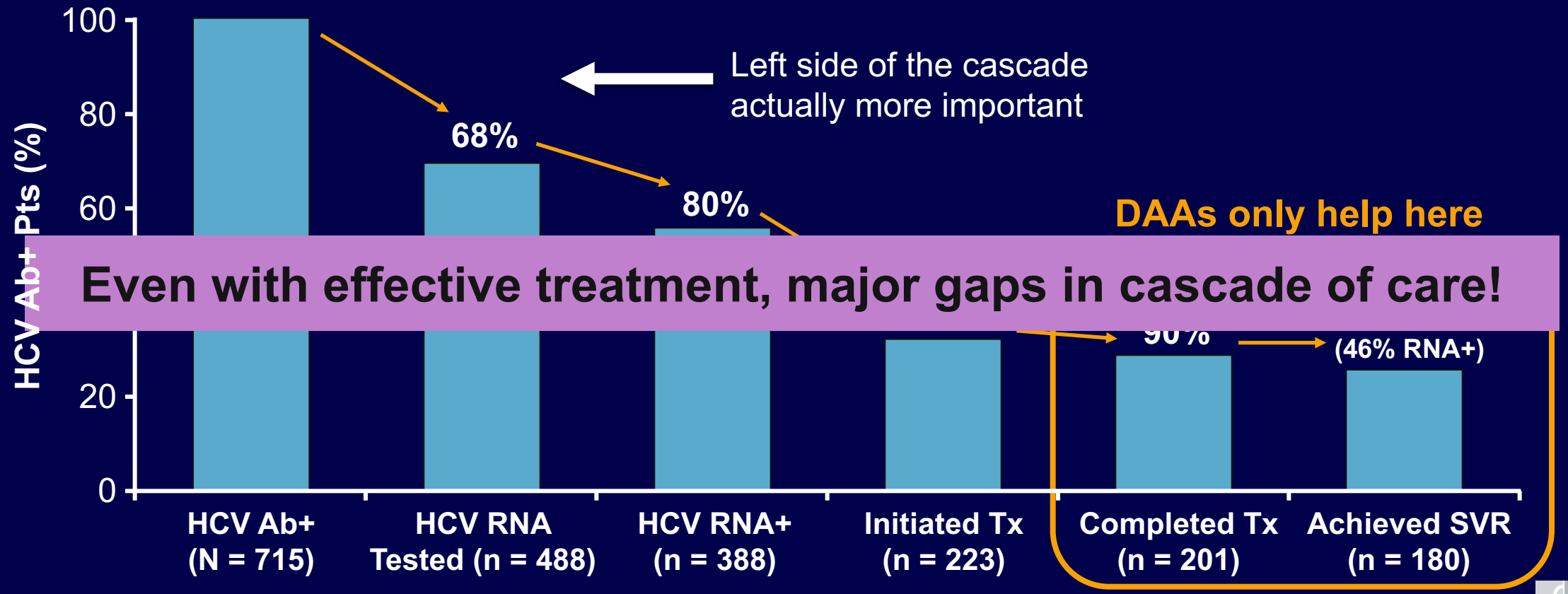



Mera J, et al. MMWR Morb Mortal Wkly Rep. 2016;65:461-466.

Slide credit: clinicaloptions.com

# HCV Screening

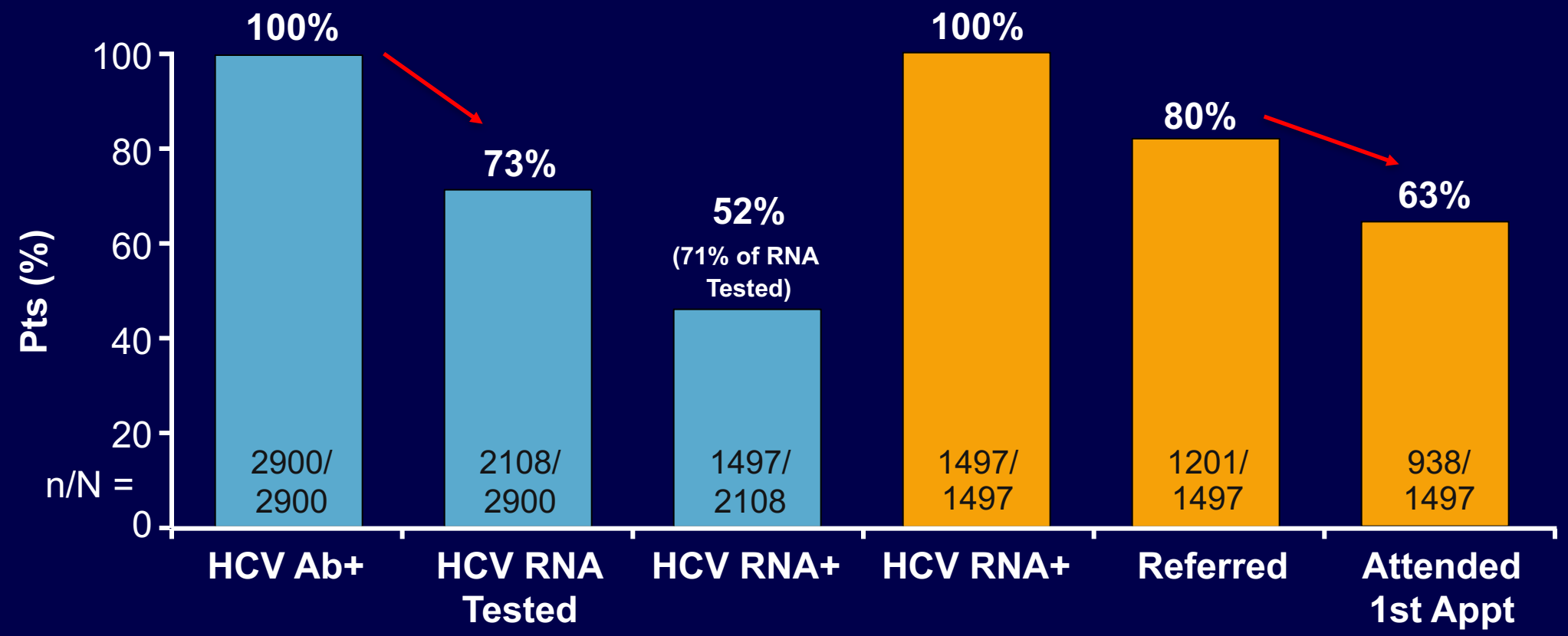
| The Where | The How | The Who |
|---|---|---|
| ▪ PCP office—birth cohort<br>▪ Hospital—ED/inpatient<br>▪ Prenatal<br>▪ OST<br>▪ Outreach—homeless shelters, supervised injection sites | ▪ Current—Ab then RNA<br>▪ Point-of-care—Ab+ then RNA<br>▪ Dried blood spot—Ab with reflex RNA<br>▪ Rapid diagnostic test—RNA | ▪ PCP—GP/RN<br>▪ ED staff<br>▪ Peer workers |

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

Slide credit: clinicaloptions.com

# Is Boomer Screening Working?

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




Patel RC, et al. Public Health Rep. 2016;131(suppl 2):12-19.

Slide credit: clinicaloptions.com

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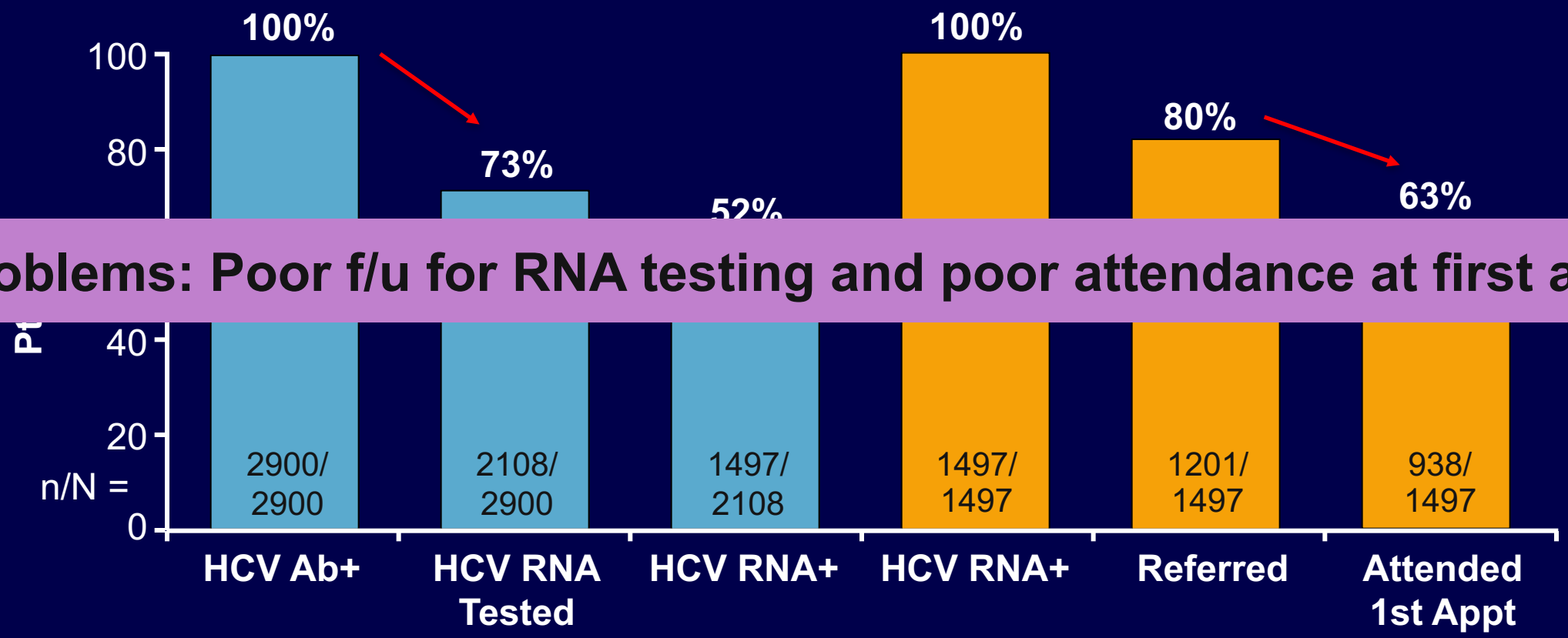


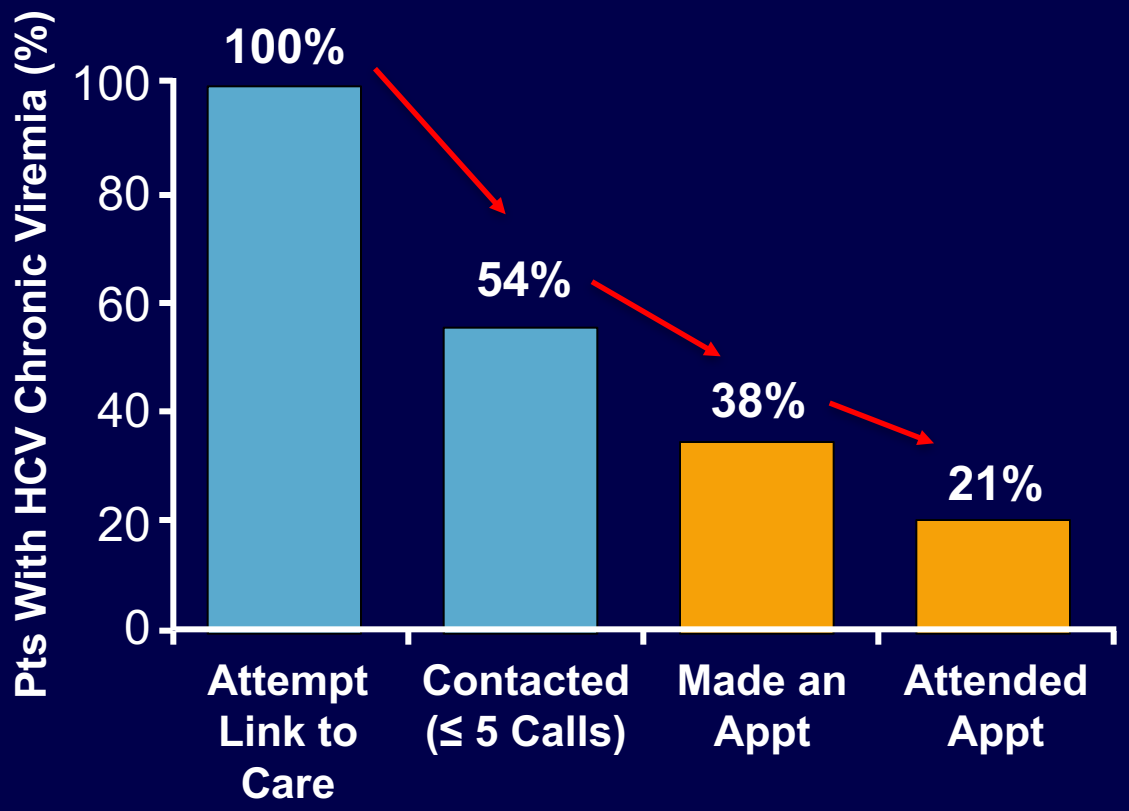

**Problems: Poor f/u for RNA testing and poor attendance at first appt**

Patel RC, et al. Public Health Rep. 2016;131(suppl 2):12-19.

Slide credit: clinicaloptions.com

# 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) |

Galbraith JW, et al. Hepatology. 2015;61:776-782.

Slide credit: clinicaloptions.com

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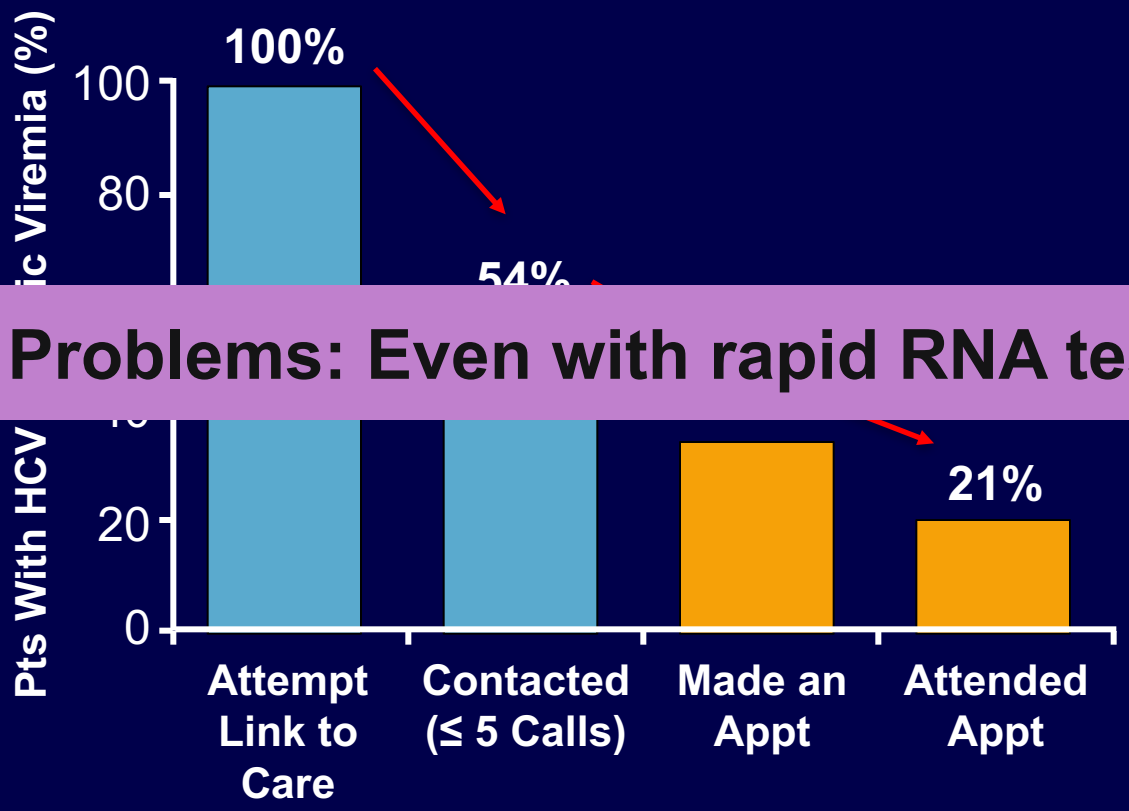


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| Insurance | |
| ▪Private | 19 (5.0) |
| ▪Public/Medicaid | 48 (16.8) |
| ▪Uninsured | 55 (16.9) |

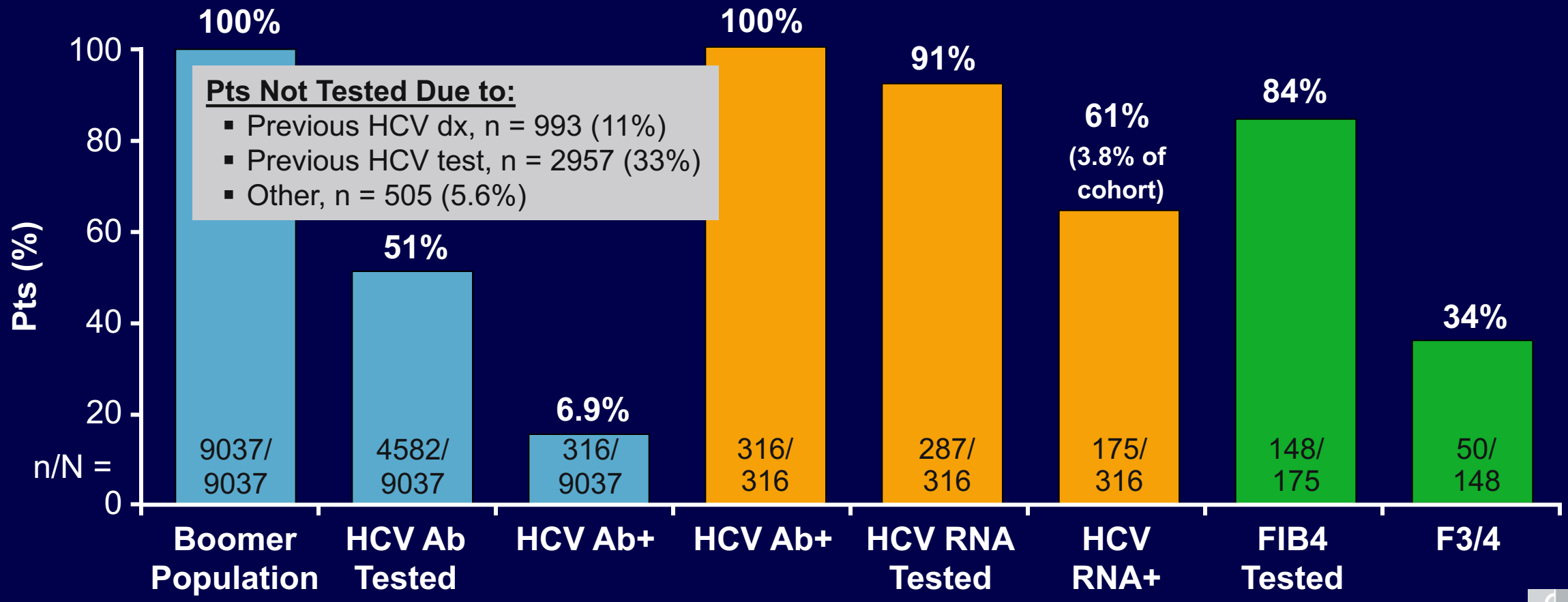
**Problems: Even with rapid RNA testing…follow-up a MAJOR problem**

Galbraith JW, et al. Hepatology. 2015;61:776-782.

Slide credit: clinicaloptions.com

# Other Settings: Hospitalized Pts

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




Turner BJ, et al. Hepatology. 2015;62:1388-1395.

Slide credit: clinicaloptions.com

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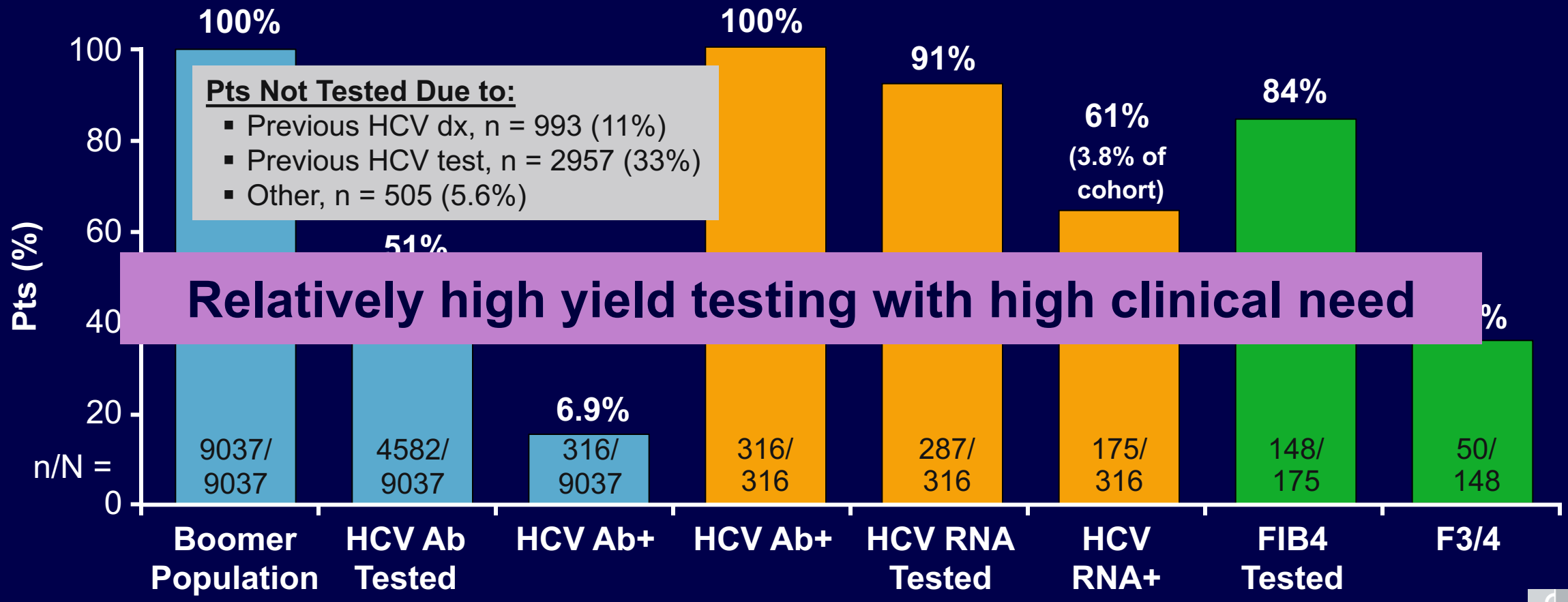


**Pts Not Tested Due to:**

- Previous HCV dx, n = 993 (11%)
- Previous HCV test, n = 2957 (33%)
- Other, n = 505 (5.6%)

**Relatively high yield testing with high clinical need**

Turner BJ, et al. Hepatology. 2015;62:1388-1395.

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# 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

Shivkumar S, et al. Ann Intern Med. 2012;157:558-566. Gupta E, et al. J Clin Virol. 2017;88:46-51. Grebely J, et al. Lancet Gastroenterol Hepatol. 2017;2:514-520. Cloherty G, et al. J Clin Microbiol. 2016;54:265-273. Ross RS, et al. Virol J. 2013;10:72.

# RDTs vs PoCT

- **Rapid diagnostic test:** rapid but requires special equipment ± trained personnel
  - Antibody (blood, serum, or saliva)
  - RNA (blood,
- **Point-of-care**
  special equipment or electricity required, easier to perform, no cold chain required
  - Antibody (blood, saliva)
  - RNA (blood)

**Not all tests are created equal!**

- **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
    test
  - me, no immediate result—need follow-up

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Slide credit: clinicaloptions.com

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

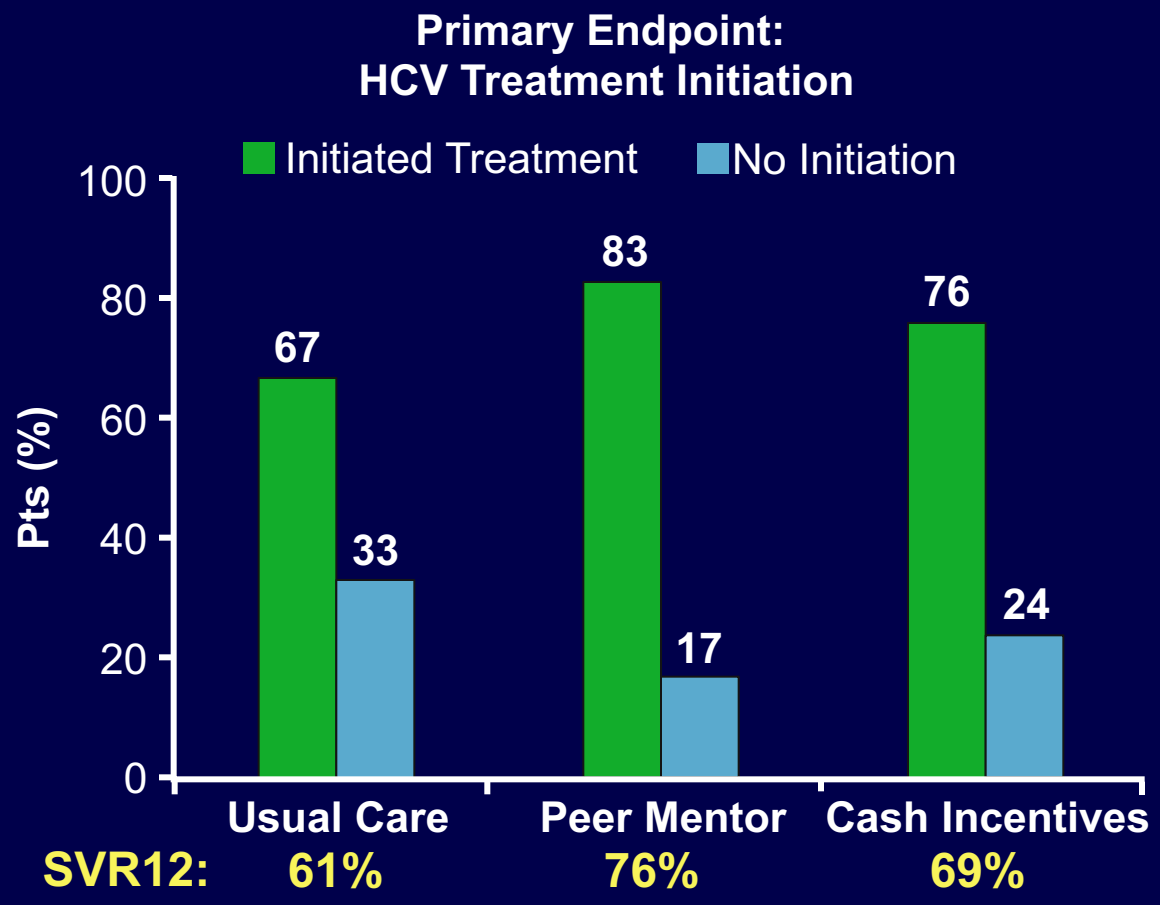
# After a Positive Test

- 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 . . .

Slide credit: clinicaloptions.com

# 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

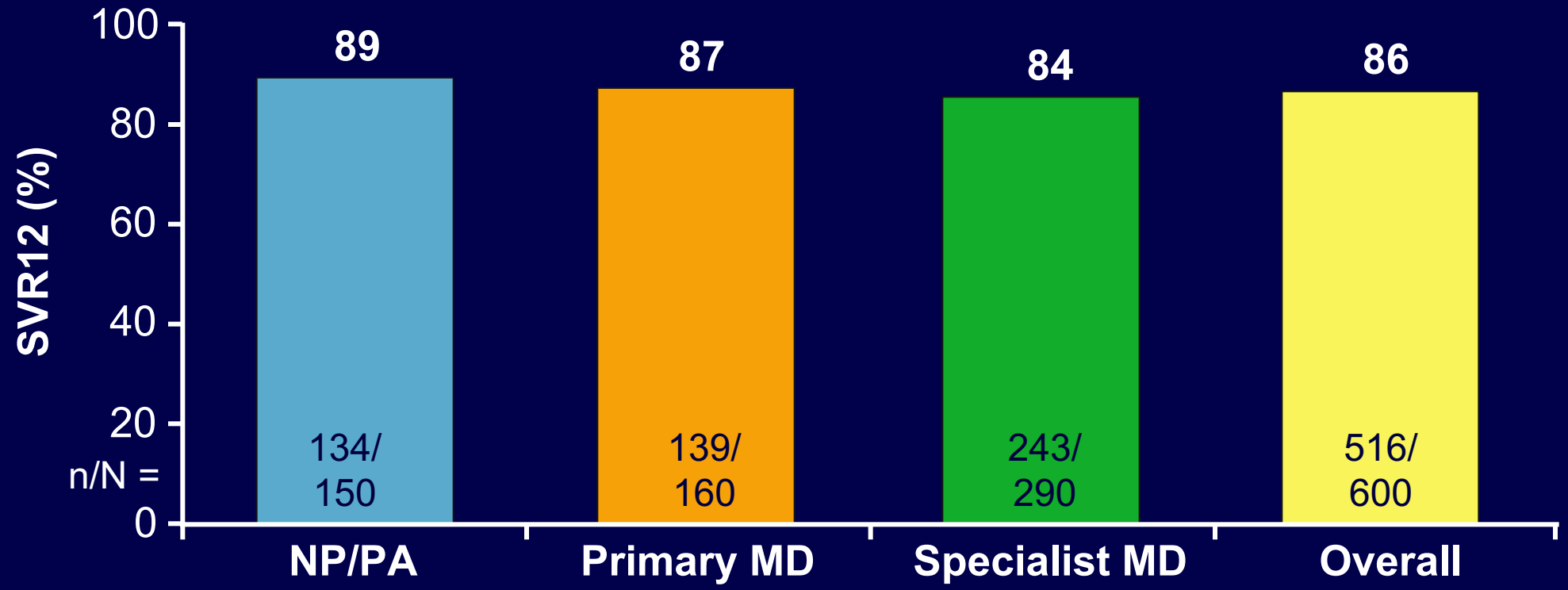



Sulkowski M, et al. AASLD 2017. Abstract 76.

Slide credit: clinicaloptions.com

# 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




Kattakuzhy S, et al. Ann Intern Med. 2017;167:311-318.

Slide credit: clinicaloptions.com

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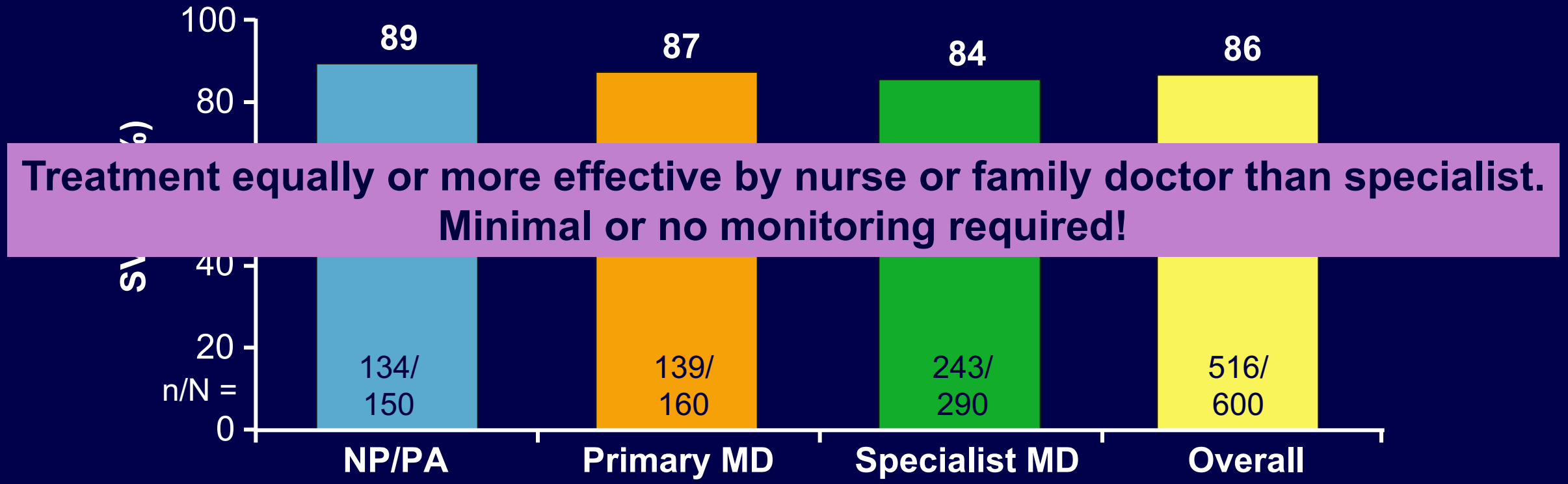
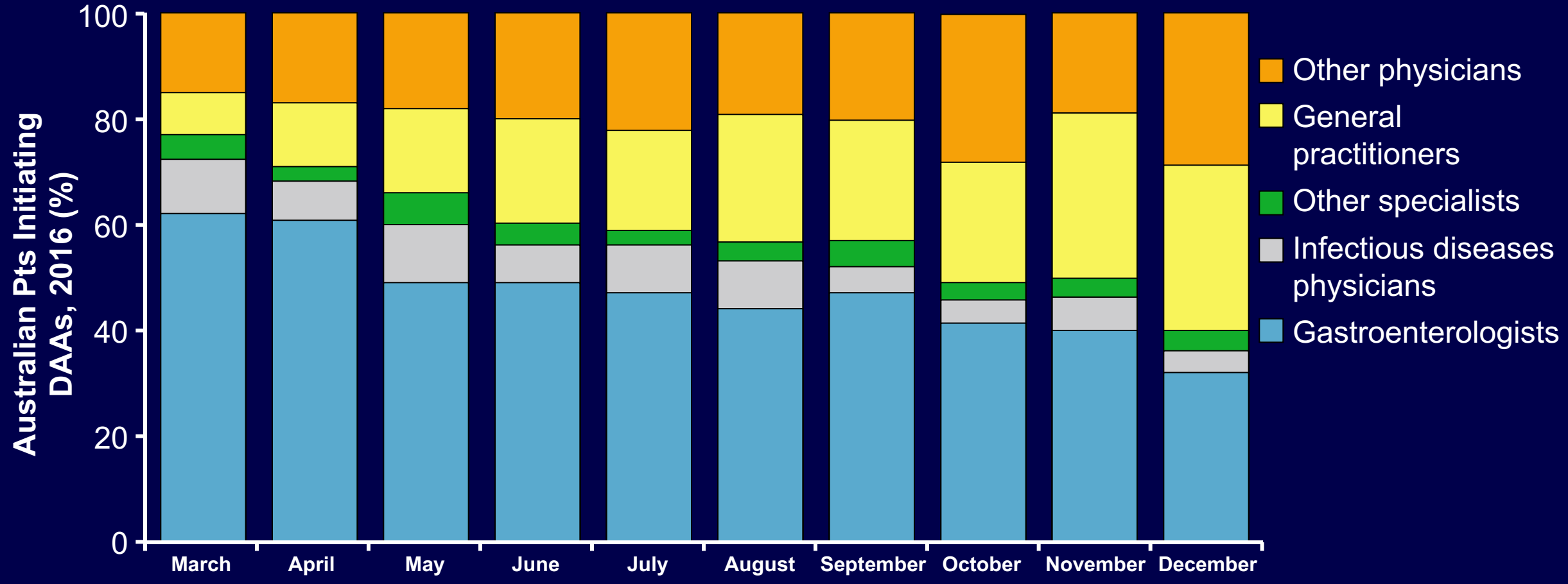



**Treatment equally or more effective by nurse or family doctor than specialist. Minimal or no monitoring required!**

Kattakuzhy S, et al. Ann Intern Med. 2017;167:311-318.

Slide credit: clinicaloptions.com

# Nonspecialists Can Effectively Treat HCV




The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 7). Available at: https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-7-july-2017.

Slide credit: clinicaloptions.com

# Project ECHO: A Key to Linkage to Care

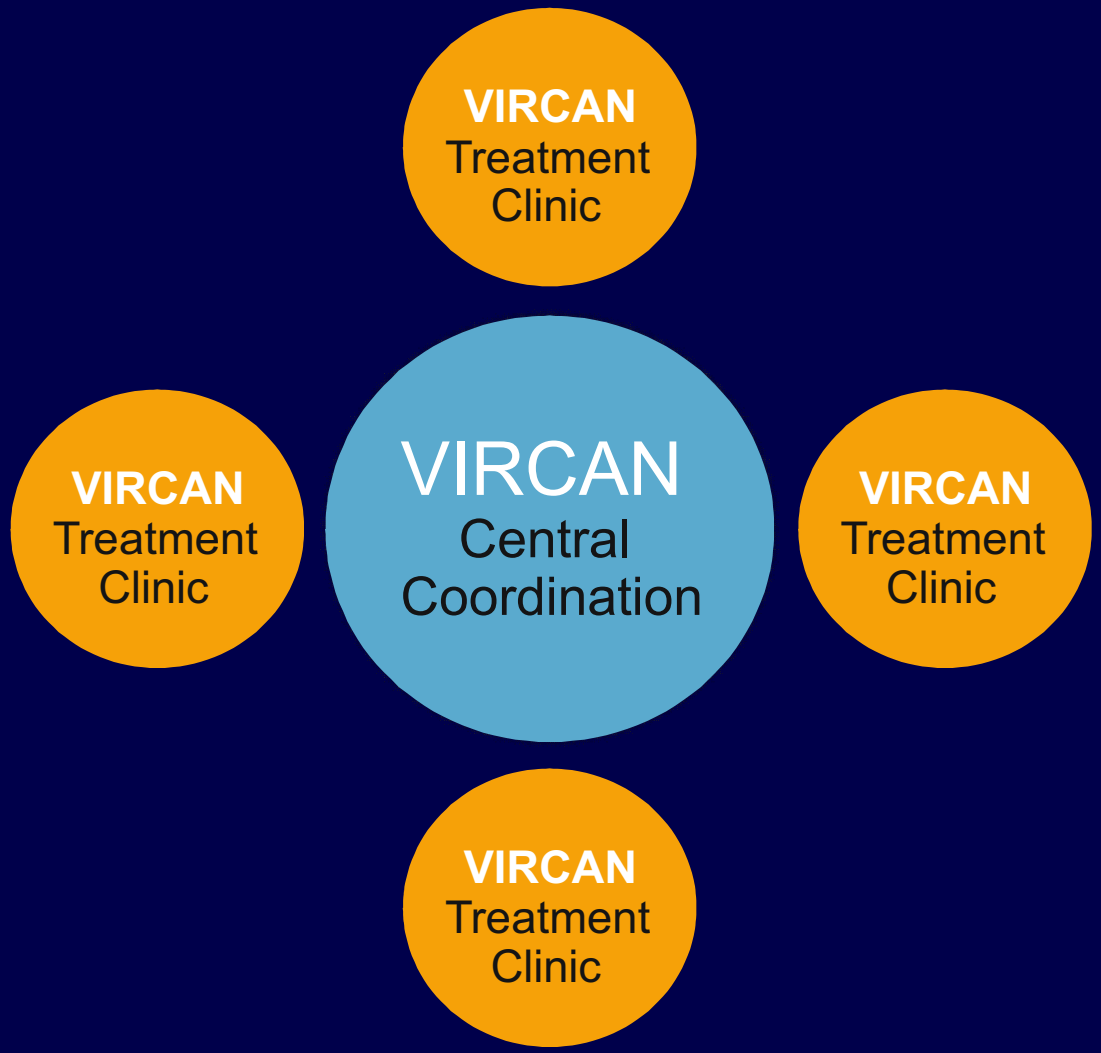
- Linking PCPs to specialists
- Program is expanding rapidly
- Expert care does not require MD
- Enables new treaters
- Knowledge translation
- Facilitates linkage to care
- Allows people to be treated by people and in settings they know and trust

**Many HCV treatment support options available**

Arora S, et al. N Engl J Med. 2011;364:2199-2207.

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# 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

Uhanova J, et al. Can J Gastroenterol. 2013;27:336-340.

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

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HEPATITIS

# Treating the 33%: Expanding Therapy to the Previously Excluded

Christian B. Ramers, MD, MPH

# Who Has Been Left Behind?

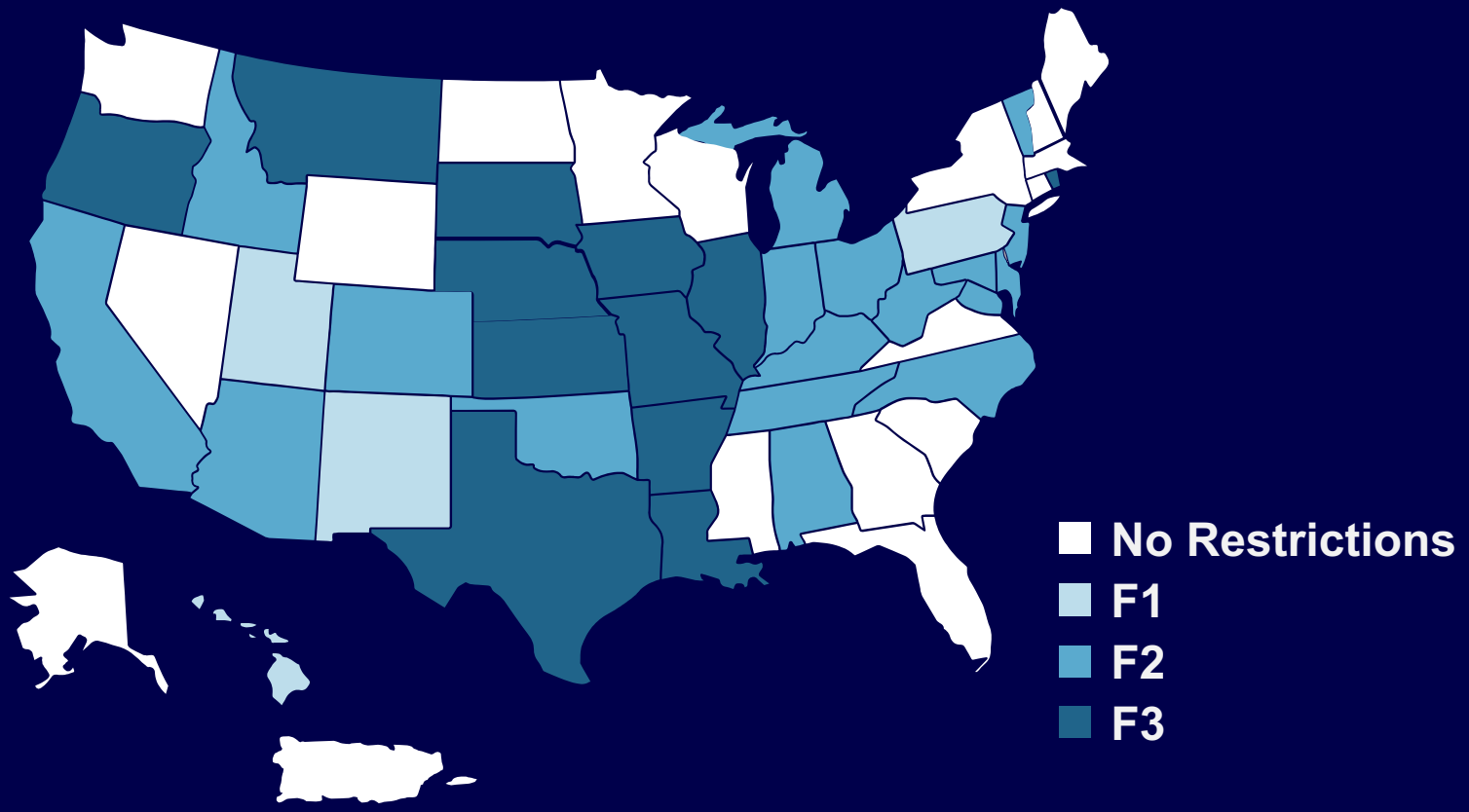
# Historical Exclusions for HCV Therapy

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

Slide credit: clinicaloptions.com

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

**2017 Medicaid FFS Liver Damage Restrictions for HCV Treatment**

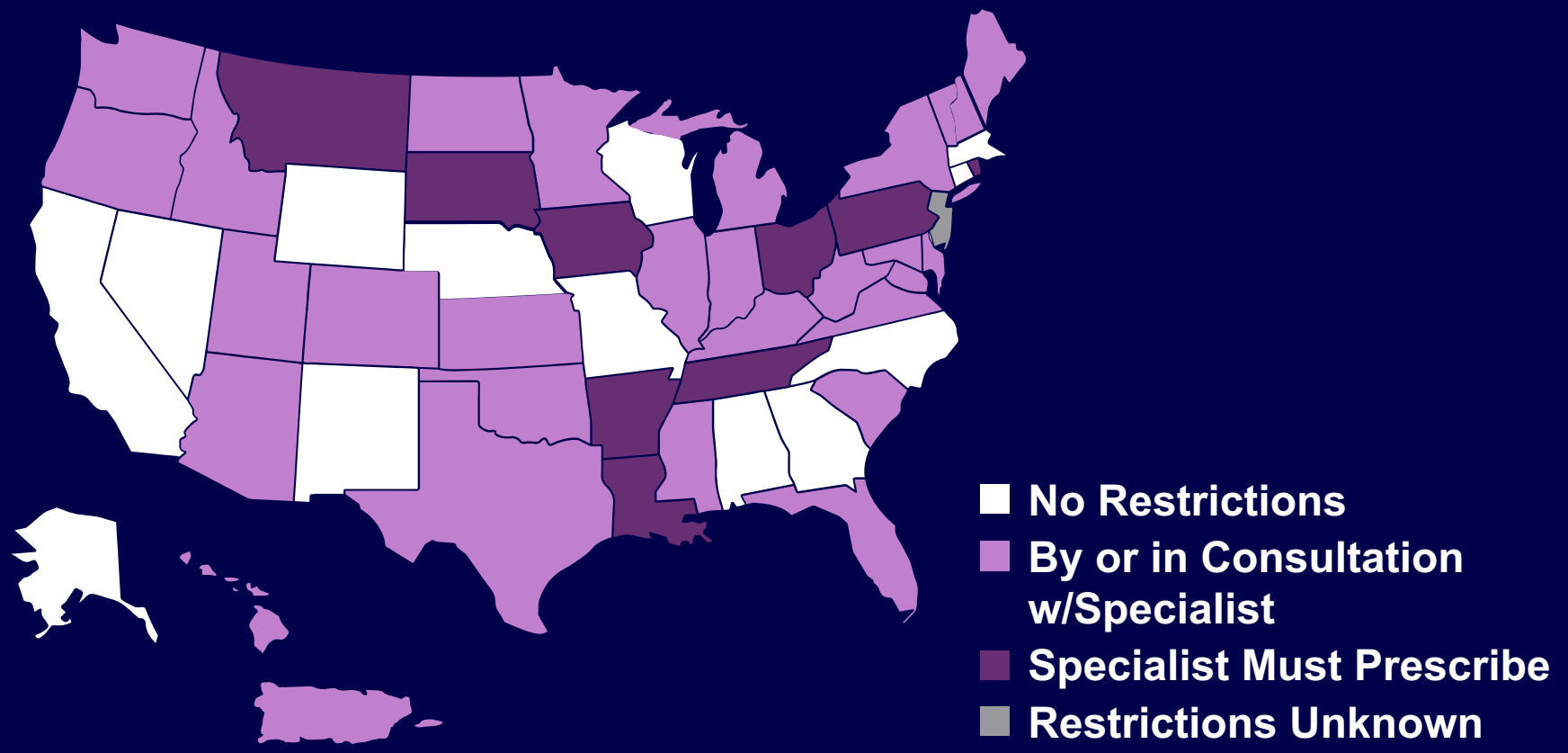



NVHR State of Hepatitis C State of Medicaid Access Report. Oct 23, 2017. https://stateofhepc.org/

Slide credit: clinicaloptions.com

# 2017 NVHR Update: Reduced Treatment Access for Pts Receiving Care From Non-Specialists

**2017 Medicaid FFS Prescriber Restrictions for HCV Treatment**

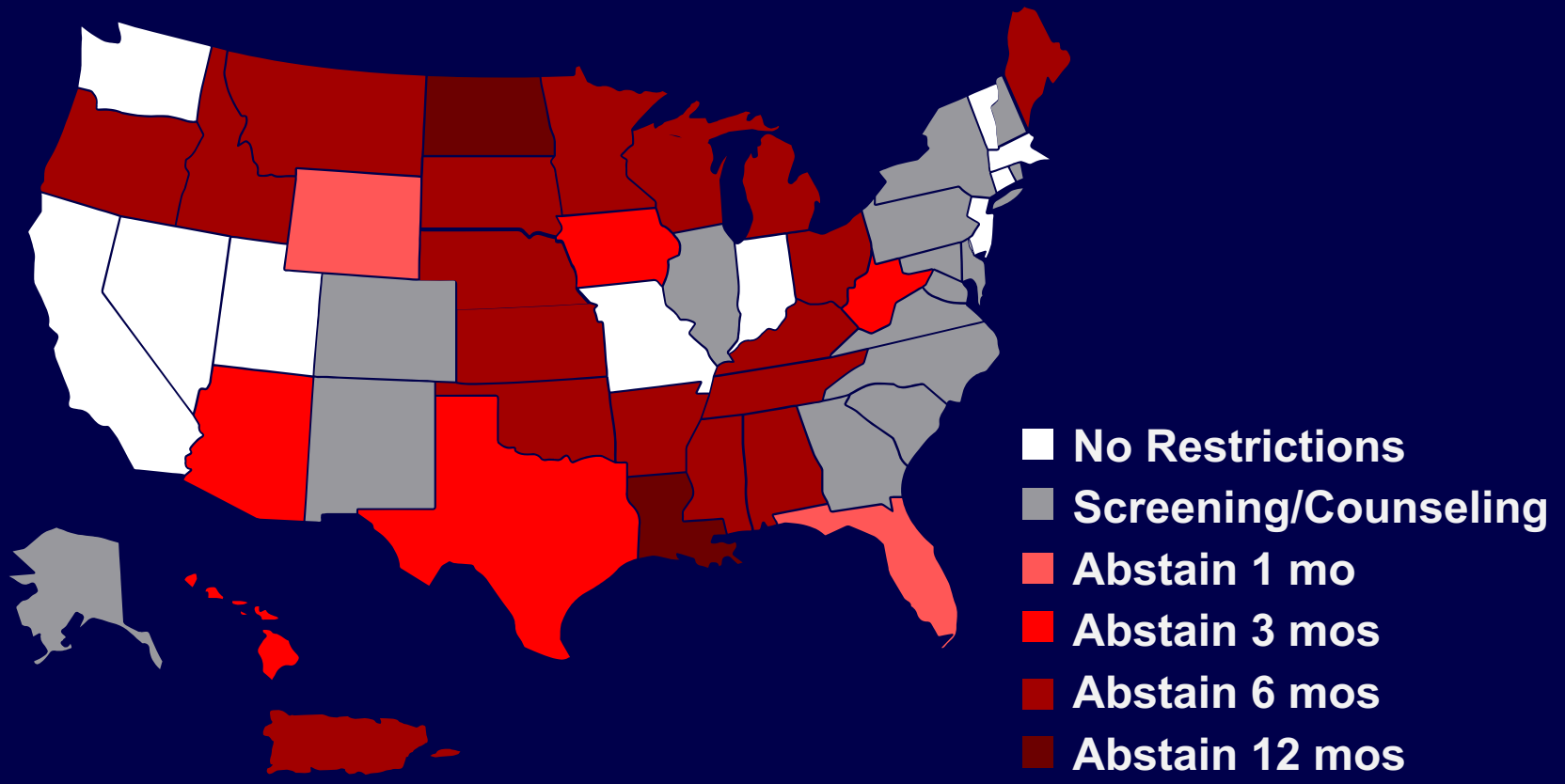



NVHR State of Hepatitis C State of Medicaid Access Report. Oct 23, 2017. https://stateofhepc.org/

Slide credit: clinicaloptions.com

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

**2017 Medicaid FFS Sobriety Restrictions for HCV Treatment**




NVHR State of Hepatitis C State of Medicaid Access Report. Oct 23, 2017. https://stateofhepc.org/

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# HCV Treatment as Prevention

# AASLD/IDSA HCV Treatment Guidelines: PWID

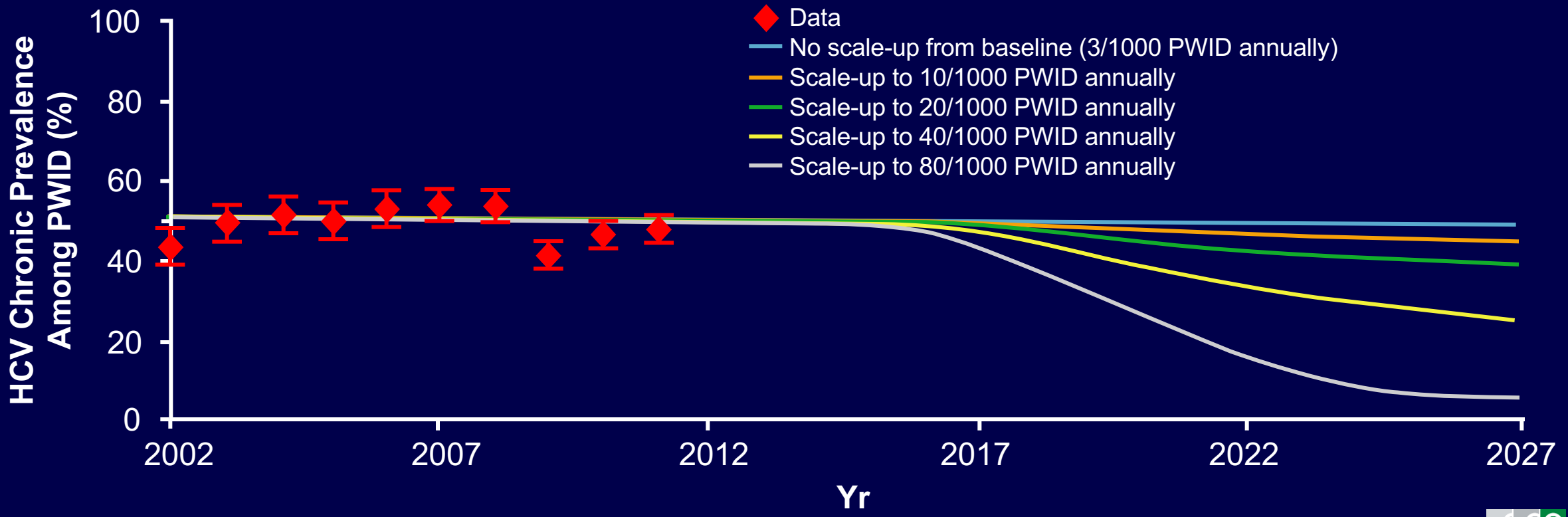
- "Recent or active IDU should not be seen as an absolute contraindication to HCV therapy"
- "Scaling up HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the US and globally"

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

# HCV Treatment Can Prevent Onward Transmission

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




Martin NK, et al. Hepatology. 2013;58:1598-1609.

Slide credit: clinicaloptions.com

# 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

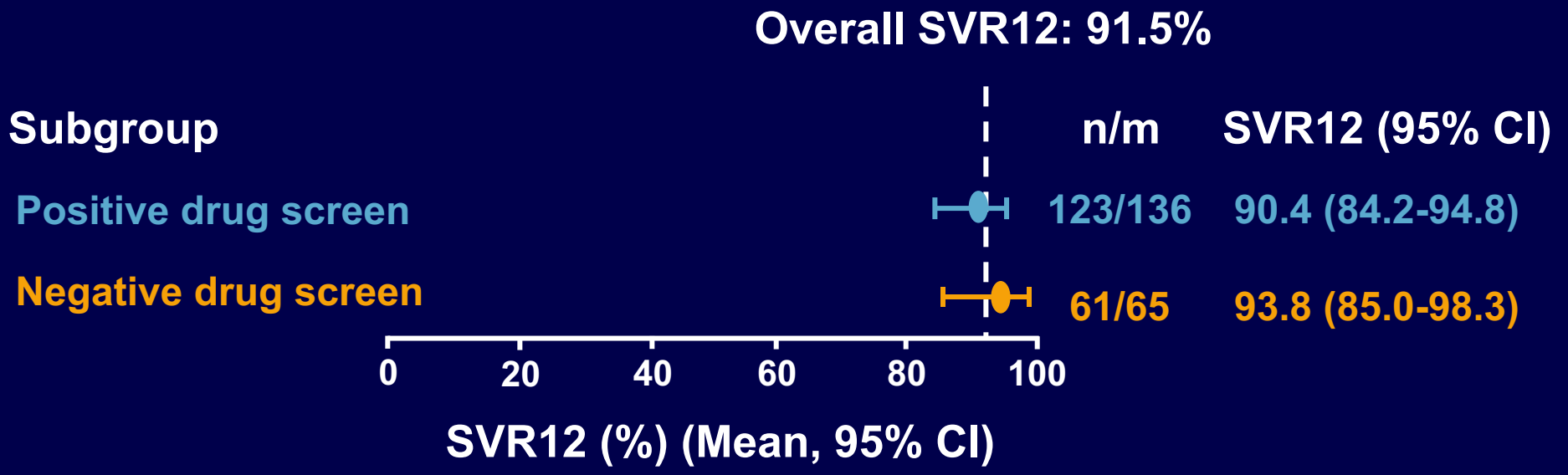
| 2030 Targets | |
|---|---|
| 90% | Diagnosed |
| 80% | Treated |
| 65% | Reduced Mortality |

WHO. Towards the elimination of hepatitis B and C by 2030.
Draft WHO Global Hepatitis Strategy, 2016-2021.

Slide credit: clinicaloptions.com

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

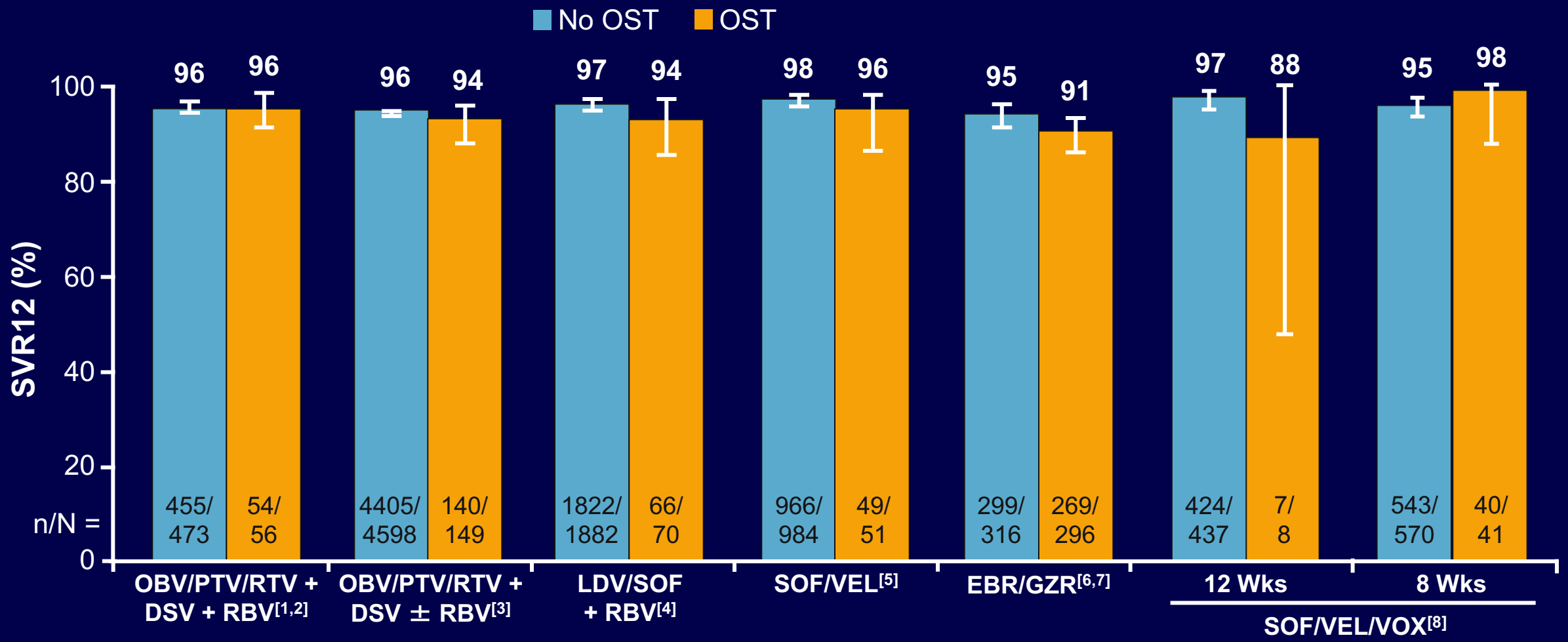
- Treatment-naive F0-4 PWID with GT1/4/6 HCV who were on OST were treated with grazoprevir/elbasvir (N = 301)
  - > 40% had injection drug use during therapy (excluding cannabinoids)




Dore GJ, et al. Ann Intern Med. 2016;165:625-634.

Slide credit: clinicaloptions.com

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



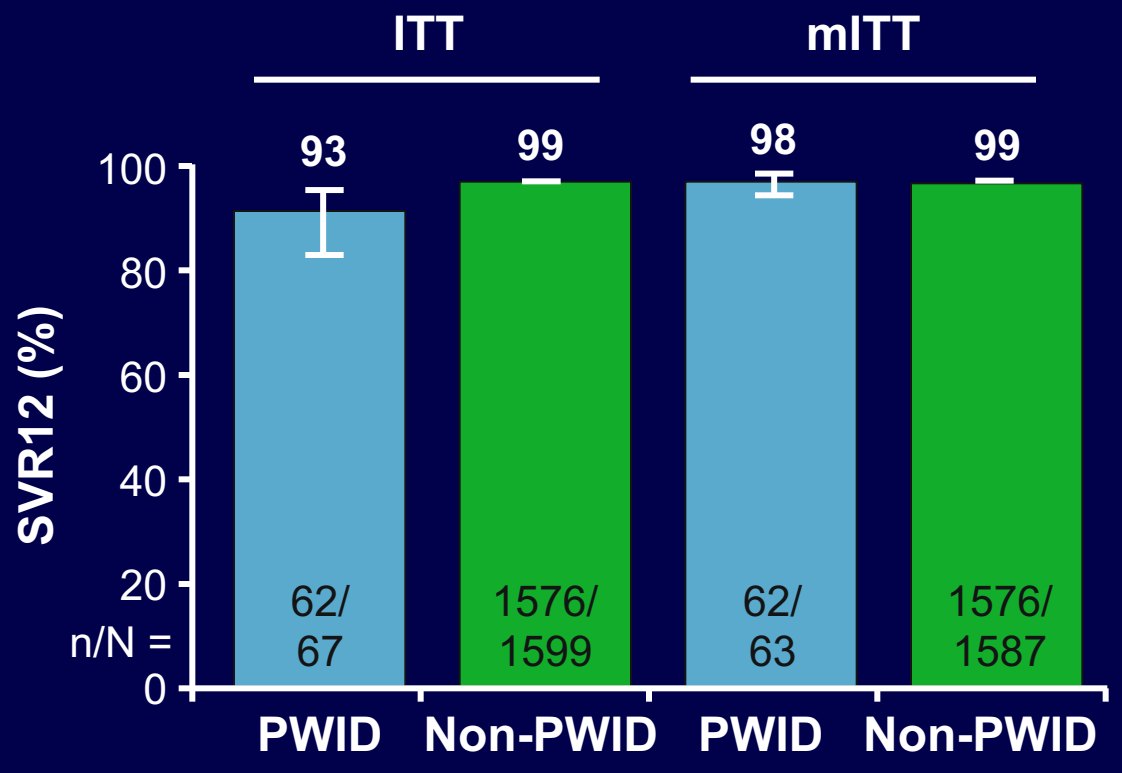

References in slidenotes.

Slide credit: clinicaloptions.com

# 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
  - ≥ 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 |




Foster GR, et al. AASLD 2017. Abstract 1182.

Slide credit: clinicaloptions.com

# 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)

Grebely J, et al. EASL 2017. Abstract FRI-234.

Slide credit: clinicaloptions.com

# 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**

Schuckit MA. N Engl J Med. 2016;375:357-368. SAMHSA. Buprenorphine waiver management. February 2017. SAMHSA. Naltrexone. September 2016.

Slide credit: clinicaloptions.com

# 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

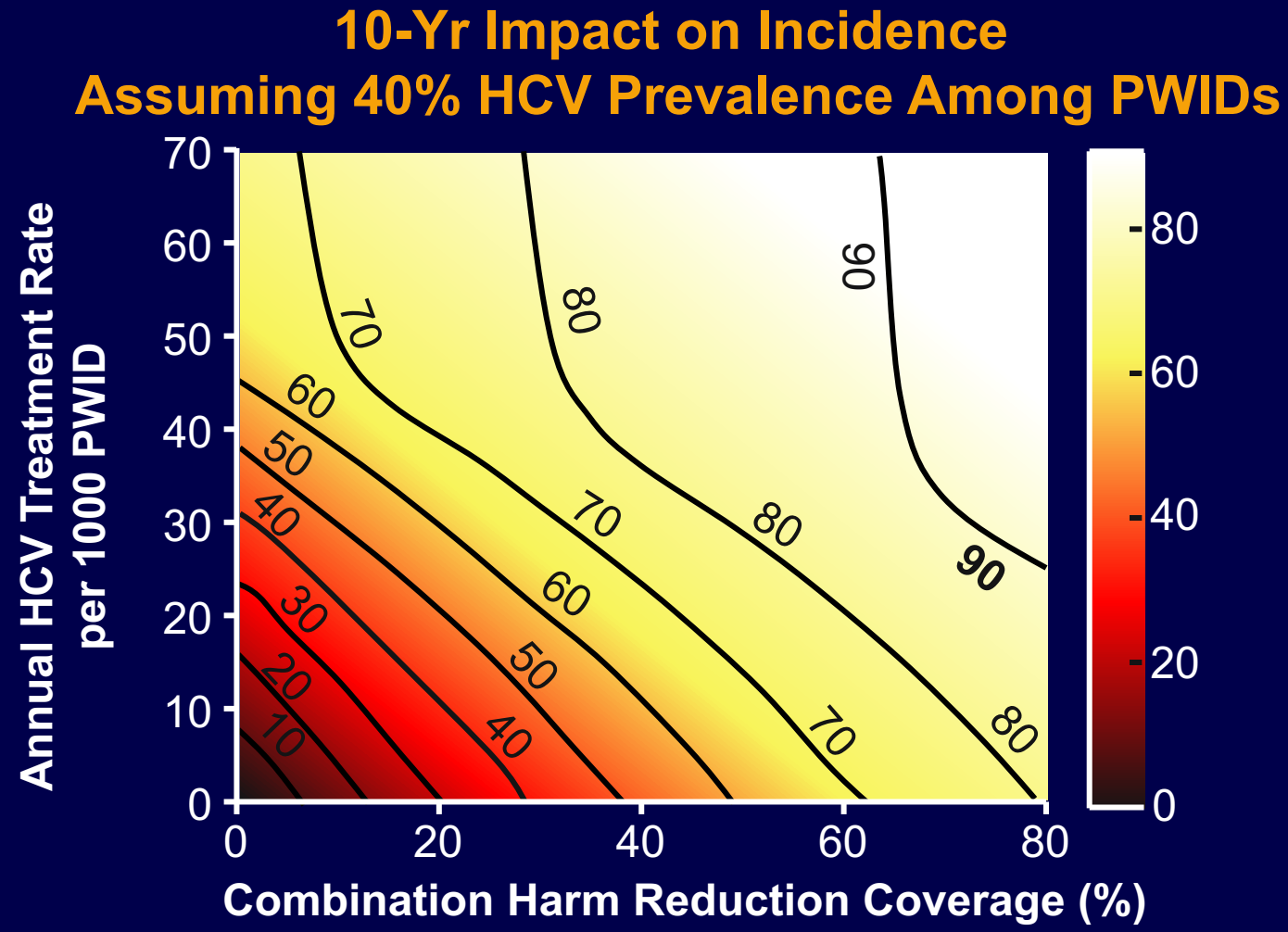
| Perceived Barriers to HCV Testing, Evaluation, Treatment | Mean Likert Scale Score* (N = 203) |
|---|---|
| Lack of funding for noninvasive liver disease testing | 2.78 |
| Lack of funding for new DAA therapies | 2.76 |
| Reimbursement restrictions based on drug and/or alcohol use | 2.73 |
| Long wait 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.

Litwin AH, et al. AASLD 2017. Abstract 1064.

Slide credit: clinicaloptions.com

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




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

Martin NK, et al. Clin Infect Dis. 2013;57(suppl 2):S39-S45.

Slide credit: clinicaloptions.com

# HCV Treatment-as-Prevention (TAP) Study

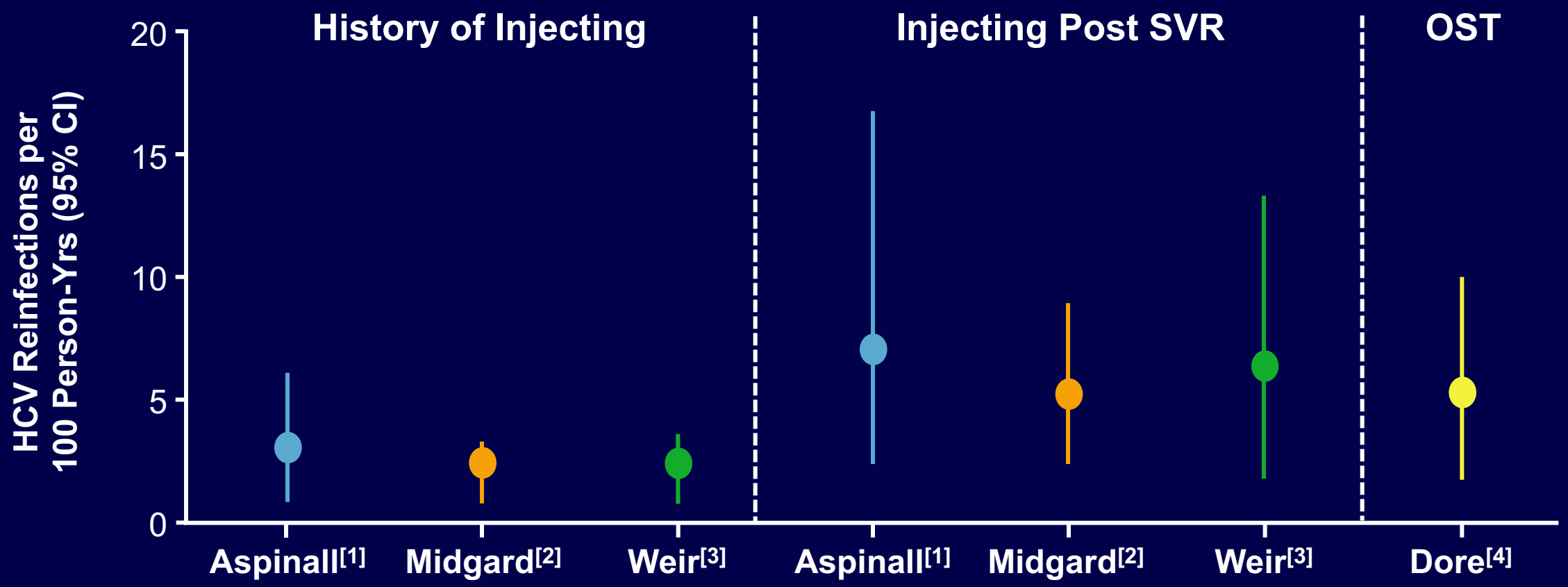
- Goal to determine if treating HCV among PWID in Melbourne reduces transmission within the community and decreases prevalence
- Community-based program using “treatment vans” to recruit and treat with nurse-led model of HCV care
- 3 HCV treatment groups
  - All participants treated at end of project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

https://www.burnet.edu.au/projects/227_treatment_and_prevention_tap_study

Slide credit: clinicaloptions.com

# 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.

# 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 |

Dore GJ, et al. AASLD 2017. Abstract 195.

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

# 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

Slide credit: clinicaloptions.com

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

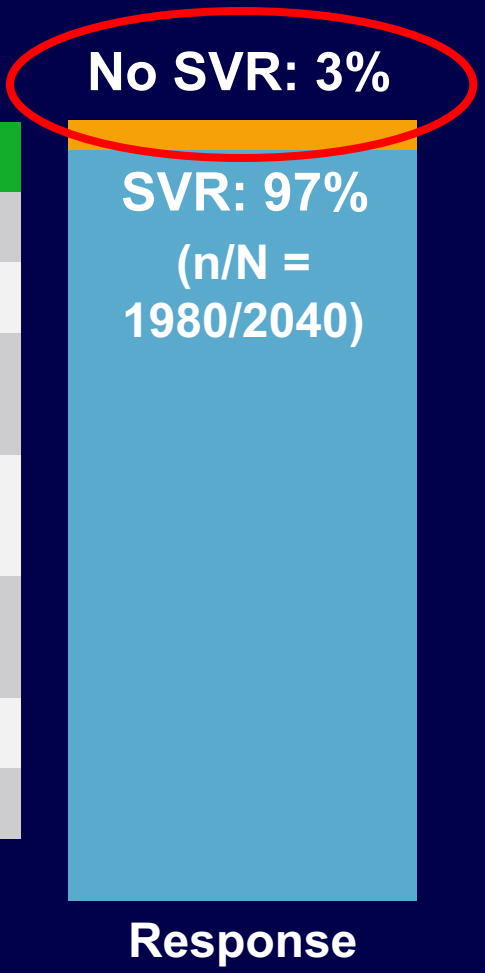
Paul Y. Kwo, MD

# 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 coinfected)[11] |

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




References in slidenotes.

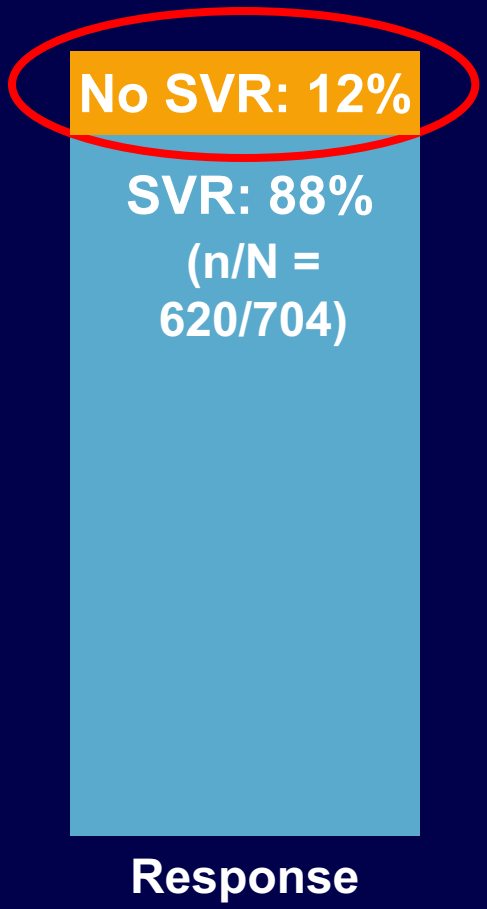
Slide credit: clinicaloptions.com

# 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**




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

Slide credit: clinicaloptions.com

# DAA Drug Classes Are Important in Planning Retreatment Strategies

| Inhibitor Class | Reminder | Examples |
|---|---|---|
| **Targeting HCV Protein Processing** | | |
| NS3/4A **pr**otease | **PR**EVIR | ▪ Glecaprevir, grazoprevir, paritaprevir, simeprevir, voxilaprevir |
| **Targeting HCV Replication** | | |
| NS5**B** polymerase | **B**UVIR | ▪ Nucleos(t)ide: sofosbuvir<br>▪ Non-nucleos(t)ide: dasabuvir |
| NS5**A** | **A**SVIR | ▪ 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

Ahmed A, et al. Viruses. 2015;7:6716-6729.

Slide credit: clinicaloptions.com

# 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<br>> 50x | > 100x / -- | NR |
| Ombitasvir | > 1000x | > 100x | < 3x<br>> 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<br>> 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

AASLD/IDSA. HCV guidance. September 2017. Ng TI, et al. Antimicrob Agents Chemother. 2017;61:e02558-16. FDA Sofosbuvir/velpatasvir. FDA Daclatasvir.

Slide credit: clinicaloptions.com

# New Options for Retreating DAA Failure

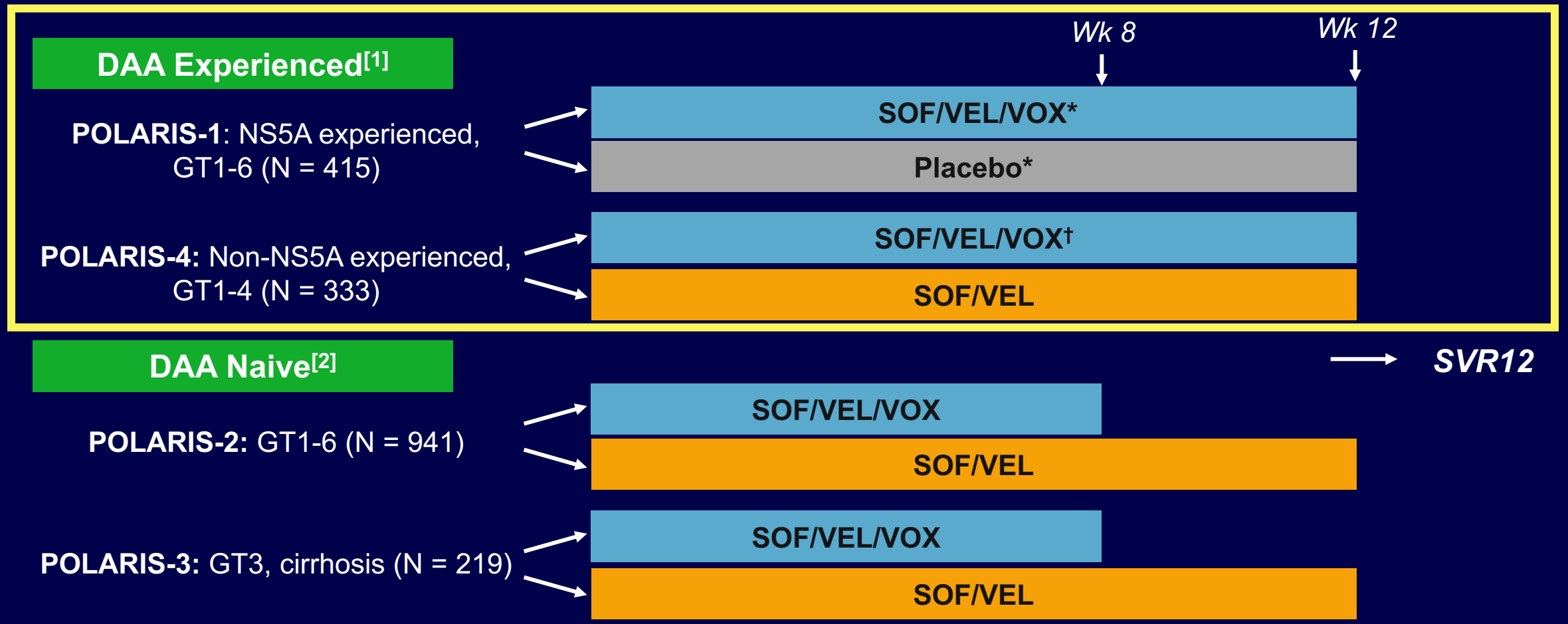
# Sofosbuvir/Velpatasvir/Voxilaprevir

- 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

FDA SOF/VEL/VOX. 2017.

Slide credit: clinicaloptions.com

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

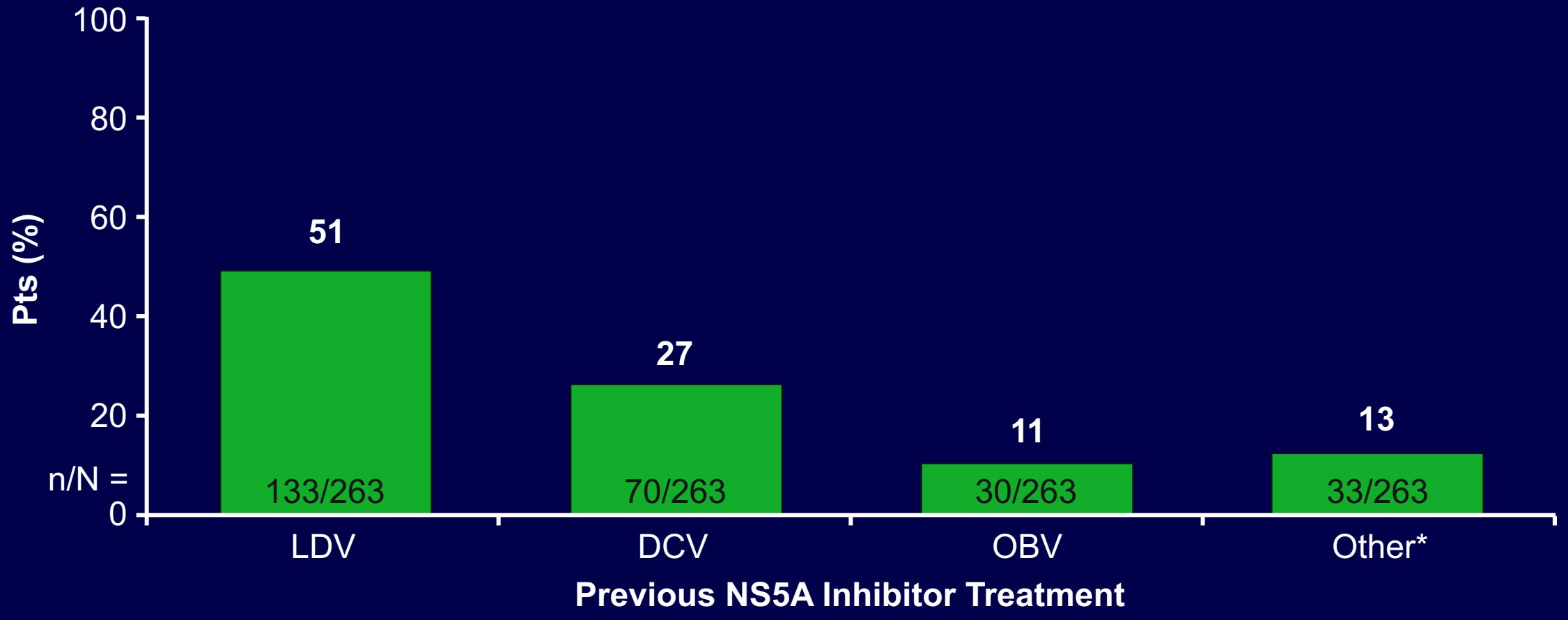



*Only pts with GT1 infection randomized to SOF/VEL/VOX vs placebo. All others received SOF/VEL/VOX.
†All pts with GT4 infection received SOF/VEL/VOX.


1. Bourlière M, et al. N Engl J Med. 2017;376:2134-2146.
2. Jacobson IM, et al. Gastroenterology. 2017;153:113-122.


Slide credit: clinicaloptions.com

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



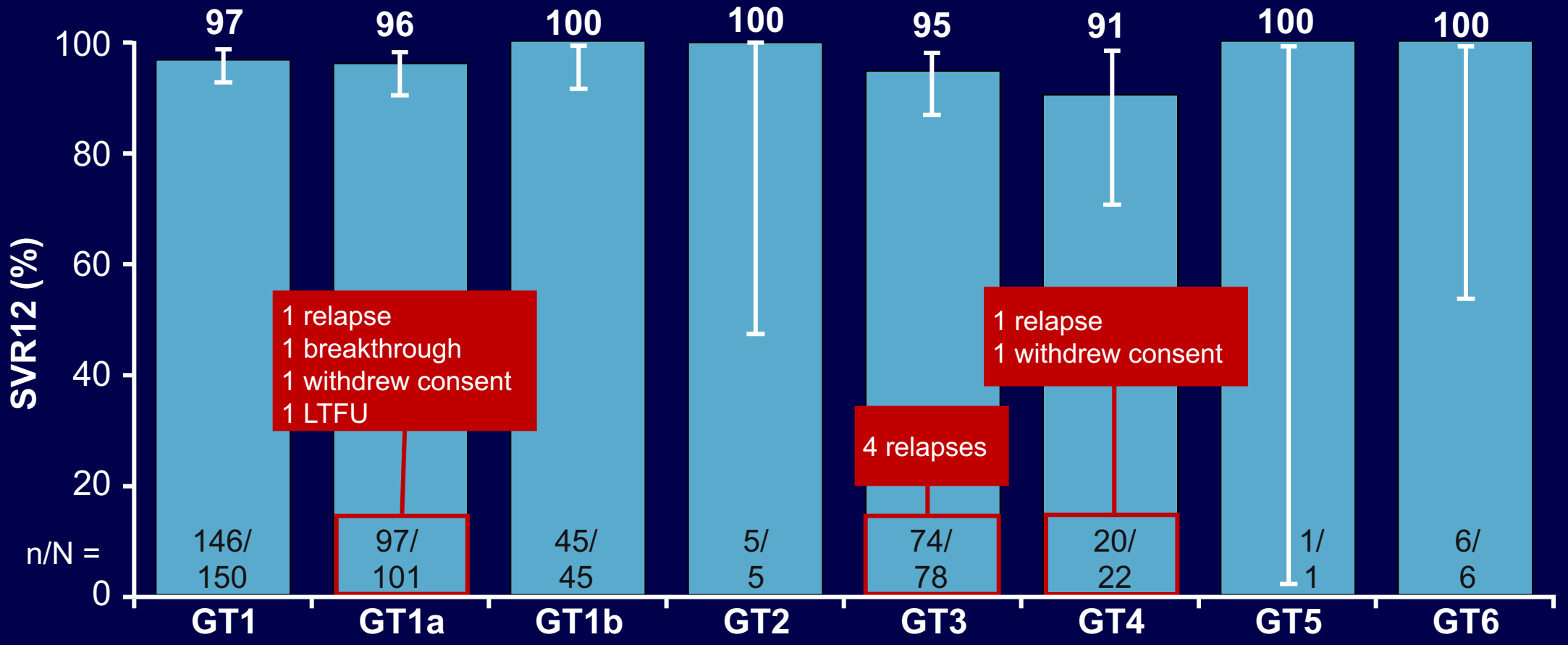

*Included SOF/VEL, EBR/GZR, and other investigational combinations and/or medications from discontinued programs.
Three pts received both LDV and DCV.

Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

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

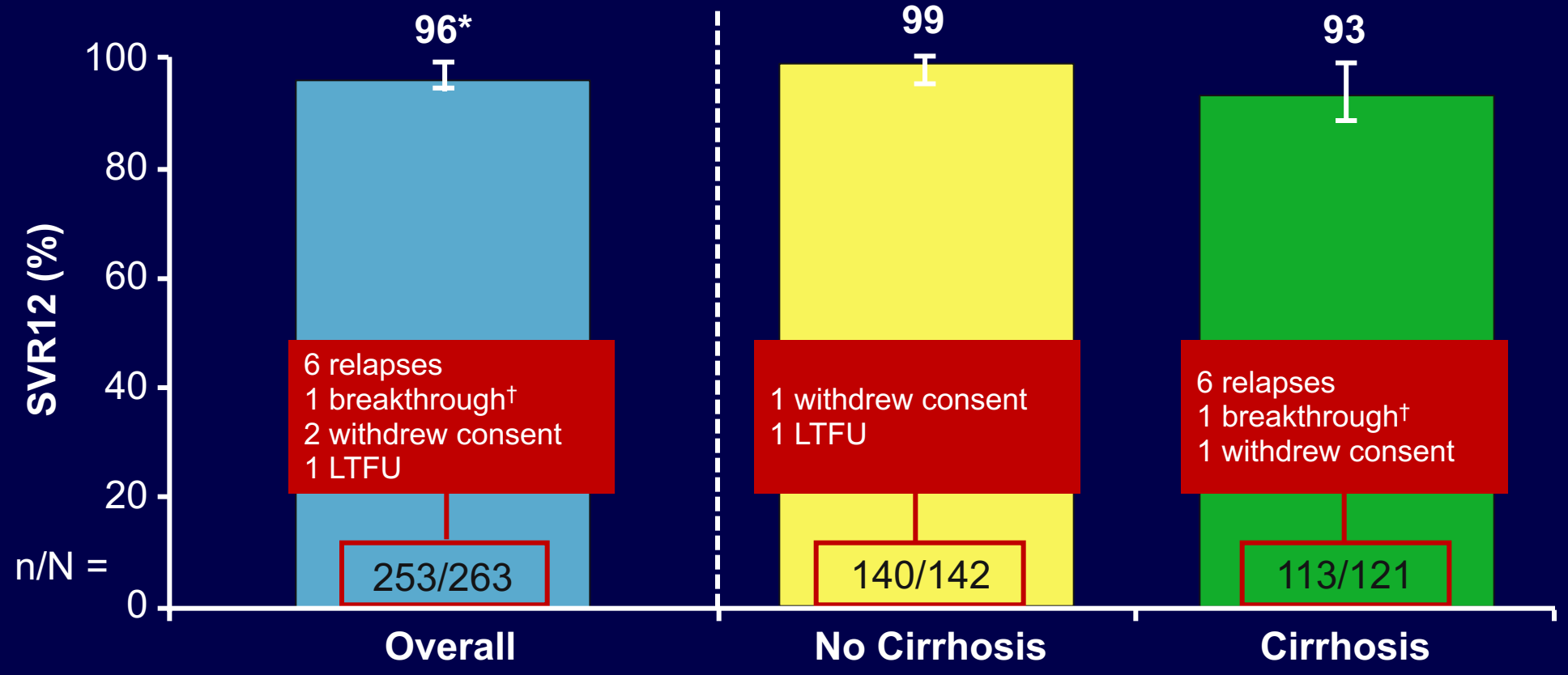
- Only 1 GT4 pt developed a treatment-emergent RAS (NS5A Y93H)




Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

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

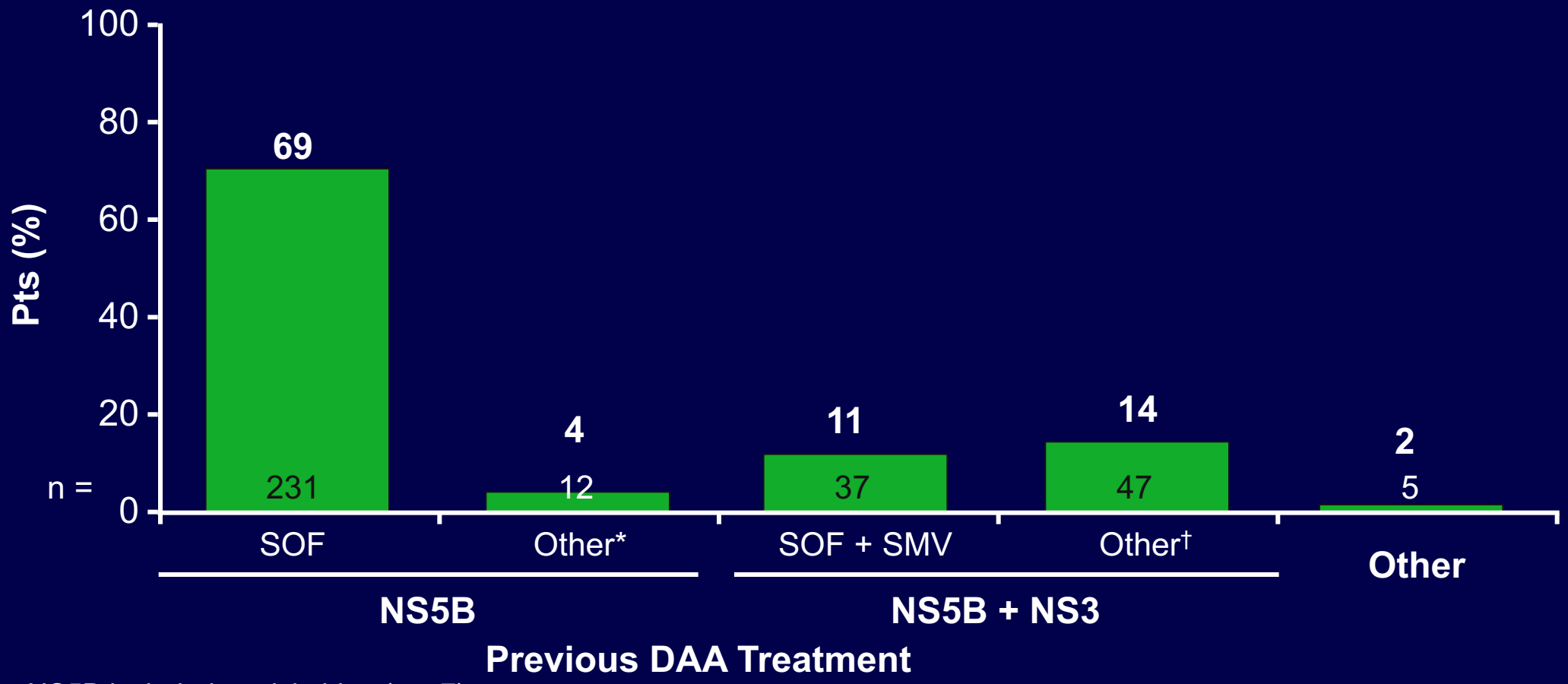



*$P$ < .001 for superiority vs prespecified 85% performance goal for SOF/VEL/VOX.
†Exposure was consistent with nonadherence.

Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Bourlière M, et al. AASLD 2016. Abstract 194.

Slide credit: clinicaloptions.com

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



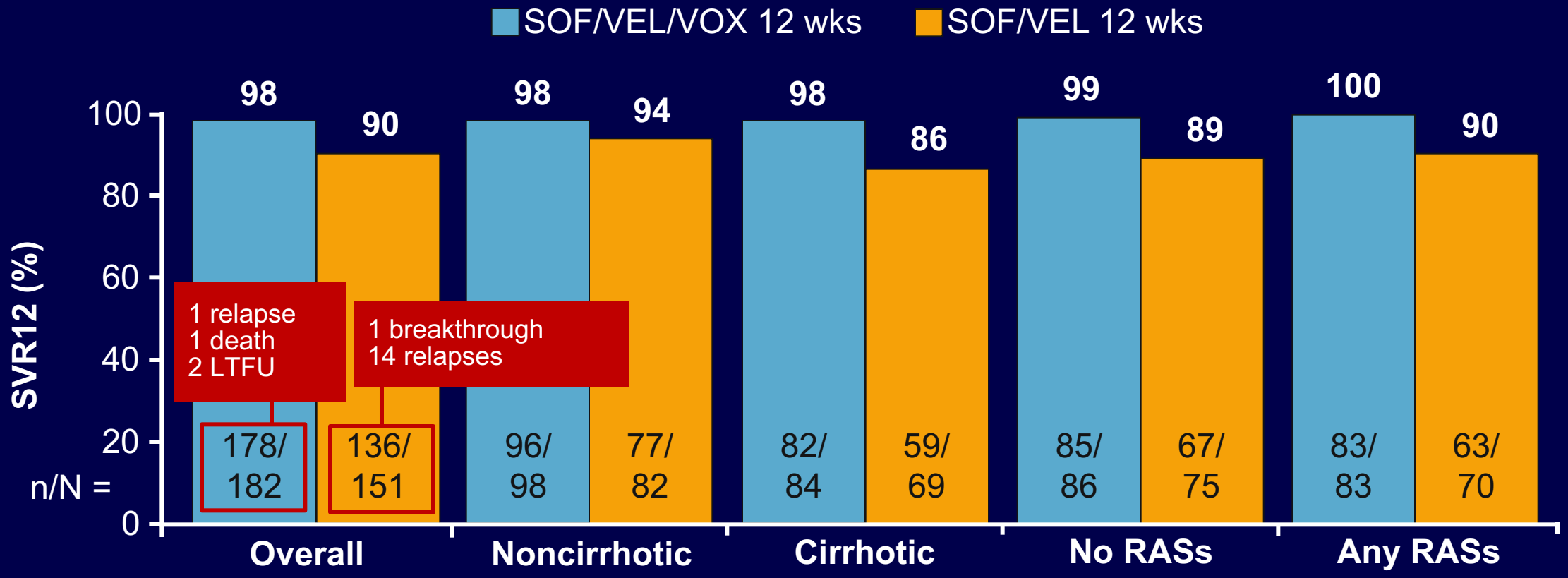

*Other NS5B included mericitabine (n = 7).
†Other NS5B + NS3 included deleobuvir + faldaprevir (n = 14), mericitabine + danoprevir (n = 8), and SOF + telaprevir (n = 6).
One pt without previous DAA exposure excluded.

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

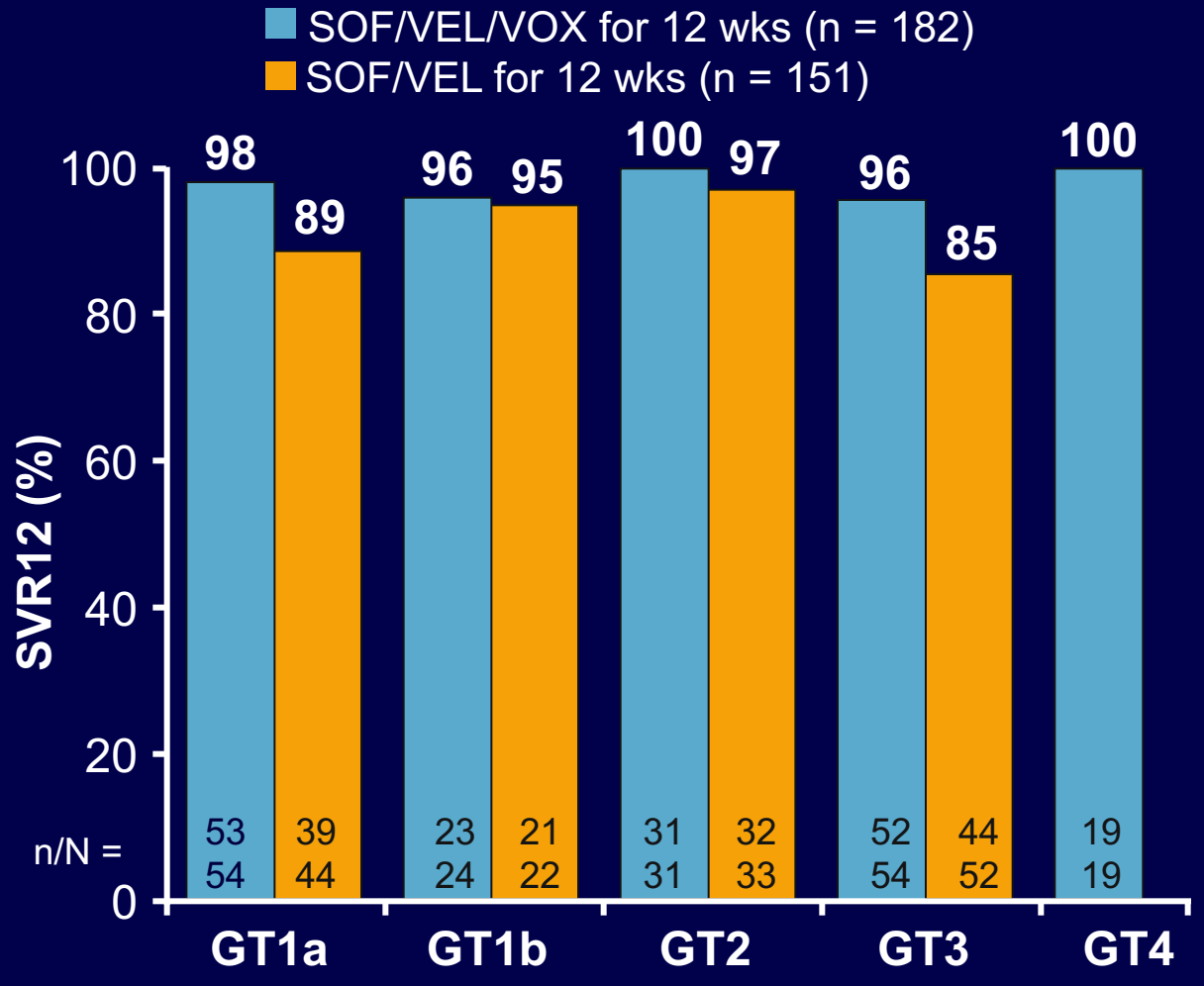
- SOF/VEL/VOX: $P < .001$ for superiority vs prespecified 85% goal; SOF/VEL: $P = .09$




Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Zeuzem S, et al. AASLD 2016. Abstract 109.

Slide credit: clinicaloptions.com

# POLARIS-4: SVR12 by Genotype and Other Outcomes



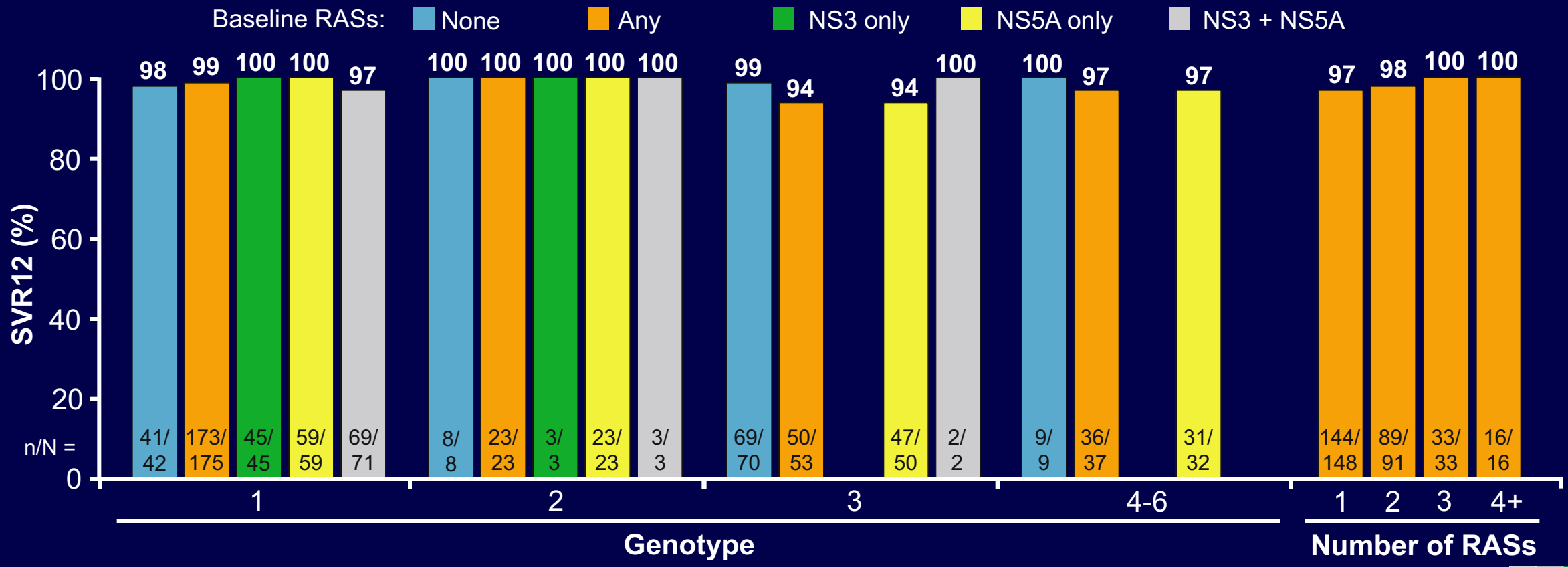

- Treatment emergent RASs
  - SOF/VEL/VOX: none
  - SOF/VEL: 11 of 15 with Y93H
- 4 serious AEs in each arm; no discontinuation for AE with SOF/VEL/VOX
- VOX associated with increase in diarrhea (20%) vs SOF/VEL alone (5%) and trend toward more nausea
  - All mild and no discontinuations

Bourlière M, et al. N Engl J Med. 2017;376:2134-2146. Zeuzem S, et al. AASLD 2016. Abstract 109.

Slide credit: clinicaloptions.com

# 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




Sarrazin C, et al. EASL 2017. Abstract THU-248.

Slide credit: clinicaloptions.com

# Glecaprevir/Pibrentasvir

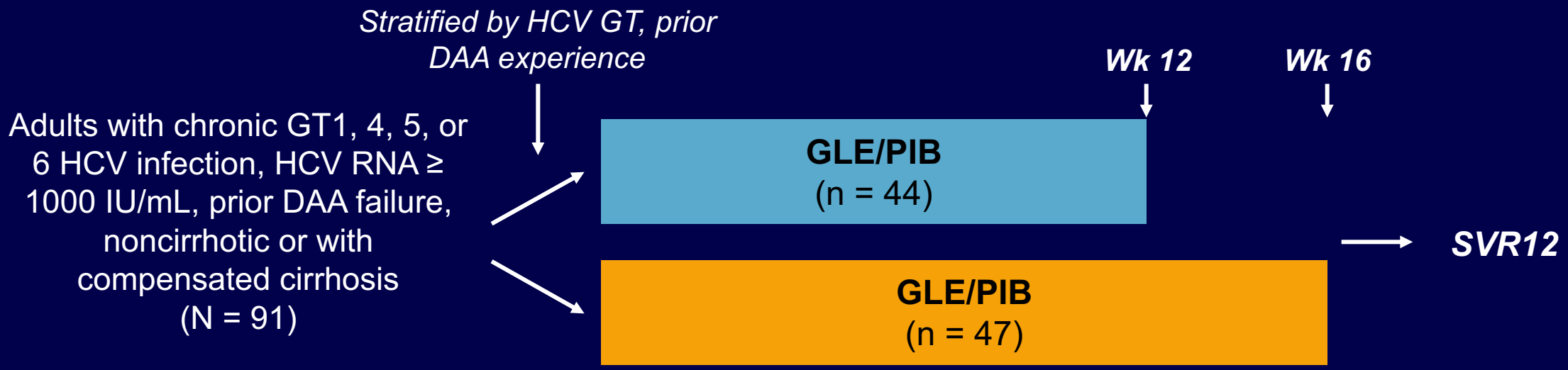
- GLE: potent pangenotypic NS3/4A protease inhibitor
- PIB: potent pangenotypic NS5A inhibitor
- **GLE/PIB**: once daily (taken as 3 tablets with food), oral, fixed-dose combination (100/40 mg) for GT1-6

FDA GLE/PIB. 2017.

Slide credit: clinicaloptions.com

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

- Randomized, open-label study



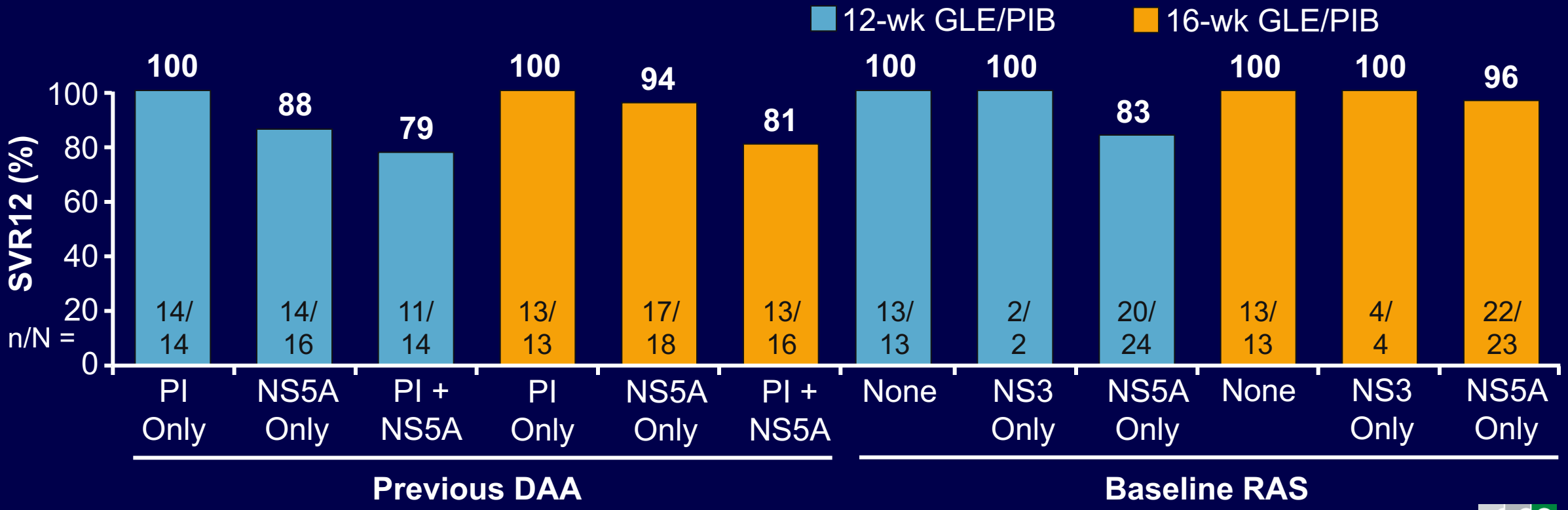

- BL characteristics of 12-wk vs 16-wk arms well balanced by sex, race, BMI, previous DAA regimen and response, RASs
  - GT1a, 80% vs 71%; compensated cirrhosis, 34% vs 26%

Poordad F, et al. EASL 2017. Abstract PS-156.

Slide credit: clinicaloptions.com

# 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




Poordad F, et al. EASL 2017. Abstract PS-156.

Slide credit: clinicaloptions.com

# 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)

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

- NS5A inhibitor experienced (regardless of NS3 inhibitor experience) ± compensated cirrhosis:
  - SOF/VEL/VOX for 12 wks

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

AASLD/IDSA. HCV guidance. September 2017. FDA GLE/PIB. 2017

Slide credit: clinicaloptions.com

# 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

AASLD/IDSA. HCV guidance. September 2017.

Slide credit: clinicaloptions.com

# 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]
  - AALSD/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**

1. FDA GLE/PIB. 2017. 2. AASLD/IDSA. HCV guidance. September 2017. 3. FDA SOF/VEL/VOX. 2017.

Slide credit: clinicaloptions.com

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