# Highlights From EASL 2019

## CCO Independent Conference Coverage*

of the *2019 International Liver Congress; April, 10-14, 2019*

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# Faculty Disclosures

**Nancy Reau, MD, FAASLD, AGAF,** has disclosed that she has received consulting fees from Abbott, AbbVie, Gilead Sciences, and Merck and funds for research support from Genfit, Intercept, and Shire.

**Zobair M. Younossi, MD, MPH, FACP, FACG, AGAF, FAASLD,** has disclosed that he has received consulting fees or funds for research support from Allergan, Bristol-Myers Squibb, Gilead Sciences, Intercept, Novartis, Novo Nordisk, and Shionogi.

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# Treatment of HCV Infection

# English Hepatitis C Registry: Efficacy of HCV Treatment in a Large Clinical Cohort

- Anonymized data extracted from registry in January 2019 (N = 37,693)
  - DAA-treated adults (n = 21,436)
  - Completed valid treatment (n = 16,756)
  - Outcome recorded (n = 14,603)
- Most patients were of white race
- Patients with GT3 HCV were significantly younger than those with non-GT3 HCV across all fibrosis stages and compensated cirrhosis ($P < .01$)
- Key endpoint: SVR12
  - Cirrhosis assessed clinically, fibrosis by *FibroScan*

Drysdale. EASL 2019. Abstr LB-07.

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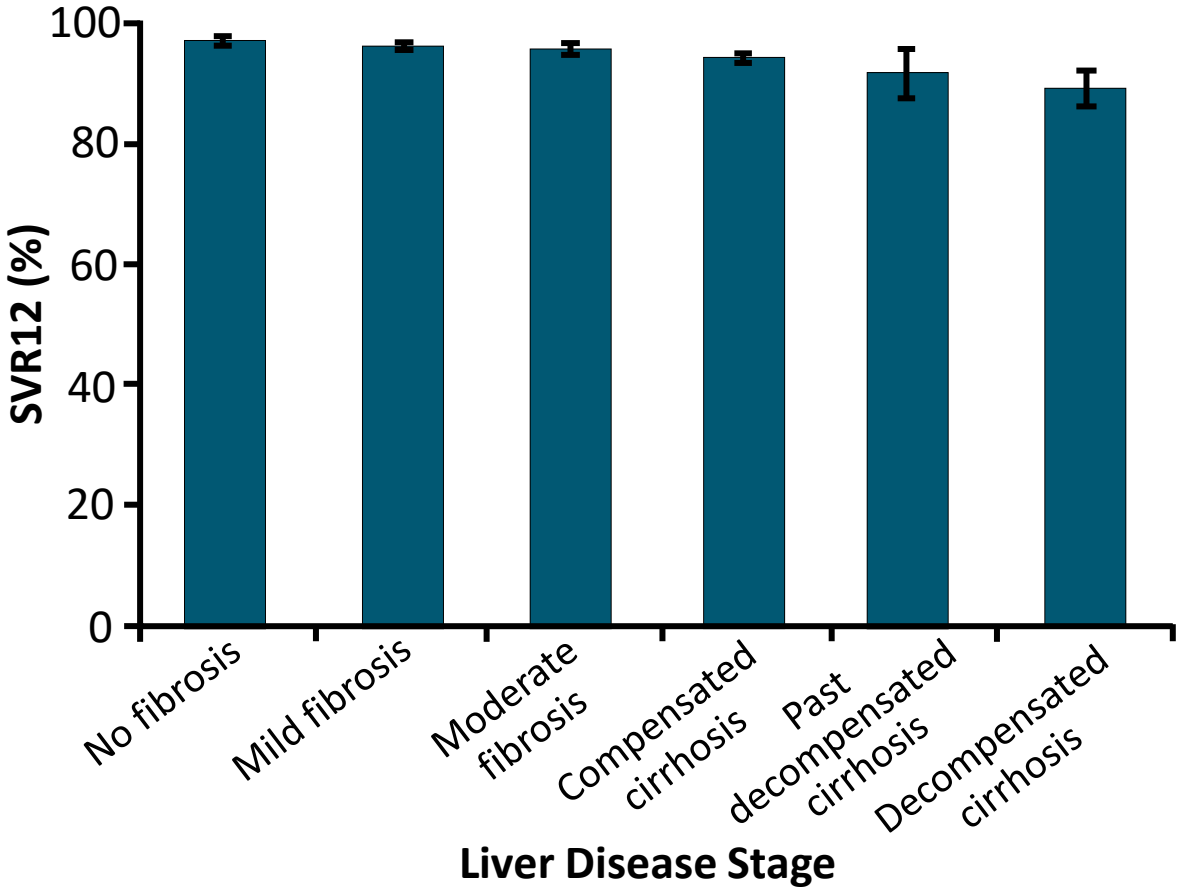
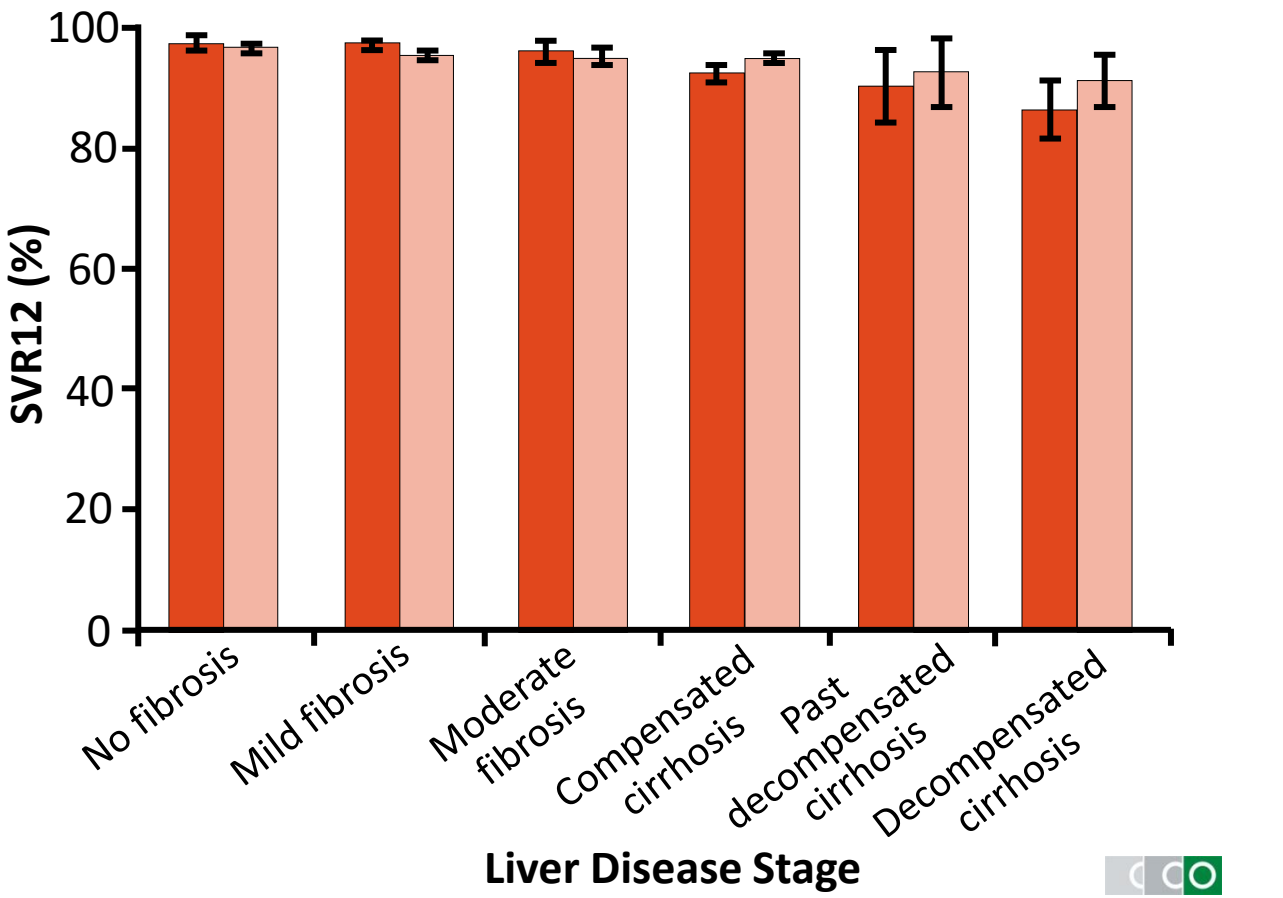
# English Hepatitis C Registry: SVR12

- SVR12 for **all patients**: 95.59%




- SVR12 for **GT3 patients**: 95.04%

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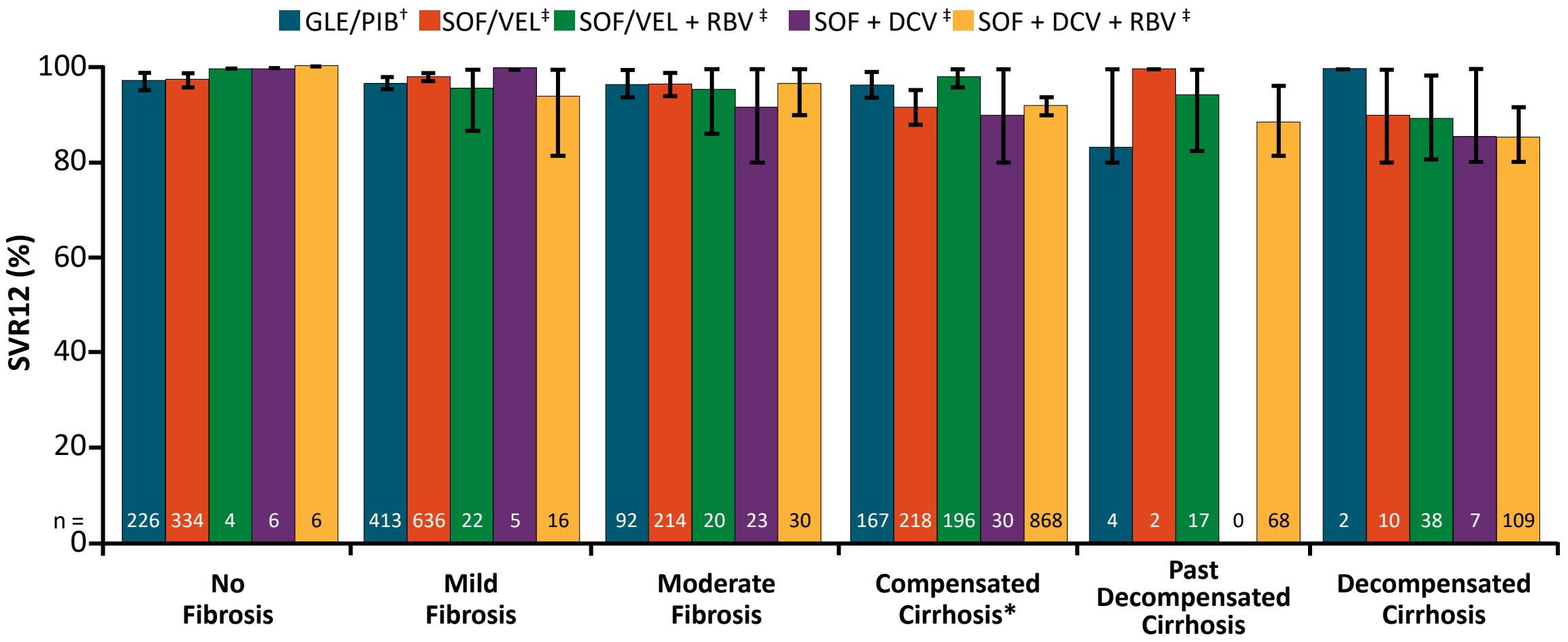
# English Hepatitis C Registry: SVR12 in GT3 by Regimen and Severity of Liver Disease




*SVR significantly improved with SOF/VEL + RBV vs SOF/VEL or SOF + DCV + RBV in this subgroup.

†8 wks if no, mild, or moderate fibrosis; 12 wks if compensated cirrhosis. ‡12 wks if no, mild, or moderate fibrosis.

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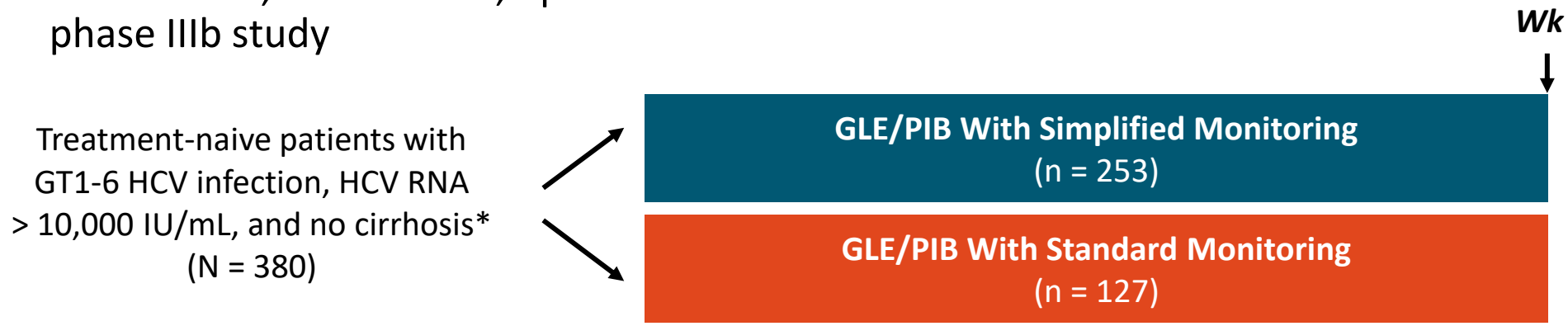
# SMART-C: Monitoring During GLE/PIB in Treatment-Naive Patients With GT1-6 HCV Infection

- Multicenter, randomized, open-label phase IIIb study




AEs and adherence assessed by study nurse via phone contact at Wks 4 and 8 in all patients. GLE/PIB dosed orally at 300/120 mg QD.
*Exclusion criteria: anticipated poor adherence, IDU within past 6 mos, positive urine drug screen.

- **Simplified monitoring:** Medication dispensed at BL; no on-treatment clinic visits
- **Standard monitoring:** Medication dispensed at BL and Wk 4; clinic visits with physician, study nurse, and pathology at Wks 4 and 8

- **Primary endpoint:** SVR12 in ITT population (6% noninferiority margin)
- **Secondary endpoints:** SVR12 in mITT and PP populations, adherence by Wk 20 pill count, treatment discontinuation and completion, safety

Dore. EASL 2019. Abstr PS-178.

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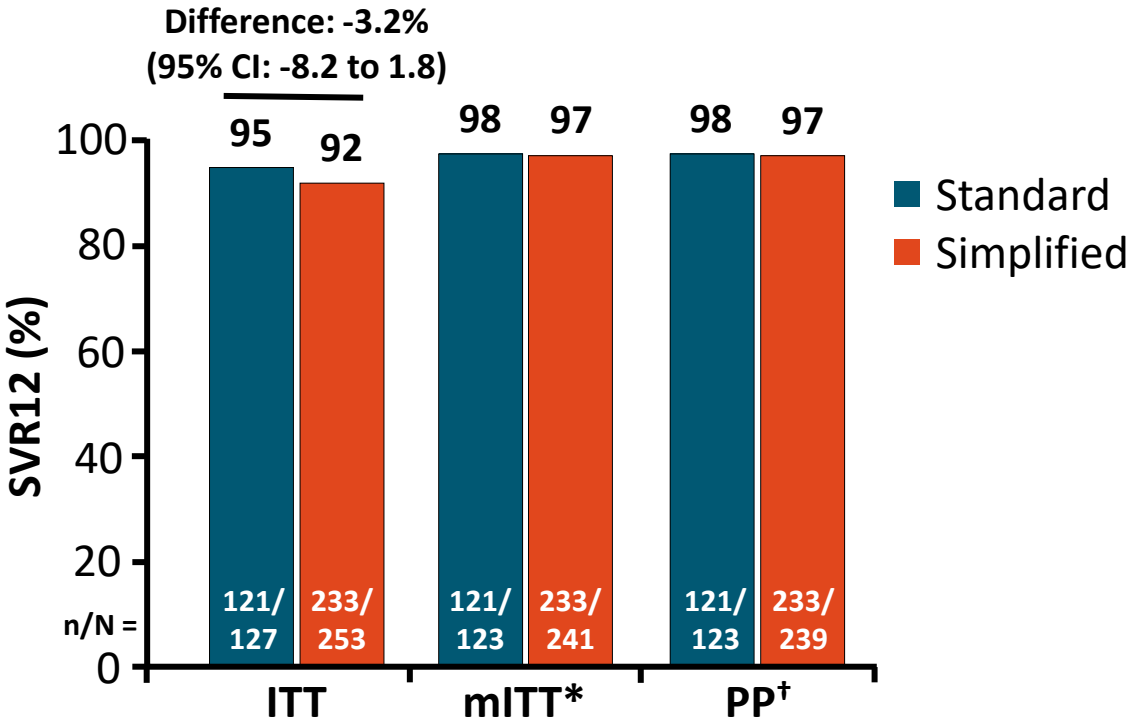
# SMART-C: Efficacy and Safety




*Excludes death (n = 1), LTFU (n = 14), or missing HCV RNA (n = 1).
†Excludes discontinuation (n = 2) in addition to mITT exclusions.

- VF: 2 (1.6%) standard vs 6 (2.4%) simplified
- Adherence > 95%: 98% standard vs 96% simplified

| Treatment-Emergent AEs, n (%) | Standard (n = 127) | Simplified (n = 253) |
|---|---|---|
| AEs | 70 (55) | 133 (53) |
| ▪ Grade 1/2 | 69 (54) | 131 (52) |
| ▪ Grade 3 | 1 (0.8) | 2 (0.8) |
| ▪ Grade 4 | 0 | 0 |
| Common AEs (> 5%) | | |
| ▪ Fatigue | 30 (14) | 52 (15) |
| ▪ Headache | 26 (12) | 43 (13) |
| ▪ Nausea | 25 (12) | 17 (5) |
| Serious AEs | 0 | 3 (1.2) |
| Unscheduled visits | | |
| ▪ On treatment | 3 (2) | 11 (4) |
| ▪ Total | 8 (6) | 20 (8) |

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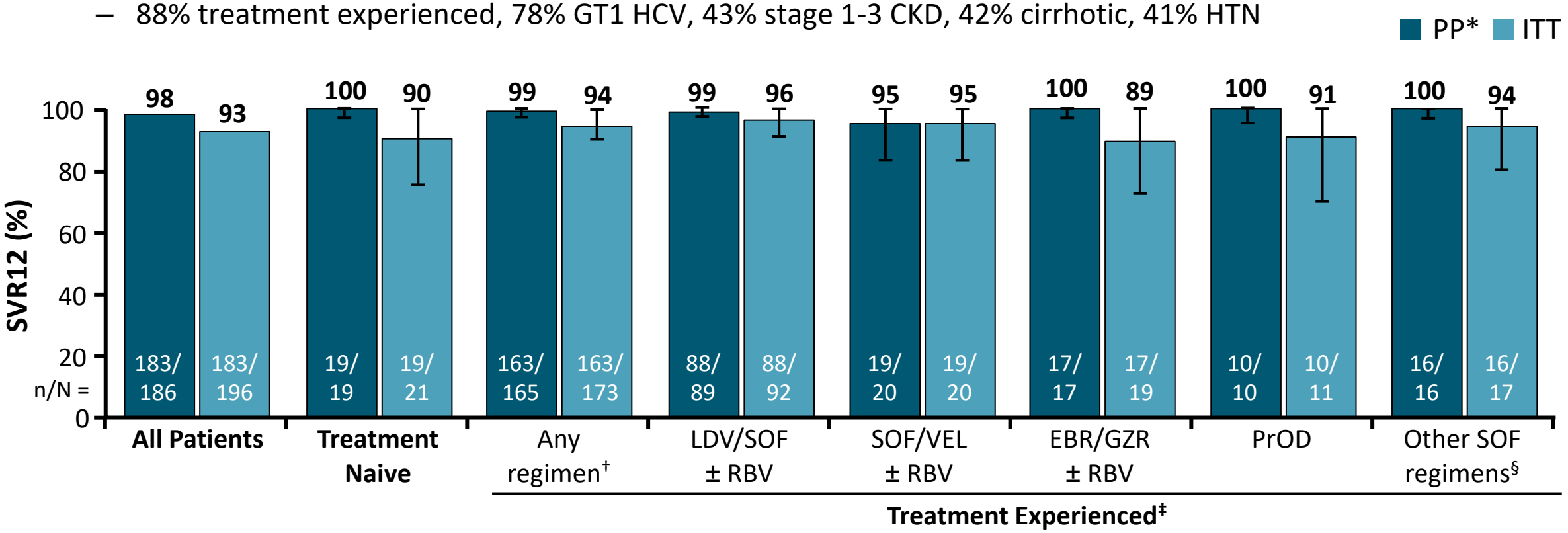
# TRIO Network: SOF/VEL/VOX Efficacy in US Practice

- Real-world data from providers and specialty pharmacies in the TRIO Health disease management program on SOF/VEL/VOX for 12 wks initiated between July 2017 and April 2018 (N = 196)
  - 88% treatment experienced, 78% GT1 HCV, 43% stage 1-3 CKD, 42% cirrhotic, 41% HTN




*Primary endpoint. †One patient with prior GLE/PIB achieved SVR. ‡Regimens prior to SOF/VEL/VOX.
§Includes DCV + SOF (n = 10), SOF + RBV (n = 6), PegIFN + SOF + RBV (n = 1).

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# TRIO Network: Discontinuation and Virologic Failure

- 8/196 (4%) patients discontinued SOF/VEL/VOX; all were Medicare recipients
  - Treatment naive, n = 2; treatment experienced, n = 6 (SOF + RBV, pegIFN + RBV, EBR/GZR, PrOD, n = 1 each; LDV/SOF, n = 2)
  - GT1, n = 6; GT3, mixed GT, n = 1 each
  - F0-2, n = 5; F4 (cirrhosis), n = 2; score unknown (no cirrhosis), n = 1
- Virologic failure in n = 3 patients

| Pt With VF* | BL HCV RNA | HCV | Fibrosis Score | Comorbidities | Prior Regimen | Insurance |
|---|---|---|---|---|---|---|
| 57/M, white | 826,651 | GT1a | 4, cirrhosis | HTN | SOF/VEL | Commercial |
| 71/M, white | 13,051,000 | GT1a | 4, cirrhosis | HLD, HTN, CKD† | LDV/SOF + RBV | Medicare |
| 69/F, black | 11,218,601 | GT1 | 2, moderate | Depression, HTN, CKD† | Not specified | NR |

*Did not achieve SVR. †Stage 2.

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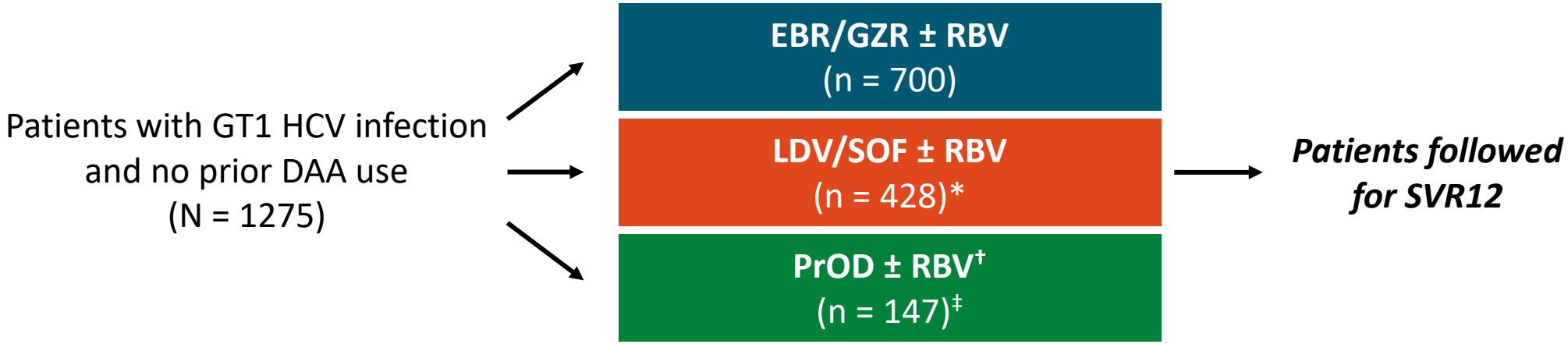
# PRIORITIZE: Oral Regimens for DAA-Naive Patients With GT1 HCV Infection

- Pragmatic, randomized, open-label trial




Treating physician selected treatment duration and use of RBV; monitoring per local standards.
*Includes 20 patients randomized to LDV/SOF, treated with EBR/GZR.
†Randomization to PrOD arm closed early in December 2017 following change in SoC for GT1 HCV per AASLD guidelines.
‡Includes 1 patient randomized to PrOD, treated with LDV/SOF.

- Primary endpoint: HCV RNA < LLOQ ≥ 12 wks after EOT in mITT patients
- Secondary endpoints: patient-reported outcomes, safety

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# PRIORITIZE: Treatment Outcomes

| Outcome (mITT) | EBR/GZR | | LDV/SOF | | Treatment Difference, % (95% CI) |
|---|---|---|---|---|---|
| | n/N | % (95% CI) | n/N | % (95% CI) | |
| SVR | 551/700 | 78.7 (75.5-81.7) | 347/428 | 81.1 (77-84.7) | -2.4 (-7 to 2.5) |
| Non-SVR | 30/700 | 4.3 (2.9-6.1) | 11/428 | 2.6 (1.3-4.6) | 1.7 (-0.6 to 3.8) |
| Missing | 119/700 | 17.0 (14.3-20) | 70/428 | 16.4 (13-20.2) | 0.6 (-4 to 5) |

- SVR > 94% across most subgroups in missing = excluded analysis
- Overall safety profiles similar between EBR/GZR and LDV/SOF arms
  - No difference in liver-related, serious, or severe AEs, or in AEs leading to d/c
  - Use of RBV associated with increased toxicity

Sulkowski. EASL 2019. Abstr THU-182.

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# Progress Toward HCV Elimination

# HCV Care Cascade: Analysis Across US Specialties

- Retrospective review of 2 de-identified national laboratory datasets, January 2013 - December 2016
  - Patients screened with HCV Ab test, then diagnosed if HCV RNA positive
    - Linkage to care evidenced by physician visit for LFT and/or HCV genotype test and receipt of treatment (inferred from change in HCV RNA, not direct observation)
- Patient number and proportion at each stage of care cascade calculated across physician specialties
  - Flow of patients across specialties represented with Sankey diagrams, in which width of arrow/arm is proportional to quantity of patient flow

Rege. EASL 2019. Abstr PS-066.

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# HCV Care Cascade: Gaps

| HCV Care Cascade Stage | Definition of Stage | Frequency, n | Proportion of Indicated Population, % |
|---|---|---|---|
| Screening | 1st Ab test | 17,177,546 | |
| ▪ Detection | 1st Ab+ test | 974,277 | 5.7 |
| ▪ Confirmatory test | 1st HCV RNA test after Ab+ test | 527,340 | **54.1** |
| ▪ HCV RNA+ | 1st HCV RNA+ test after Ab+ test | 337,846 | 64.1 |
| Awareness | 1st HCV RNA test* | 1,721,020 | |
| ▪ Diagnosis | 1st HCV RNA+ test* | 913,529 | 53.1 |
| ▪ Genotype test | 1st HCV genotype test after HCV RNA+ test | 487,263 | **53.3** |
| ▪ LFT | 1st LFT after HCV RNA+ test | 390,162 | **42.7** |
| Diagnosis/linkage to care | HCV RNA+ test and ≥ 2 HCV RNA lab tests | 172,835 | |
| ▪ Treatment | Occurring after diagnosis | 18,220 | **10.5** |

Bolded values represent gaps/places for intervention. *Regardless of Ab test.

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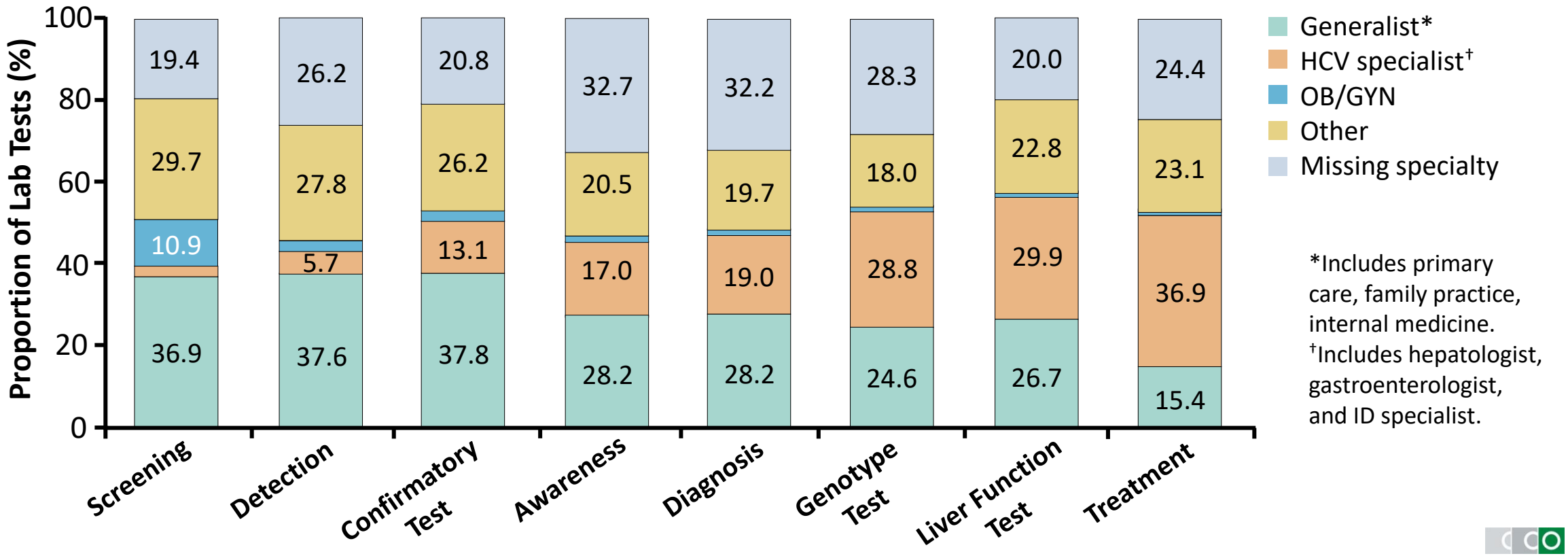
# HCV Care Cascade: Lab Test Orders by Physician Type

- Proportion of lab tests ordered by generalists and OB/GYN decreased over cascade, whereas those ordered by HCV specialists increased

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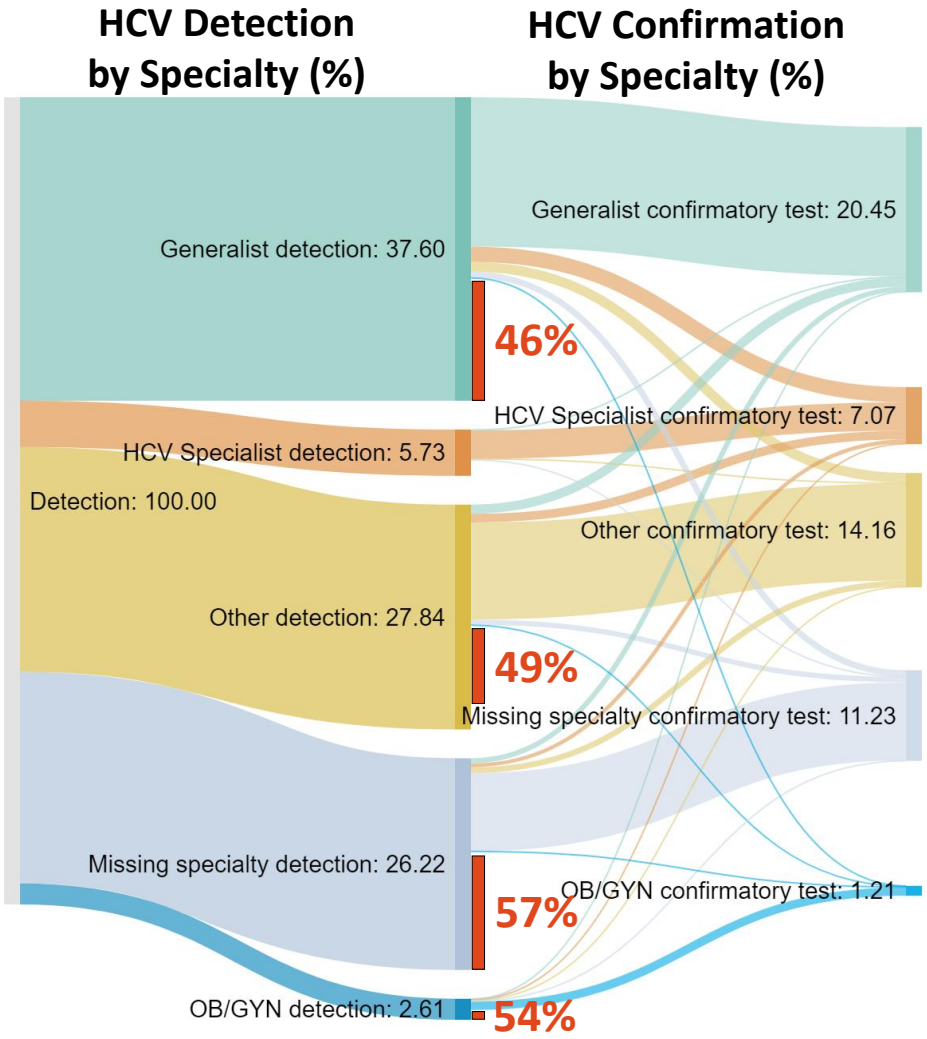
# HCV Care Cascade: Diagnosis Gaps by Physician Type




**Gap:** Ab+ patients seen by physician group who **did not have confirmatory HCV RNA testing** by that physician group

**46% of Ab+ patients received no HCV RNA test**

- Generalist*
- HCV specialist†
- OB/GYN
- Other
- Missing specialty

*Includes primary care, family practice, internal medicine.
†Includes hepatologist, gastroenterologist, and ID specialist.

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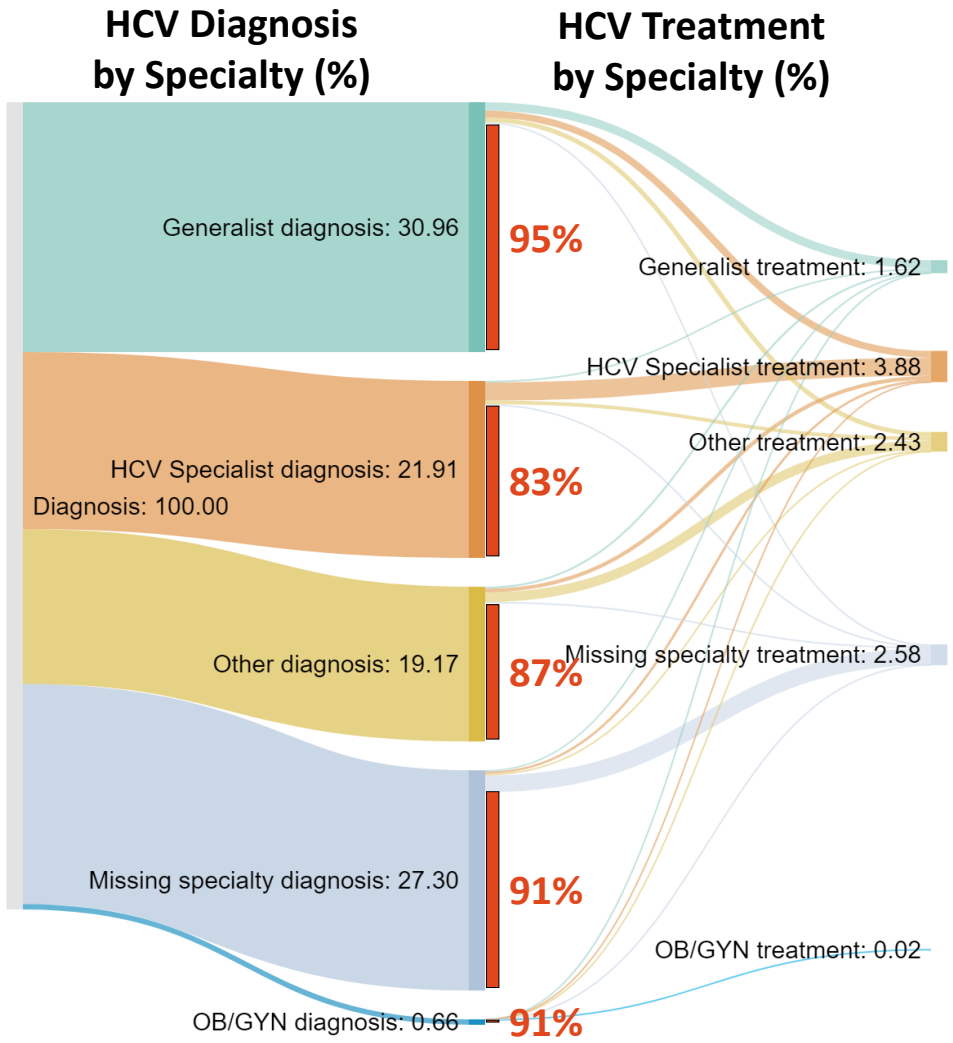
# HCV Care Cascade: Treatment Gaps by Physician Type




**Gap:** patients with ≥ 2 HCV RNA tests by physician group but **did not receive treatment** from that physician group

**90% of diagnosed patients received no HCV therapy**

- Generalist*
- HCV specialist†
- OB/GYN
- Other
- Missing specialty

*Includes primary care, family practice, internal medicine.
†Includes hepatologist, gastroenterologist, and ID specialist.

Rege. EASL 2019. Abstr PS-066.

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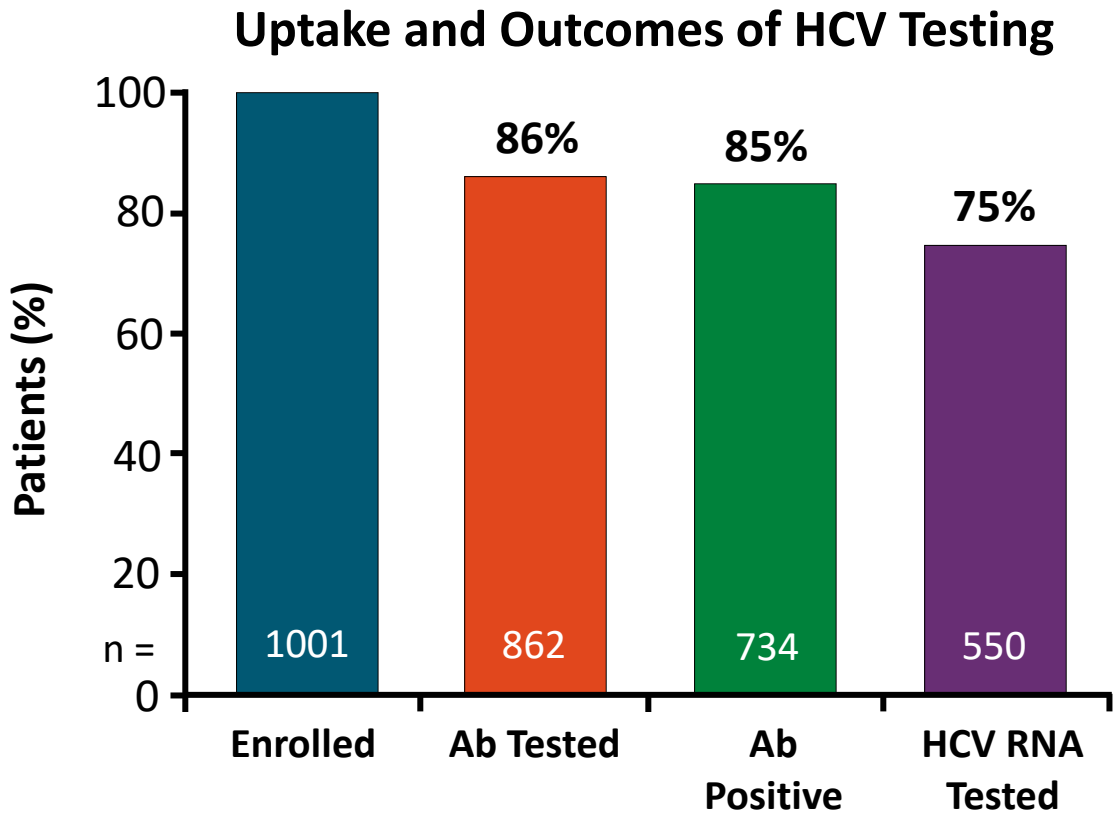
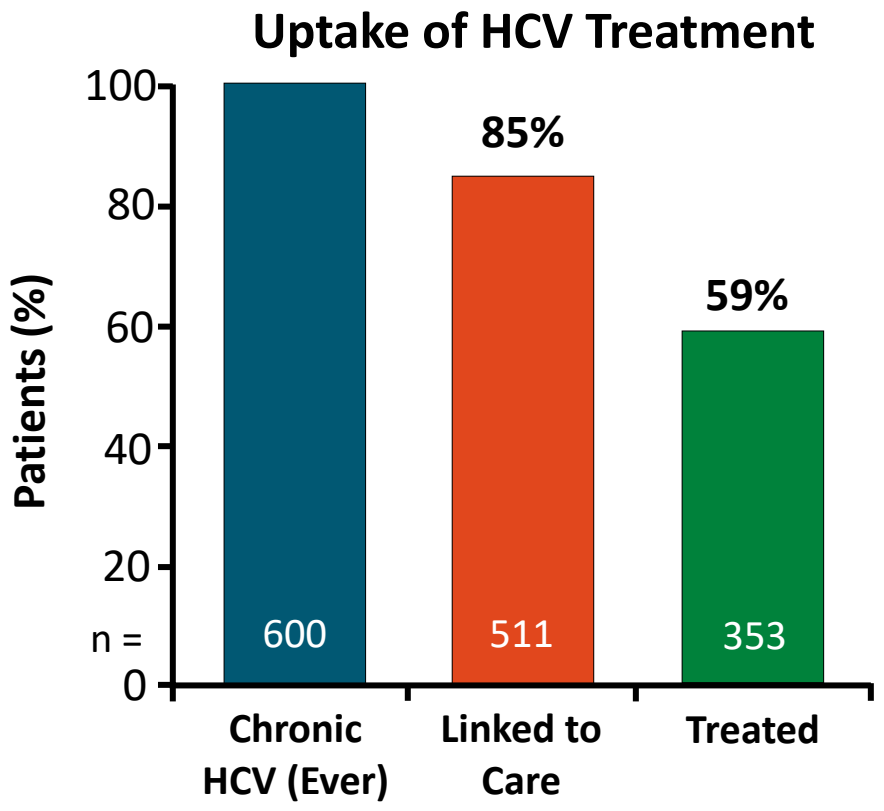
# ETHOS Engage: HCV Testing and Treatment Among PWID in Australia

- Observational cohort study of PWID recruited at OST clinics, drug and alcohol treatment centers, needle and syringe exchange sites
  - Target N = 1500 with recruitment ongoing since May 2018
- Main inclusion criteria: ≥ 18 yrs of age, informed consent, history of IDU, IDU in past 6 mos or current OST, not pregnant
  - Among 1001 patients as of March 15, 2019, 72% receiving OST, 70% with history of incarceration, 63% male, 57% consuming excessive alcohol
- Assessments: demographics, IDU history, HCV experience, noninvasive liver stiffness test, HCV PoC testing, clinical assessment

Valerio. EASL 2019. Abstr PS-070.

# ETHOS Engage: Uptake of HCV Testing and Treatment




- In PWID with past or current chronic HCV infection, female sex and no current OST use associated with decreased uptake of HCV therapy

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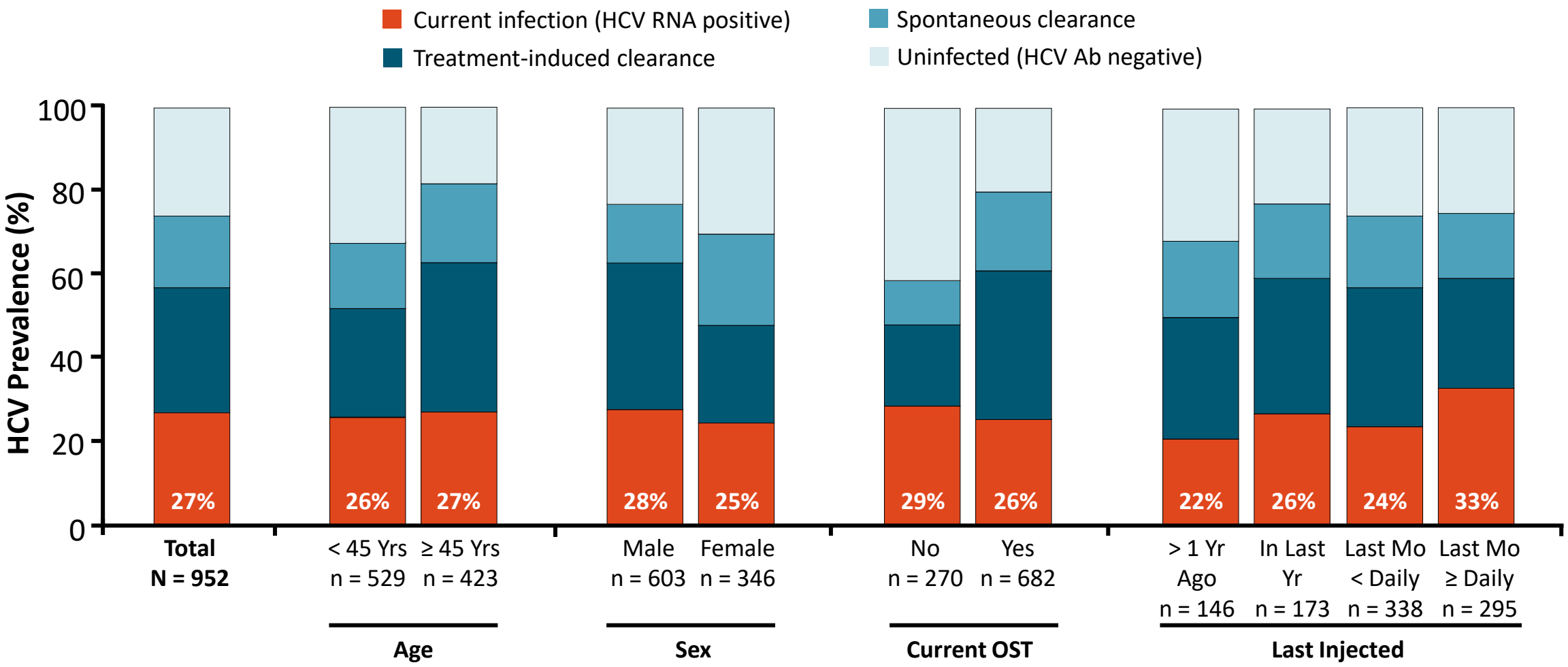
# ETHOS Engage: Current HCV Prevalence

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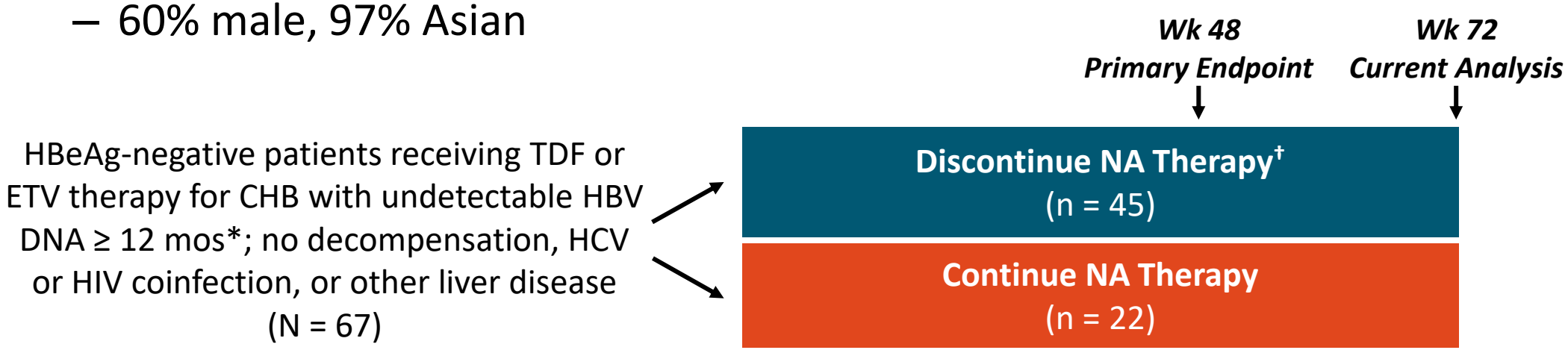
# Treatment of HBV Infection

# STOP: Evaluation of ALT Flares in HBeAg-Negative Patients Discontinuing NA Therapy for CHB

- Single-center, prospective, randomized, open-label phase IV trial
  - 60% male, 97% Asian




*If HBeAg positive at start of NA therapy, required to have HBeAg seroconversion and undetectable HBV DNA for 12 mos; if HBeAg negative at start of NA therapy, required to have undetectable HBV DNA for 36 mos. †Patients retreated for HBeAg seroreversion, HBV DNA > 20,000 IU/mL at 2 visits, or HBV DNA > 2000 IU/mL with ALT > 5 x ULN at 2 visits or > 15 x ULN at any visit.

- Endpoints: cumulative incidence of ALT > 5 x ULN, predictors of off-therapy ALT > 5 x ULN

Liem. EASL 2019. Abstr FRI-190. Liem. AASLD 2018. Abstr 268.

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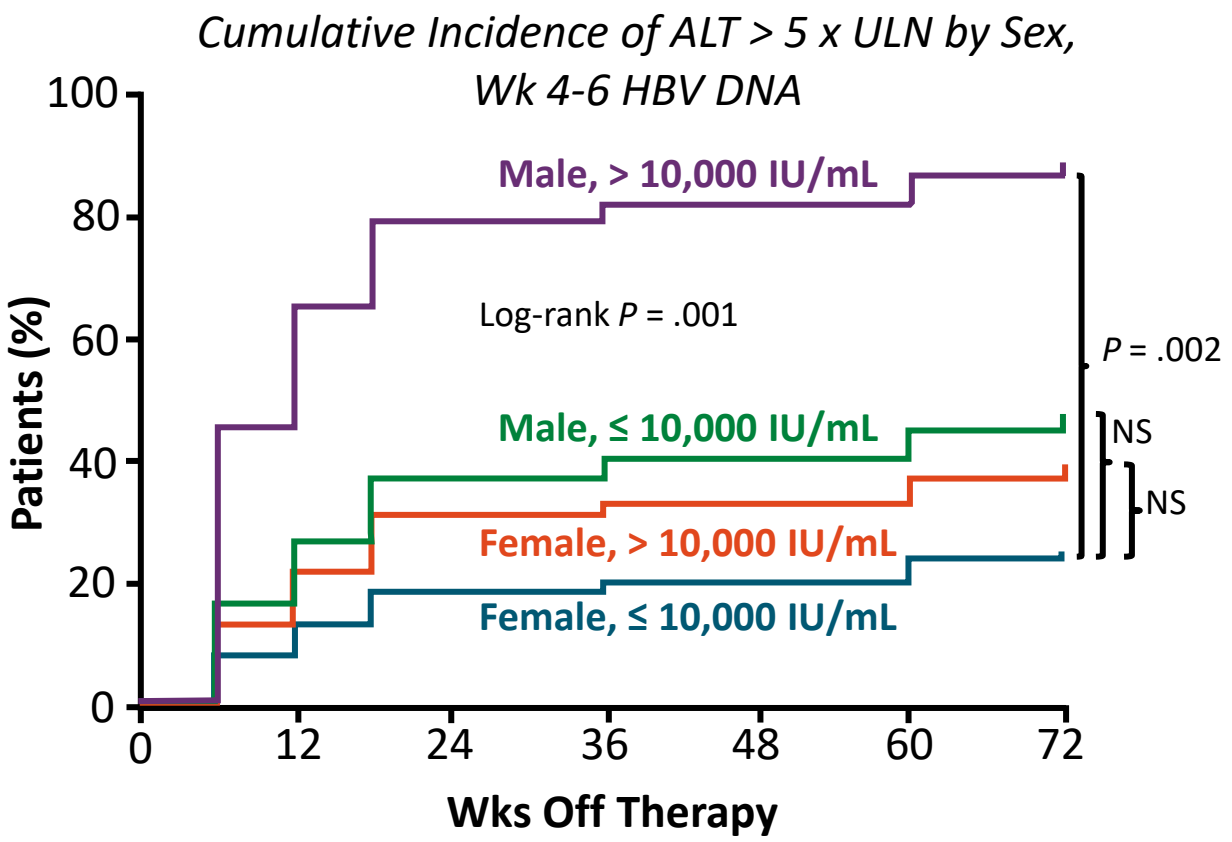
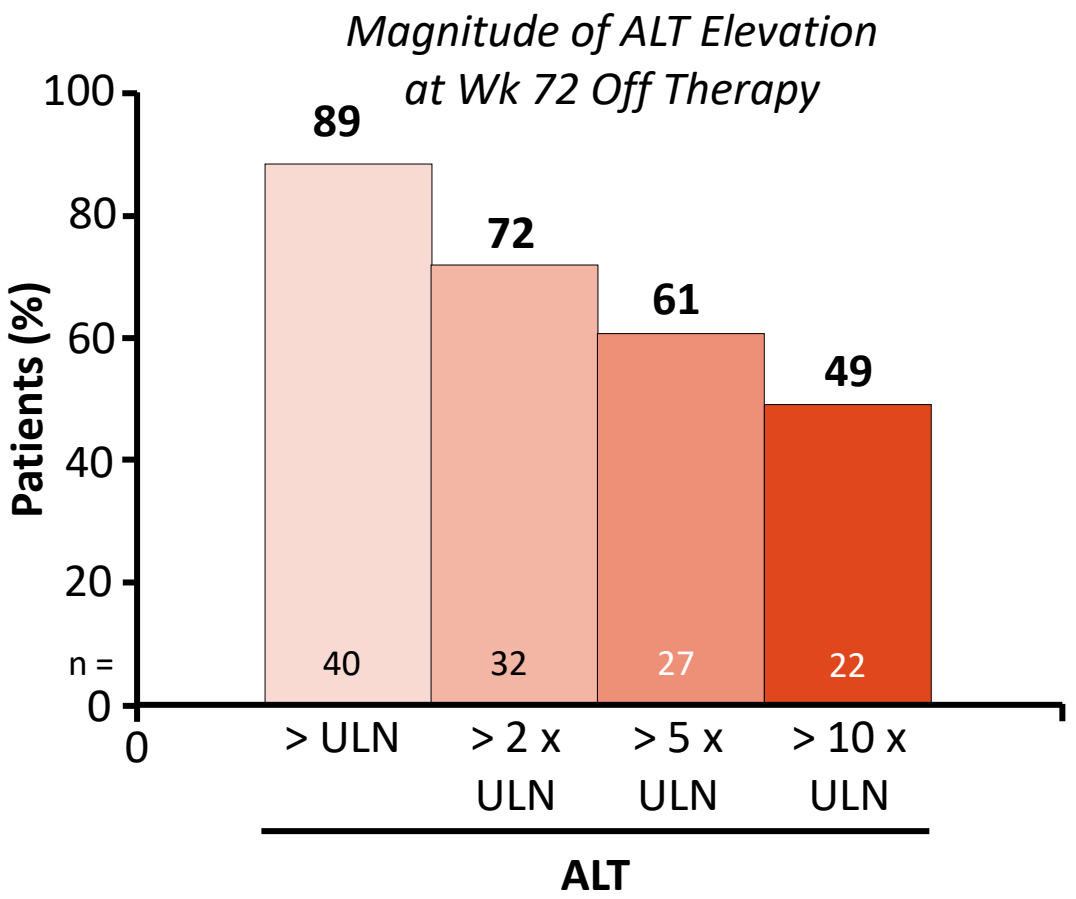
# STOP: Incidence, Magnitude of Off-Therapy ALT Flares

**Endpoint in Patients Discontinuing NA Therapy (n = 45)**

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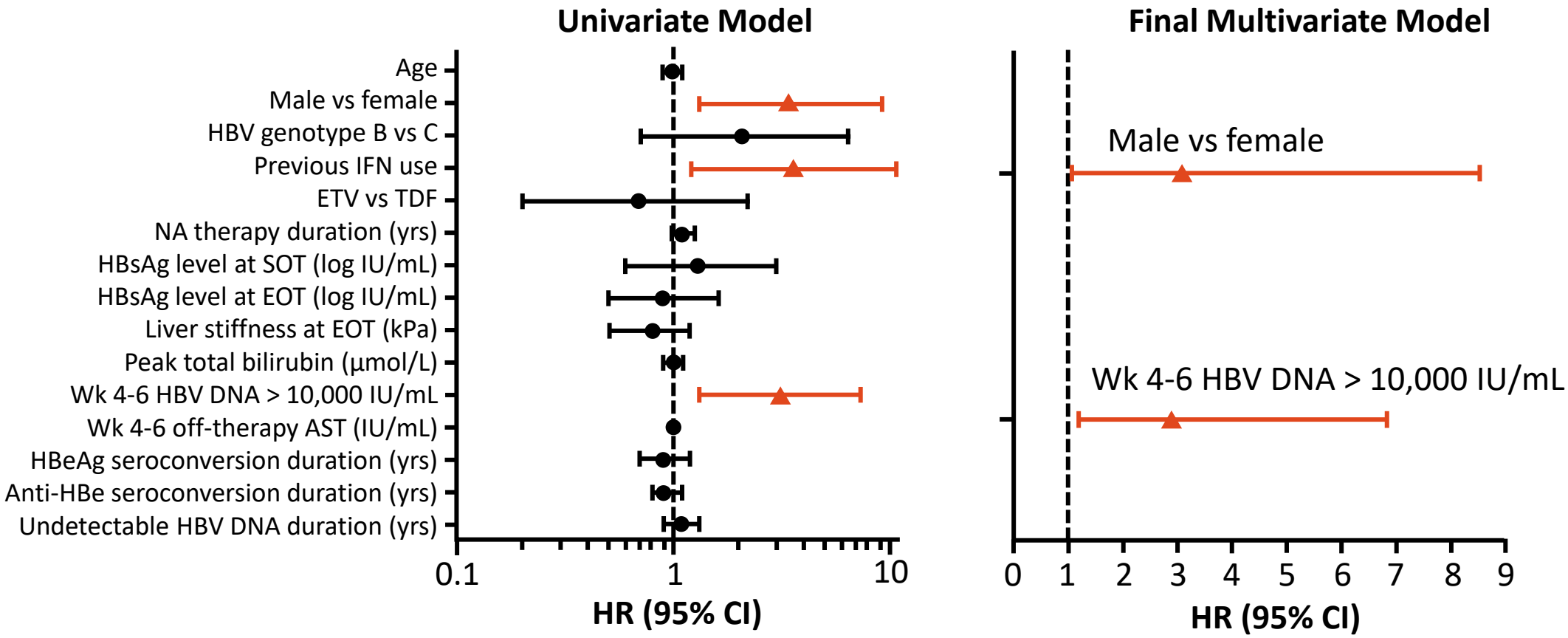
# STOP: Predictors of Off-Therapy ALT Flares

**Cox Proportional Hazards Model: Likelihood of ALT > 5 x ULN in Patients Discontinuing NA Therapy (n = 27 with ALT > 5 x ULN by Wk 72)**

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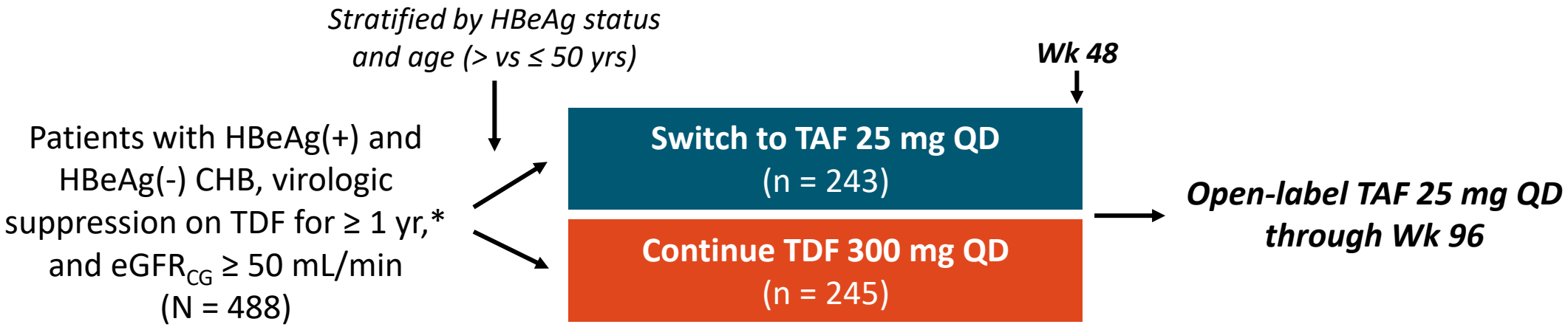
# Study 4018: Switch to TAF vs Continued TDF in Virologically Suppressed Patients With CHB

- Multicenter, randomized, double-blind phase III trial




*Patients eligible if receiving TDF ≥ 48 wks with HBV DNA < LLOQ by local lab for ≥ 12 wks before screening, HBV DNA < 20 IU/mL at screening.

- Primary endpoint: HBV DNA ≥ 20 IU/mL at Wk 48 by FDA modified snapshot analysis (4% noninferiority margin)
- Secondary endpoints: ALT normalization, HBeAg and HBsAg loss/seroconversion, change in quantitative HBsAg, resistance, AEs, markers of bone and renal disease

Lampertico. EASL 2019. Abstr FRI-183.

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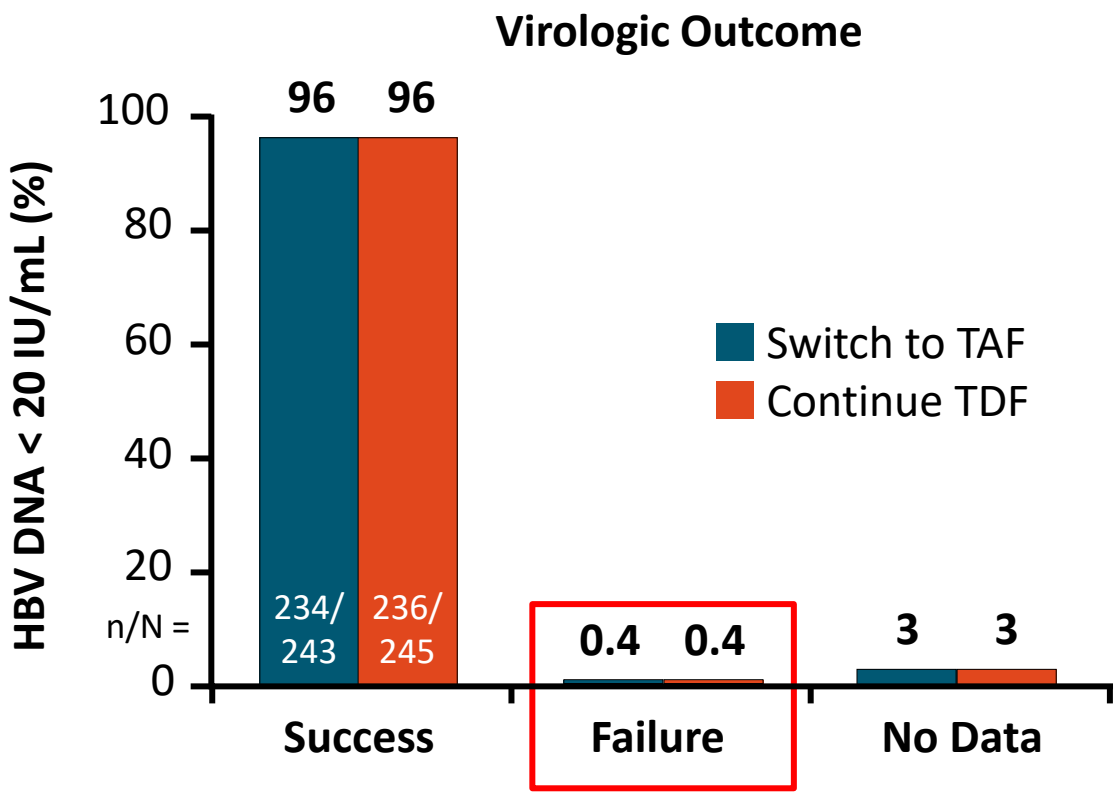
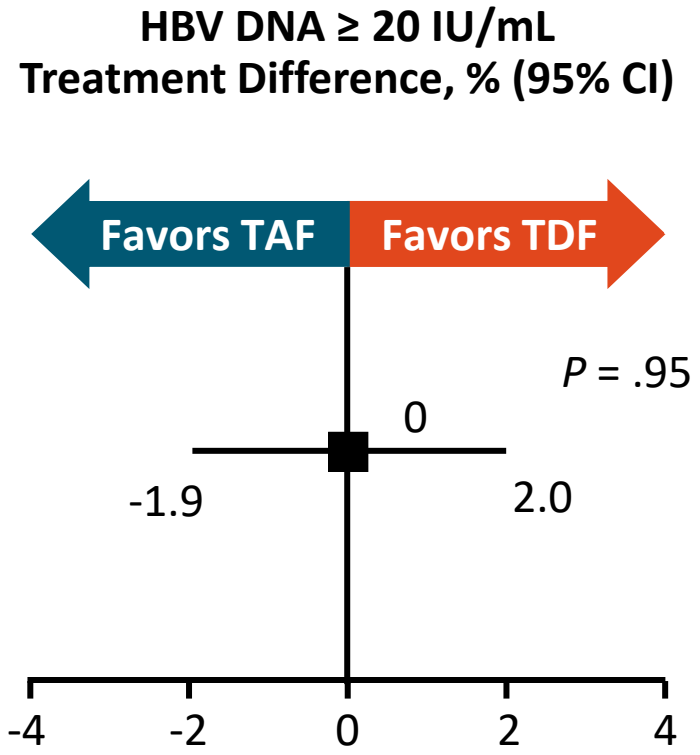
# Study 4018: HBV DNA ≥ 20 IU/mL at Wk 48 (Primary Endpoint)




- No virologic breakthroughs or resistance detected in either arm

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# Study 4018: Secondary Endpoints at Wk 48

- No HBsAg seroconversion in either arm through Wk 48
  - Similar quantitative HBsAg declines

| Endpoint, n/N (%) | Switch to TAF | Continue TDF | *P* Value |
|---|---|---|---|
| ALT normalization | | | |
| ▪ Central lab* | 16/32 (50) | 7/19 (37) | .34 |
| ▪ AASLD criteria† | 26/52 (50) | 14/53 (26) | .014 |
| HBeAg, % | | | |
| ▪ Loss | 6/78 (8) | 5/78 (6) | .73 |
| ▪ Seroconversion | 2/78 (3) | 0 | .13 |
| HBsAg loss, % | 0 | 5/245 (2) | .03 |

*ULN (U/L): men, 43 if 18-68 yrs, 35 if ≥ 69 yrs; women, 34 if 18-68 yrs, 32 if ≥ 69 yrs. †ULN (U/L): men, 35; women, 25.

- At Wk 48, switch to TAF associated with:
  - Significant improvements in hip and spine BMD, renal function (eg, $eGFR_{CG}$, CKD stage)
  - Significant decreases in markers of bone turnover and proteinuria

| Safety Endpoint, n (%) | Switch to TAF (n = 243) | Continue TDF (n = 245) |
|---|---|---|
| AEs | 126 (52) | 118 (48) |
| Grade 3/4 AEs | 8 (3) | 4 (2) |
| Serious AEs‡ | 11 (5) | 3 (1) |
| D/c due to AEs | 2 (< 1) | 0 |
| Grade 3/4 lab abnormalities§ | 23 (10) | 18 (7) |

‡None drug related. §TAF, n = 242; TDF, n = 243.

Lampertico. EASL 2019. Abstr FRI-183.

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# HCC Risk With TDF vs ETV in Patients With CHB

- Study of patients from Clinical Data Analysis and Reporting System, large database covering public hospitals and clinics in Hong Kong
  - Eligibility: Chinese adults with CHB receiving TDF or ETV between January 2008 and June 2018
  - Exclusion criteria: HCV, HDV, or HIV coinfection; cancer or liver transplantation before or < 6 mos from starting HBV treatment; HBV treatment duration < 6 mos; prior pegIFN or other NAs (eg, 3TC, adefovir, telbivudine)
- Analyses: multiple imputation, propensity score (weighting and matching), competing risk, negative control outcome
- N = 29,350 included; n = 1309 TDF vs n = 28,041 ETV (HCC cases: 8 vs 1386, respectively)
  - Overall: 64% male, 31% HBeAg positive, 13% cirrhosis
  - Baseline characteristics well balanced after propensity score weighting

Yip. EASL 2019. Abstr LB-03.

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# HCC Risk With TDF vs ETV in Patients With CHB: Results

- Among treatment-naive patients with CHB in Hong Kong, risk of HCC lower with use of TDF vs ETV

| 5-Yr Cumulative HCC, % (95% CI) | TDF | ETV |
|---|---|---|
| Univariate* | 1.1 (0.5-2.3) | 7.0 (6.6-7.3) |
| PS weighting | 1.2 (0.5-2.4) | 3.1 (1.9-4.8) |
| PS matching | 1.2 (0.6-2.5) | 2.3 (1.4-4.0) |

*$P < .001$

| Analysis | HCC Risk With TDF vs ETV | |
|---|---|---|
| | SHR (95% CI) | *P* Value |
| Multivariate | 0.32 (0.16-0.65) | .002 |
| PS weighting | 0.36 (0.16-0.80) | .013 |
| PS weighting† | 0.35 (0.12-0.98) | .045 |
| PS matching | 0.42 (0.17-1.04) | .060 |

†Adjusted for HBV DNA suppression, ALT normalization (< 35 U/L for men, < 25 U/L for women) at Yr 1.

- No associations observed between HBV treatment and negative control outcomes (ie, lung cancer, acute MI)

Yip. EASL 2019. Abstr LB-03.

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# Select Agents Under Early-Phase Investigation for HBV

| Agent | MoA | Phase | Key Findings |
|---|---|---|---|
| JNJ-56136379[1] | Capsid assembly modulator | I | 75 mg QD for 4 wks provided potent antiviral activity, was well tolerated in 15 TN CHB patients |
| RO7049389*[2] | Core protein allosteric modulator | I | Significant decrease in HBV DNA and HBV RNA observed across dosing cohorts in 21 TN CHB patients; well tolerated |
| ABI-H0731[3] | Core protein allosteric modulator | IIa | Faster, deeper HBV DNA decline in TN CHB patients with NA combo vs NA alone; HBV DNA undetectable in virologically suppressed patients with combo but not NA alone; well tolerated |
| Inarigivir[4] | RIG-I agonist | II | Dose-dependent response seen in HBeAg-positive and HBeAg-negative TN patients; treatment well tolerated; HBsAg response in 26% of patients |
| JNJ-3989[5] | RNA interference | II | 88% of 40 TN CHB patients achieved HBsAg ≤ 100 IU/mL; 100% gained ≥ 1.0 $\log_{10}$ IU/mL HBsAg decrease after 3 doses; well tolerated |
| Bulevirtide[6] | NTCP inhibitor | II | 6/15 HDV/HBV-coinfected patients had HBsAg response at Wk 72 with 2 mg bulevirtide + pegIFN |
| T101[7] | Therapeutic vaccine | I | Reduced HBsAg and stimulated HBV-specific T-cell immune response in CHB patients with HBV DNA < 20 IU/mL on NAs; SC injections well tolerated |

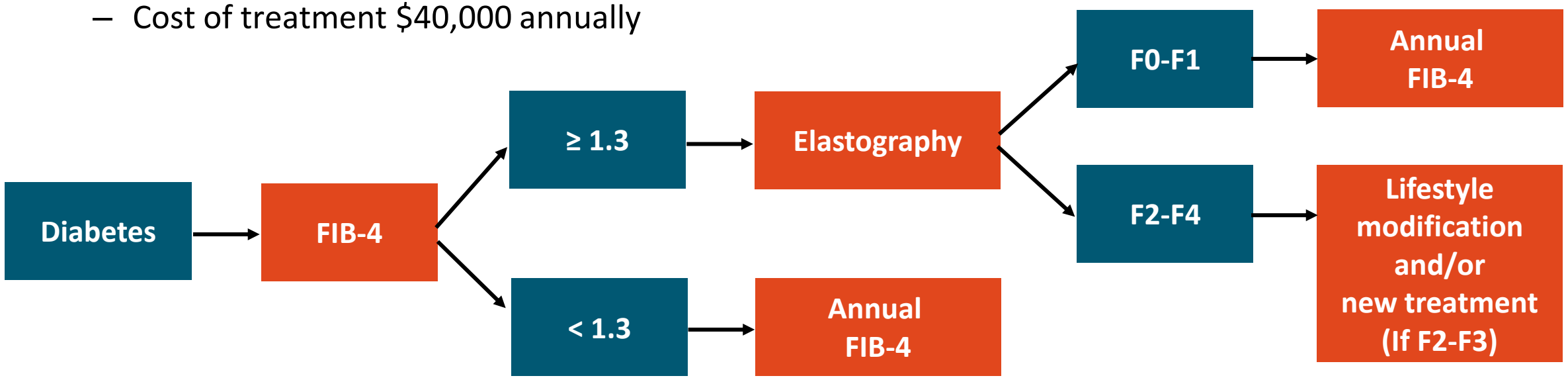
*Abstract data only.

1. Yogaratnam. EASL 2019. Abstr FRI-217. 2. Gane. EASL 2019. Abstr FRI-219. 3. Ma. EASL 2019. Abstr LB-06. 4. Yuen. EASL 2019. Abstr GS-12. 5. Yuen. EASL 2019. Abstr PS-080. 6. Wedemeyer. EASL 2019. Abstr GS-13. 7. Hu. EASL 2019. LBP-25.

# NAFLD/NASH Impact

# Screening for NAFLD in People With Diabetes: Modeling Analysis

- Model developed to assess impact of screening for liver fibrosis using routine variables and elastography in people with diabetes
- Assumptions regarding hypothetical new treatment for people 50 yrs of age with F2-F3 disease
  - Reduces annual progression rate by 15%, increases regression rate by 15%
  - Cost of treatment $40,000 annually




Maor. EASL. Abstr PS-063.

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# Screening for NAFLD in People With Diabetes: Cost-Effectiveness

| Strategy | Total Cost, USD | Incremental Cost, USD | Total QALY | Incremental QALY | ICER, USD per QALY |
|---|---|---|---|---|---|
| No screening | $94,791 | -- | 15.25 | -- | -- |
| Screening | $21,347 | $118,556 | 15.86 | 0.61 | $195,481 |

- Changing treatment cost and effectiveness alters ICER in sensitivity analysis

| Screening Strategy, Assuming 115% Regression Rate | ICER, USD per QALY |
|---|---|
| Treatment $20,000/yr | $90,874 |
| Treatment $100,000/yr | $509,301 |

| Screening Strategy, Assuming 125% Regression Rate | ICER, USD per QALY |
|---|---|
| Treatment $20,000/yr | $42,205 |
| Treatment $40,000/yr | $105,839 |
| Treatment $100,000/yr | $296,740 |

- Incremental cost-effectiveness ratio of screening for NAFLD in patients with diabetes is high
- Screening could be cost-effective if new treatments are highly effective in reducing fibrosis and if costs are reasonable

Maor. EASL. Abstr PS-063.

Slide credit: clinicaloptions.com

# Economic and Clinical Burden of NASH in US Patients With T2DM Primarily Driven by T2DM

- According to Markov modeling analysis, even though **NASH population with T2DM** ~ 10 x smaller than non-NASH NAFLD population, it accounts for **~ 3 x more adverse clinical outcomes**

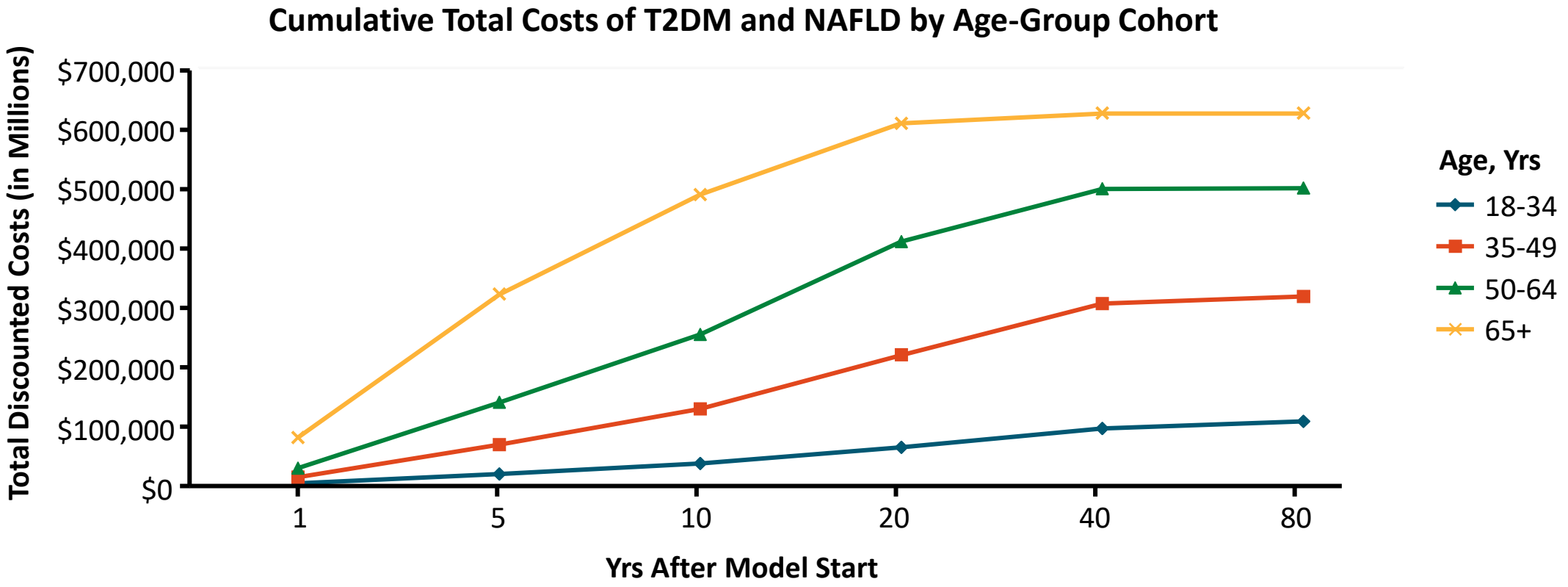
| | Incident Population (New Cases) | | Prevalent Population (All Cases) | All NAFLD |
|---|---|---|---|---|
| | Non-NASH NAFLD | NASH | NASH | |
| Total lifetime cost | $1,302,831,600,693 | $63,666,986,969 | $181,061,807,397 | $1,547,560,395,059 |
| Diabetes-attributable costs | $1,283,803,681,082 | $48,984,471,501 | $127,143,233,665 | $1,459,931,386,248 |
| % of total | 98.5% | 76.9% | 70.2% | 94.3% |
| NAFLD-attributable costs | $19,027,919,611 | $14,682,515,468 | $53,918,573,732 | $87,629,008,811 |
| % of total | 1.46% | 23.1% | 29.8% | 5.66% |
| Liver transplants | 19,170 | | 79,386 | 98,556 |
| Liver-related deaths | 96,133 | | 261,089 | 357,222 |
| Decompensated cirrhosis person-yrs | 138,160 | | 330,918 | 469,078 |
| Hepatocellular carcinoma person-yrs | 37,775 | | 93,262 | 131,037 |
| Cardiovascular deaths | 834,532 | | 189,797 | 1,024,329 |

Younossi. EASL 2019. Abstr THU-347.

Slide credit: clinicaloptions.com

# Economic and Clinical Burden of NASH in US Patients With T2DM According to Age Group

- Older age-group cohorts (50+ yrs) account for majority of costs over time, largely due to high prevalence of both T2DM and NAFLD




Younossi. EASL 2019. Abstr THU-347.

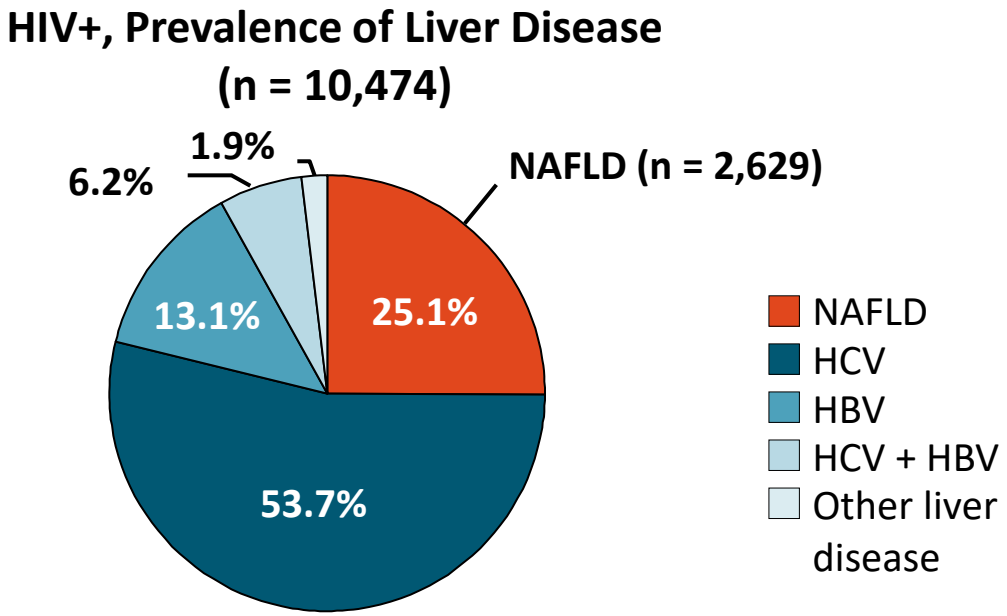
Slide credit: clinicaloptions.com

# NAFLD Prevalence, Mortality in US Medicare Recipients With HIV

- Study of 5% random sample of all Medicare recipients with HIV from 2006-2016 (N = 47,062)[2]

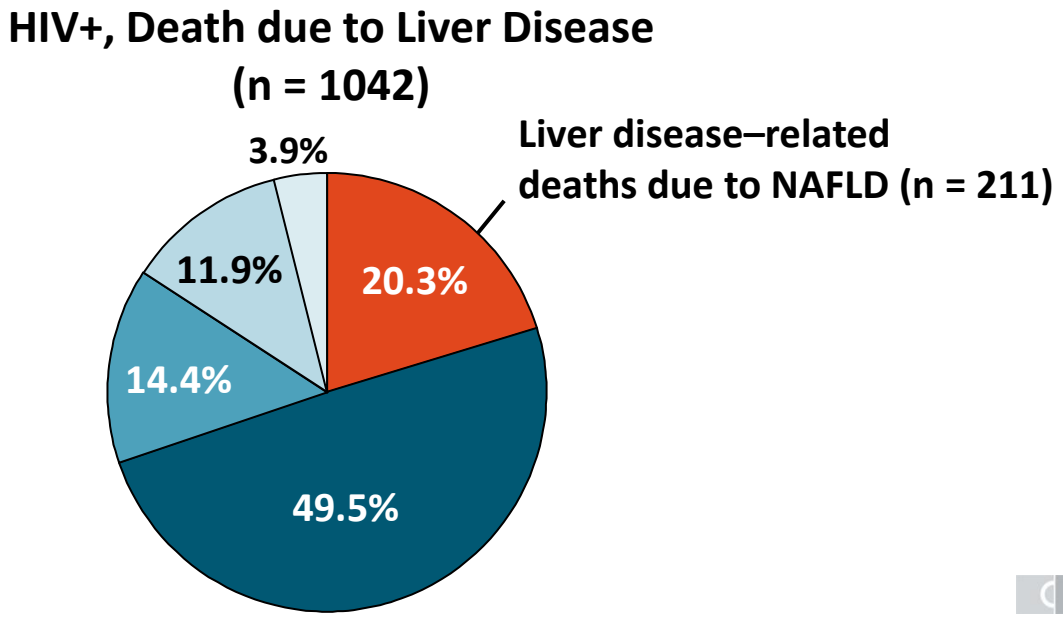
## Liver Disease Prevalence

- 22.3% had liver disease (n = 10,474)




## Liver Disease Mortality

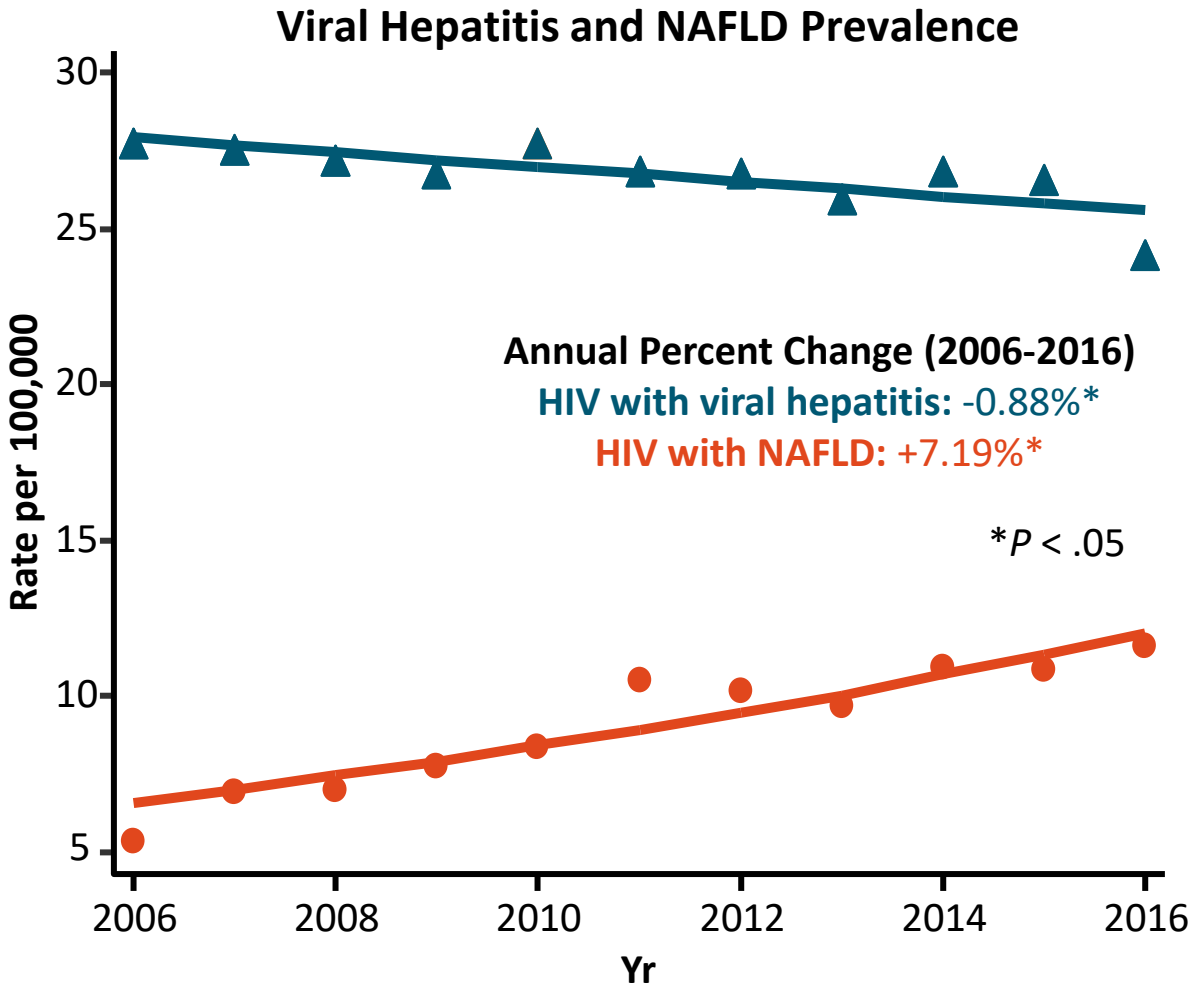
- Within 1 yr, 63.8% of deaths (1042/2882) were related to liver disease

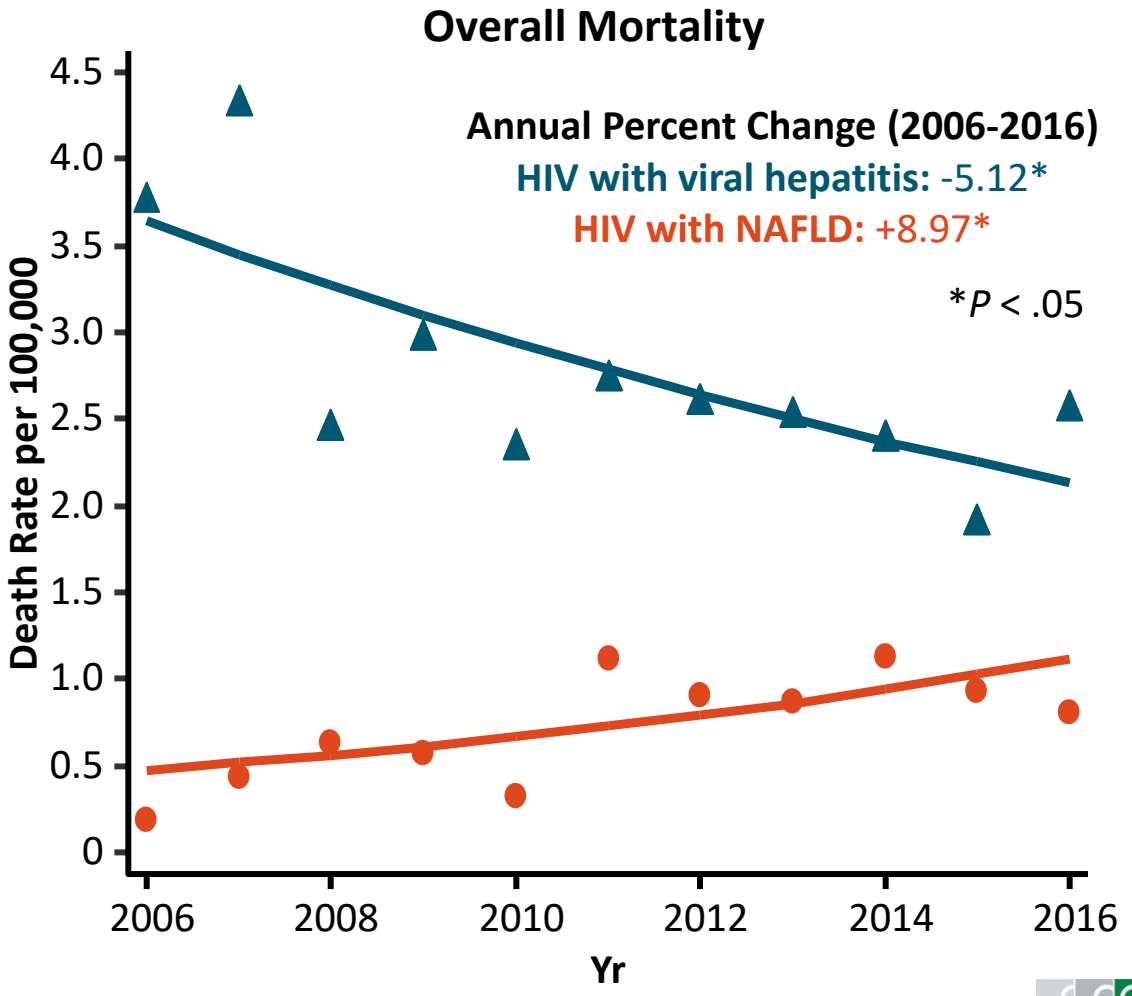



Paik. EASL 2019. Abstr PS-062.

Slide credit: clinicaloptions.com

# NAFLD Prevalence, Mortality in US Medicare Recipients With HIV: Changes From 2006 to 2016




Paik. EASL 2019. Abstr PS-062.

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# Association of NAFLD With Mortality and Resource Utilization in US Medicare Recipients With HIV

- In multivariate analysis (adjusted for calendar yr, age, sex, race/ethnicity, region, and beneficiary entitlement), **each liver disease in HIV** independently associated with **higher risk of 1-yr mortality, longer length of stay,** and **greater inpatient and outpatient costs** (all *P* values vs no liver disease in HIV < .05)

| HIV Patient Group | 1-Yr Mortality, OR (95% CI) | Length of Stay, % Change (95% CI) | Total Charges | |
|---|---|---|---|---|
| | | | Inpatient, % Change (95% CI) | Outpatient, % Change (95% CI) |
| No liver disease | Reference | Reference | Reference | Reference |
| NAFLD | 1.54 (1.33-1.80) | 19.28 (16.96-21.66) | 27.33 (17.50-37.98) | 55.08 (47.20-63.38) |
| HCV without HBV | 1.89 (1.69-2.11) | 23.89 (22.30-25.50) | 31.18 (24.24-38.50) | 47.95 (42.60-53.49) |
| HBV without HCV | 2.25 (1.85-2.72) | 44.06 (41.01-47.18) | 40.43 (27.39-54.80) | 78.20 (65.75-91.58) |
| HCV and HBV | 4.17 (3.31-5.24) | 81.47 (77.37-85.67) | 77.86 (58.02-100.19) | 122.44 (96.05-152.37) |

- Regardless of the etiology, liver disease in HIV is also associated with increased resource utilization

Paik. EASL 2019. Abstr PS-062.

# Patient-Reported Outcomes Among Patients With NASH and Advanced Fibrosis or Compensated Cirrhosis

- Analysis of NASH patients with **bridging fibrosis** or **compensated cirrhosis (NASH CRN stages F3-F4)** enrolled on 2 phase III STELLAR trials evaluating ASK1 inhibitor selonsertib (N = 1667)
- Patient-reported outcomes collected before treatment initiation using
  - Chronic Liver Disease Questionnaire (CLDQ NASH)
  - EQ-5D
  - Short Form-36 (SF-36)
  - Work Productivity and Activity Index (WPAI:SHP)

Younossi. EASL 2019. Abstr SAT-151.

# Independent Predictors of Poorer Patient-Reported Outcomes in NASH

| Independent Predictors of Poorer Scores* | Beta, % of PRO Range Size |
|---|---|
| Age, per yr | -0.19 to 0.46 |
| Male sex | 3.0 to 9.2 |
| Black vs white | -15.8 to -14.0 |
| Asian vs white | 4.2 to 9.9 |
| US enrollment | 3.9 to 9.9 |
| Current smoker | -7.5 to -3.2 |
| BMI, per kg/m$^2$ | -0.99 to -0.15 |

| Independent Predictors of Poorer Scores* | Beta, % of PRO Range Size |
|---|---|
| Cirrhosis vs bridging fibrosis | -3.6 to -3.3 |
| Type 2 diabetes mellitus | -6.3 to -2.8 |
| GI disorders | -7.4 to -3.0 |
| Musculoskeletal and connective tissue disorders | -11.2 to -3.3 |
| Nervous system disorders | -5.7 to -2.8 |
| Psychiatric disorders | -13.1 to -2.4 |

*All $P < .05$ after bidirectional stepwise selection of clinical and demographic predictors.

Younossi. EASL 2019. Abstr SAT-151.

Slide credit: clinicaloptions.com

# Patient-Reported Outcomes Worse in NASH and With Select Comorbid Conditions

- Physical health–related PROs significantly lower for NASH patients vs population norms (all $P < .01$)
- **Musculoskeletal disorders, higher BMI** significantly associated with (all $P < .05$):
  - Worse physical health
  - Increased fatigue
  - Decreased vitality
- **Comorbid psychiatric disorder** (anxiety, depression, bipolar, sleep disorder) was the only predictor of decreased work productivity ($P < .01$)

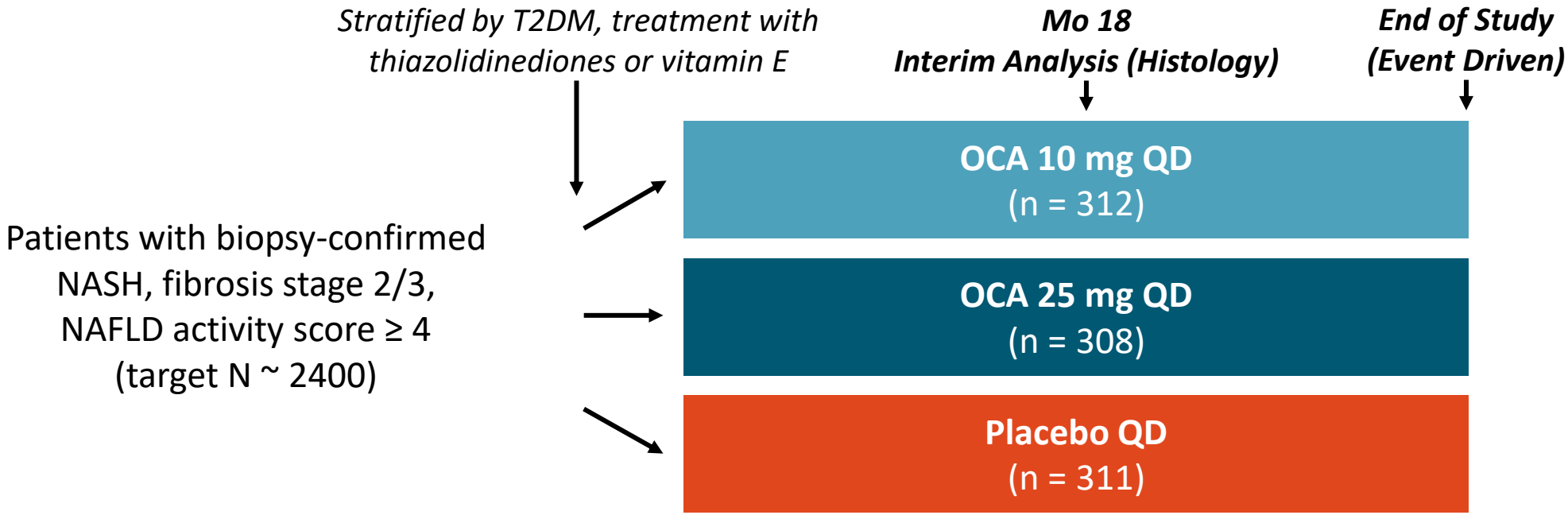
Younossi. EASL 2019. Abstr SAT-151.

Slide credit: clinicaloptions.com

# Treatment of NASH

# REGENERATE: Study Design

- International, randomized, double-blind phase III study of FXR agonist obeticholic acid



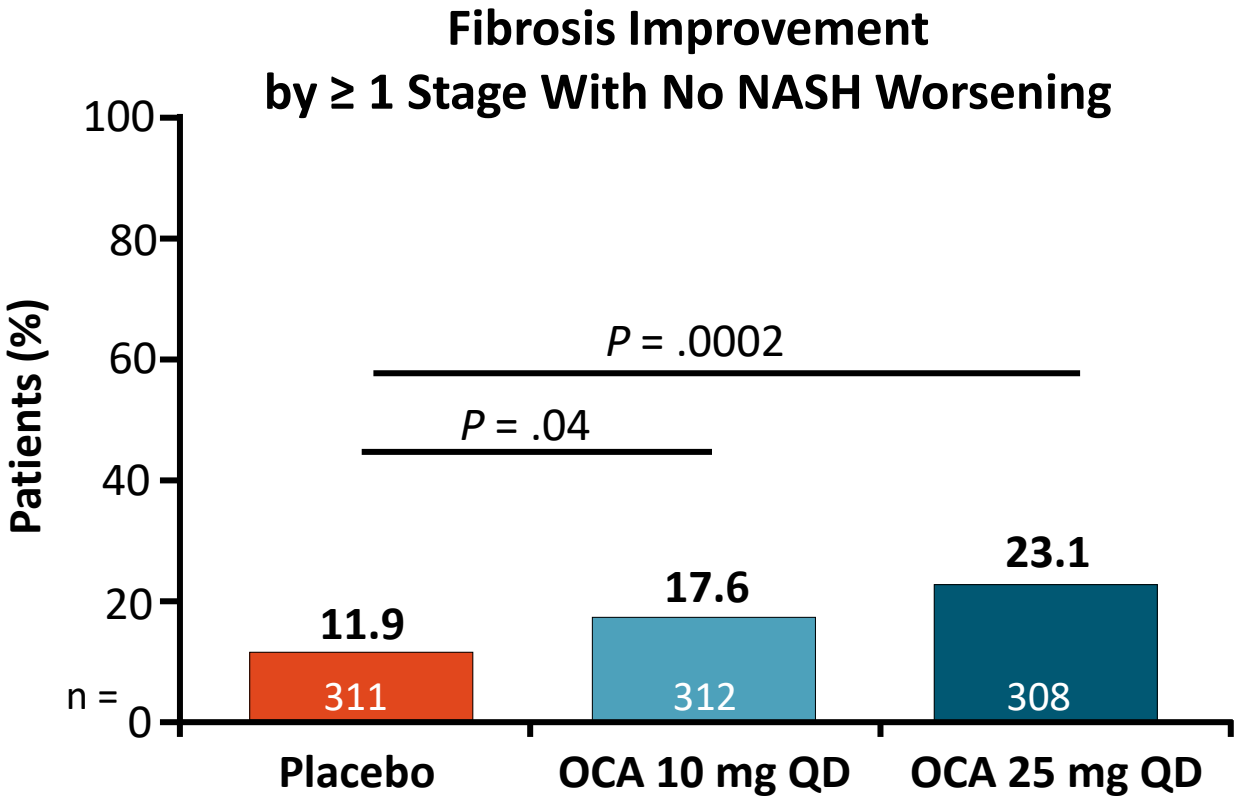

- Primary endpoint at interim analysis by paired biopsy: either **fibrosis improvement by ≥ 1 stage without NASH worsening** or **NASH resolution without fibrosis worsening**

Younossi. EASL 2019. Abstr GS-06. Ratziu. EASL 2016. Abstr THU-488.

Slide credit: clinicaloptions.com

# REGENERATE Primary Endpoint: Fibrosis Improvement

- Study met fibrosis primary endpoint at 18 mos (ITT)



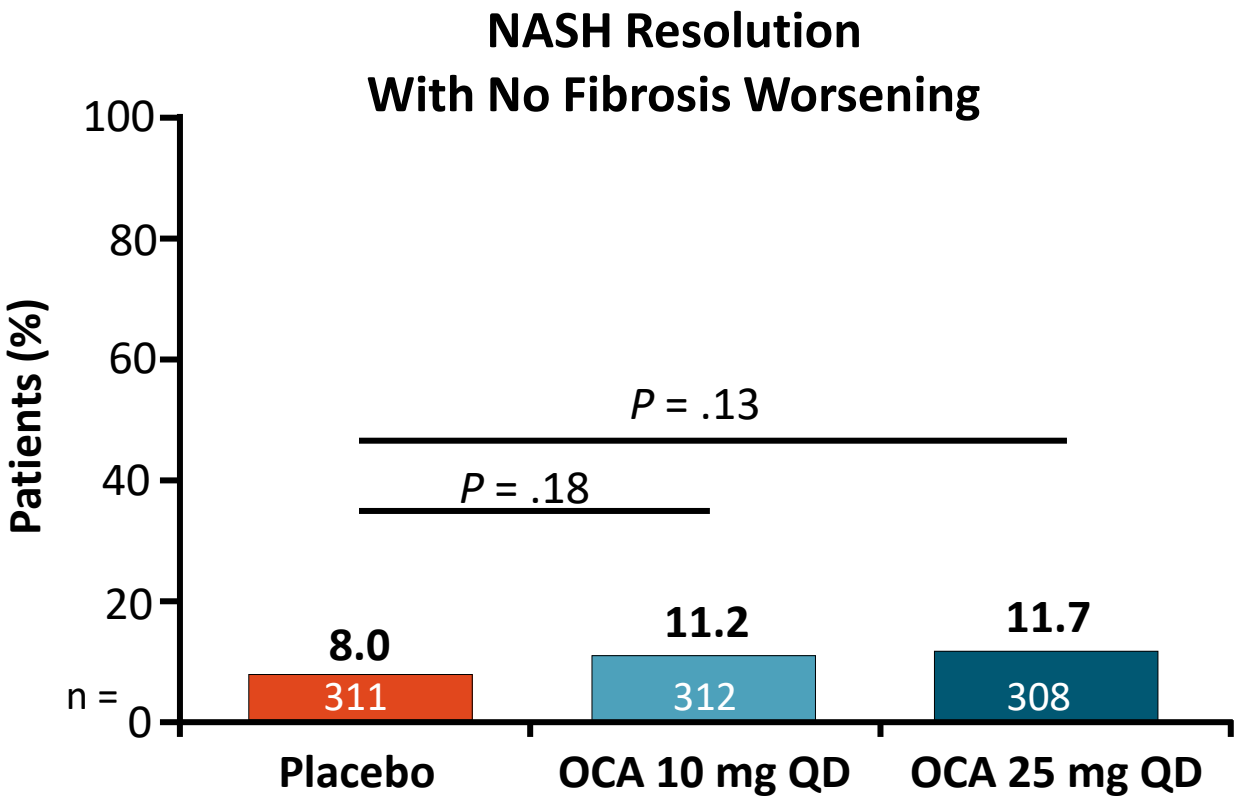

- **In PP analysis,** OCA 25 mg QD also associated with fibrosis improvement across subgroups defined by fibrosis stage, NAS, T2DM status

Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

# REGENERATE Primary Endpoint: NASH Resolution

- Study did not meet NASH resolution primary endpoint at 18 mos (ITT)



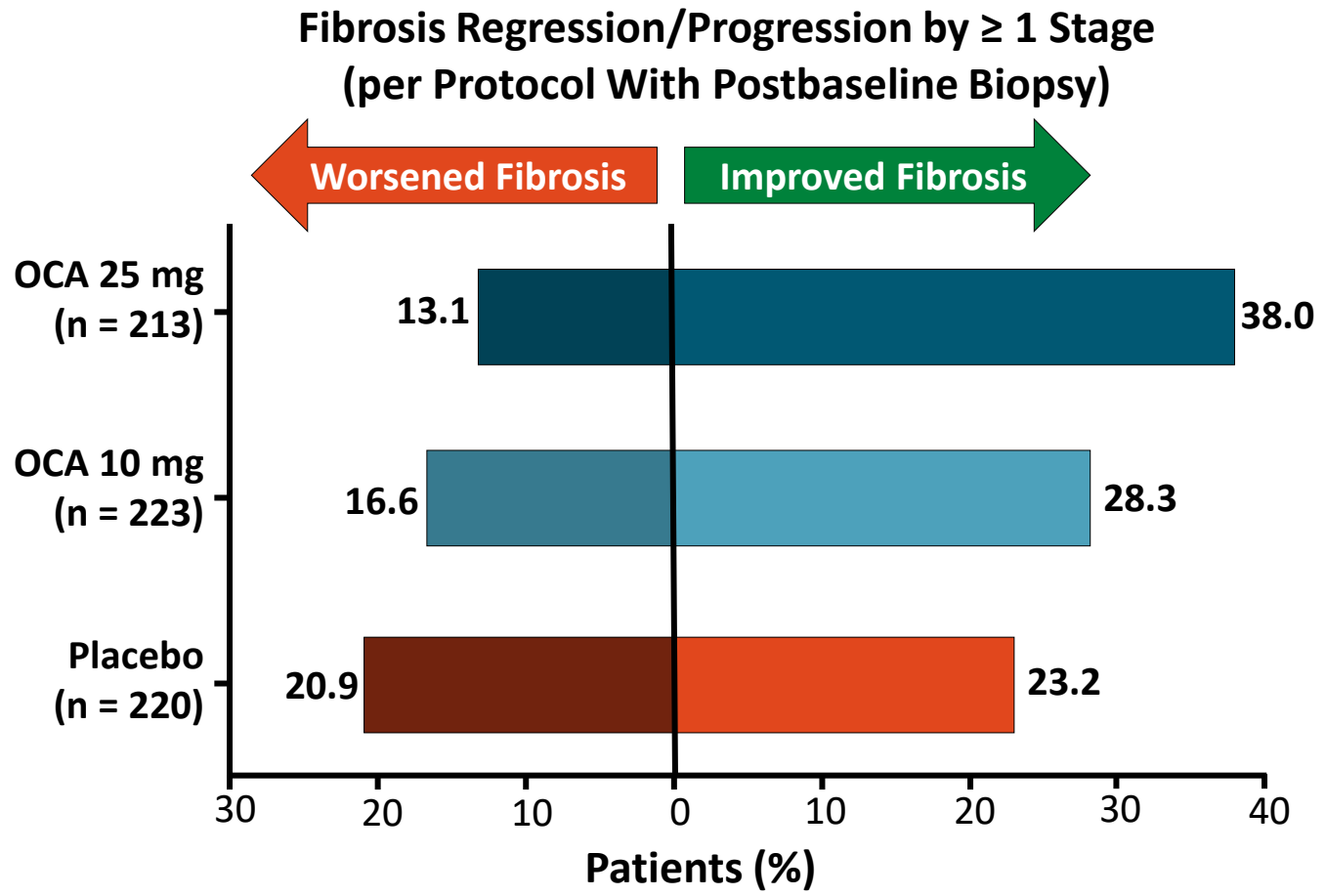

- **In post hoc analysis,** OCA 25 mg QD associated with steatohepatitis resolution* (placebo, 12.2%; OCA 10 mg, 16.3%; OCA 25 mg 23.1%; *P* < .001 for OCA 25 mg vs placebo)
- OCA 25 mg QD also associated with improvement of NAS score, grade of ballooning, and inflammation

*According to overall assessment by pathologists.

Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

# REGENERATE Secondary Endpoints: Changes in Fibrosis




- OCA also associated with improvement in fibrosis staging, NAS parameters, ALT, AST, GGT

Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

# REGENERATE: Safety

- **Pruritus** incidence peaked within first 3 mos before declining
- In OCA 25 mg arm, 9% discontinued due to pruritus, mostly protocol driven
  - Rates comparable between arms
- **Cardiovascular AE rates** ≤ 2% in all arms
- **LDL increased** and **HDL decreased** early with OCA; recovered with clinical management
- **Hepatic TEAE** rates similar across arms
  - Hepatic serious AEs in < 1%, numerically more cases in OCA 25 mg arm
  - Low rates of cholelithiasis, cholecystitis AEs

| TEAEs Occurring in ≥ 10% of Patients in Any Arm, n (%) | OCA 10 mg (n = 653) | OCA 25 mg (n = 658) | Placebo (n = 657) |
|---|---|---|---|
| Pruritus | 183 (28) | 336 (51) | 123 (19) |
| LDL increased | 109 (17) | 115 (17) | 47 (7) |
| Nausea | 72 (11) | 83 (13) | 77 (12) |
| Fatigue | 78 (12) | 71 (11) | 88 (13) |
| Constipation | 65 (10) | 70 (11) | 36 (5) |
| Abdominal pain | 65 (10) | 67 (10) | 62 (9) |
| Diarrhea | 44 (7) | 49 (7) | 79 (12) |

Younossi. EASL 2019. Abstr GS-06.

Slide credit: clinicaloptions.com

# Phase II Data on Investigational NAFLD/NASH Therapies Presented at EASL 2019

| Agent | MoA | N | Study Population |
|---|---|---|---|
| Lubiprostone[1] | Chloride type 2 channel activator | 150 | NAFLD |
| NGM313[2] | FGF21 analogue | 25 | NAFLD |
| VK2809[3] | THR-β agonist | 59 | NAFLD, liver fat ≥ 8%, elevated LDL-C and TG |
| MSDC-0602K[4] | mTOT modulator | 402 | NASH (NAS ≥ 4 including ballooning, inflammation ≥ 1, F1-F3) |
| Emricasan[5] | Pan-caspase inhibitor | 263 | NASH cirrhosis and severe portal hypertension |
| MGL-3196[6] | THR-β agonist | 107 | NASH, hepatic fat fraction ≥ 10% |
| Firsocostat (GS-0976), cilofexor (GS-9674)[7] | ACC inhibitor, FXR agonist | 40 | NASH |

1. Kessoku. EASL 2019. GS-01 2. DePaoli. EASL 2019. PS-108. 3. Loomba. EASL 2019. LBP-20. 4. Harrison. EASL 2019. PS-111. 5. Garcia-Tsao. EASL 2019. LB-01. 6. Harrison. EASL 2019. SAT-347. 7. Lawitz. EASL 2019. SAT-352.

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