ICHEP EXPERT PERSPECTIVES

Highlights on HCV from AASLD 2016

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Endorsed by:

American College of Gastroenterology

CLDF
Chronic Liver Disease Foundation

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HCV Treatment: Innovation

- Overall, ~4% failure rate with currently approved regimens
  - Sofosbuvir/ledipasvir
  - Paritaprevir/ritonavir/ombitasvir + dasabuvir +/- ribavirin
  - Simeprevir/sofosbuvir
  - Elbasvir/grazoprevir
  - Sofosbuvir/velpatasvir
- Very promising late-stage regimens for patients who fail current DAA therapy
  - AbbVie (glecaprevir/pibrentasvir)
  - Gilead (sofosbuvir/velpatasvir/voxilaprevir)
  - Merck (MK-3682/grazoprevir/ruzasvir)

HCV Treatment: Past Challenges

- Failures with NS5A substitutions
  - Present in >80% of patients prior to retreatment
  - ≥95% SVR12 attained when retreating with regimens in late stage development
  - Fail with a similar resistance profile
  - Treat all patients since salvage therapies will be available

HCV Treatment: Past Challenges

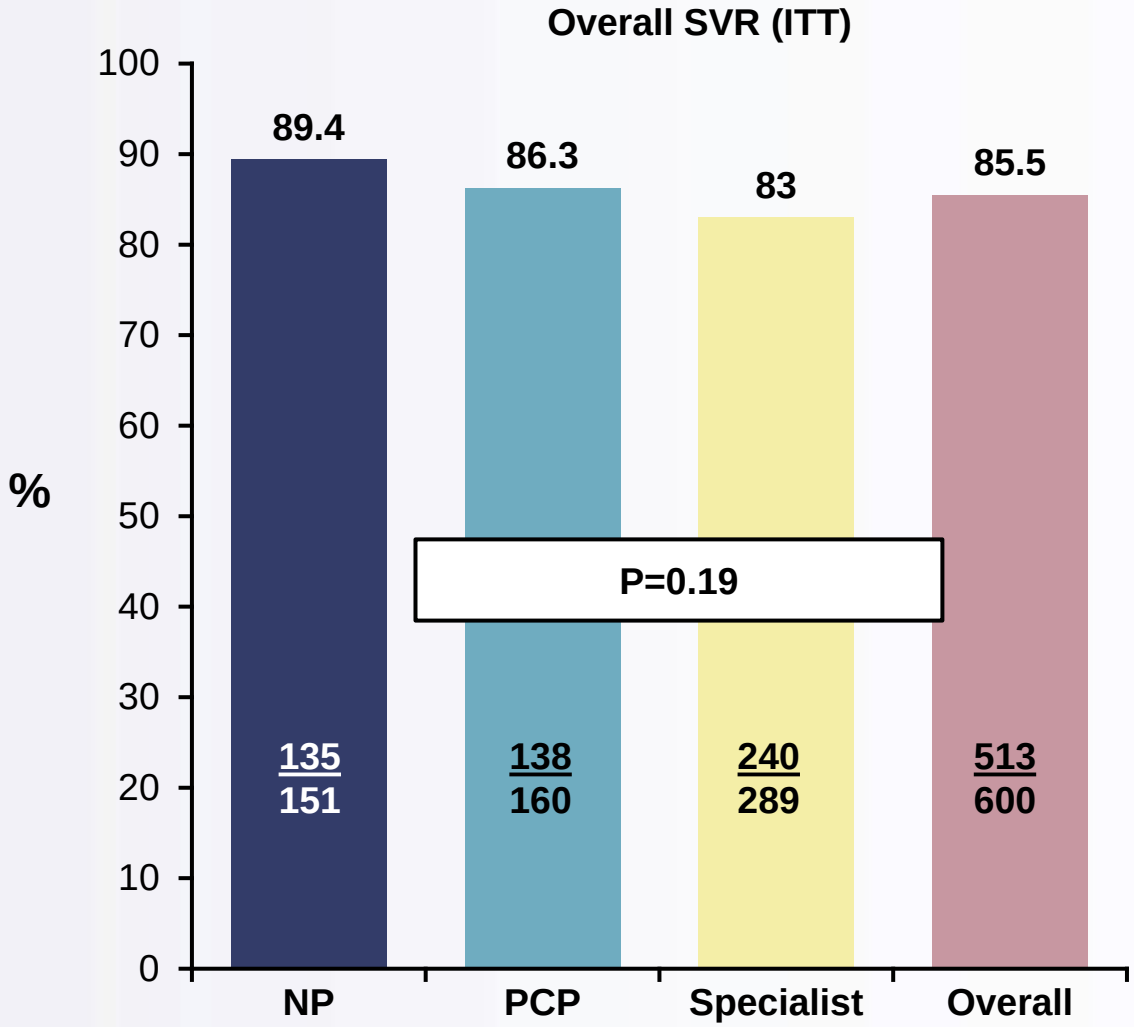
- Past vs Current Clinical Research
  - Peginterferon/ribavirin clinical trials did not reflect real world patients
  - Cherry picked patients
  - Current clinical trials are as close to real world
  - Include patients with negative predictive factors including cirrhosis, prior treatment failures, HCV/HIV coinfection, etc

HCV Treatment: GT3

- ASTRAL (sofosbuvir/velpatasvir)
  - High SVR12 rates across all genotypes
  - Even GT3 cirrhotics respond well
  - Y93H identified as resistance associated substitution (RAS) of some concern
- POLARIS-3 (sofosbuvir/velpatasvir/voxilaprevir) (Foster et al., Abstract #258)
  - 100% (20/20) of patients with baseline NS5A RASs achieved SVR12 with 8 weeks of therapy
    - Includes 6/6 with Y93H RAS

Real World Evidence and Current Practice

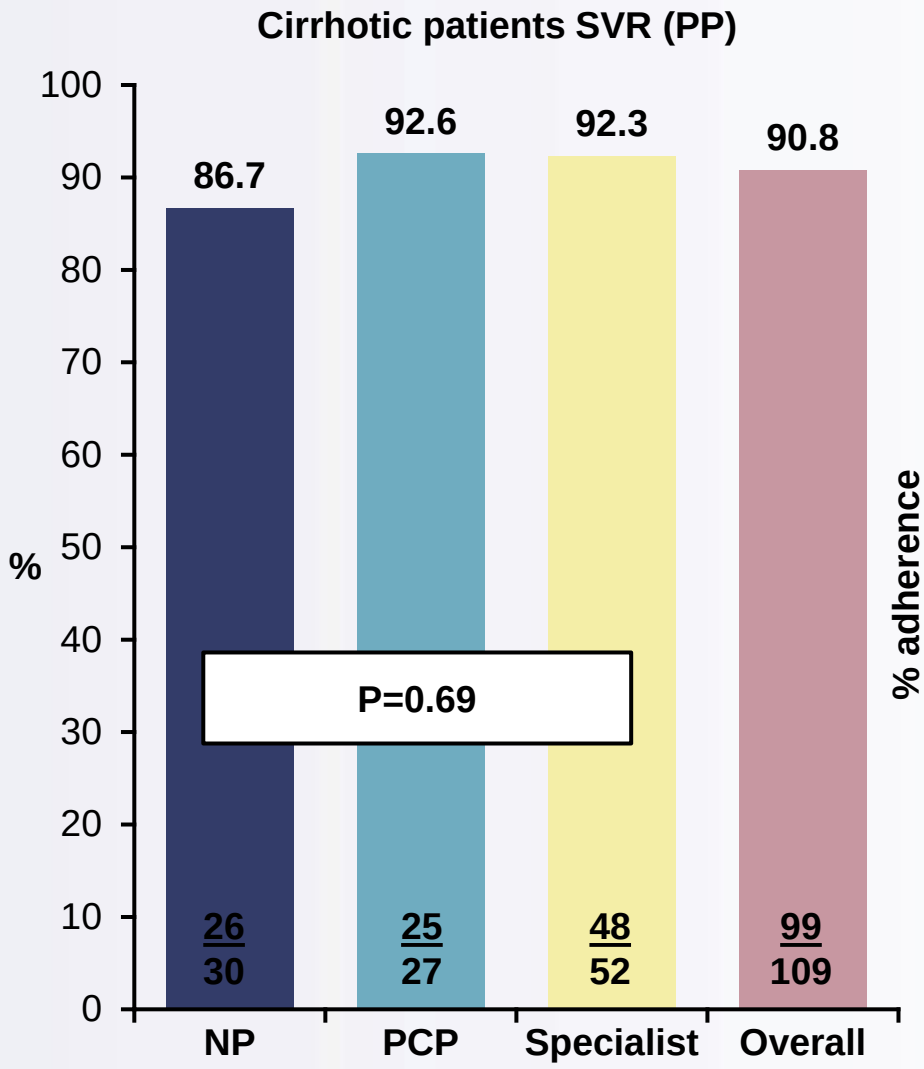
High Efficacy in Real-World Treatment of Cirrhotic Patients by Non-Specialist Providers

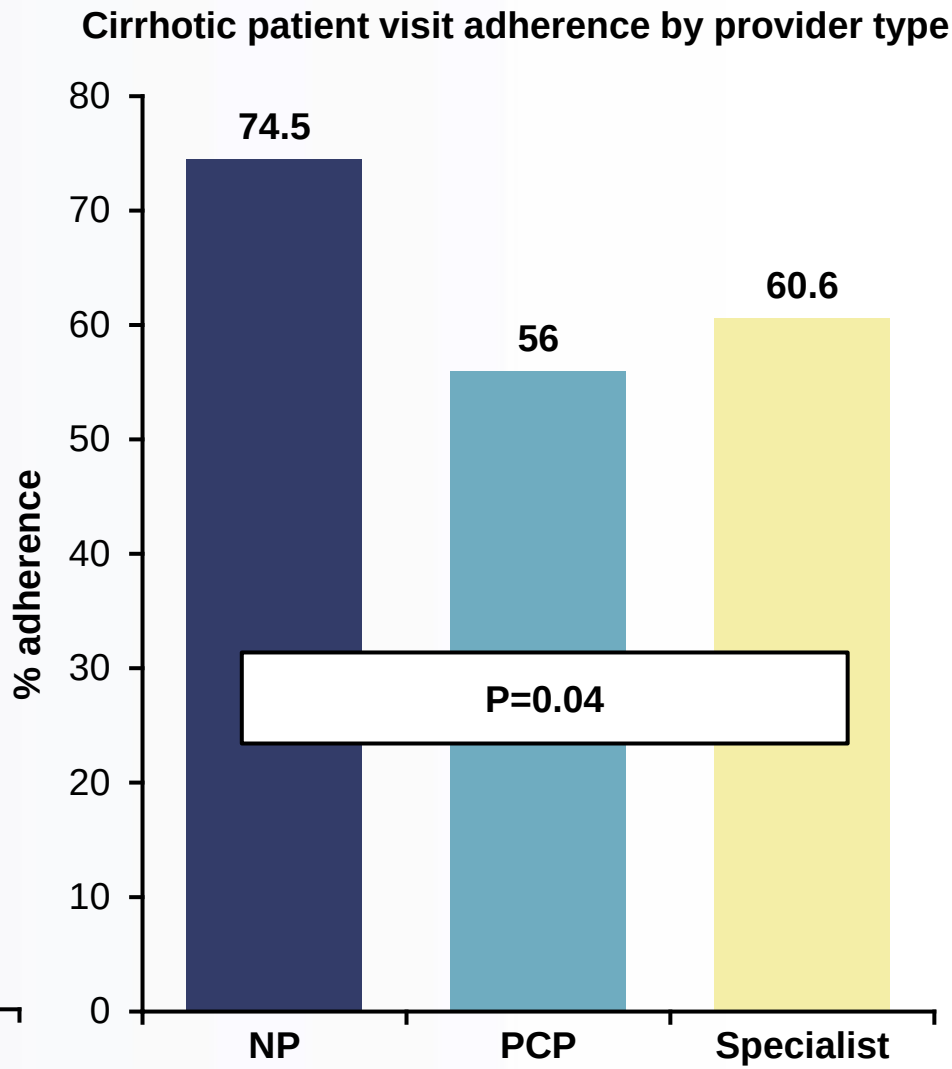


Emmanuel B, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 22.

High Efficacy in Real-World Treatment of Cirrhotic Patients by Non-Specialist Providers

International Coalition of Hepatology Education Providers





Emmanuel B, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 22.

HBV Reactivation Associated with DAA Therapy for HCV: A Review of Spontaneous Post-Marketing Cases

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Age in years (n=29)	Mean (60.7) Median (58) Range (36-85)
Sex	Male (n=13) Female (n=16)
Country of Report	USA (n=5) Japan (n=19) Other (n=5)
Days to Event (n=28)	Mean (53) Median (46) Range (14-196)
Treatment Delay	Yes (n=7) Possible (n=7) No delay (n=2) No treatment given or treatment not stated (n=13)
HCV Genotype	Genotype 1 (n=16) Other genotype (n=2) Not reported (n=11)
Baseline HBV Viral Parameters	HBsAg (+) n=13 HBsAg (-) n=4 HBsAg Not reported n=12 HBcAb (+) n=6 HBcAb Not reported n=23 HBsAb (-) n=3 HBsAb Not reported n=26 HBV DNA undetectable n=16 HBV DNA detectable n=9 HBV DNA baseline either not reported or detectability status unclear n=4
Outcome	Death (n=2); Transplant (n=1); Hospitalization (n=6); Other (n=20)
DAA Therapy	Discontinued (n=10); Completed (n=13); Not Reported (n=6)
Treatment for HBV	Entecavir (n=9); Tenofovir (n=6), Tenofovir/Emtricitabine (n=1); Not Reported (n=6); No Treatment (n=7)

Bersoff-Matcha S, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. LB-17.

Routine Screening

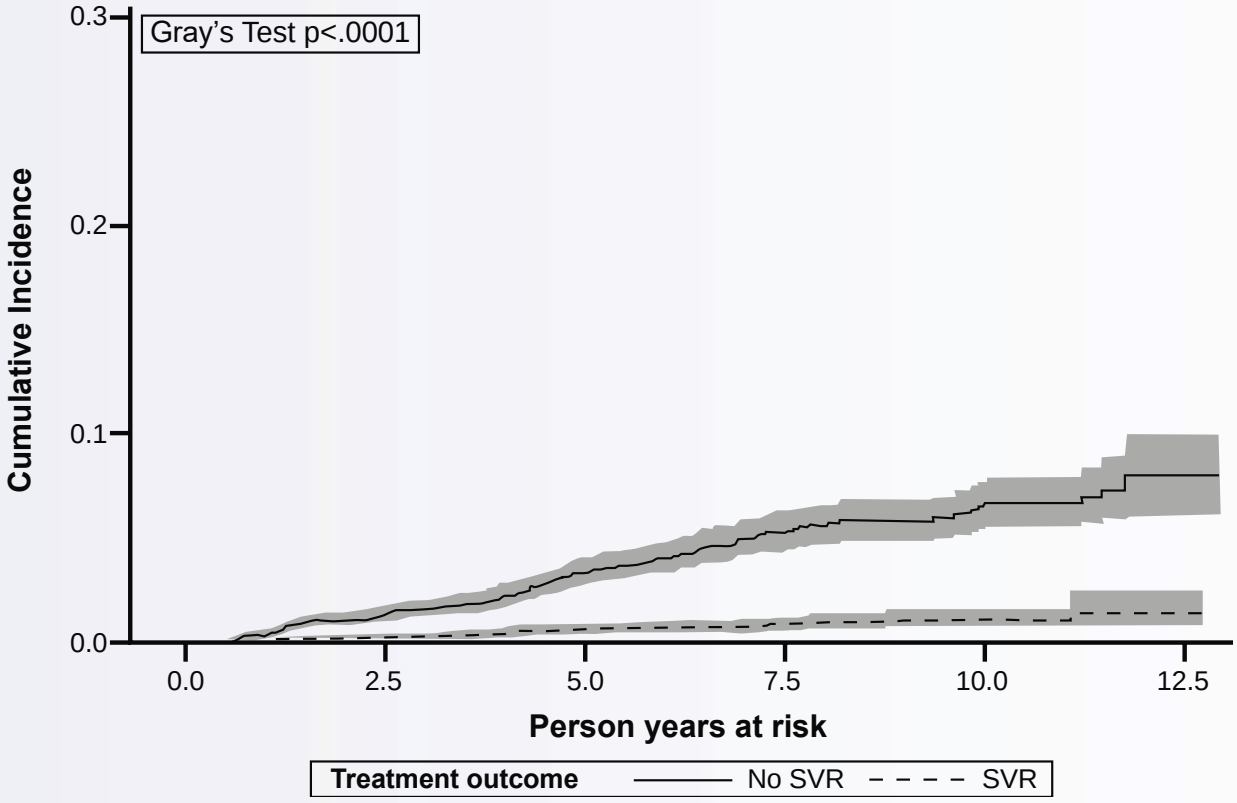
- Screen for HBV
- Ethanol use
- Screen for HIV
- Fatty Liver
  - 30% of patients who achieve SVR have fatty liver that can progress over time to NASH
  - Include in NASH clinical trials

Phase 3 Platform

- Shortening duration
  - <8 weeks: very selective population with lower complexity
- Why do we need shorter therapy?
  - Adherence improvement?
    - Is there a difference between 8 and 12 weeks?
  - Provider pool
    - More patients can get treated
- Use shortened therapy?
  - If you are willing to accept complexity of identifying a short duration subject, you could treat with a very short duration knowing you have salvage therapy
  - More simplistic model that minimizes mistakes is more realistic

SVR Substantially Reduces, But Does Not Eliminate, the Risk of HCC

Cumulative HCC Incidence by SVR



- HCC incidence rate (IR) was 1.1/1000 person-yr (PY) in the SVR and 7.2/1000 PY in the no-SVR groups.
- The IR was higher among those with cirrhosis at treatment (SVR: 6.4, no-SVR: 21.0/1000 PY).
- In those with SVR, cirrhosis (HR=3.16), older age (50-59 yr: HR=4.73; 60+yr: HR=5.44 vs. ≤49 yr), and being male (HR=3.3) were associated with higher HCC risk.

Janjua N, et al. Abstract #175, AASLD 2016.

Do DAA-treated Patients Have a Higher Rate of Liver Cancer Compared to Interferon-treated Patients?

- Not enough information thus far
- “SVR is SVR”
- SVR decreases risk of liver related mortality and liver cancer

Three Treatment Outcomes to Consider

- Clinical Outcome
  - SVR (cure, surrogate of survival)
  - Clear evidence
- Patient Reported Outcome
  - Surrogate of patient experience
- Economic Outcome
  - Surrogate for resource utilization

Patient Report Outcomes Improvement with SOF/VEL vs Placebo (ASTRAL-1)

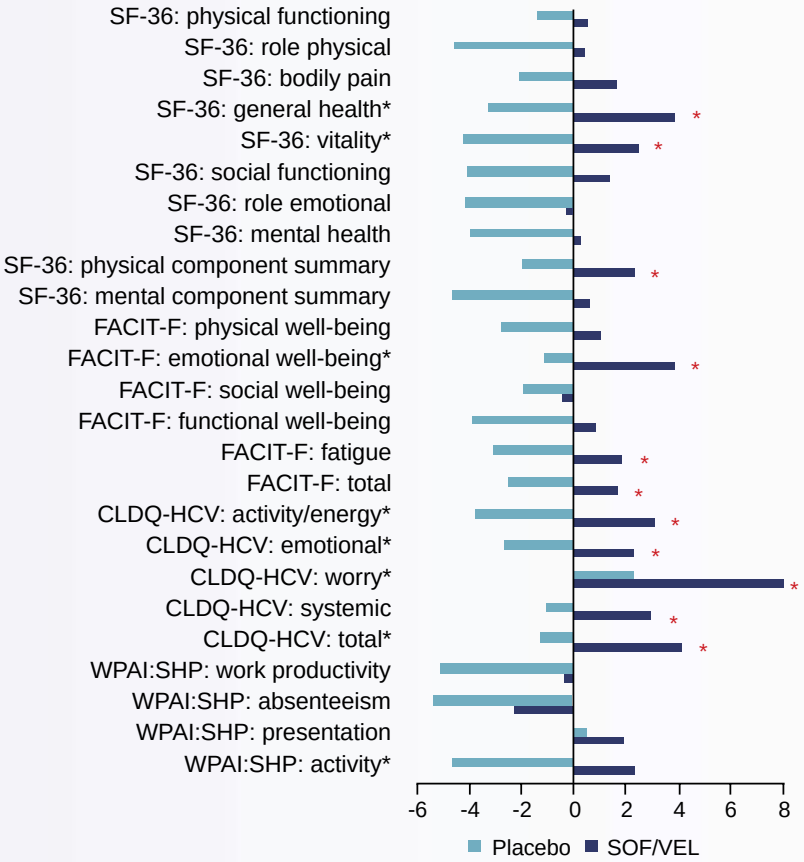
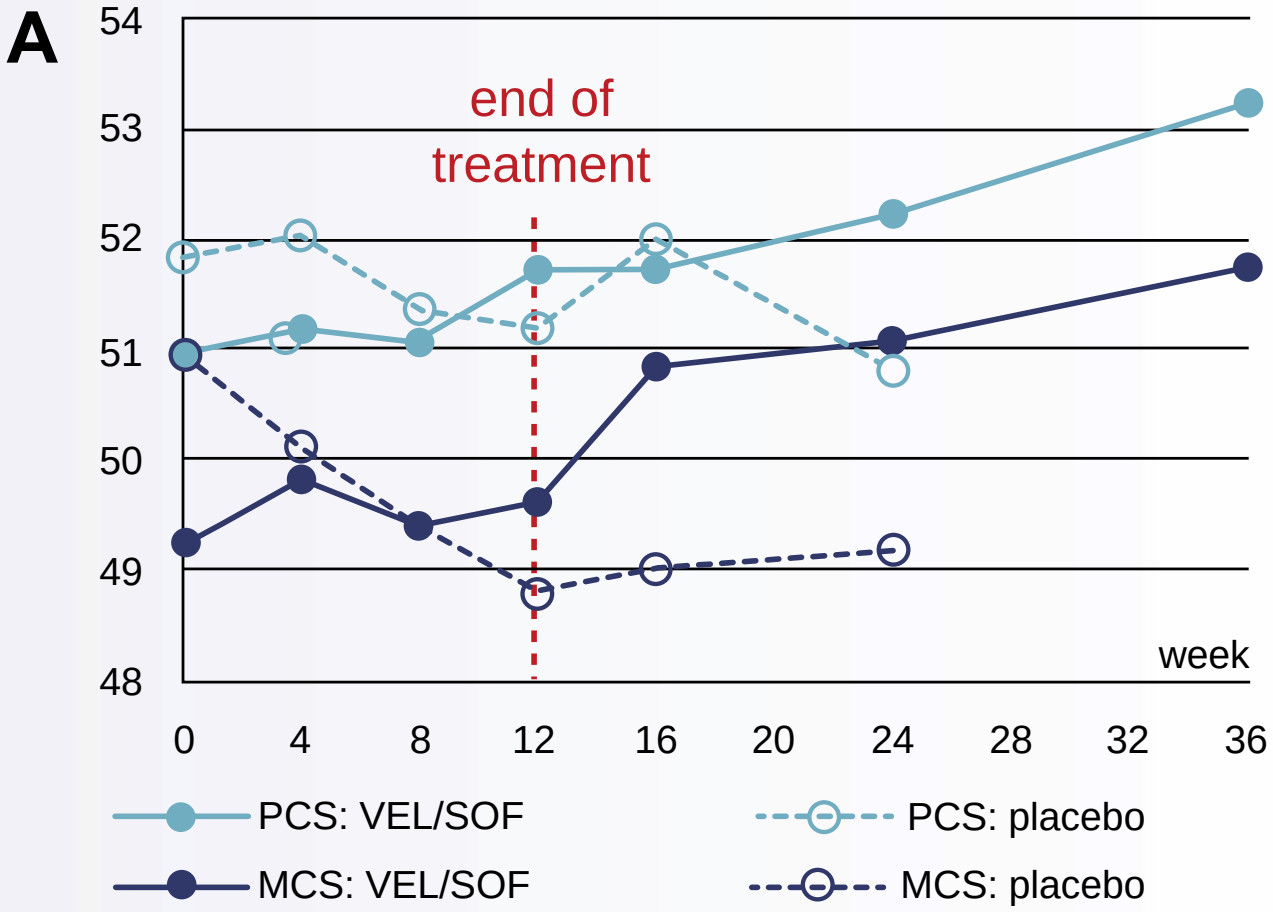


Fig. 2. Treatment-emergent changes in PROs in patients after receiving SOF/VEL and placebo for 12 weeks. A grey asterisk indicated statistically significant difference between the study arms (p <0.005); a red asterisk indicates statistically significant change from the baseline level (difference from zero). All PROs were transformed to a uniform 0-100 scale. A zero height bar indicates no change from the baseline level.

Younossi Z, et al. *J of Hepatology*, 2016: 65:1, 33-39.

Long-term Improvement in PROs After SOF/VEL Treatment (ASTRAL-1)



PCS, physical component summary of SF-36; MCS, mental component summary of SF-36

Younossi Z, et al. *J of Hepatology*, 2016: 65:1, 33-39.

Long-term Value of Cure Compared to no Treatment for HCV GT1 at Different QALY Thresholds

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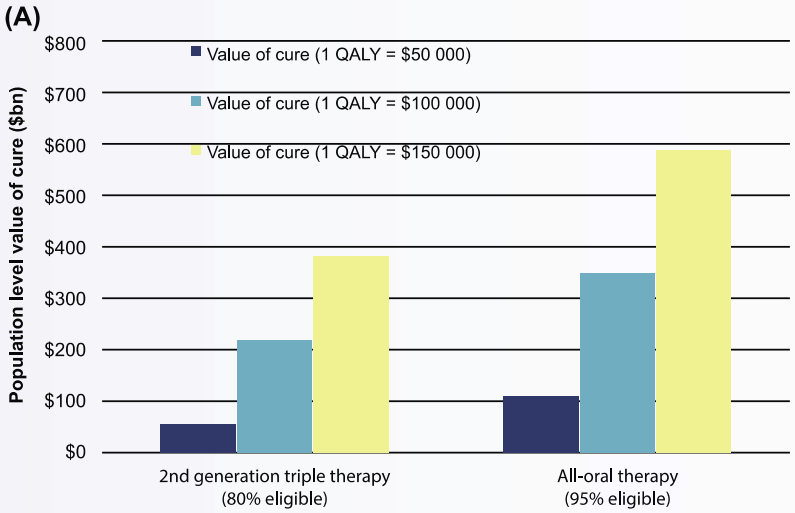
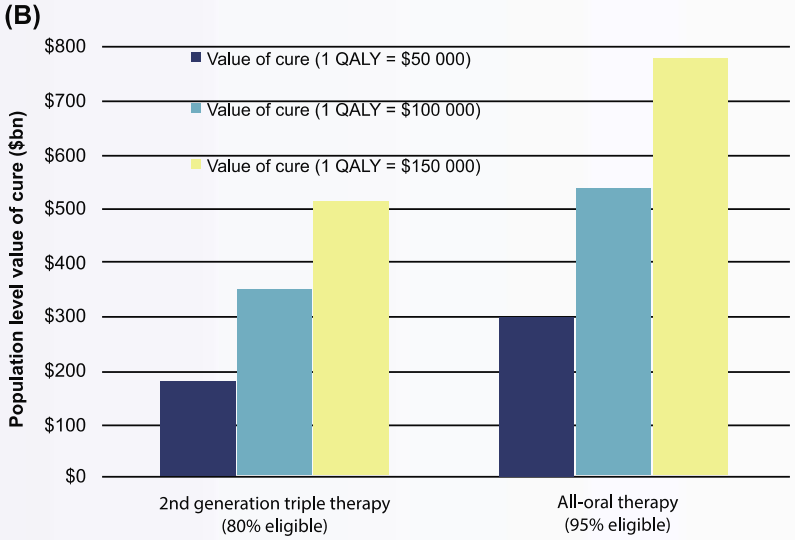
Drug Costs Only



Total Lifetime Costs

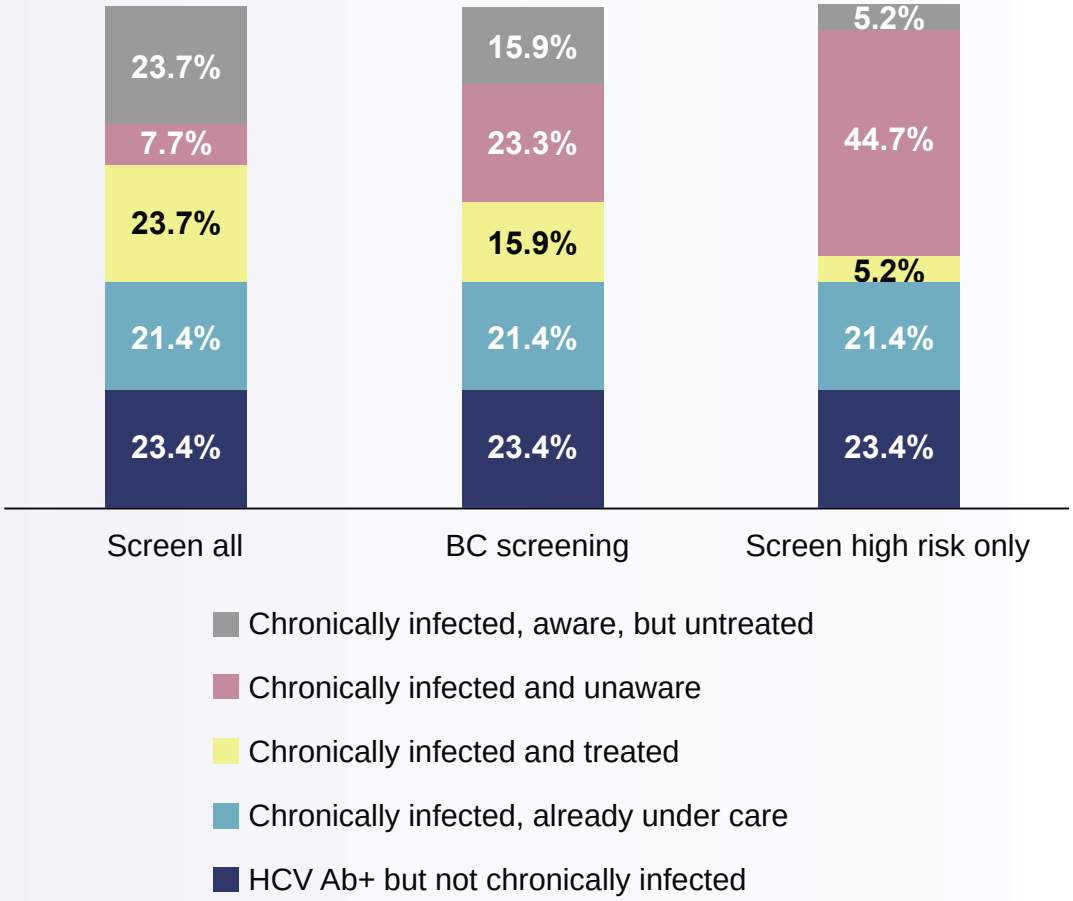


QALY = Quality Adjusted Life Year

Younossi Z, et al. *Liver International*. 2016 Nov 2. doi: 10.1111/liv.13298.

Markov Model: Hepatitis C Screening Options in US

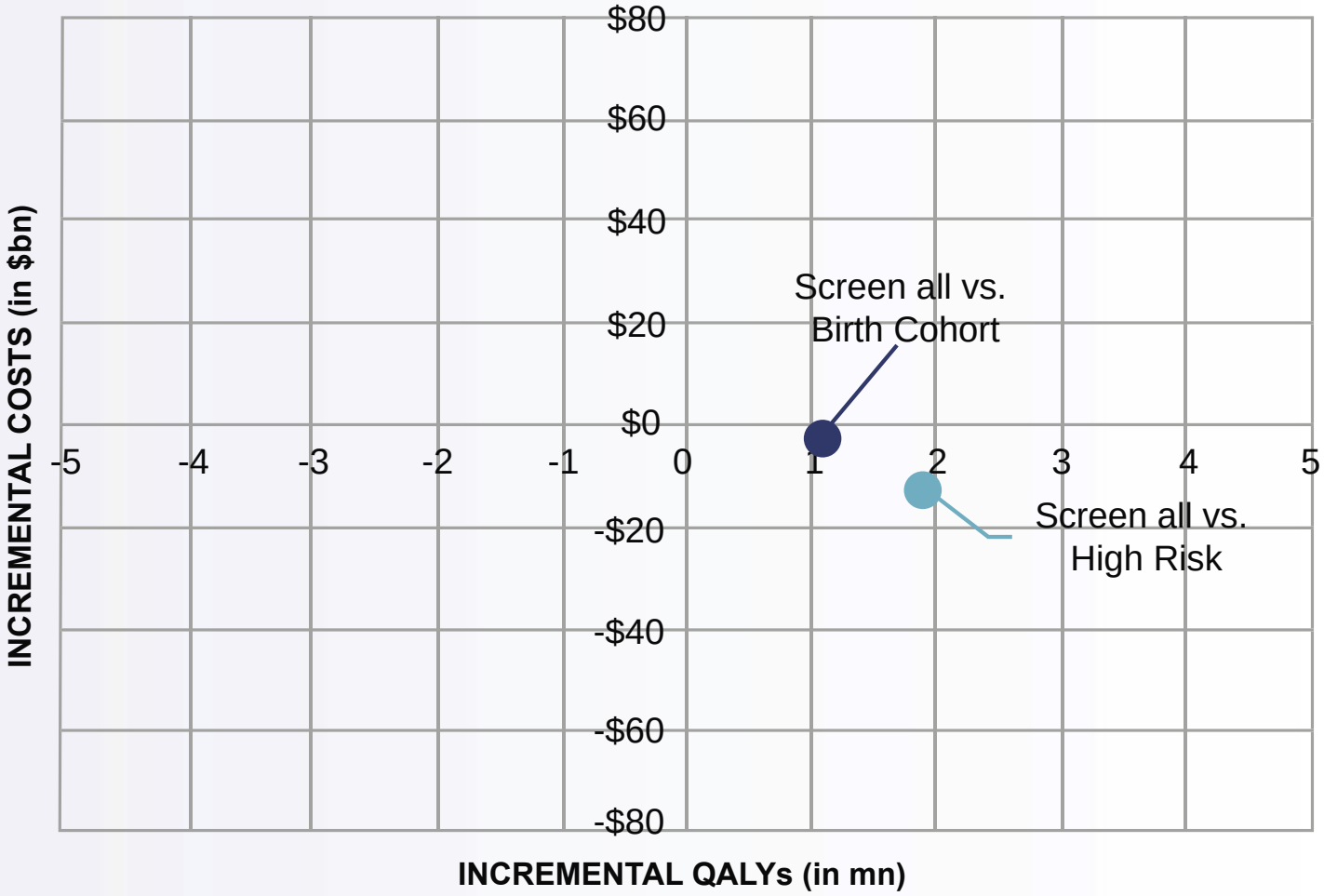
Figure 1. Model Results: Awareness and Treatment Status of Infected Patients, by Screening Strategy



Younossi Z, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 745.

Screening All US Population is Most Cost Effective

Figure 3. Model Results: Cost-effectiveness of the 'Screeb All' Strategy



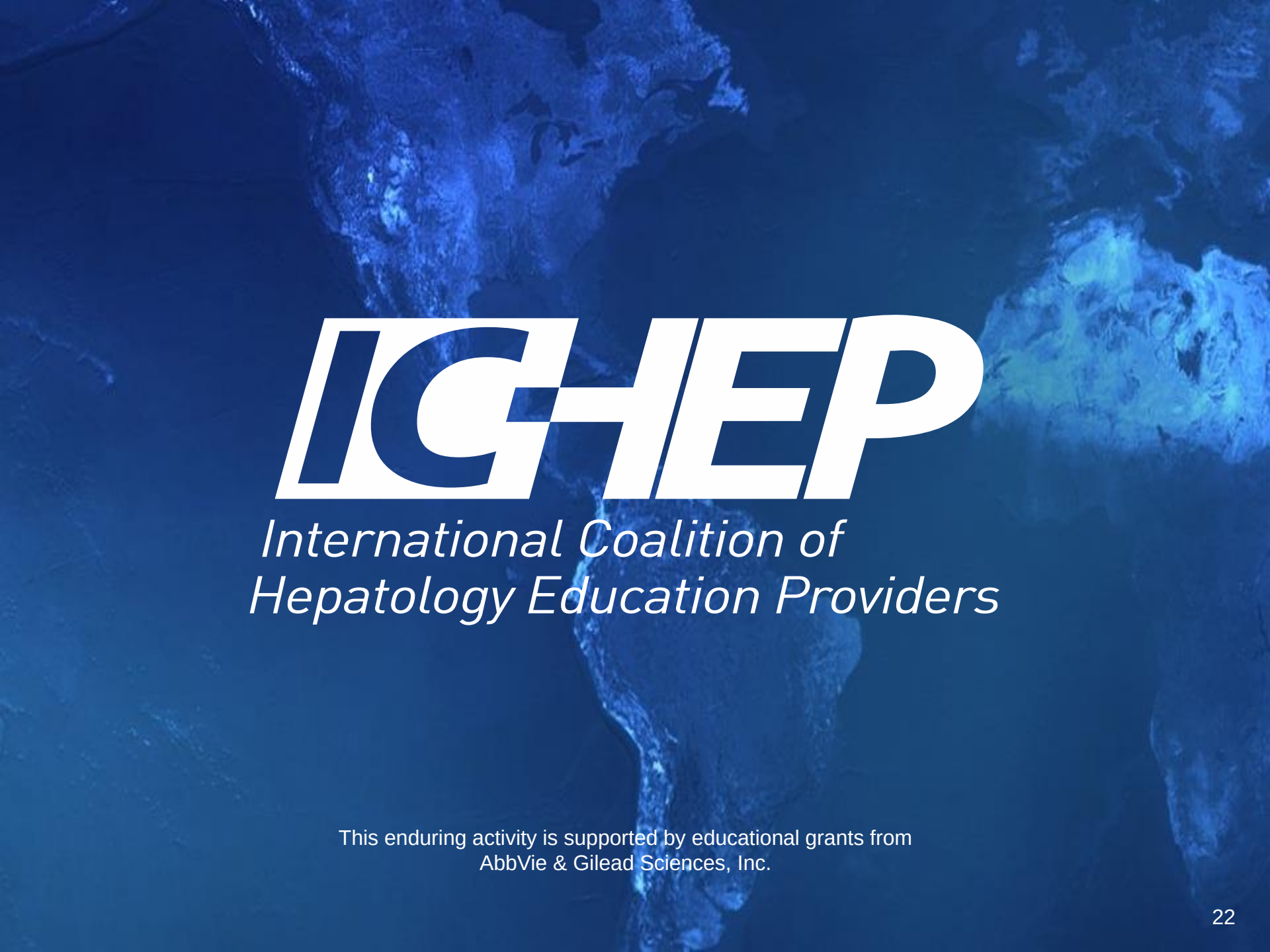
Younossi Z, et al. 67th AASLD; Boston, MA; November 11-15, 2016; Abst. 745.

Patient Management Post SVR

- Vaccination: Hepatitis A and B
- Counseling on alcohol consumption
- Recognition of cirrhosis
  - Very well compensated cirrhotics may be without lab triggers
  - Lifestyle choices may increase risk of progressive liver disease

Chronic Hepatitis C is a Systemic Disease

- Extrahepatic manifestations such as
  - Diabetes
  - Cryoglobulinemia
  - Fatigue
- Patient with mild disease likely will benefit beyond SVR
- Cost of extrahepatic manifestations to society is substantial



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