Hepatitis C / HIV & Aging

New Drugs for Old (er) People

EATG Berlin 2016

Tracy Swan

Treatment Action Group

OVERVIEW

Aging & the liver

Aging & HCV

Aging & HIV/HCV

HIV & polypharmacy

Drug-drug interactions

HIV/HCV clinical trials in people >50

New drugs in the pipeline

GLOSSARY

DAA = direct-acting antivirals; HCV drugs

DDI = drug-drug interaction

HCC= hepatocellular carcinoma; liver cancer

HCV = hepatitis C virus

NAFLD = non-alcoholic fatty liver disease; excessive fat in the liver- can lead to NASH

NASH = excessive fat in the liver, with inflammation and cell damage

RAV = resistance-associated variant

AGING & THE LİVER
BAD NEWS & GOOD NEWS

- Vicious cycle: stress/response ➔ liver cell senescence (to reduce cancer risk) ➔ liver dysfunction

- Increases vulnerability to hepatic metabolic disorders (NAFLD, NASH) that lead to cirrhosis and HCC

BUT: HCC incidence dramatically decreases among people >70

Hoare et al; J Hepatol 2010; Sheedfar et al; Aging Cell 2013

AGİNG & HCV

Liver damage from HCV worsens w/aging

- Thymus slowdown
- Duration of infection
- Lifestyle
- Common comorbidities (steatosis, obesity, metabolic disorders)

For women, menopause-related estrogen loss increases vulnerability to NAFLD, HCC and liver damage from HCV

Brady; World J Gastroentero 2015

HCV EPİ

In the US and Western Europe, ~70% of HCV cases among people born between 1945 -- 1965

Saab et al; Hepatology 2016

HIV/HCV & AGİNG

Menopausal women with HIV//HCV are at risk for rapidly-worsening liver disease

Aging increases the risk of drug-related liver injury -- and older people are likely to be taking more medications

Some ARVs can be hard on the liver, especially “d” drugs, AZT, nevirapine, tipranavir, maraviroc

Nasta; Acta Biomend 2011; Sesion, Deckx; AIDS Rev 2015; Tajiri, Shimizu; World J Gastroenterlo 2013

HIV AND POLYPHARMACY (USE OF ≥5 MEDİCATİONS)

More likely in HIV-positive (vs. HIV-negative) people

Common among HIV-positive people who are >50 years old

Prescriptions for medications with DDIs or contraindications more likely for HIV-positive people who are >50 years old

Gimeno-Gracia et al; HIV Clin Tirals 2015; Holtzman et al; J Gen Intern Med 2013

DRUG-DRUG İNTERACTİONS

HIV-positive people may be on many other medicines that interact with DAAs (statins, proton pump inhibitors, anti-depressants, cardiovascular drugs)—important to check them and discuss with your doctor

DAAs may interact with recreational drugs

	SIM	DCV	SOF	SOF/ LDV	3D
Amphetamine	•	•	•	•	•
Cannabis	•	•	•	•	•
Cocaine	•	•	•	•	•
Diamorphine	•	•	•	•	•
Diazepam	•	•	•	•	•
Gamma-hy-droxybutyrate	•	•	•	•	•
Ketamine	•	•	•	•	•
MDMA (ecstasy)	•	•	•	•	•
Methamphetamine	•	•	•	•	•
Phencyclidine (PCP)	•	•	•	•	•
Temazepam	•	•	•	•	•

EASL 2015 http://www.easl.eu/medias/cpg/HEPC-2015/Summary.pdf

DRUG-DRUG İNTERACTİONS: DAAS & ART

Drug-drug interactions with HCV DAAs and ARVs (especially boosted protease inhibitors and efavirenz) may complicate HCV treatment

Certain ARVs are less likely to interact with DAAs (raltegravir, dolutegravir and most NRTIs)

This has implications for HIV and HCV treatment access

		SIM	DCV	SOF	SOF/ LDV	3D
NRTIs	Abacavir	•	•	•	•	•
	Didanosine	•	•	•	•	•
	Emtricitabine	•	•	•	•	•
	Lamivudine	•	•	•	•	•
	Stavudine	•	•	•	•	•
	Tenofovir	•	•	•	•	•
	Zidovudine	•	•	•	•	•
NNRTIs	Efavirenz	•	•	•	•*	•
	Etravirine	•	•	•	•	•
	Nevirapine	•	•	•	•	•
	Rilpivirine	•	•	•	•*	•
Protease inhibitors	Atazanavir; atazanavir/ritonavir	•	•	•	•*	•
	Darunavir/ritonavir; darunavir/cobicistat	•	•	•	•*	•
	Fosamprenavir	•	•	•	•*	•
	Lopinavir	•	•	•	•*	•
	Saquinavir	•	•	•	•*	•
Entry/ Integrase inhibitors	Dolutegravir	•	•	•	•	•
	Elvitegravir/cobicistat	•	•	•	•*	•
	Maraviroc	•	•	•	•	•
	Raltegravir	•	•	•	•	•

EASL 2015 http://www.easl.eu/medias/cpg/HEPC-2015/Summary.pdf

SAFETY, EFFICACY AMONG OLDER PEOPLE İN HCV CLİNİCAL TRİALS (FROM DAA PRESCRİBİNG İNFORMATİON)

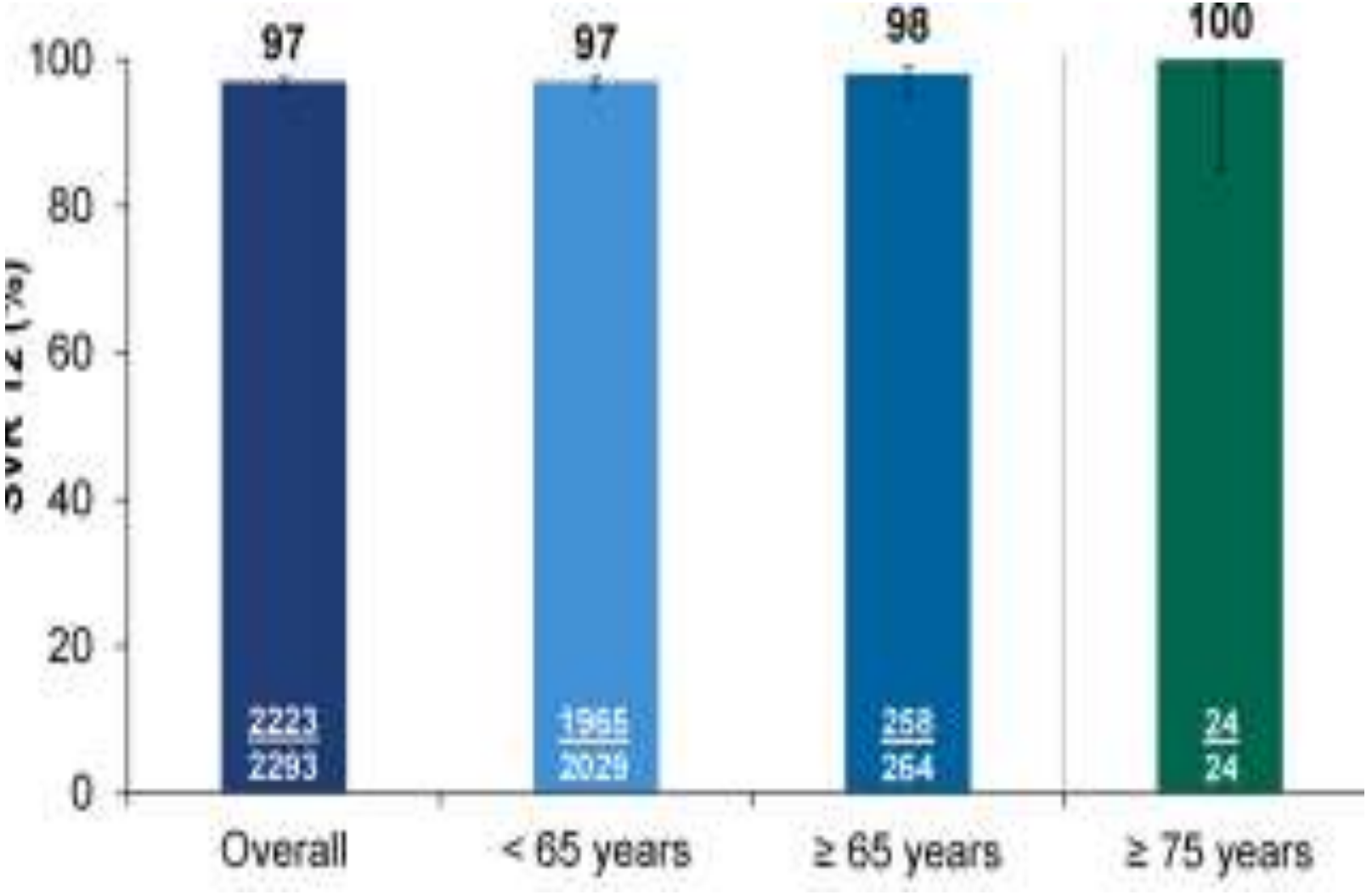
- **DAKLINZA:** 83 people (or 7%) ≥65 **No difference in safety, effectiveness**

- **HARVONI** : 264 people (or 12%) ≥65 **No difference in safety, effectiveness (98% SVR, discontinuation rates similar across age groups) but more AEs from RBV in older people**

- **OLYSIO: did not include "sufficient numbers" to determine difference in response**

Saab et al; Hepatology 2016

HARVONI: SVR BY AGE



Saab et al; Hepatology 2016

SAFETY, EFFICACY AMONG OLDER PEOPLE İN HCV CLİNİCAL TRİALS (FROM DAA PRESCRİBİNG İNFORMATİON)

- **VIEKIRA PAK**: 174 (8.5%) ≥65
  No difference in safety, effectiveness

- **SOVALDI :** 90 people (or 7.5%) ≥65
  No difference in effectiveness (safety not mentioned)

- **ZEPATIER:** 187 people (or 16%) ≥65 **higher drug concentrations and risk of late ALT elevations (vs. within first 4 weeks of treatment)**

AVERAGE AGE İN HIV/HCV CLİNİCAL TRİALS

ION-4 (Harvoni) median age: **52 (48-58)**

TURQUOISE-1 (Vikerax /Exviera) mean age: **50.9**

ALLY-2 (Sovaldi and Daklinza)**: up to 75;** median age varied by treatment group**; 51 to 57**

C-EDGE coinfection (Zepatier)**: average age 49**

Naggie et al; NEJM 2015; Rockstroh et al; AASLD 2015; Sulkowski et al; JAMA 2015; Wyles et al; NEJM 2015

ZEPATIER
GRAZOPREVİR + ELBASVİR

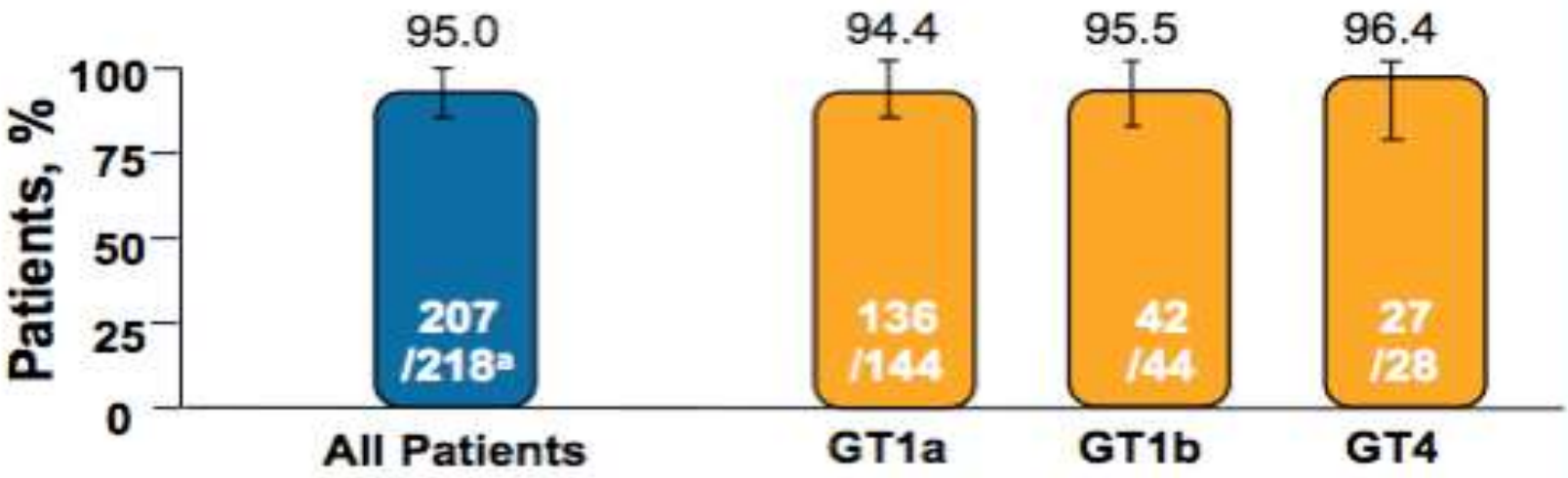
FDA-approved for genotypes 1 and 4, for 12 or 16 weeks, with or without RBV

Subtyping needed; Baseline NS5A RAV testing recommended in G1A

Trials in HIV/HCV, people with renal impairment, treatment-experienced (with an HCV protease inhibitor), cirrhosis

C-EDGE COİNFECTİON: 12 WEEKS O F ZEPATIER, HIV/HCV G1 AND G4, HCV TREATMENT-NAÏVE

Figure 2. SVR12 (full analysis set).

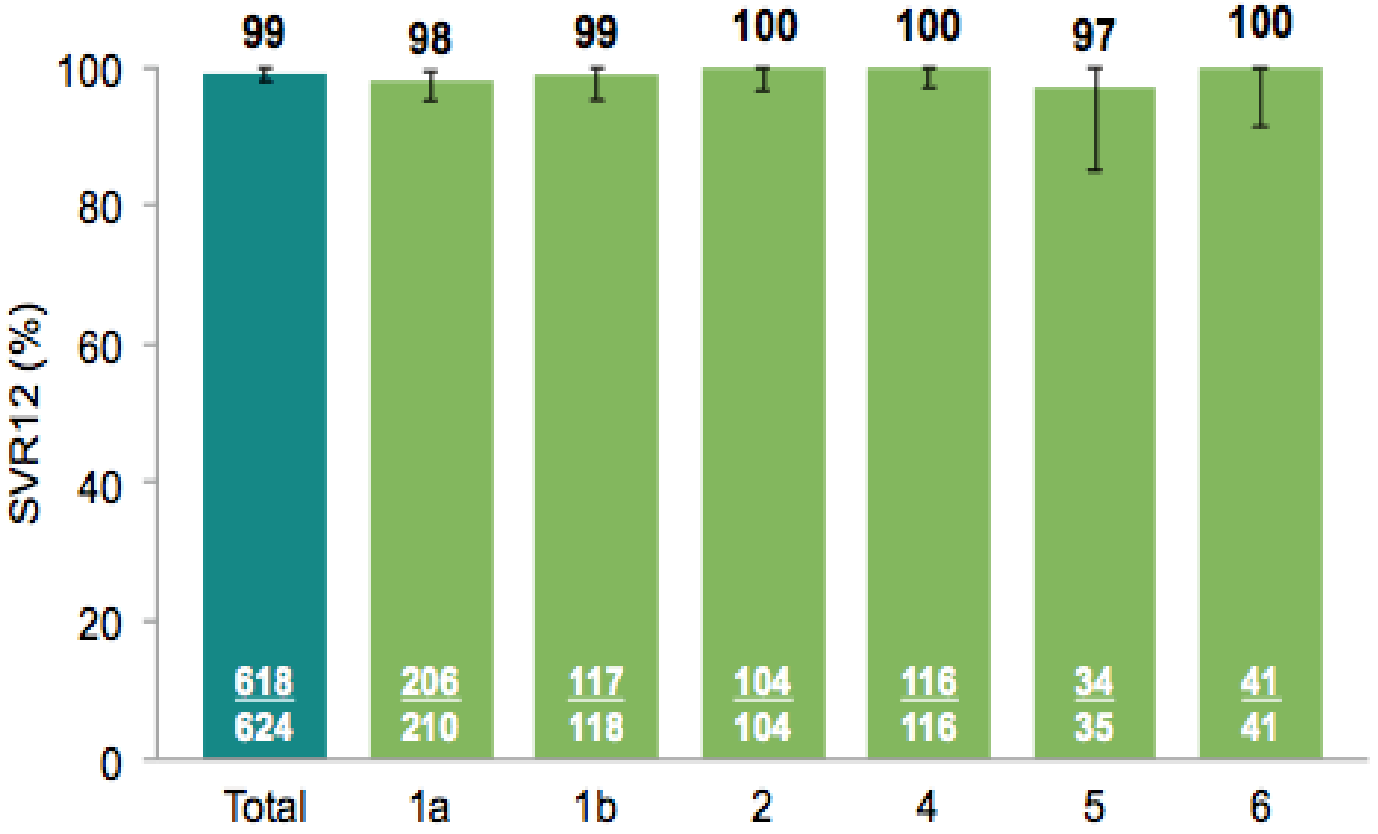


LTFU or discontinued unrelated to VF	4	3	1	0
Breakthrough	0	0	0	0
Relapse	6	4	1	1
Reinfection	1	1	0	0

ARVS: dolutegravir, raltegravir, rilpivirine

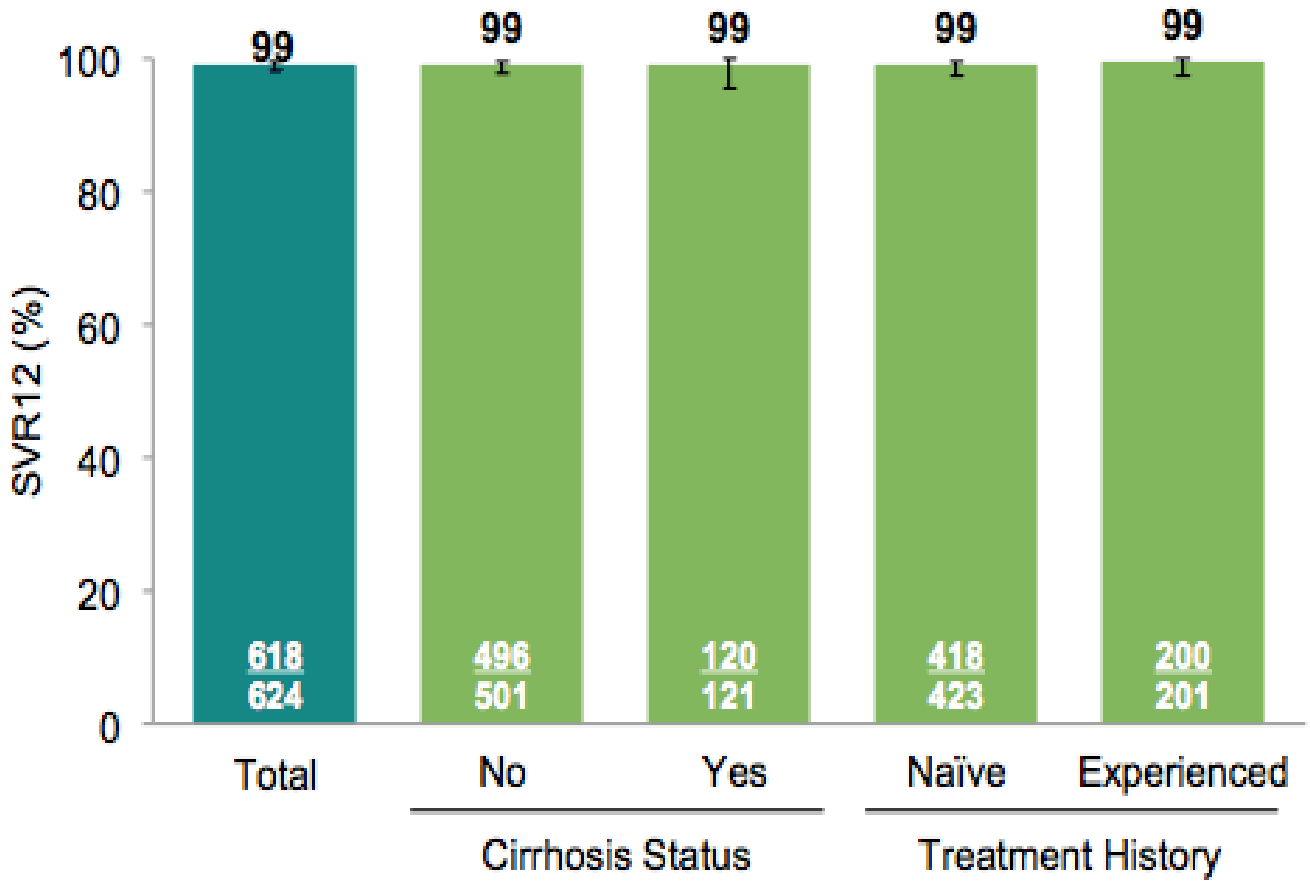
Rockstroh et al; AASLD 2015

ASTRAL-1: SOF + VELPATASVİR 12 WEEKS, GENOTYPES 1, 2, 4, 5, 6



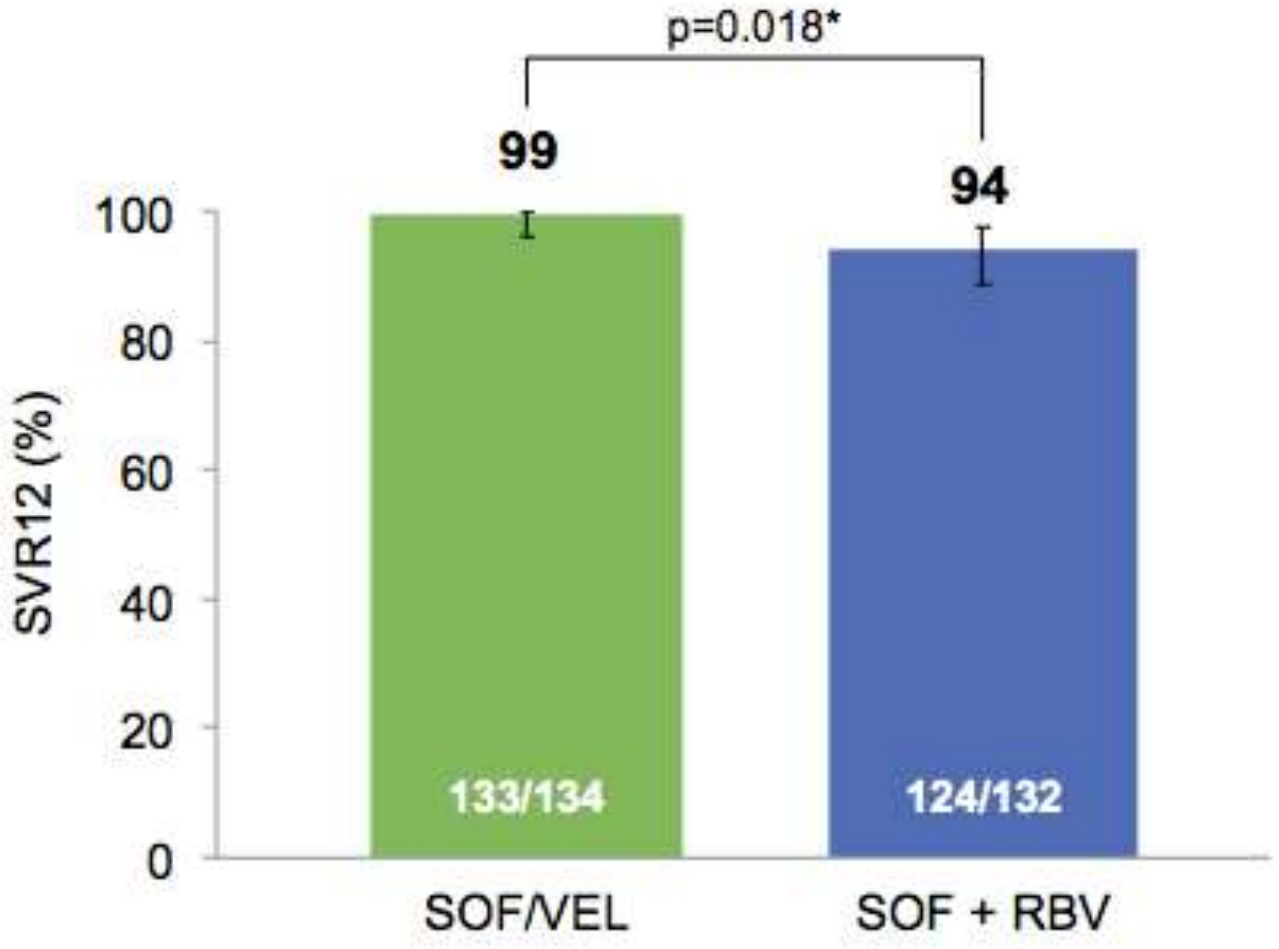
Feld et al; AASLD 2015

ASTRAL-1: CURE RATES
BY CİRRHOSİS AND TREATMENT HİSTORY



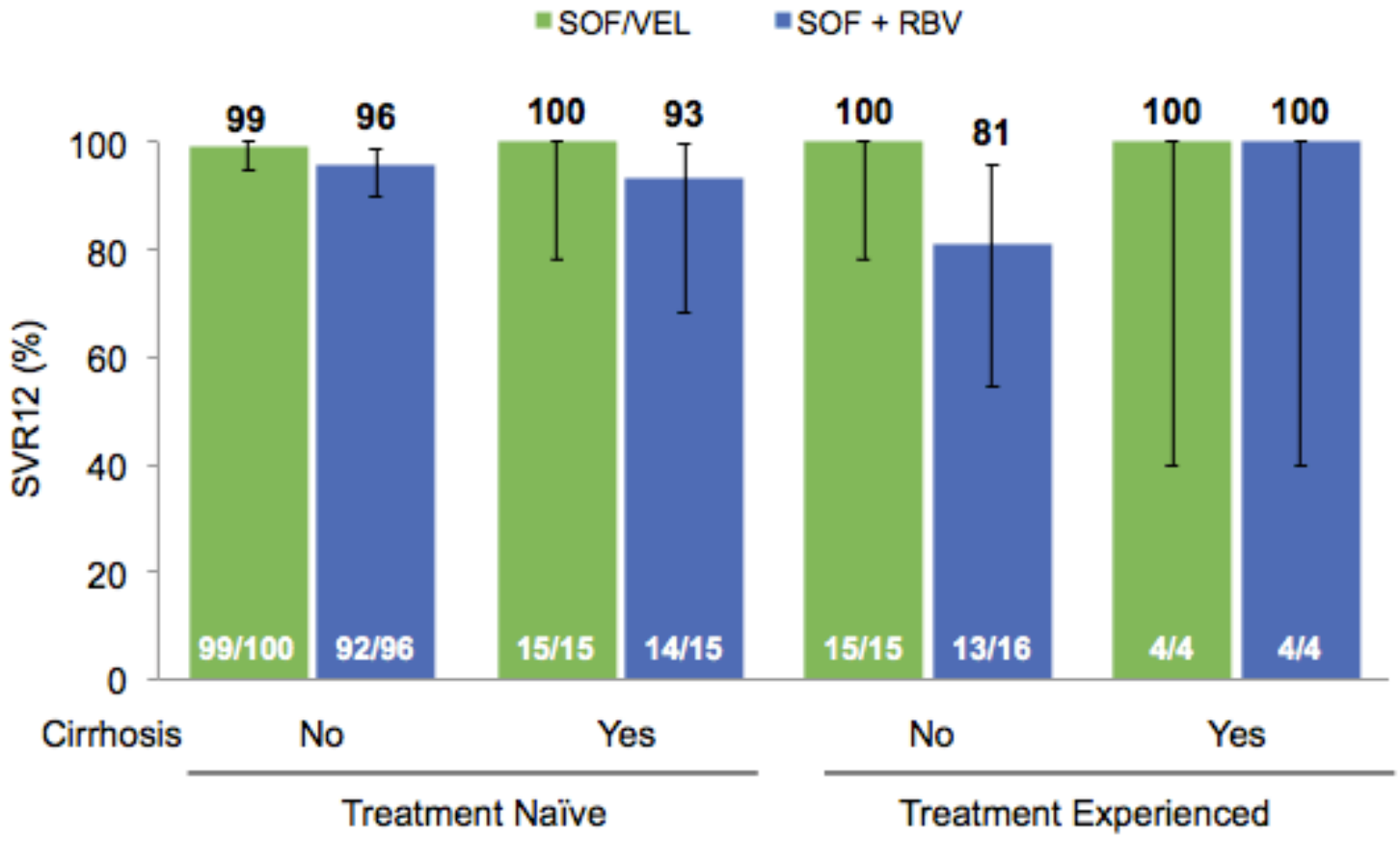
Feld et al; AASLD 2015

ASTRAL-2: SOF + VELPATASVIR, 12 WEEKS VS. 24 WEEKS OF SOF/RBV, G2



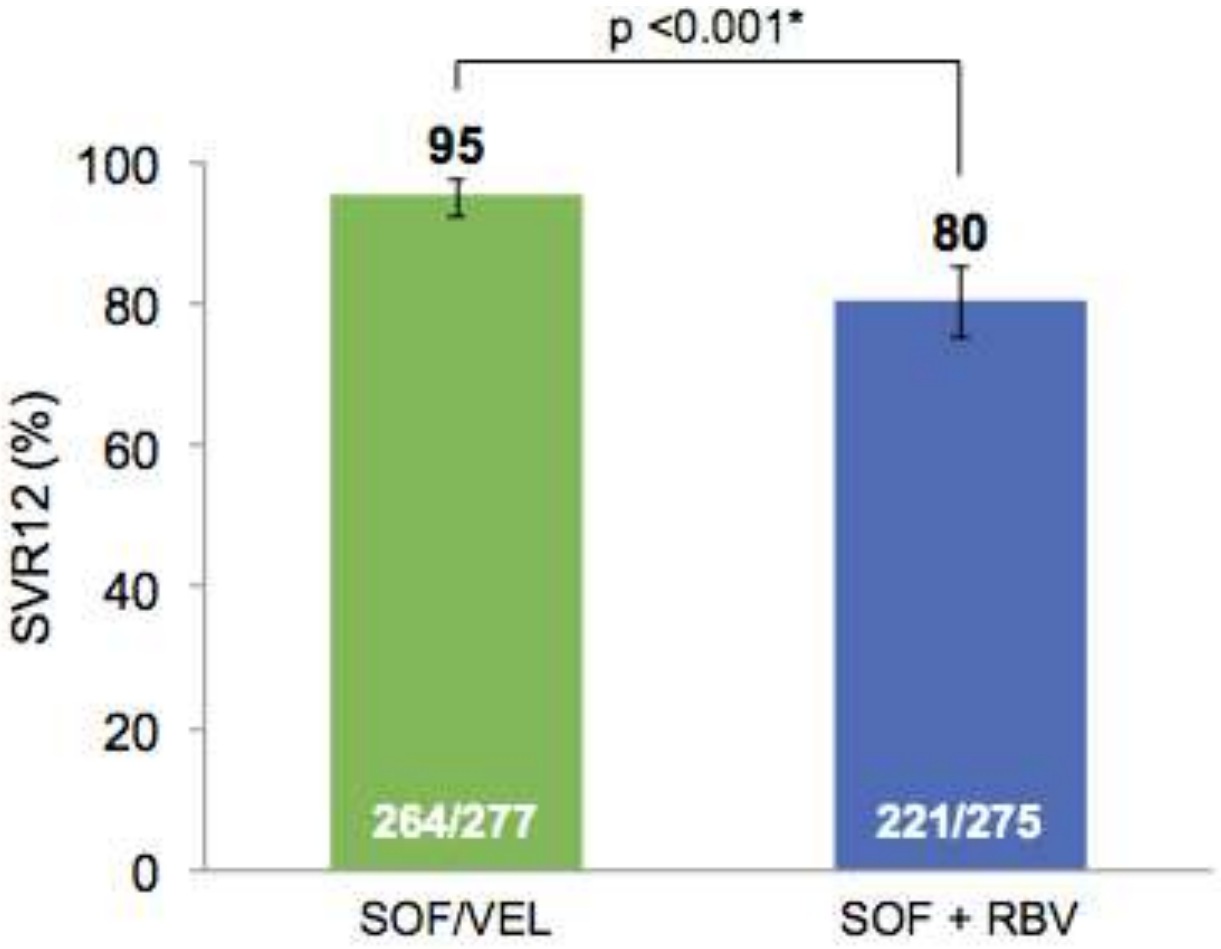
Sulkowski et al, AASLD 2015

ASTRAL-2: CURE RATES BY CİRRHOSİS AND TREATMENT HİSTORY



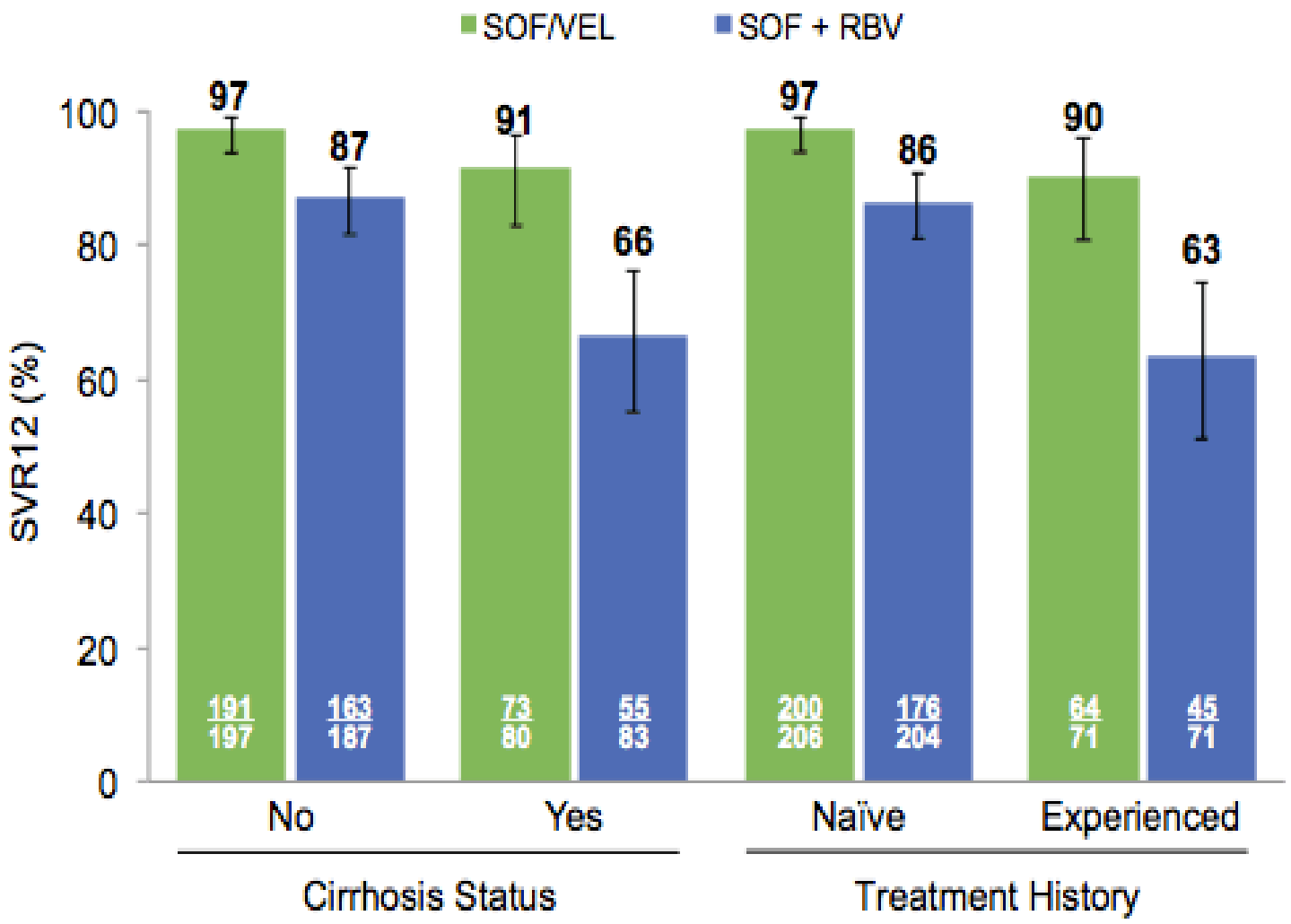
Sulkowski et al, AASLD 2015

ASTRAL-3: SOF + VELAPTASVIR, G3
FOR 12 WEEKS VS. 24 WEEKS OF SOF + RBV



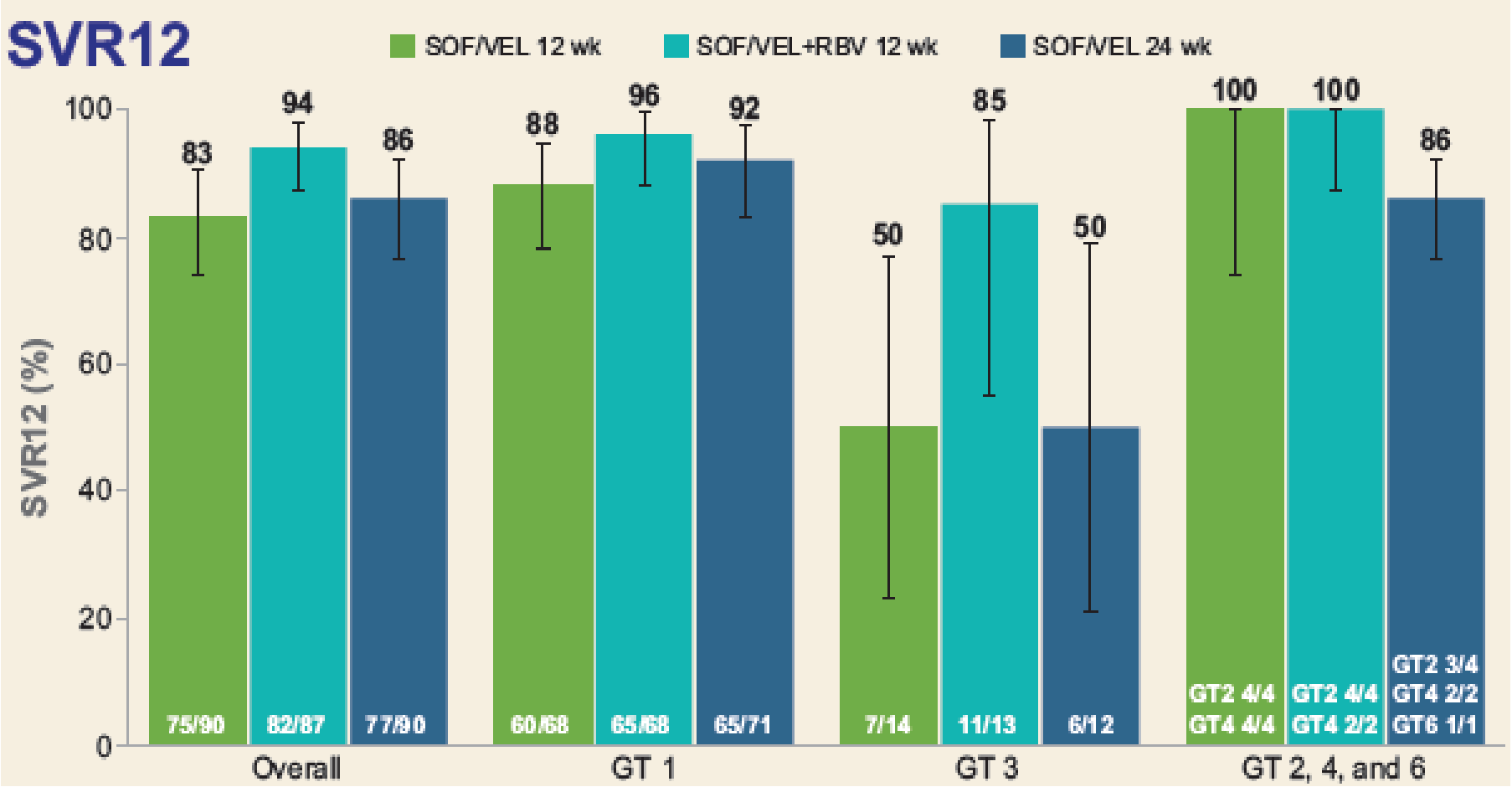
Mangia, et al; AASLD 2015

ASTRAL-3: SOF + VELAPTASVIR, G3
FOR 12 WEEKS VS. 24 WEEKS OF SOF + RBV



Mangia, et al; AASLD 2015

ASTRAL-4: SOF + VELPATASVİR FOR 12 WEEKS (± RBV) OR 24 WEEKS, İN DECOMPENSATED CİRRHOSİS



Charlton, et al; AASLD 2015

WHAT'S NEXT

DOUBLES:

ABBVIE: NS5A + PROTEASE

TRIPLETS:

MERCK: NS5A + PROTEASE + NUCLEOTIDE

GILEAD NS5A + PROTEASE + SOF

How much better can it get?