

Hepatitis C Virus (HCV) Treatment

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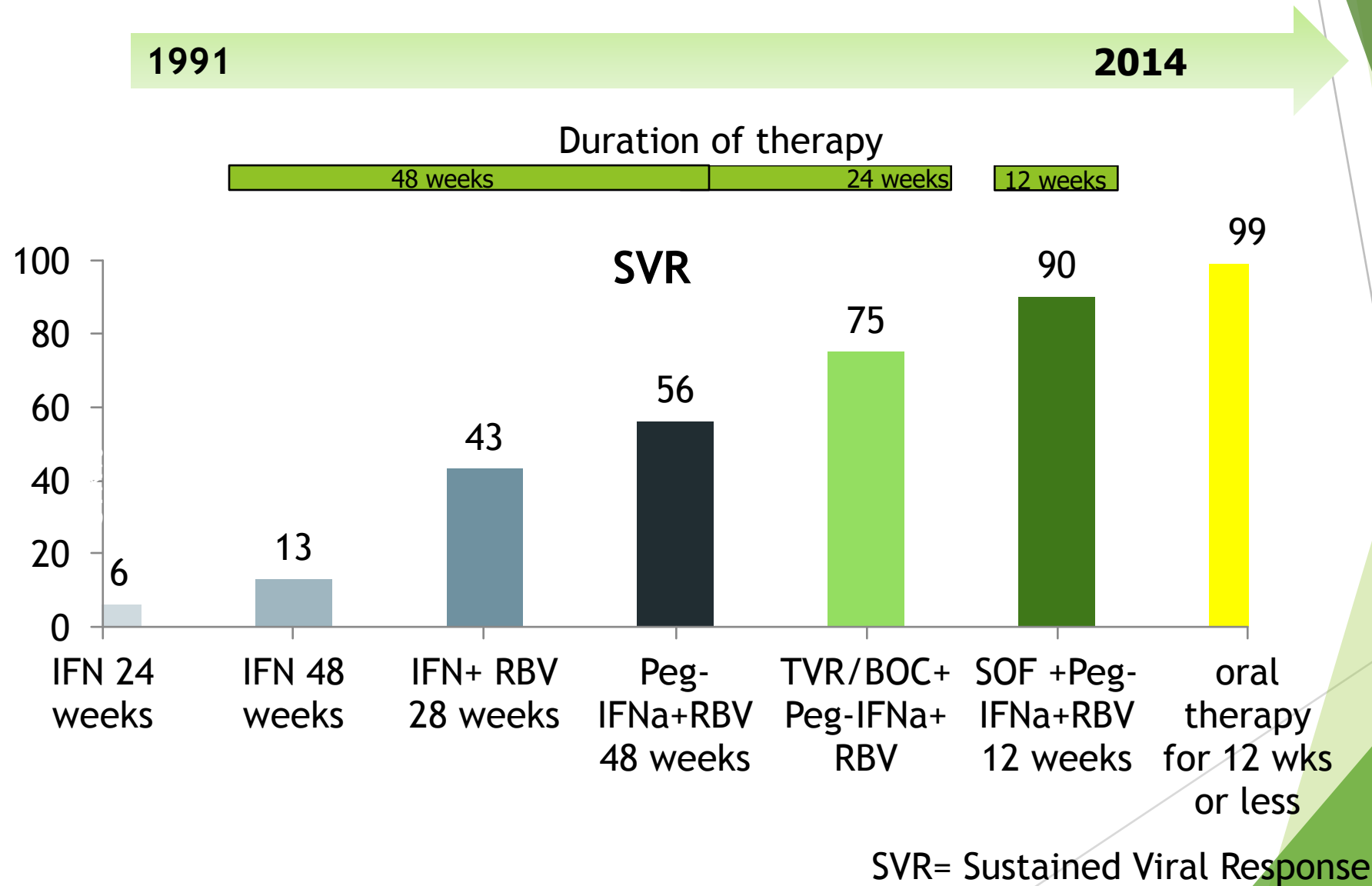


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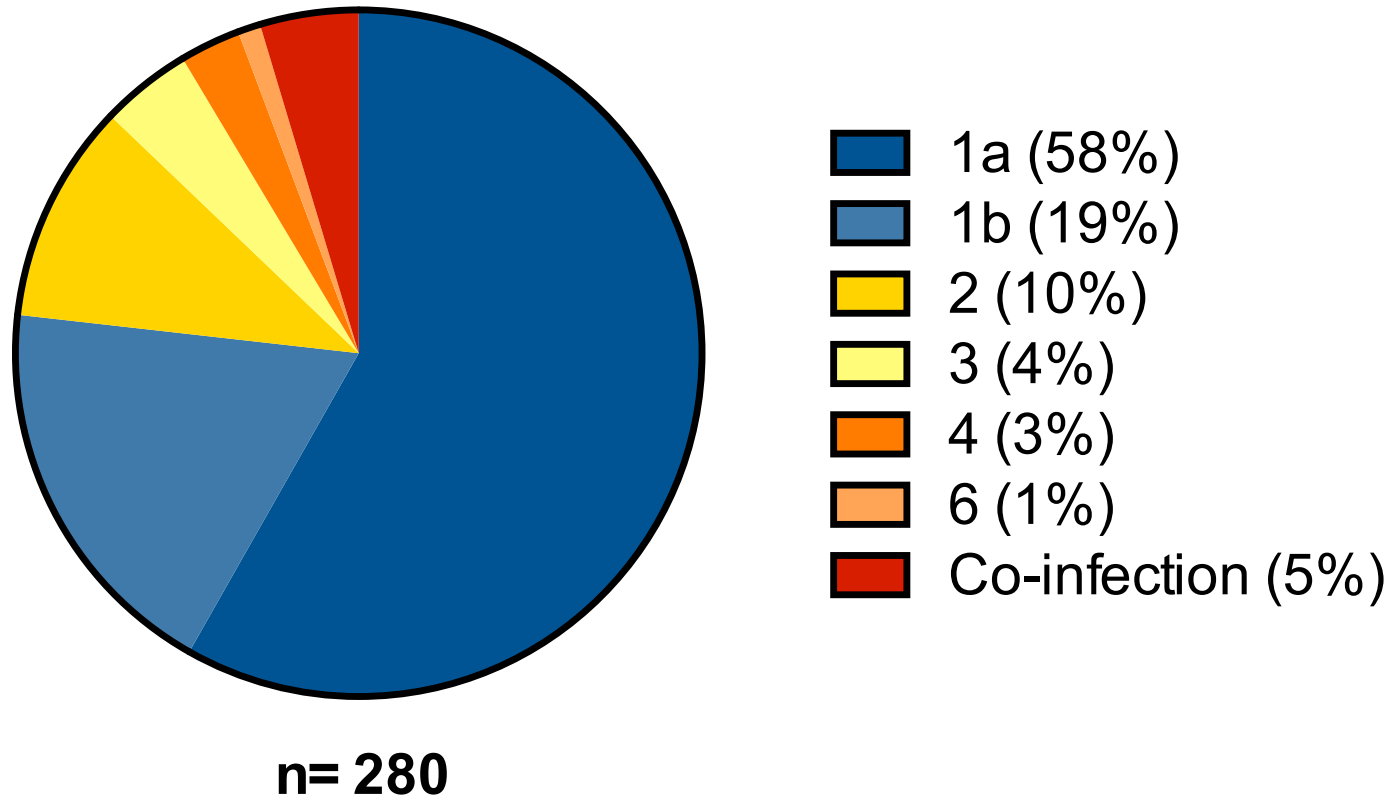
Learning Objectives

- ▶ List common classes of direct-acting, all-oral drug medications for HCV
- ▶ Define how to measure a sustained viral response
- ▶ List 3 HCV treatments that can be used for genotype 1
- ▶ Identify general patterns of differences in treatment based on genotype, presence of cirrhosis, and prior anti-HCV treatment
- ▶ List several common side effects of HCV medications

Evolving HCV Treatment Paradigm



HCV Genotype 1a: Most common in US and at Parkland



Directly Acting Antivirals

- ▶ **NS5A polymerase inhibitors (-asvir)**
 - ▶ High potency
 - ▶ Pan-genotypic, but inhibition by genotype may vary by molecule
 - ▶ Intermediate **barrier** to resistance (Barrier is how many mutations it takes to develop resistance; low barrier is 1 mutation and high barrier is multiple mutations)
- ▶ **NS5B polymerase inhibitors (-busvir)**
 - ▶ Intermediate potency
 - ▶ Some are pan-genotypic, others not
 - ▶ High barrier to resistance, but some are not
- ▶ **NS3/4A Protease Inhibitors (-evir)**
 - ▶ High potency
 - ▶ Limited genotypic coverage
 - ▶ Low barrier to resistance

Combination Therapy

- ▶ Because of risk of HCV developing resistance, combination therapy should be used when treating hepatitis C

Definition of Cure

- ▶ A person is considered to be cured of hepatitis C if the HCV RNA is undetectable 12 weeks after the completion of therapy

Sofosbuvir/Ledipasvir: Genotype targets

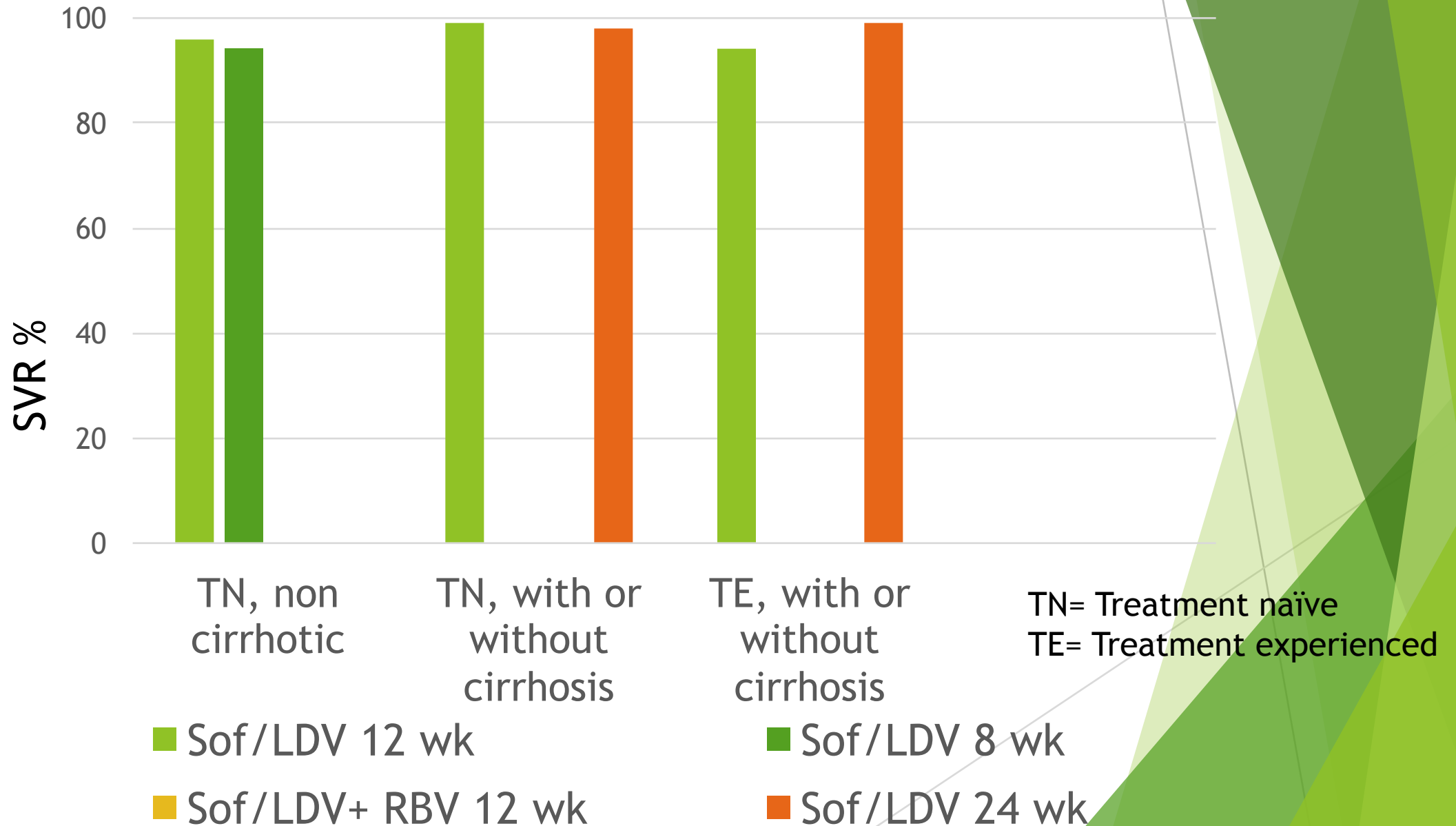
- ▶ Sofosbuvir = nucleoside NS5B inhibitor and pan-genotypic
- ▶ Ledipasvir = NS5A inhibitor with activity for genotypes 1, 4, 5, and 6
- ▶ Combination for genotypes 1, 4, 5, and 6
- ▶ One pill once a day
- ▶ Can not use with Cr Cl <30 ml/min



Sofosbuvir/Ledipasvir: Duration of Therapy

- ▶ Treatment naïve or non-cirrhotic treatment experienced
 - ▶ 12 weeks
 - ▶ Except: 8 weeks for genotype 1 with HCV RNA <6 million and early stage disease
 - ▶ Risk of relapse if patient has advanced fibrosis
- ▶ Treatment-experienced cirrhotic
 - ▶ 24 weeks
 - ▶ 12 weeks if you add ribavirin

Sofosbuvir/Ledipasvir: Efficacy



Sofosbuvir/Ledipasvir: Drug Interactions

- ▶ Acid reducing medication : PPI (prescription strength) can reduce efficacy
 - ▶ Alternative - H2 blockers 12 hours apart
- ▶ Anticonvulsants: decrease efficacy
- ▶ Antimycobacterial therapy (including rifamycins): decrease efficacy
- ▶ HIV medications
 - ▶ Truvada and boosted PI combination
 - ▶ Increases tenofovir levels
 - ▶ Tipranavir
- ▶ St. John's Wort: decrease efficacy

Sofosbuvir/Ledipasvir: Side Effects

- ▶ Fatigue (13-18%)
- ▶ Headaches (11-17%)
- ▶ Nausea (6-9%)
- ▶ Diarrhea (3-7%)
- ▶ Insomnia (3-6%)

Other side effects not in package insert

- ▶ Increased appetite
- ▶ Occasional increase in creatinine

Sofosbuvir and Ribavirin

- ▶ Sofosbuvir -- a NS5A inhibitor
- ▶ Ribavirin -- guanosine analog (mechanism of action unknown)
- ▶ Sofosbuvir: one pill once a day
- ▶ Ribavirin dose is weight-based
- ▶ If >75 kg give 1200 mg daily
 - ▶ 200 mg tablets give 3 in AM and 3 in PM
- ▶ If ≤ 75 kg give 1000 mg daily
 - ▶ 200 mg tablets give 3 in AM and 2 in PM

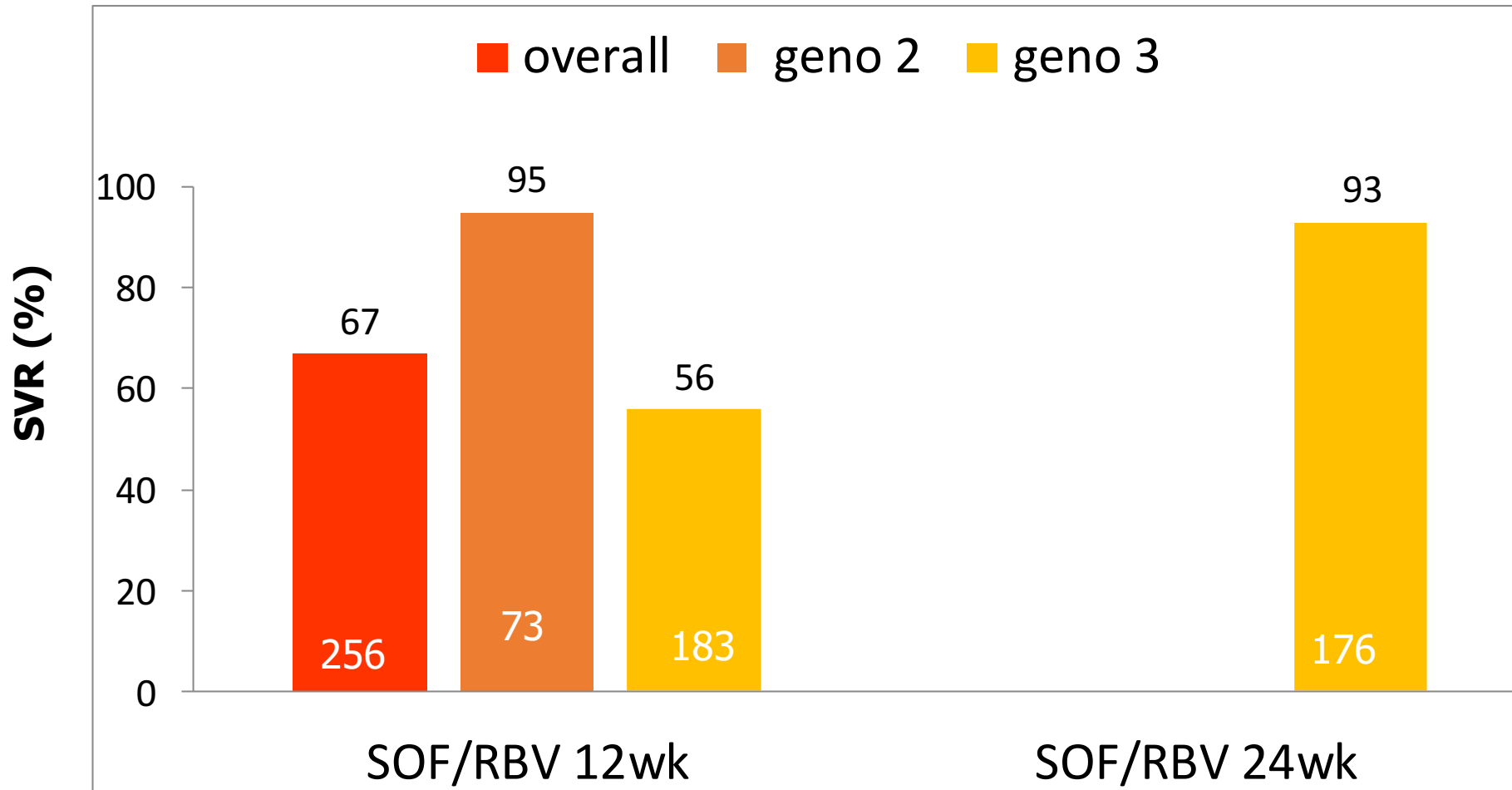
Sovaldi and Ribavirin



Sofosbuvir and Ribavirin: Duration of Therapy

- ▶ Genotype 2: Sofosbuvir 400 mg daily with weight-based ribavirin 12 weeks
 - ▶ With cirrhosis - treat for 16 weeks
- ▶ Genotype 3: Sofosbuvir 400 mg daily with weight-based ribavirin for 24 weeks
 - ▶ With cirrhosis, not as effective especially in treatment-experienced cirrhotics

Sofosbuvir and Ribavirin: Efficacy



Sofosbuvir and Ribavirin:

- ▶ Sofosbuvir and ribavirin are have renal clearance
- ▶ Do not use sofosbuvir in patients with cr cl <30 ml/min
- ▶ Ribavirin dosing should be modified for renal insufficiency

- ▶ Efficacy of Sofosbuvir will be decreased if used with
 - ▶ Rifampin
 - ▶ St. John's Wort

Sofosbuvir and Ribavirin:

- ▶ Fatigue (30-38%)
- ▶ Headache (24-30%)
- ▶ Nausea (13-22%)
- ▶ Insomnia (15-15%)
- ▶ Pruritus (11-27%)
- ▶ Anemia (6-10%)
- ▶ Asthenia (6-21%)
- ▶ Irritability (10%)
- ▶ Rash (8-9%)

Sofosbuvir and Ribavirin: Side Effects

- ▶ Ribavirin
 - ▶ Anemia
 - ▶ Rash
 - ▶ Irritability
 - ▶ Insomnia

Ribavirin rash



Ribavirin rash management

- ▶ Use topical steroids
- ▶ Reduce dose of ribavirin, reduce to 600 mg daily
- ▶ If severe, stop ribavirin and re-introduce 2 weeks later if rash resolved
- ▶ For pruritis, prescribe atarax

Ribavirin anemia monitoring and management

- ▶ Check CBC at 2 and 4 weeks and if stable then q4 weeks
- ▶ Reduce dose to 600 mg (monitor q 2 weeks)
 - ▶ If Hgb <10 g/dl without known cardiac disease
 - ▶ If >2 g/dl decrease within 4 weeks with history of stable cardiac disease
- ▶ Stop ribavirin
 - ▶ If Hgb <8.5 g /dL without known cardiac disease
 - ▶ If <12 g/dl after 4 weeks at reduced dose with known stable cardiac disease

Ombitasvir, paritaprevir/ritonavir and dasabuvir (O/P/D)

- ▶ Ombitasvir (NS5A)/Paritaprevir (PI), fixed dose combination
- ▶ Dasabuvir (NS5B)
- ▶ Combination therapy: 2 Ombitasvir/paritaprevir once a day plus 1 Dasbuvir twice a day
- ▶ Ritonavir has no HCV activity and is used to boost paritaprevir levels
- ▶ Used for genotype 1 and 4 (but not dasbuvir for genotype 4)



Ombitasvir, Paritaprevir/ritonavir and Dasabuvir (O/P/D): Duration of therapy

Genotype

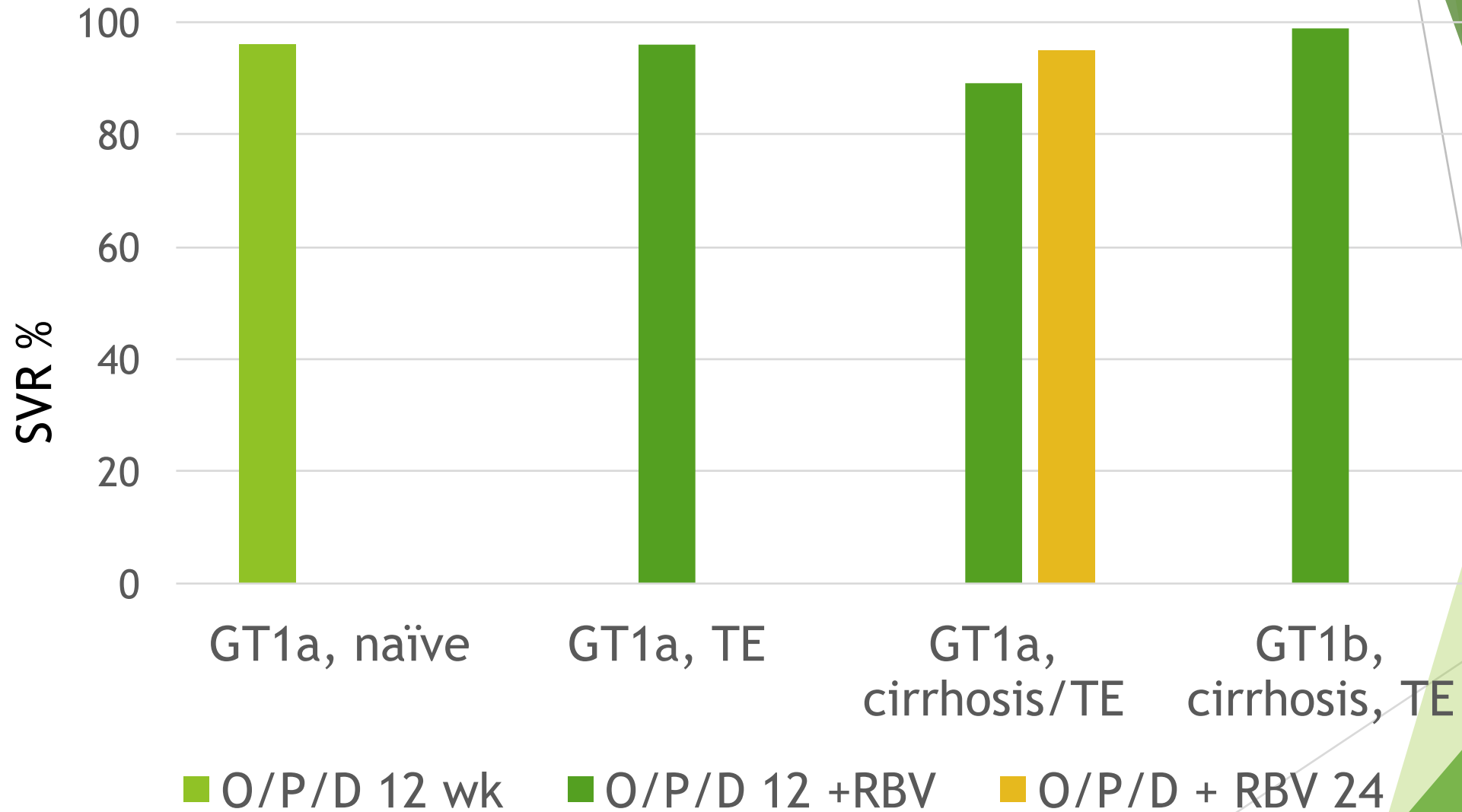
1a: O/P/D + Ribavirin weight-based for 12 weeks

1a with cirrhosis: O/P/D & Ribavirin for 24 weeks

1b: O/P/D for 12 weeks

1b with cirrhosis: O/P/D for 12 weeks

Ombitasvir, Paritaprevir/ritonavir and Dasabuvir: Efficacy



Ombitasvir, Paritaprevir/ritonavir and Dasabuvir: Drug Interactions

- ▶ The following drugs or class of drugs will decrease efficacy
 - ▶ Anticonvulsants
 - ▶ HIV medication: Efavirenz
 - ▶ Rifamycins
 - ▶ Sedatives
 - ▶ St. John's wort
- ▶ Do not use with ethinyl- estradiol as it can cause liver enzyme elevation

Ombitasvir, paritaprevir/ritonavir and Dasabuvir: Side effects

With ribavirin

- ▶ Fatigue (34%)
- ▶ Nausea (16-22%)
- ▶ pruritus (13-18%)
- ▶ skin reactions (16%)
- ▶ insomnia (12-14%)
- ▶ asthenia (9-14%)

Without ribavirin

- ▶ Nausea (8%)
- ▶ Pruritus (7%)
- ▶ insomnia (5%)
- ▶ Asthenia (4%)

Daclatasvir/Sofosbuvir

- ▶ Daclatasvir: NS5A
- ▶ Sofosbuvir: NS5B
- ▶ Both are pangenotypic: for all genotypes
- ▶ FDA Approved for genotype 3 and if HIV infected for genotype 1 and 3
- ▶ Daclatasvir 60 mg once a day
 - ▶ Strong CYP 3a inhibitors: use 30 mg (HIV PI)
 - ▶ Because HIV PI will boost level of daclatasvir
 - ▶ Moderate CYP 3a inducers: use 90 mg (HIV NNRTI such as efavirenz)
 - ▶ Because efavirenz will decrease daclatasvir levels
- ▶ Combination: 400 mg once a day



Daclatasvir/Sofosbuvir: Genotype and Duration

- ▶ Genotype 1:
 - ▶ Daclatasvir/sofosbuvir for: Treatment naive or Treatment experienced without cirrhosis or compensated cirrhotics → 12 weeks
- ▶ Genotype 3:
- ▶ Daclatasvir/sofosbuvir: no cirrhosis → 12 week
- ▶ Daclatasvir/sofosbuvir + Ribavirin: cirrhosis or decompensated → 12 weeks



Daklinza and Sovaldi:

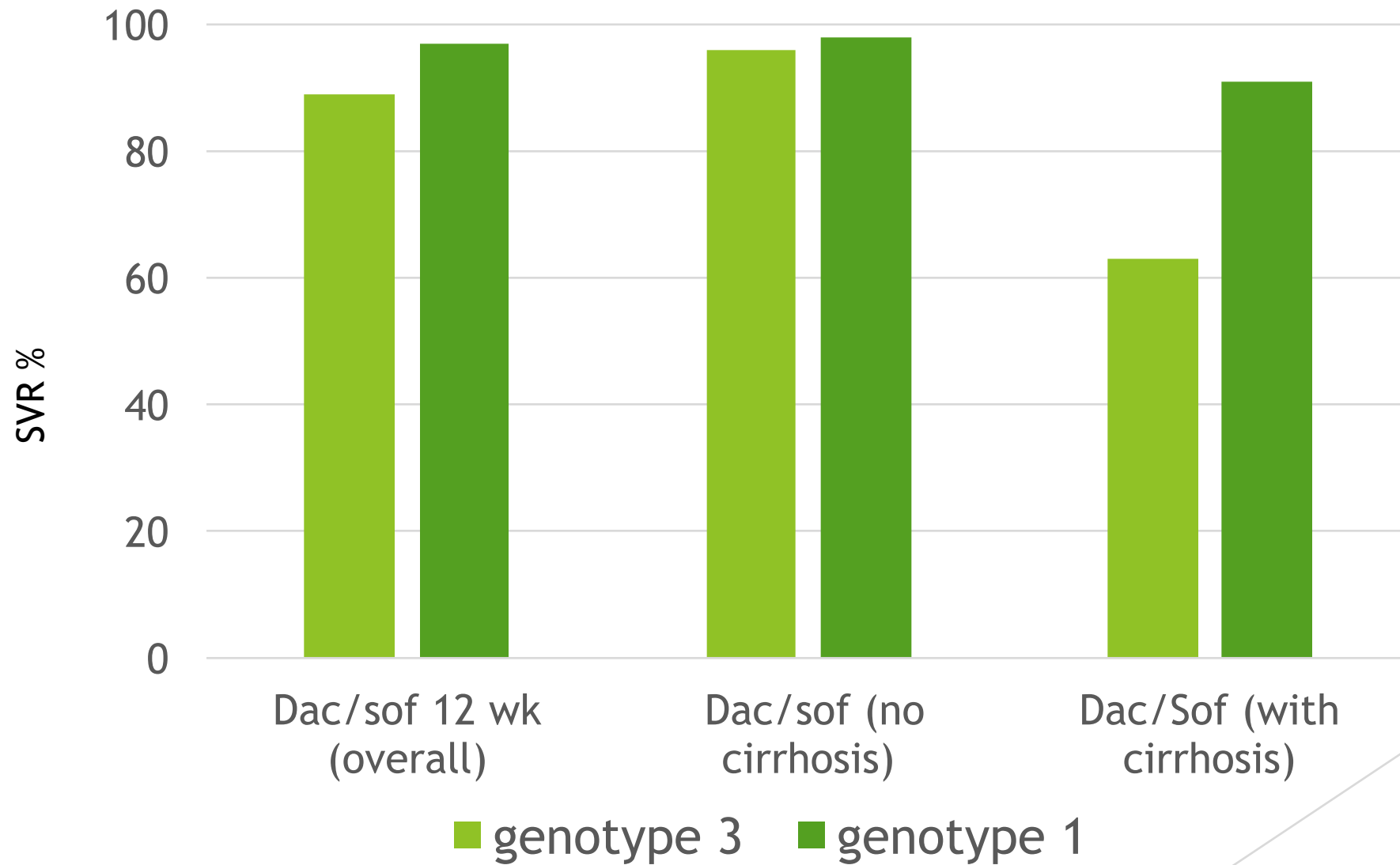
Daclatasvir /Sofosbuvir:

- ▶ Drug Interactions:
- ▶ amiodarone can cause bradycardia (sofosbuvir)
- ▶ cyp 3A inhibitors/inducers (daclatasvir)
 - ▶ You have to adjust the dose of daclatasvir based on if you have a drug that is a strong inhibitor or inducer

Daclatasvir / Sofosbuvir:

- ▶ Side effects
 - ▶ headache (8-14%)
 - ▶ Fatigue (14-15%)
 - ▶ Nausea (8-9%)
 - ▶ Diarrhea (5-7%)

Daclatasvir / Sofosbuvir: Efficacy



Elbasvir/Grazoprevir:

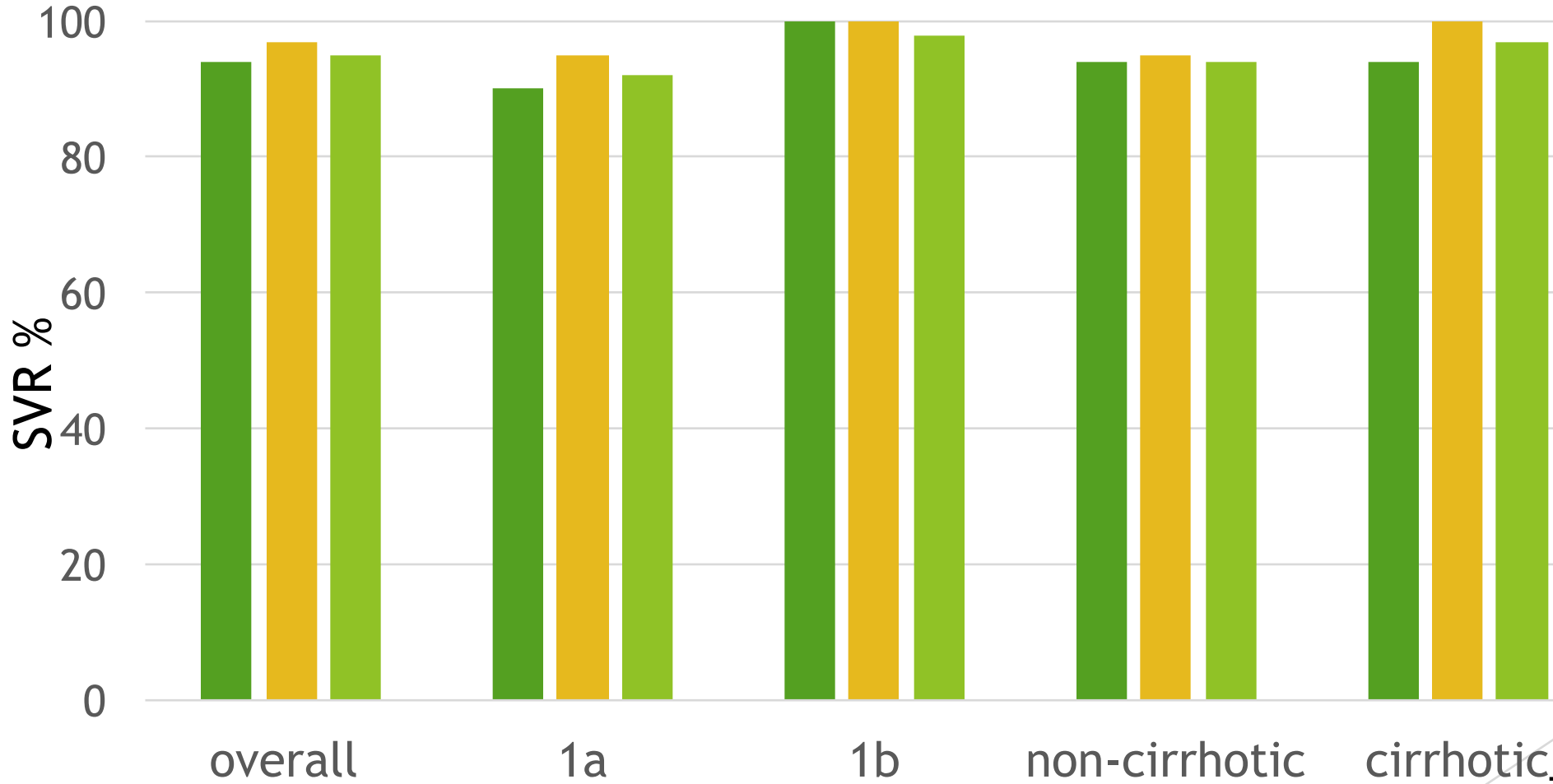
- ▶ Elbasvir is a NS5A polymerase inhibitor
- ▶ Grazoprevir is a NS3/4A protease inhibitor
- ▶ One pill once a day
- ▶ Effective for genotype 1 and 4



Elbasvir/Grazoprevir: Duration of Therapy

- ▶ Genotype 1a Treatment Naïve or Experienced:
 - ▶ without NS5A mutations: 12 weeks
 - ▶ with NS5A mutations: + ribavirin for 16 weeks
- ▶ Genotype 1b Treatment naïve/experienced: 12 weeks
- ▶ Genotype 1a or 1b Treatment experience with PI: + ribavirin for 12 weeks
- ▶ Genotype 4 Treatment naïve: 12 weeks
- ▶ Genotype 4 Treatment experienced: + ribavirin for 16 weeks

Elbasvir/Grazoprevir: Efficacy



TN= Treatment naïve

TE= Treatment experienced

■ TE: E/G 12 wk

■ TE: E/G + RBV 16 wk

■ TN: E/G 12 wk

Elbasvir/Grazoprevir: Use in renal disease and drug interactions

- ▶ Can be used with renal insufficiency or dialysis
- ▶ Avoid with the following drugs due to drug interactions which will decrease efficacy:
 - ▶ Anticonvulsants
 - ▶ Antimycobacteria agents such as rifamycins
 - ▶ St. John's Wort
 - ▶ HIV medications such as Efavirenz, HIV Protease Inhibitor
 - ▶ Cyclosporine

Elbasvir/Grazoprevir: Side Effects

▶ Without ribavirin:

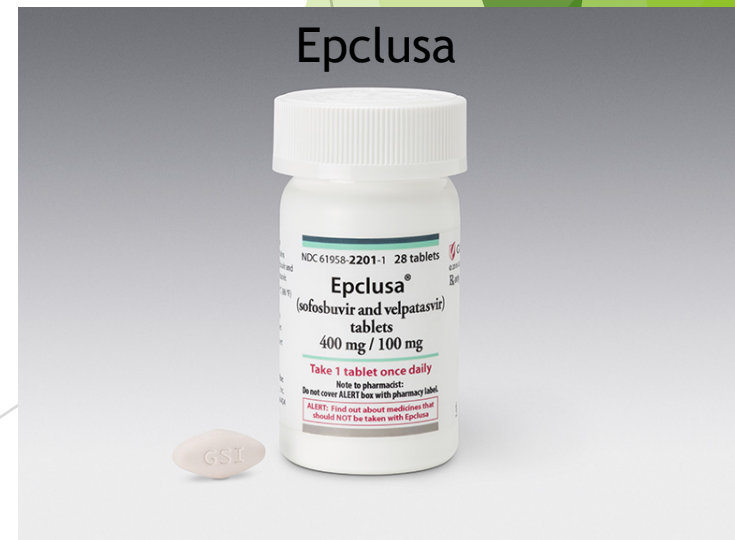
- ▶ Fatigue (5-11%)
- ▶ headache (10%)
- ▶ abd pain/diarrhea (2%)
- ▶ Irritability (1%)
- ▶ Depression (1%)

▶ With ribavirin:

- ▶ Anemia (8%)
- ▶ Headache (6%)
- ▶ Fatigue (4%)
- ▶ Dyspnea (4%)
- ▶ Rash & Pruritus (4%)
- ▶ Irritability (3%)
- ▶ Abd pain (2%)
- ▶ Depression (1%)
- ▶ Arthralgia (2%)

Sofosbuvir/Velpatasvir:

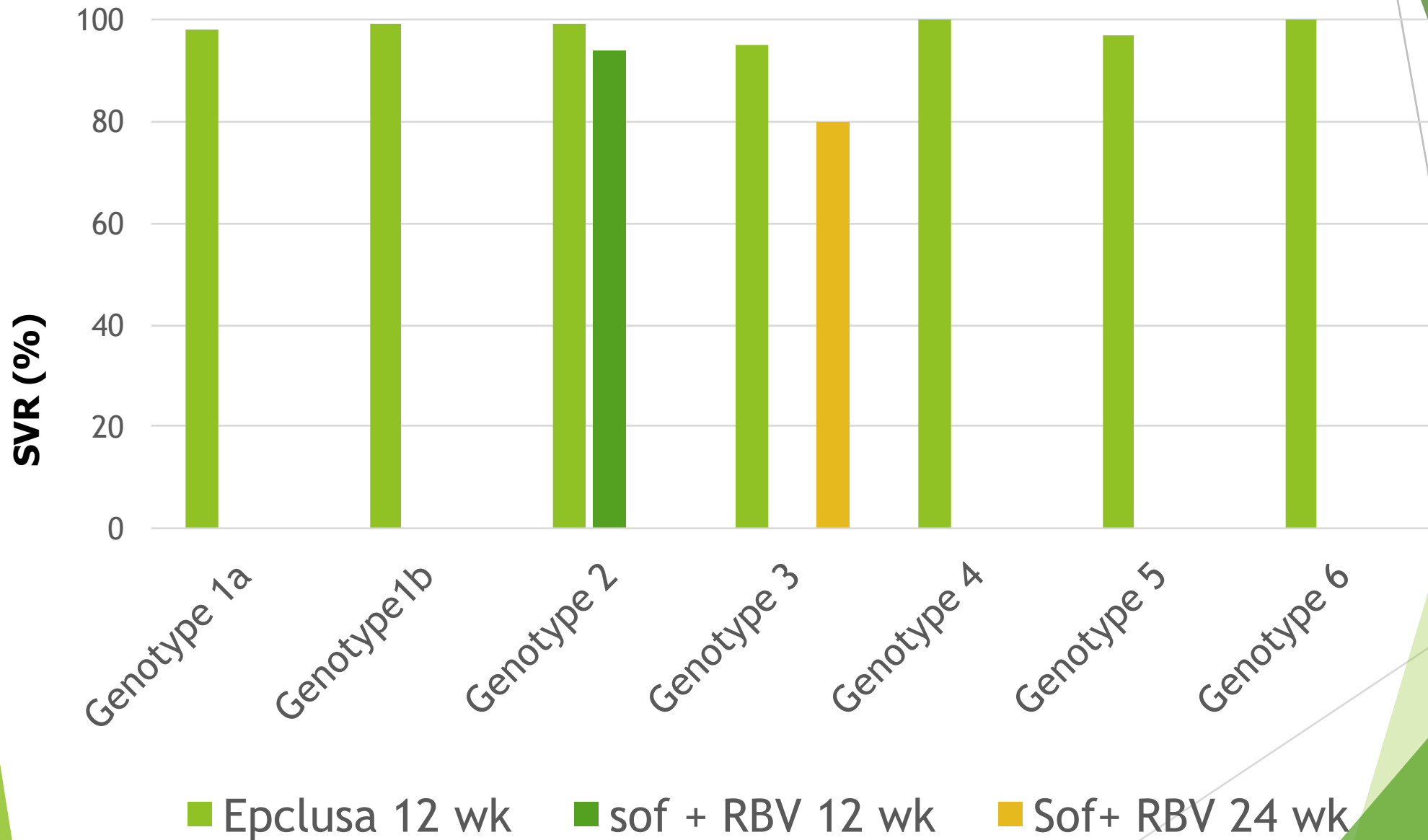
- ▶ Sofosbuvir is nucleoside NS5B inhibitor and pan-genotypic
- ▶ Velpatasvir is NS5A inhibitor and pangenotypic
- ▶ Can be used for all genotypes 1,2,3, 4, 5, and 6
- ▶ One pill once a day



Sofosbuvir/Velpatasvir: Indications

- ▶ Without cirrhosis or with compensated cirrhosis (Child-Pugh A): 12 weeks (regardless of genotype)
- ▶ Decompensated cirrhosis (Child-Pugh B and C) + ribavirin (weight-based) for 12 weeks
- ▶ Can not use with Cr Cl <30 ml/min

Sofosbuvir/Velpatasvir: Efficacy



Sofosbuvir/Velpatasvir: Drug Interactions

- ▶ Amiodarone - symptomatic bradycardia
- ▶ Rifampin, St. John's wort, carbamazepine: may decrease concentration of drug
- ▶ Drugs decreasing velpatasvir dose
 - ▶ Antacids: take least 4 hours apart
 - ▶ H2 blockers: take 12 hours apart
 - ▶ No PPI: except take this drug with food at least 4 hours before omeprazole 20 mg
 - ▶ HIV meds: do not use with Efavirenz, Tipranavir/ritonavir

Sofosbuvir/Velpatasvir: Side Effects

Sofosbuvir/Velpatasvir

- ▶ Headache (22%)
- ▶ Fatigue (15%)
- ▶ Nausea (9%)
- ▶ Asthenia (5%)
- ▶ Insomnia (5%)

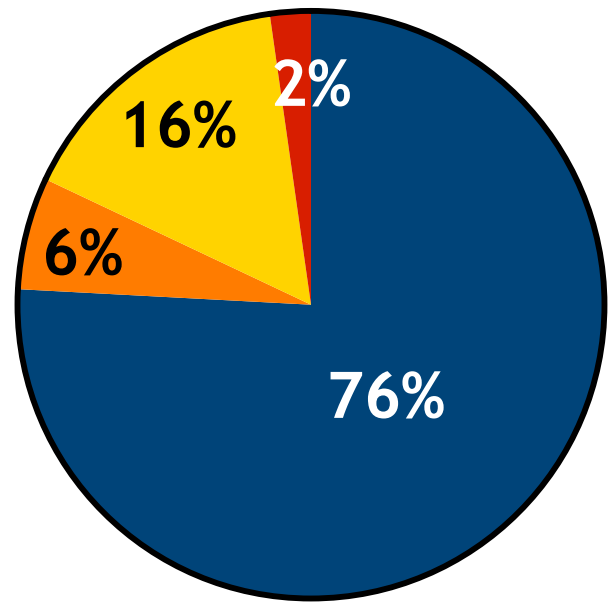
With Ribavirin

- ▶ Fatigue (32%)
- ▶ Anemia (26%)
- ▶ Nausea (15%)
- ▶ Headache (11%)
- ▶ Diarrhea (10%)

Effectiveness of HCV medications at Parkland

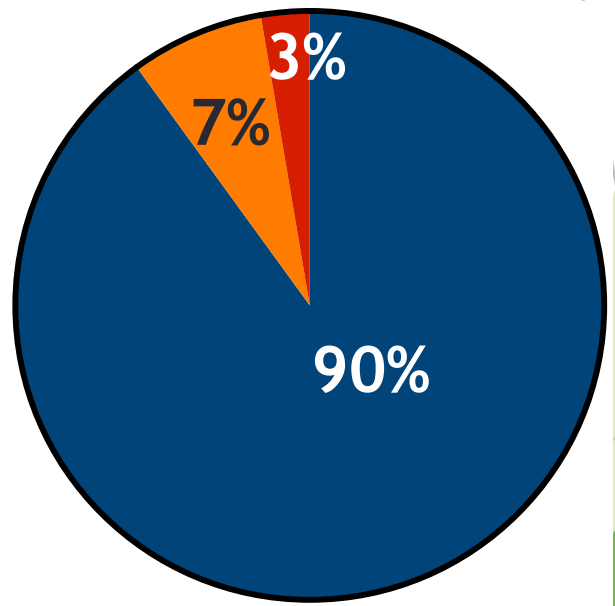
Including 16% who failed to return for the last HCV viral load 12 weeks after completing treatment

Including those who completed all follow-up testing



n= 178

- SVR 12
- Relapse
- Lost to F/U
- Other



n= 150

HCV Treatment: Labs

- ▶ Baseline HCV RNA, LFTS, electrolytes, Bun, cr, CBC
- ▶ Week 2 CBC (if on ribavirin)
- ▶ 4 week HCV RNA, LFTS, (add CBC if on ribavirin)
- ▶ 8 week HCV RNA, LFTS, (add CBC if on ribavirin)
- ▶ 12 week HCV RNA, LFTS, (add CBC if on ribavirin)
- ▶ 12 week post-treatment HCV RNA, LFTS, CBC

- ▶ Can omit week 8 and 12 if cost is an issue
- ▶ But must obtain CBCs if on ribavirin



Thank you for your Attention!

STOP HCC by Treating HCV