Treatment of HCV

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Cherokee Nation

OBJECTIVES

- Rationale and goals for the universal need of HCV treatment
- Describe FDA approved antivirals used in HCV treatment, their strengths and weaknesses
- Interpret decision trees to determine treatment options

GOAL OF TREATMENT

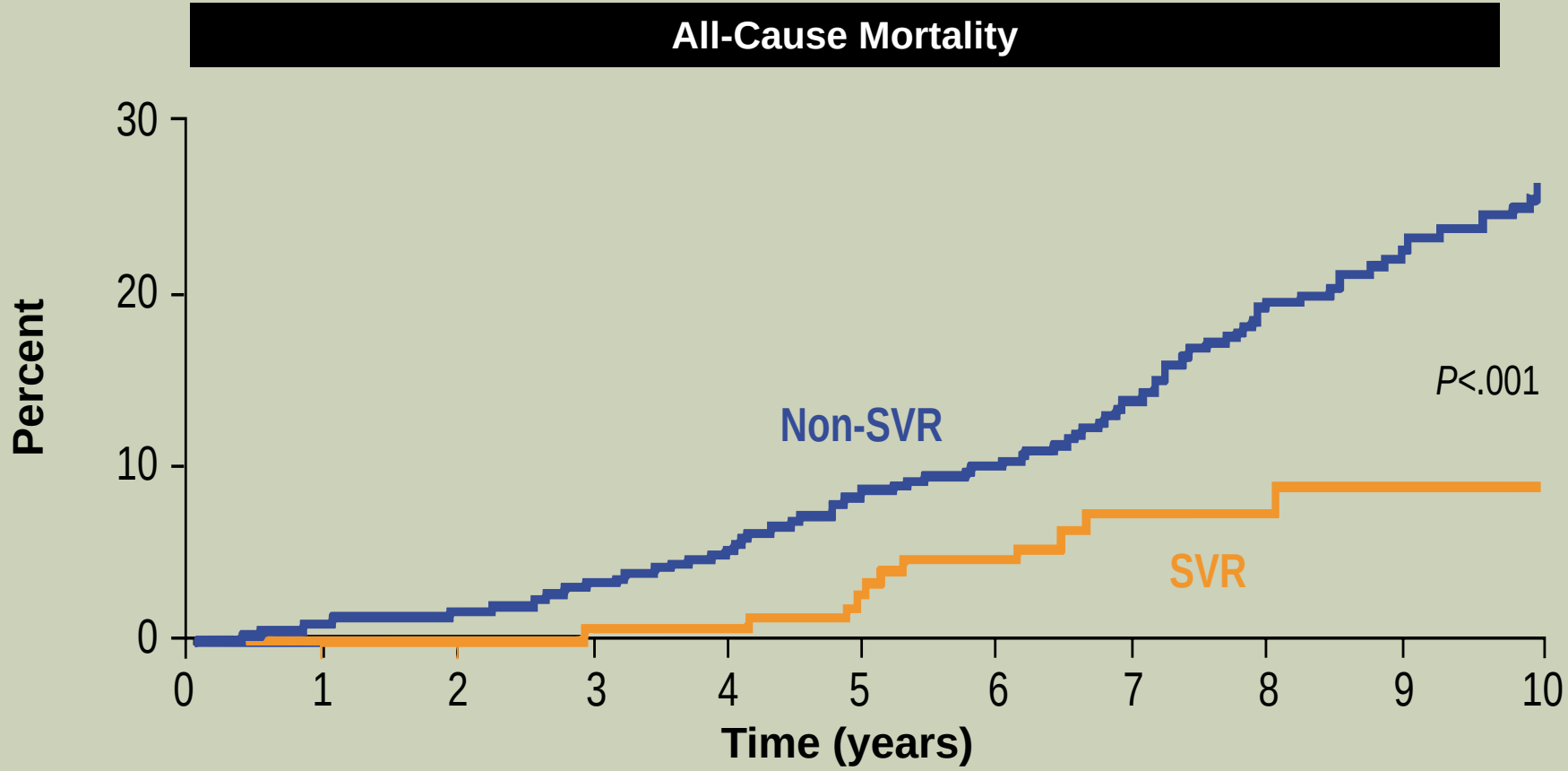
*"The goal of treatment of HCV-infected persons is to **reduce all-cause mortality** and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the **achievement of virologic cure** as evidenced by an SVR"*

SVR: sustained virological response

hcvguidelines.org

Treatment

SVR WAS ASSOCIATED WITH REDUCED LONG-TERM RISK OF ALL-CAUSE MORTALITY IN AN INTERNATIONAL, MULTICENTER STUDY



International, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Europe and Canada. Patients with chronic HCV infection started an interferon-based treatment regimen between 1990 and 2003 (n=530).

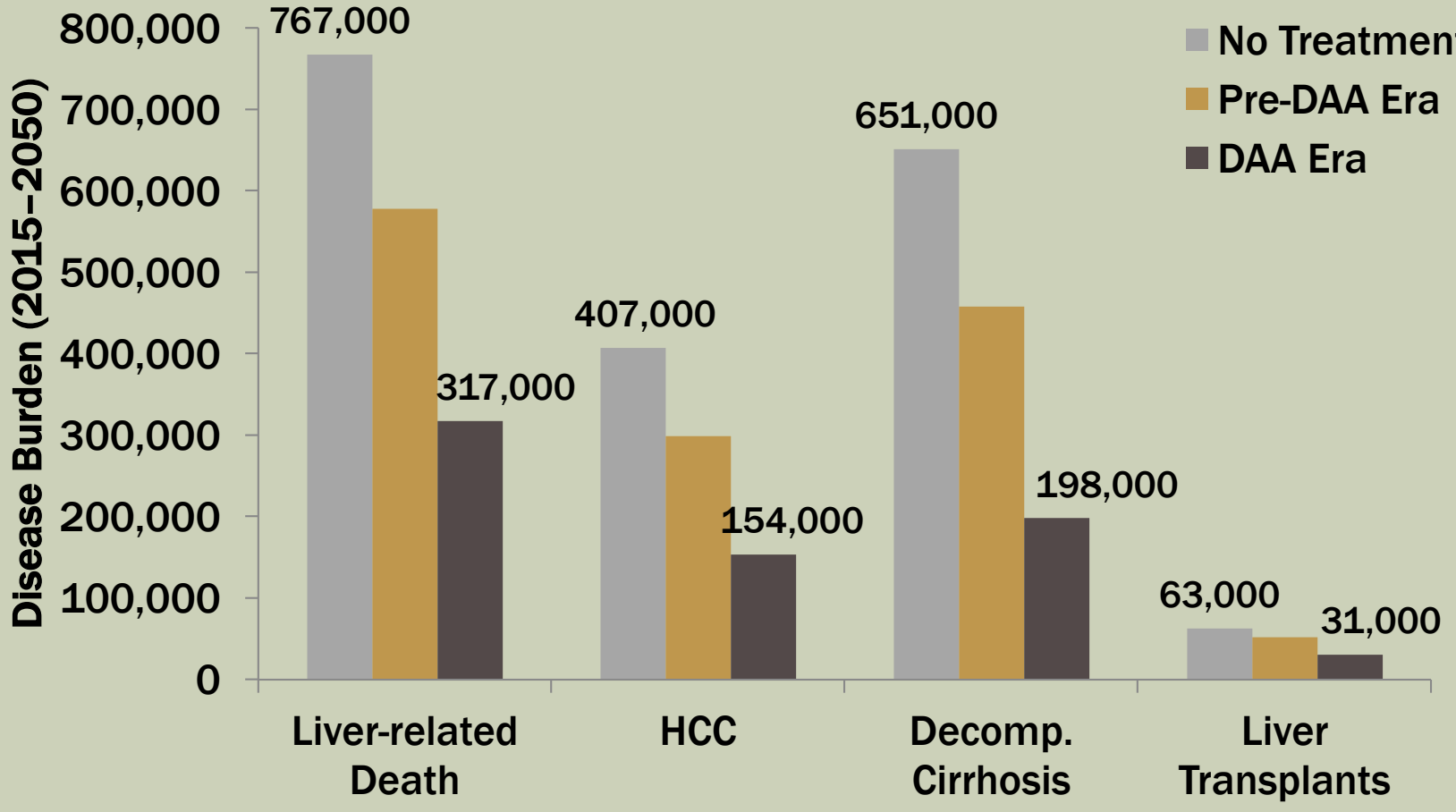
van der Meer AJ, et al. *JAMA*. 2012;308:2584-2593.

WHY DO WE NEED TO TREAT HCV

- **SVR (cure) of HCV** is associated with:
  - 70% Reduction of Liver Cancer
  - 50% Reduction in All-cause Mortality
  - 90% Reduction in Liver Failure

Lok A. NEJM 2012; Ghany M. Hepatol 2009; Van der Meer AJ. JAMA 2012

HCV-ASSOCIATED DISEASE BURDEN (2015–2050)



50–70% reduction in HCV-associated disease burden

Chhatwal et al. AASLD 2015 Abstract 104

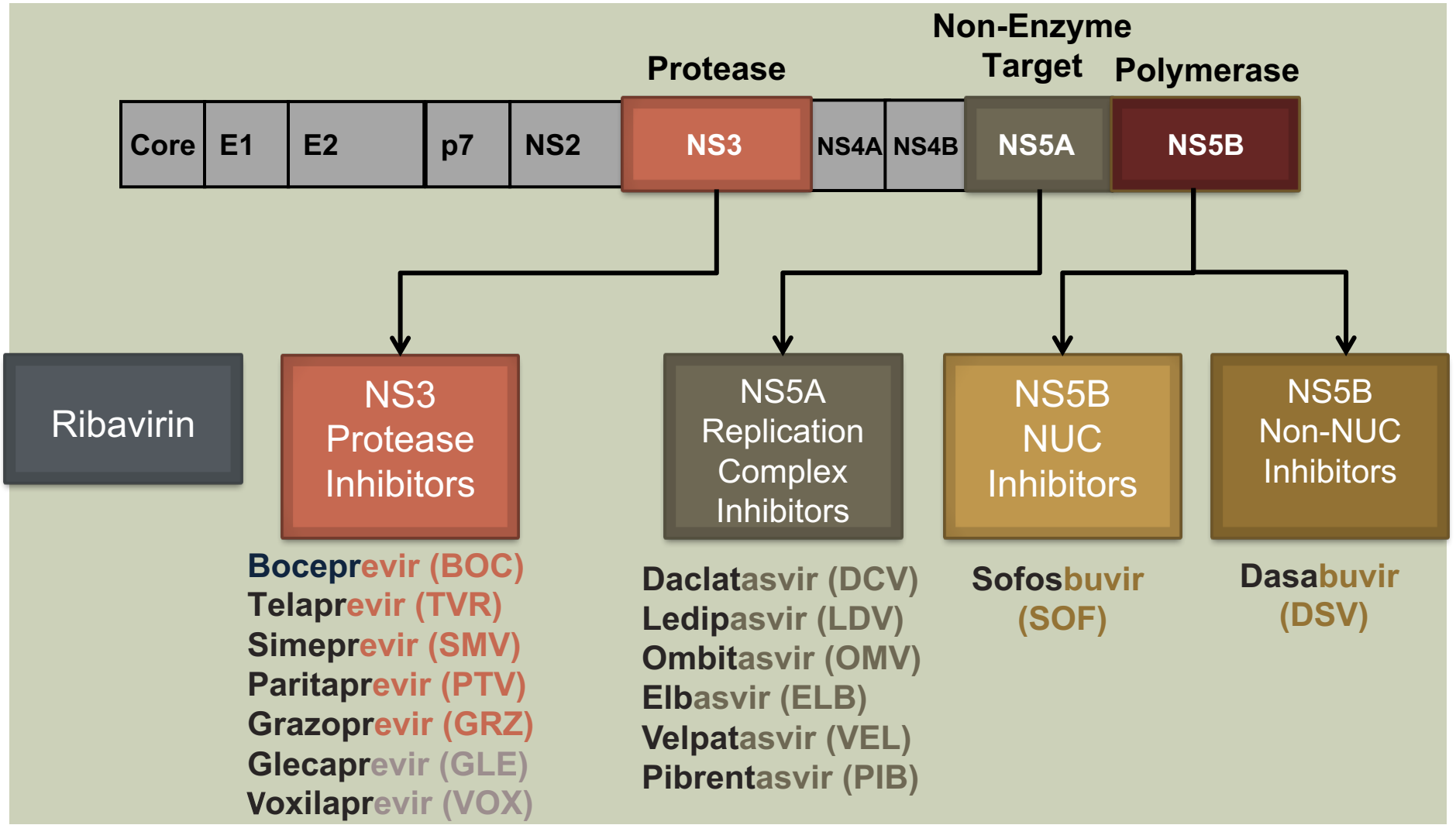
IMPACT OF TREATMENT COMPARED TO OTHER COMMON DISEASES

- HCV cirrhosis risk = 40% over 30 years
- Hepatocellular carcinoma (HCC) risk in HCV Cirrhosis = 17% over 5 years
- When we **cure 30 patients** with HCV we will prevent:
  - **12 cases of HCV related cirrhosis**
  - **2 case of HCV related HCC**

If we treat 104 patients with hypercholesterolemia with statins (For 5 years), we will prevent **1** first time heart attack and ¾ of a stroke

www.thennt.com

DIRECT-ACTING ANTIVIRAL AGENTS (DAA): KEEPING THEM STRAIGHT



HCV THERAPIES - DAAS

Medication	NS5B	NS5A Inh	NS3 PI	Other
Sovaldi®	sofosbuvir			
Harvoni®	sofosbuvir	ledipasvir		
Epclusa®	sofosbuvir	velpatasvir		
Zepatier®		elbasvir	grazoprevir	
Viekira Pak®	dasabuvir	ombitasvir	paritaprevir	ritonavir
Daklinza®		daclatasvir		
Olysio®			simeprevir	
Ribavirin				ribavirin
Vosevi®	sofosbuvir	velpatasvir	voxilaprevir	
Mavyret®		pibrentasvir	glecaprevir	

SOFOSBUVIR (SOVALDI®)

- NS5B nucleotide inhibitor
- Few drug interactions
- Genotypes 1,2,3,4
- Contraindicated in patients with GFR < 30
- Most common reported SE
  - Headache
  - Fatigue (with ribavirin)
- Pangenic in combination
  - Not used as monotherapy

SE: Side Effects

Sovaldi® [package insert]. Gilead Sciences, Foster City, CA

Treatment

LEDIPASVIR/SOFOSBUVIR (HARVONI®)

- Once daily single oral tablet
- Genotype 1 and 4
- Minimal DDIs, no food effect
- 8 week treatment available
  - Naïve/Non cirrhotic/VL < 6 million
- **Do not use in patients with GFR < 30**
- Avoid use with anti acids
  - May use with 20 mg of omeprazole ***if necessary***

LDV NS5A inhibitor

SOF - NS5B nucleotide polymerase inhibitor

Approved: Oct 10, 2014

DDI: Drug-Drug Interactions

Harvoni® [package insert]. Gilead Sciences, Foster City, CA

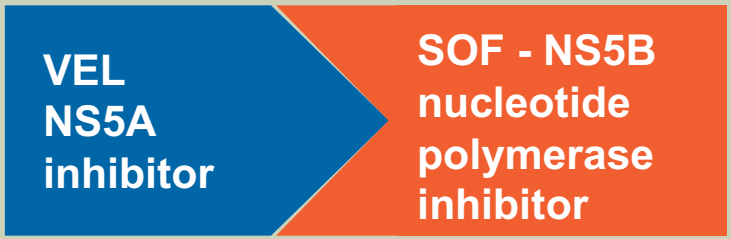
Treatment

VELPATASVIR/SOFOSBUVIR (EPCLUSA®)

- Once daily single oral tablet

Approved: June 28, 2016

- Minimal DDIs, no food effect



- Genotype 1,2,3,4

- Do not co-administer with PPI
  - *If medically necessary, take Epclusa with food 4 hours before omeprazole 20 mg*
- Do not use in patients with GF<30

DDI: Drug-Drug Interactions

Epclusa® [package insert]. Gilead Sciences, Foster City, CA

Treatment

OBV/PTV/R AND DSV (VIEKIRA PAK)

2 tablets of ombitasvir/paritaprevir/ ritonavir (12.5/75/50 mg) combination tablet every am
1 dasabuvir 250 mg tablet every am and pm

- Includes 3 direct acting antivirals and ritonavir, triple therapy or PrOD
  - Ombitasvir, paritaprevir, dasabuvir
- Ritonavir (No HCV activity)
  - Used to boost the paritaprevir
- Genotype 1 and 4
- Administer orally twice a day with food
- Many pharmacological interactions
- GT1a requires addition of RBV
- May use with GFR < 30

VIEKIRA PAK [package insert]. North Chicago, IL: AbbVie Inc.

FDA approval Dec 19, 2014

OBV/PTV/R AND DSV XR (VIEKIRA XR)

- Extended Release
  - All 3 tablets at the same time
  - Take with food

    Same precautions as Viekira Pak
  - Do not split, crush or chew
  - Alcohol should not be consumed within 4 hours of taking VIEKIRA XR

DACLATASVIR (DAKLINZA)

- NS5A inhibitor
- High barrier to resistance
- Once daily oral tablet
  - ***In combination with sofosbuvir***
- With or without food
- Genotype 1,2,3,4
- May use with antiacids

No DDIs:	60 mg once daily
DDIs with strong CYP3A inhibitors:	30 mg once daily
DDIs with moderate CYP3A inducers:	90 mg once daily

Daklinza [package insert]. Princeton, NJ: Bristol-Myers Squibb Company

DDI: Drug-Drug Interaction

Treatment

ELBASVIR/GRAZOPREVIR ZEPATIER

- Genotypes 1 and 4
- Elbasvir/Grazoprevir
  - NS5A inhibitor - NS3/4A protease inhibitor
- Oral and once daily
- **Must perform resistance testing in genotype 1A**
  - ***If resistance present must add Ribavirin and extend therapy from 12 to 16 weeks***
- **DO NOT use in advanced liver disease (Child Pugh B or C**
- **May use with GFR < 30 ml/min**
- **May use in Dialysis**
- **May use with PPI**

FDA-approved Jan 28, 2016

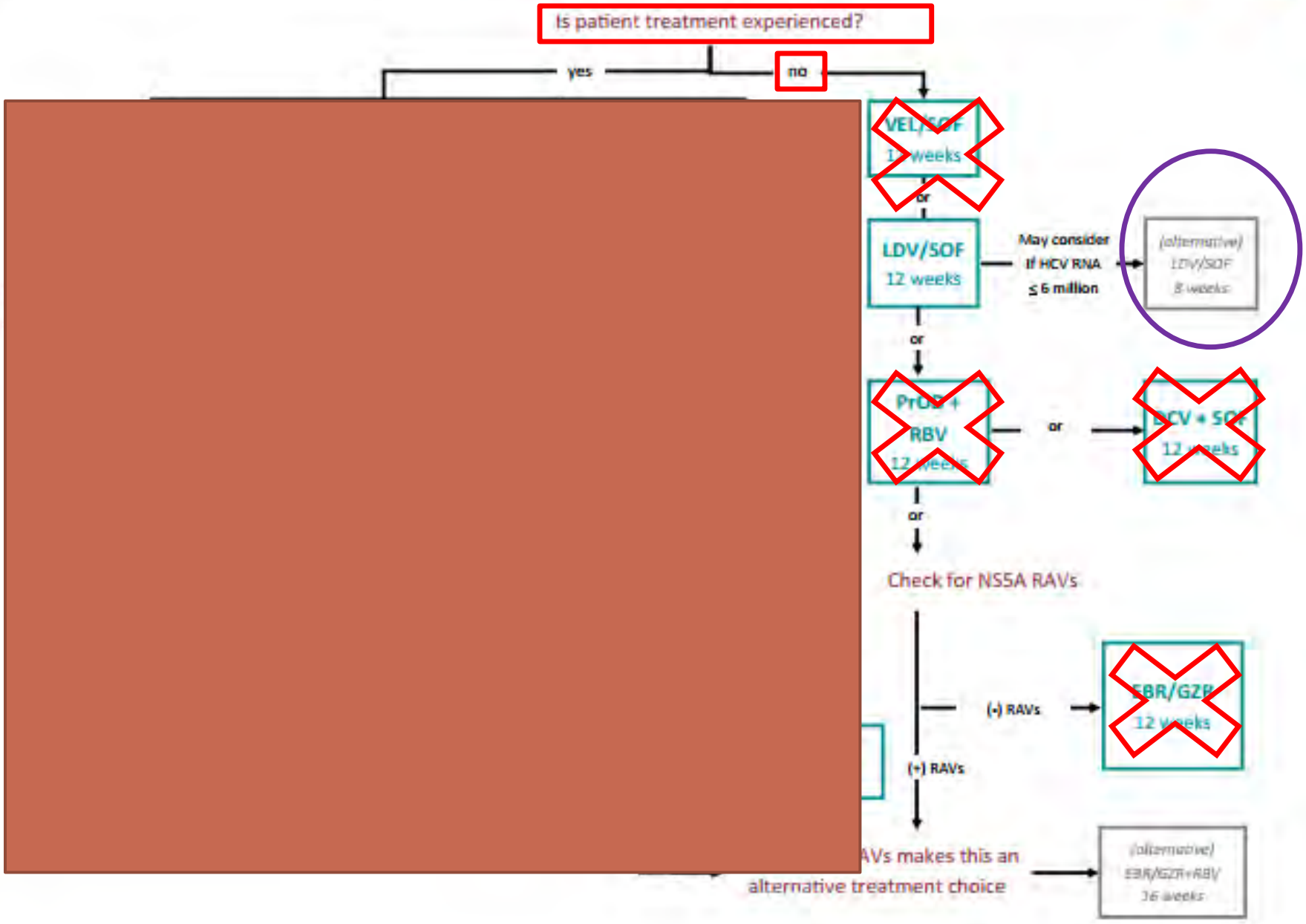
Treatment

CLINICAL CASE #1

- 55 year old HCV positive male with a hx of IVDU 10 years ago
- Genotype 1a
- VL 2.4 million/ML
- Treatment naïve
- Fibrosis Stage F0-F1
- Labs: GFR of 65 ml/min, Hg 13 Platelets 245
- Other medical conditions
  - HTN on amlodipine
- What are your options?

Version: 7/25/2016

Hepatitis C : Genotype 1a Non-Cirrhotic Treatment Regimen



Treatment

SOFOSBUVIR/LEDIPASVIR (HARVONI) AND ACID SUPPRESSING AGENTS

Antacids

- aluminum hydroxide
- magnesium hydroxide

- Separate administration by four hours

H_2RAs

- famotidine
- ranitidine

- Administer concurrently or 12 hours apart
- Not to exceed doses >40 mg famotidine twice daily

Harvoni® [package insert]. Gilead Sciences, Foster City, CA

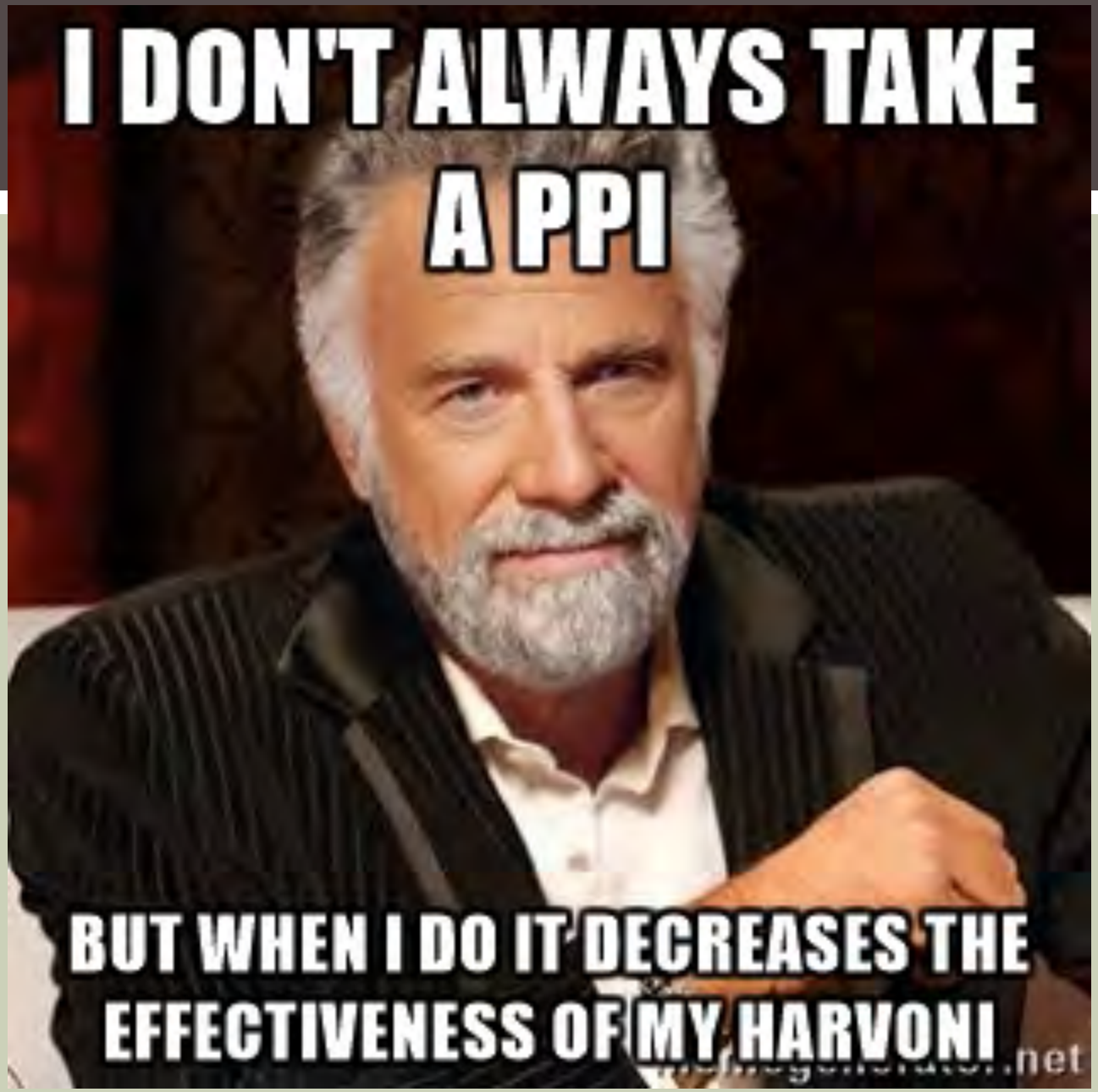
Treatment

SOFOSBUVIR/LEDIPASVIR (HARVONI) AND PROTON PUMP INHIBITORS

- Consider discontinuation of acid suppression therapy if patient is able to tolerate
  - Reduce PPI by 50% per week to lowest dose, then discontinue to minimize rebound acid hypersecretion
- If you have to use a PPI and Harvoni is the best option
  - Administer simultaneously on an empty stomach
    - Only doses ≤ omeprazole 20 mg
    - Pantoprazole mg ≠ omeprazole mg

Harvoni® [package insert]. Gilead Sciences, Foster City, CA

Treatment


I DON'T ALWAYS TAKE A PPI
BUT WHEN I DO IT DECREASES THE EFFECTIVENESS OF MY HARVONI
.net

Treatment

CLINICAL CASE # 2

- 65 year old HCV positive female with a hx of a post partum blood transfusion 40 years ago

- Genotype 1a
- VL 8.8million/ML
- Treatment naïve
  - Fibrosis Stage **F3-F4**
  - **No** history of
    - Esophageal varices/ encephalopathy or ascitis
  - Labs: **GFR of 28 ml/min**, Hg 13 **Platelets 109**
  - Other medical conditions
    - Barrett's esophagus (on **omeprazole 40 mg** once a day)

- What are your options?

Version: 7/25/2016

Hepatitis C : Genotype 1a Cirrhotic Treatment Regimen

Does the patient have decompensated cirrhosis?

yes

no

eatment experienced?

no

or

or

or

Check NSSA RAVs

(-) RAVs

(+) RAVs

EBR/GZR
12 weeks

RAVs
ternative
hoice

*EBR/GZR and PrOD are contraindicated with CTP Class B or C cirrhosis

Treatment

ELBASVIR/GRAZOPREVIR ZEPATIER

- Genotypes 1 and 4
- Elbasvir/Grazoprevir
  - NS5A inhibitor - NS3/4A protease inhibitor
- Oral and once daily w or wo food
- **Must perform resistance testing in genotype 1A**
  - ***If resistance present must add Ribavirin and extend therapy from 12 to 16 weeks***
- **DO NOT use in advanced liver disease (Child Pugh B or C**
- **May use with GFR < 30 ml/min**
- **May use in Dialysis**
- **May use with PPI**

FDA-approved Jan 28, 2016

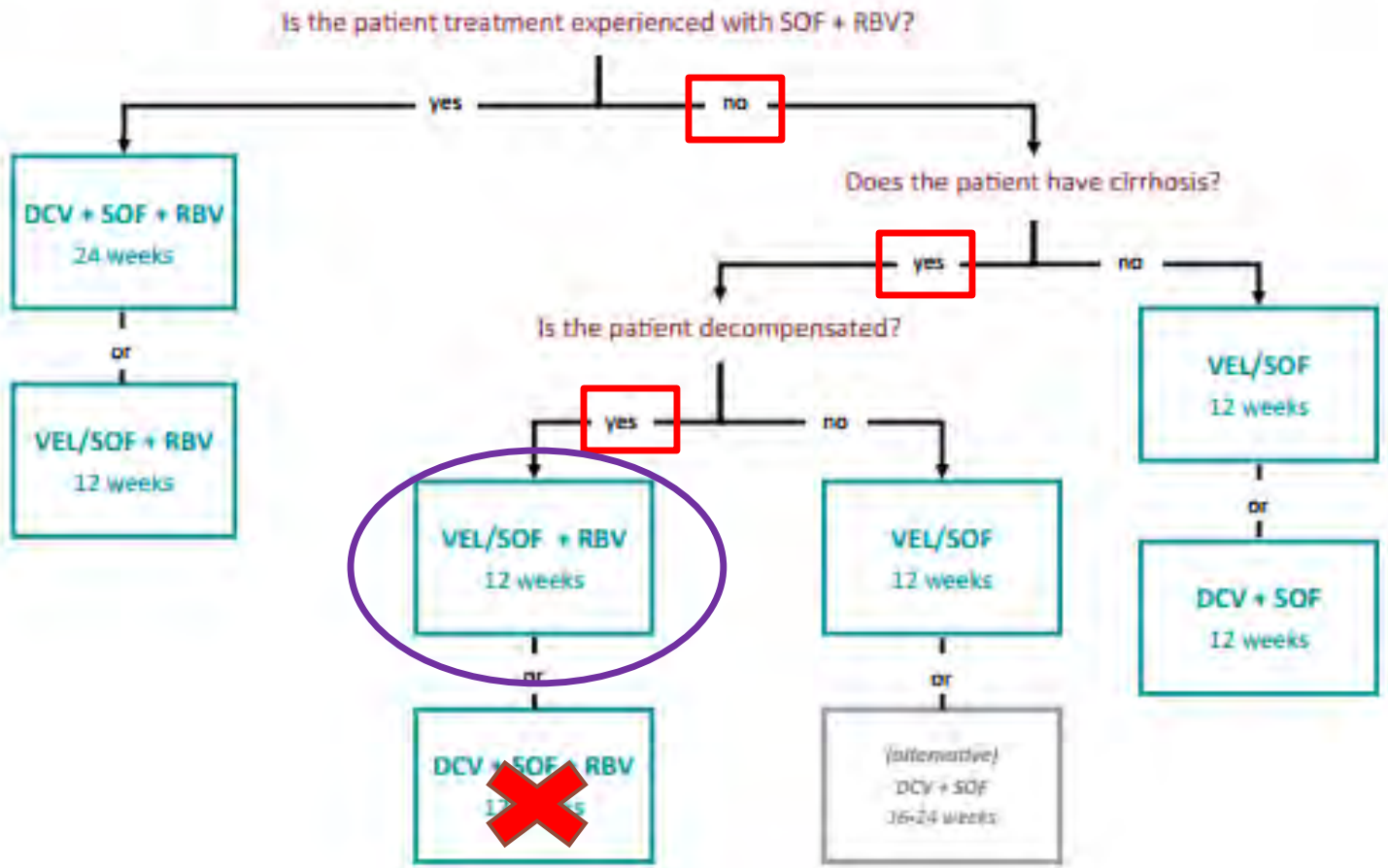
CLINICAL CASE # 3

- 73 year old HCV positive male with no risk factors
  - Genotype **2**
  - VL 3.4 million/ML
  - Treatment **naïve**
  - Fibrosis Stage **F3-F4**
  - History of **ascites**
  - Labs: GFR of 69 ml/min, Hg 13.4, Platelets 88
  - Other medical conditions
    - Prediabetes/40 pack/year smoking/HTN on amlodipine Hypercholesteremia on atorvastatin
- What are your options?

Version: 7/25/2016

Hepatitis C Genotype 2 Treatment Regimen Decision Tree

Genotype 2 Patients



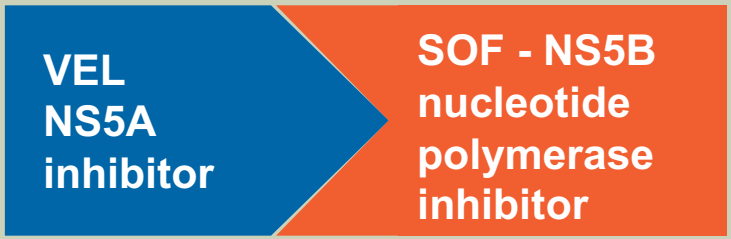
Do I need any workup before I start Ribavirin?

What are his Drug - Drug Interactions with Epclusa?

Treatment

VELPATASVIR/SOFOSBUVIR (EPCLUSA®)

- Once Daily Single Oral Tablet
- Minimal DDIs, no food effect
- **Genotype 1,2,3,4**
- **Do not co-administer with PPI**
  - *If medically necessary, take Epclusa with food 4 hours before omeprazole 20 mg andOnly doses ≤ omeprazole 20 mg*
- **Do not use in patients with GFR < 30**

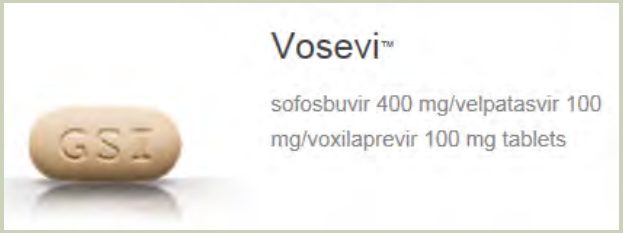


Approved: June 28, 2016

Epclusa® [package insert]. Gilead Sciences, Foster City, CA

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR (VOSEVI®)

- 400mg/100mg/100mg tablet
  - One tablet daily with food
- **sofosbuvir**
  - NS5B polymerase inhibitor
- **velpatasvir**
  - NS5A Inhibitor
- **voxilaprevir**
  - NS3/4A protease inhibitor
- Pan-genotypic
  - genotypes 1,2,3,4,5,6
- Approved for treatment failures
- FDA approved on July 20, 2017



Vosevi® [package insert]. Gilead Sciences, Foster City, CA

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR - TREATMENT FAILURES

Genotype	Previous Regimen Included	Duration of Treatment
1, 2, 3, 4, 5, 6	NS5SA inhibitor[1]	12 weeks
1a, 3	Sofosbuvir without NS5A inhibitor[2]	12 weeks

[1]—NS5A medications included in clinical trials: daclatasvir, elbasvir, ledipasvir, ombitasvir, or velpatasvir
[2]—Regimen tested in clinical trials inlcuded sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, NS3/4A protease inhibitor (boceprevir, simeprevir or telaprevir). Additional benefit of VOSEVI over sofosbuvir/velpatasvir was not shown in adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

Vosevi® [package insert]. Gilead Sciences, Foster City, CA

SOFOSBUVIR/VELPATASVIR/VOXILAPREVIR - PRECAUTIONS

- Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C)
  - Due to higher exposure to protease inhibitor voxilaprevir
- Bilirubin increased ≤ 1.5 x ULN in ~10% of patients in clinical studies
  - No jaundice
  - Levels decreased after completing treatment

Vosevi® [package insert]. Gilead Sciences, Foster City, CA

GLECAPREVIR/PIBRENTASVIR (MAVYRET®)

- 100mg/40mg tablet
  - Take 3 tablets once daily with food
- glecaprevir
  - NS3/4A protease inhibitor
- pibrentasvir
  - NS5A inhibitor
- Pan-genotypic
  - Genotypes 1,2,3,4,5,6
- Approved for some treatment failures
- No dosage adjustment in patients with mild, moderate, or severe renal impairment, including dialysis
- FDA Approval August 3, 2017

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

GLECAPREVIR/PIBRENTASVIR - TREATMENT NAÏVE

- All genotypes (no cirrhosis)
  - 8 weeks
- All genotypes (with cirrhosis - Child-Pugh A)
  - 12 weeks

GLECAPREVIR/PIBRENTASVIR - TREATMENT EXPERIENCED

Genotype	Previous Treatment	Treatment Duration (No Cirrhosis)	Treatment Duration Compensated Cirrhosis (Child-Pugh A)
1	NS5A inhibitor[1] without prior treatment with NS3/4A protease inhibitor	16 weeks	16 weeks
	NS3/4A protease inhibitor[2] without prior treatment with NS5A inhibitor	12 weeks	12 weeks
1,2,4,5,6	PRS[3]	8 weeks	12 weeks
3	PRS[3]	16 weeks	16 weeks

[1] – In clinical trials, subjects were treated with ledipasvir/sofosbuvir or daclatasvir +interferon+ribavirin

[2] – In clinical trials, subjects were treated with simeprevir+sofosbuvir, or simeprevir, boceprevir, or telaprevir with interferon+ribavirin

[3] – Prior treatment experience with interferon, ribavirin, and/or sofosbuvir, but no prior experience with NS3/4A protease inhibitor or NS5A inhibitor

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

GLECAPREVIR/PIBRENTASVIR ADVERSE EFFECTS AND CAUTIONS

- Most common adverse effects (~10%)
- Headache
- Fatigue
- Child-Pugh B
- Not Recommended
- Contraindicated in Child-Pugh C
- No additional monitoring parameters provided in package insert

GLECAPREVIR/PIBRENTASVIR - DRUG INTERACTIONS

- Glecaprevir is inhibitor of P-gp
  - May increase concentration of drugs that are substrates
    - Digoxin, dabigatran
- Ethinyl estradiol-containing products
  - Coadministration of Mavyret may increase the risk of ALT elevations and is not recommended
- Inducers of P-gp/CYP3A decrease plasma concentrations
  - rifampin, carbamazepine, efavirenz, St. John's Wort
- HIV medications – see package insert

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc

GLECAPREVIR/PIBRENTASVIR - DRUG INTERACTIONS

- HMG-CoA Reductase Inhibitors
  - Levels of statin drugs are increased; doses should be adjusted per package insert
- Omeprazole
  - Package insert states no dose adjustments required
    - 40mg daily is highest dose studied
    - 20mg: Coadminister with GLE/PIB
    - 40mg: Give one hour before GLE/PIB
- No interaction with antacids or H2 blockers

Mavyret® [package insert]. North Chicago, IL: AbbVie Inc.

RIBAVIRIN (RBV)

- Administration
  - Weight-based dosing (Twice daily)
    - 1000 mg if > 75 kg
    - 1200 mg if ≥ 75 kg
  - Take evening dose (8 hours apart) in the afternoon to keep from disturbing sleep
- Pregnancy category X
  - Contraindicated in pregnant women or male partners of pregnant women
  - Use 2 effective forms of contraception during treatment and for at least 6 months after completion of therapy (both male and female patients)

LexiComp

RIBAVIRIN

- **Adverse Events**
  - Headache
  - Fatigue
  - Nausea
  - Insomnia
  - Depression
- **Lab abnormalities:**
  - Hemolytic anemia
    - Decrease ribavirin dose by 200 mg daily for a 2g or more drop in HgB
- **Monitoring RBV**
  - CBC & CMP
  - At baseline, weeks 2 and 4, as clinically indicated
  - TSH at week 12
  - Preexisting cardiac issue
- **Ophthalmic exam**
  - Preexisting opthalmic disorders
- **HCG**
  - At baseline
  - Monthly during treatment and for 6 months after treatment

WHO TO TREAT, AND WHEN? WHO TO PRIORITIZE?

- **Who to treat?**
  - **All patients** with chronic HCV should be treated, unless:
    - Life expectancy is < 1 year that cannot be remediated by treating HCV or liver transplantation (AASLD)
    - Uncontrolled comorbidities that can cause HCV treatment discontinuation (Dr. Mera's Opinion)
- **When to Prioritize**
  - Limited resources for medication procurement
  - Limited clinical capacity to treat

WHO TO PRIORITIZE

- Prioritize treatment only if limited by clinical capacity
  - Decompensated cirrhotic
  - Non decompensated cirrhotic first, then F3, F2, F0-F1
  - HCV related nephropathy/vasculitis
  - PWID

Dr. Mera's Opinion

Highest Priority for Treatment Owing to Highest Risk for Severe Complications	Strength of Recommendation
Advanced fibrosis (Metavir F3 or F4)	Class I, Level A
Organ transplant	Class I, Level B
Type 2 or 3 essential mixed cryoglobulinemia with endo organ manifestations (vasculitis)	Class I, Level B
Proteinuria, nephrotic syndrome, or MPGN	Class IIa, Level B

AASLD/ IDSA HCV Guidelines

SPECIAL TREATMENT CONSIDERATIONS

SPECIAL TREATMENT CONSIDERATIONS DRUG-DRUG INTERACTIONS

- Most anti convulsants are contraindicated
  - Due to decreased antiviral levels
- Regimens with protease inhibitors tend to have more drug interactions
  - PrOD (Viekira Pak) (has 2 PI), Simeprevir (Olysio) elbasvir/grazoprevir (zepatier). glecaprevir/pibrentasvir (Mavyret) Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)
- Daclatasvir (Daklinza) has numerous DDI and may need dose adjustment
- Sofosbuvir/velpatasvir (Epclusa) and sofosbuvir/ledipasvir (Harvoni)
  - Decreased absorption with anti acids specially Proton Pump Inhibitors

SPECIAL TREATMENT CONSIDERATIONS RENAL AND HEPATIC IMPAIRMENT

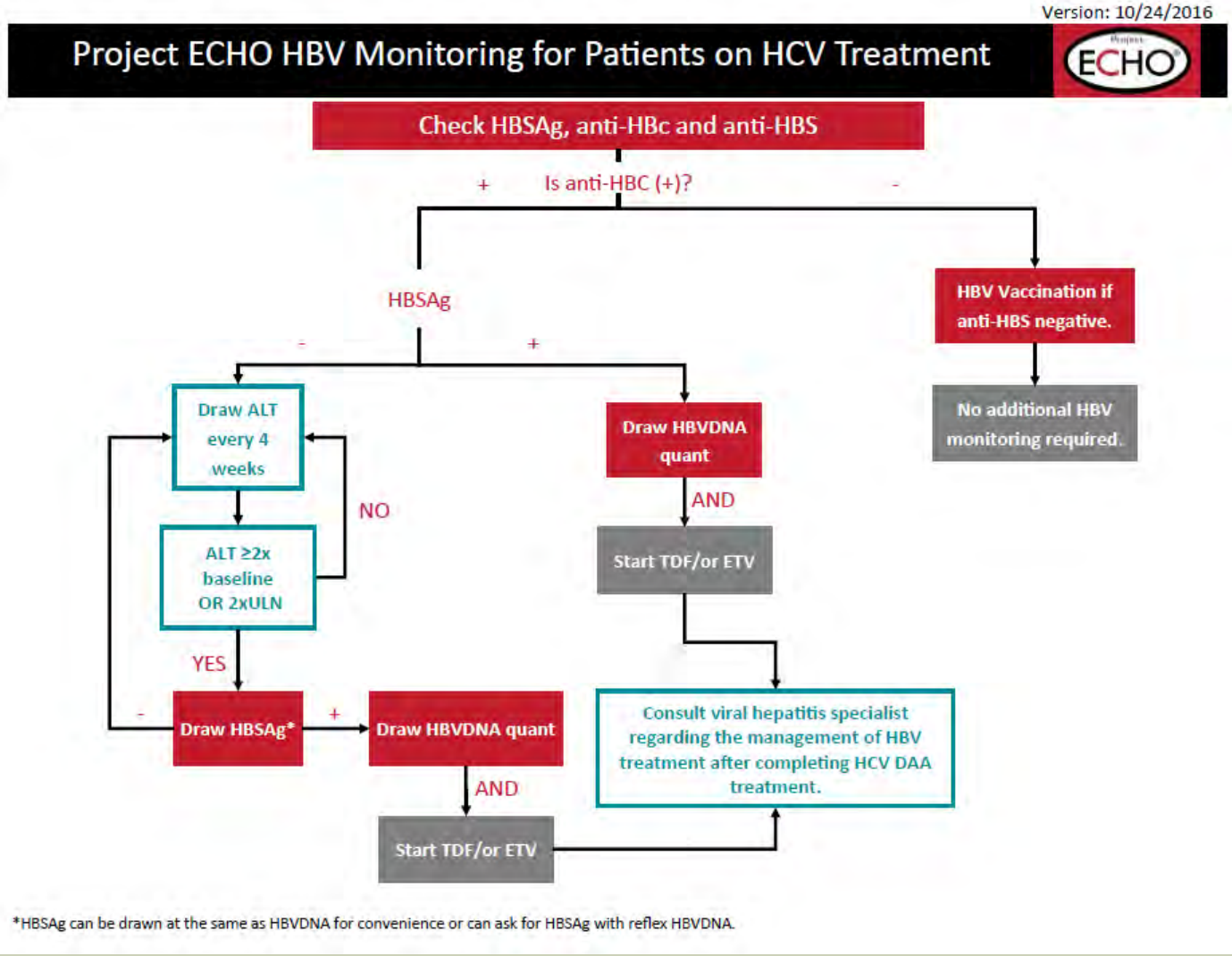
- **Renal Impairment**:
  - elbasvir/grazoprevir (Zepatier) and glecaprevir/pibrentasvir (Mavyret) is approved in ESRD and dialysis
  - PrOD (Viekira Pak) is approved with CrCl <30

- **Hepatic Impairment** (Child Pugh B/C):
  - PrOD (Viekira Pak) (has 2 PI), Simeprevir (Olysio) elbasvir/grazoprevir (zepatier) glecaprevir/pibrentasvir (Mavyret) and Sofosbuvir/velpatasvir/voxilaprevir (Vosevi) are contraindicated
  - May require addition of ribavirin or treatment extension

SPECIAL TREATMENT CONSIDERATIONS GENOTYPES

- **Genotype 1a**
  - Will require Ribavirin if PrOD (Viekira Pak) is used
  - May treat for 8 weeks with sofosbuvir/ledipasvir (Harvoni) if viral load is < 6 million, treatmente naïve and non cirrhotic
  - If elbasvir/grazoprevir (zepatier) is used resistance testing needed
  - Glecaprevir/pibrentasvir (Mavyret) recently approved.
    - 8 week treatment for patients without cirrhosis.
- **Genotype 2 and 3**
  - Sofosbuvir/velpatasvir (Epclusa) is first line therapy but PPI use and low GFR are a problem,
  - Glecaprevir/pibrentasvir (Mavyret) recently approved

SPECIAL TREATMENT CONSIDERATIONS HEPATITIS B STATUS



SUMMARY:
WHAT DO YOU NEED TO KNOW TO SELECT THE BEST TREATMENT OPTION

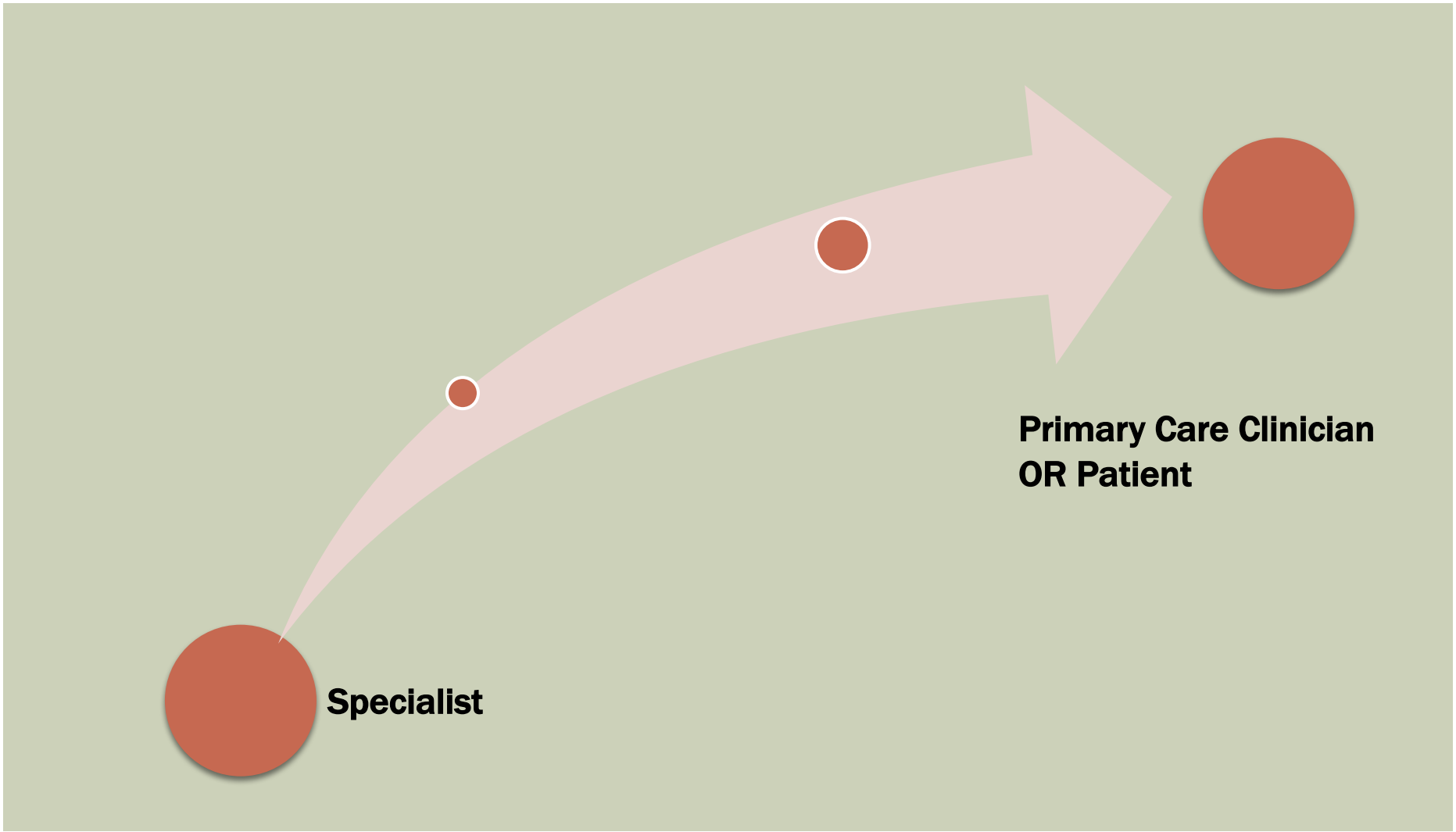
- Genotype
- Viral load for GT1a (< 6 million ?)
- Liver Fibrosis Staging
  - Cirrhosis vs no Cirrhosis
  - If Cirrhotic
    - Compensated vs Decompensated
- Previous treatment status
- Kidney function
  - CrCl < or > 30
  - Dialysis
- Drug interaction check
  - Anti seizure meds, PPI, etc.
- Check Hepatitis B status to monitor reactivation

WHAT NOW?

Join the ECHO Community and start Paving the Road to HCV Elimination in Native America

Treatment

TELEMEDICINE IMPROVES ACCESS BY USING TECHNOLOGY TO BRIDGE DISTANCE



Treatment

THE ECHO MODEL IMPROVES CAPACITY AND ACCESS SIMULTANEOUSLY

MOVING KNOWLEDGE INSTEAD OF PATIENTS

Treatment

SHARING EVIDENCE BASED BEST MEDICAL PRACTICES

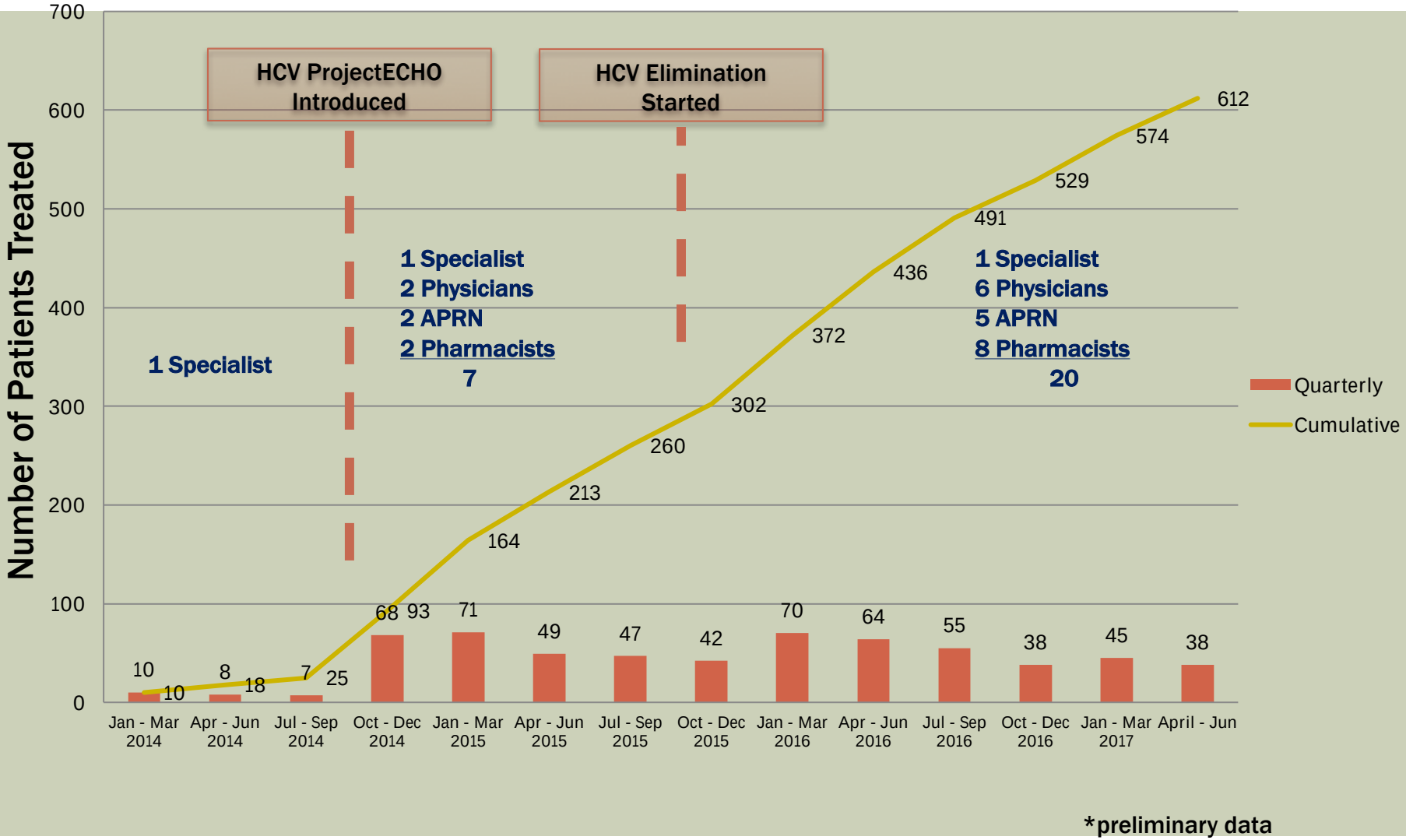
Benefits to Rural Clinicians

- Professional interaction with colleagues with similar interest
  - Less isolation with improved recruitment and retention
- A mix of work and learning
- Obtain HCV certification
- Access to specialty consultation with GI, hepatology, psychiatry, infectious diseases, addiction specialist, pharmacist, patient educator

Benefits of ECHO® model to Health System

- Quality and Safety
- Rapid Learning and best-practice dissemination
- Reduce variations in care
- Access for Rural and Underserved Patients, reduced disparities
- Workforce Training and Force Multiplier
- De-monopolize Knowledge
- Improving Professional Satisfaction/Retention
- Supporting the Medical Home Model
- Cost Effective Care- Avoid Excessive Testing and Travel
- Prevent Cost of Untreated Disease (e.g.: liver transplant or dialysis)
- Integration of Public Health into treatment paradigm

CNHS HCV PROGRAM: CLINICAL CAPACITY EXPANSION* 1/2014 – 6/2017



*preliminary data

HELPFUL RESOURCES

- http://www.hcvguidelines.org/
- http://www.hepatitisc.uw.edu/
  - On-line curriculum on liver disease and HCV, includes clinical studies, clinical calculators, slide lectures
- ECHO guidelines

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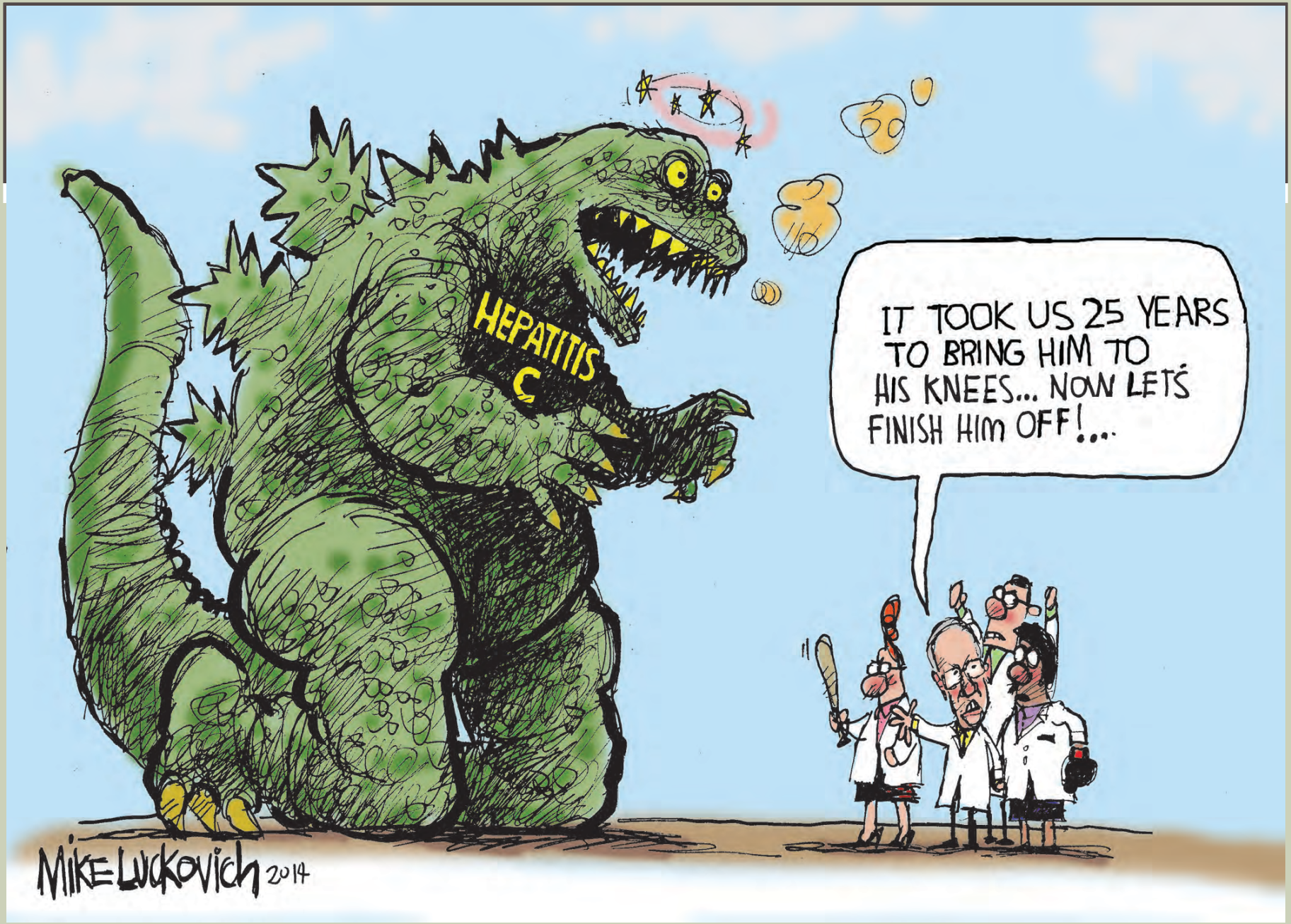
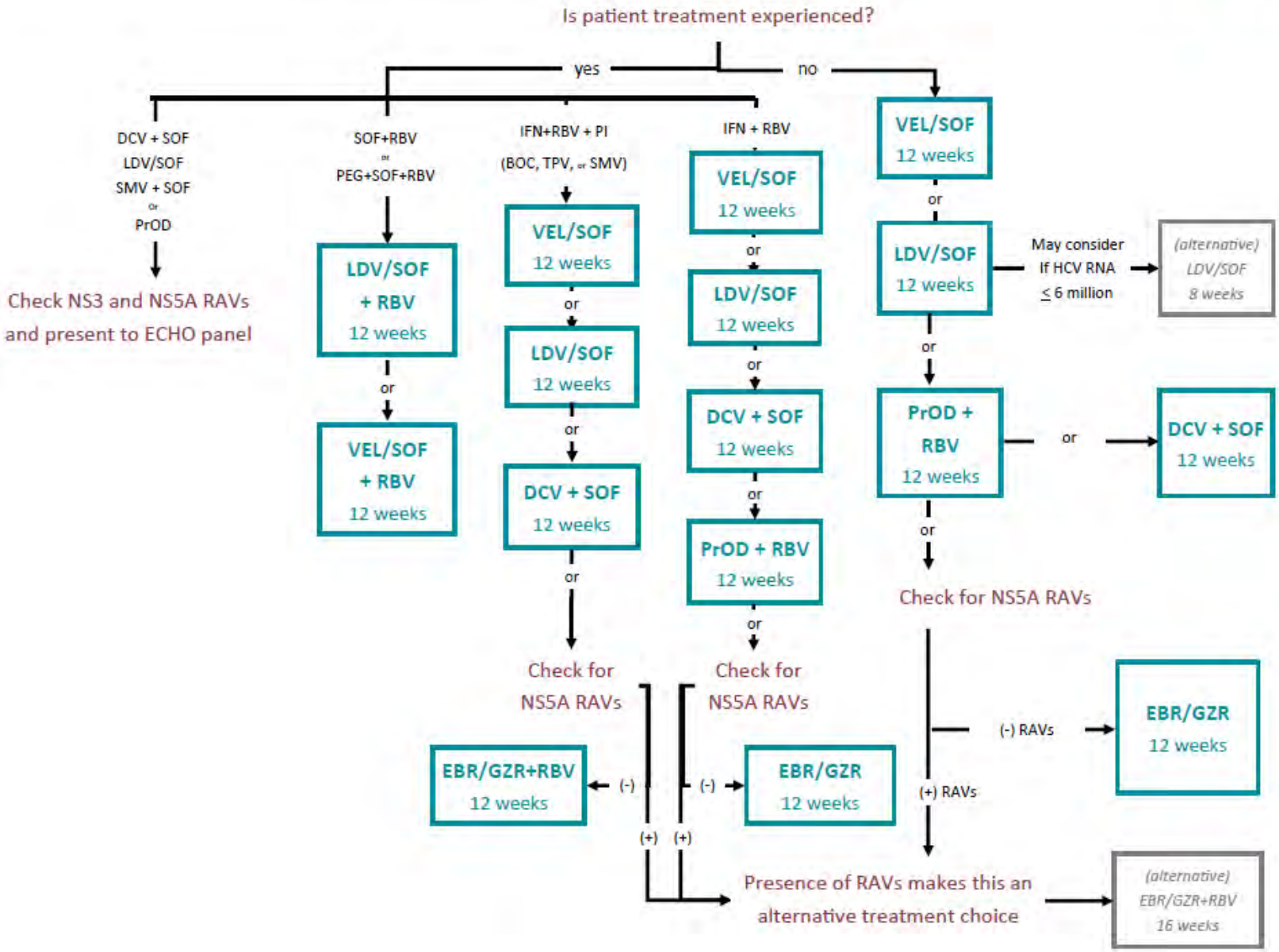

HEPATITIS C
IT TOOK US 25 YEARS TO BRING HIM TO HIS KNEES... NOW LETS FINISH HIM OFF!...
MIKE LUCKOVICH 2014

ECHO DECISION TREES

Version: 7/25/2016

Hepatitis C : Genotype 1a Non-Cirrhotic Treatment Regimen



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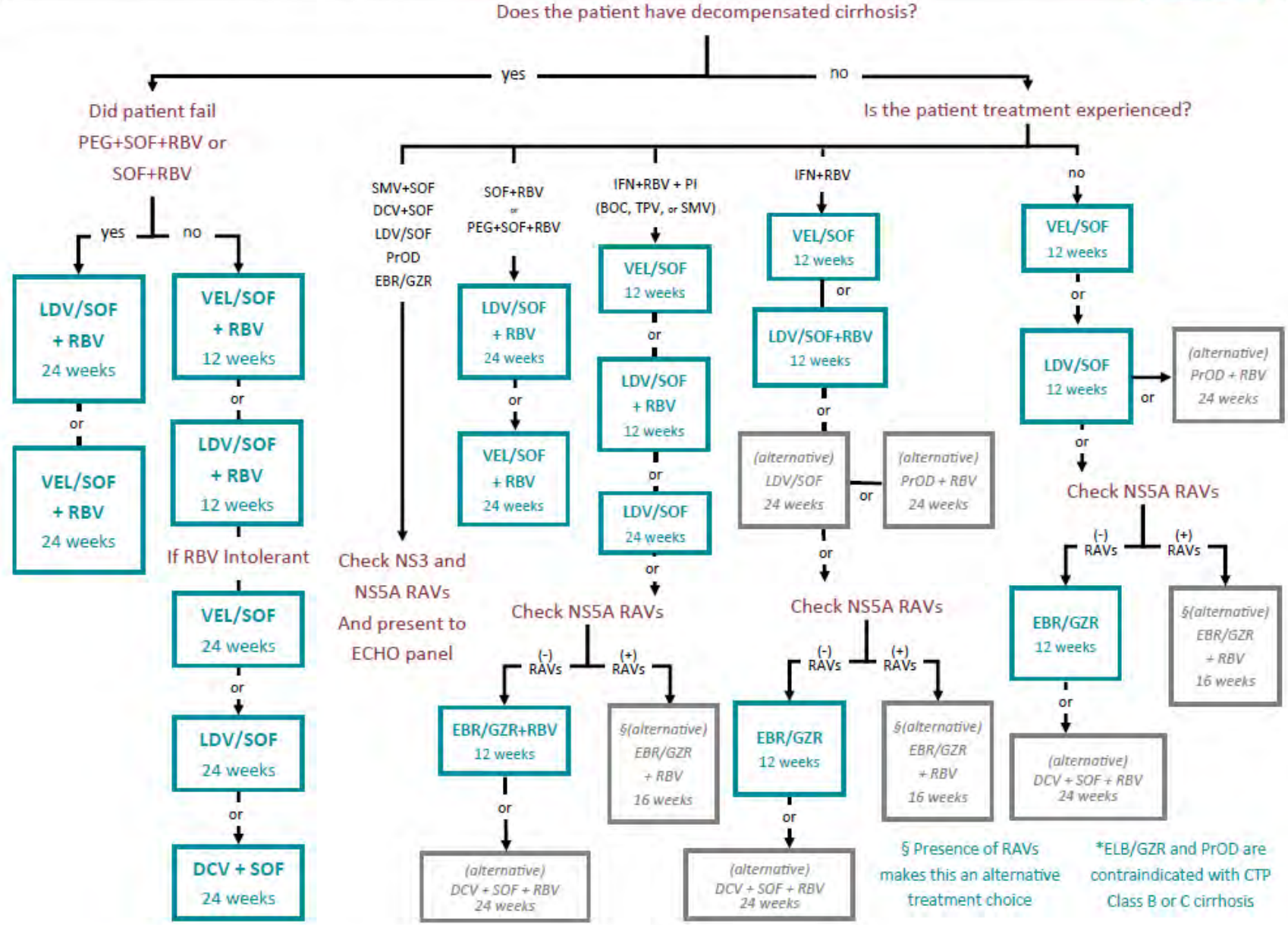
Hepatitis C : Genotype 1a Cirrhotic Treatment Regimen



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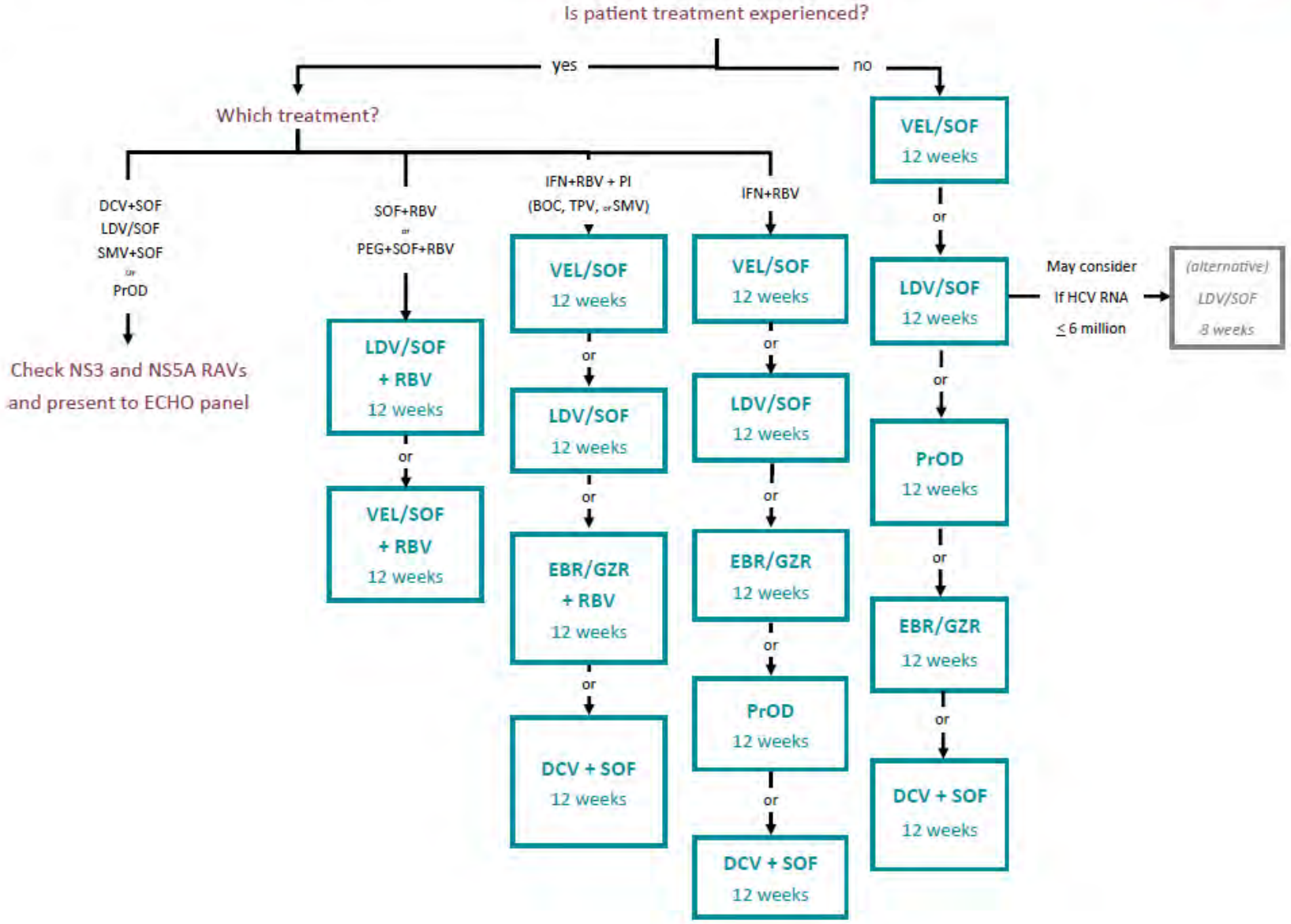
Hepatitis C : Genotype 1b Non-Cirrhotic Treatment Regimen



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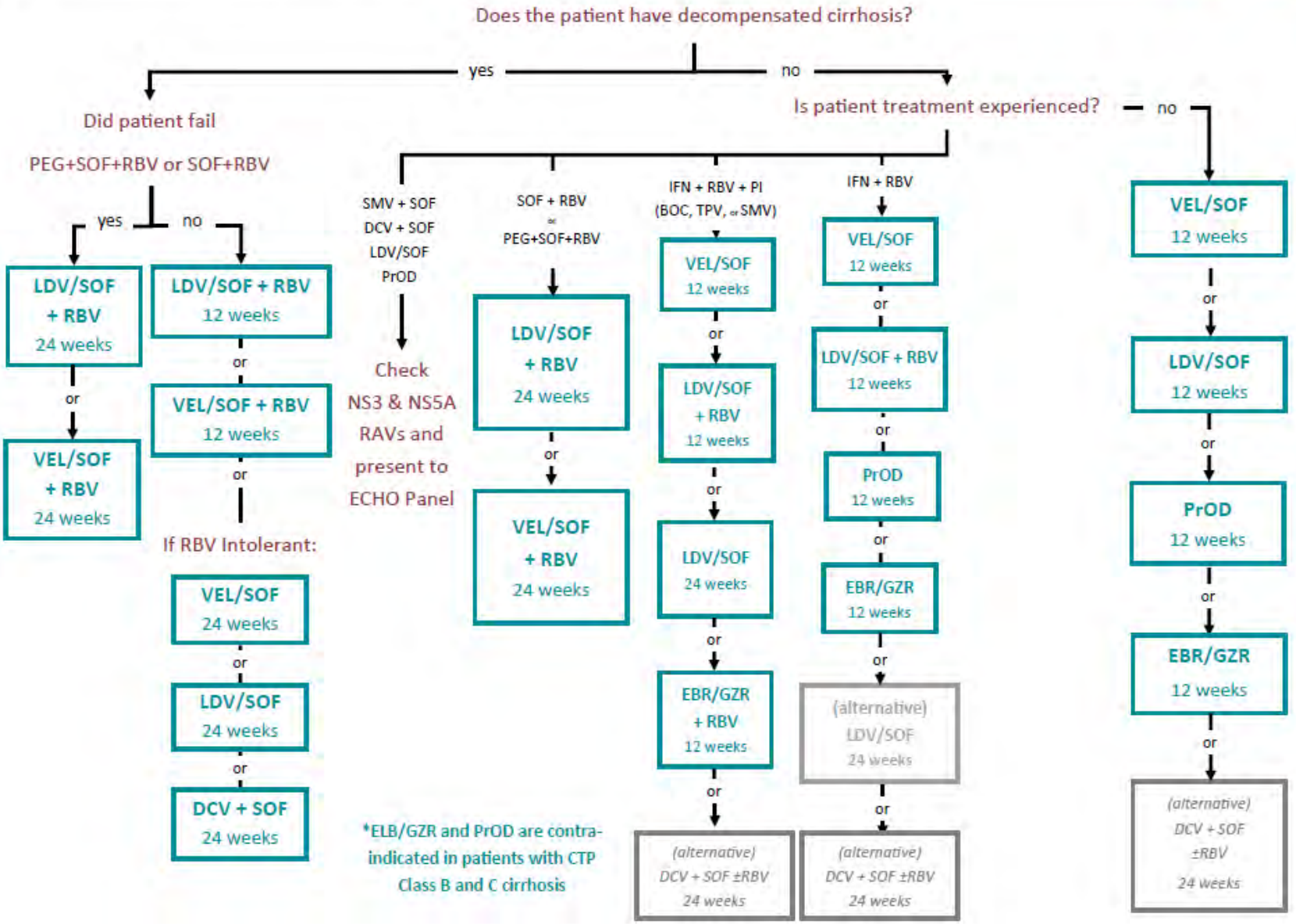
Hepatitis C : Genotype 1b Cirrhotic Treatment Regimen



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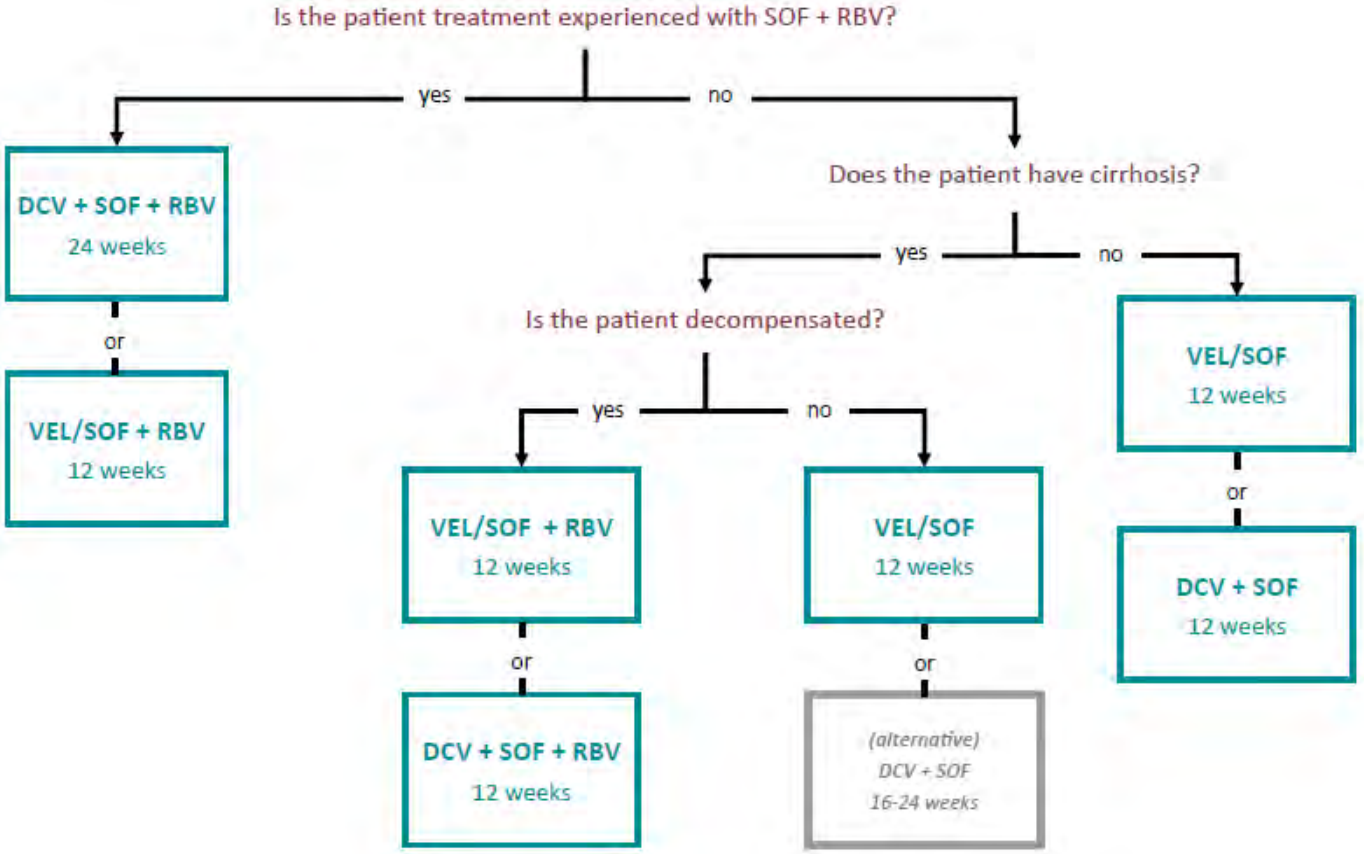
Hepatitis C Genotype 2 Treatment Regimen Decision Tree

Genotype 2 Patients



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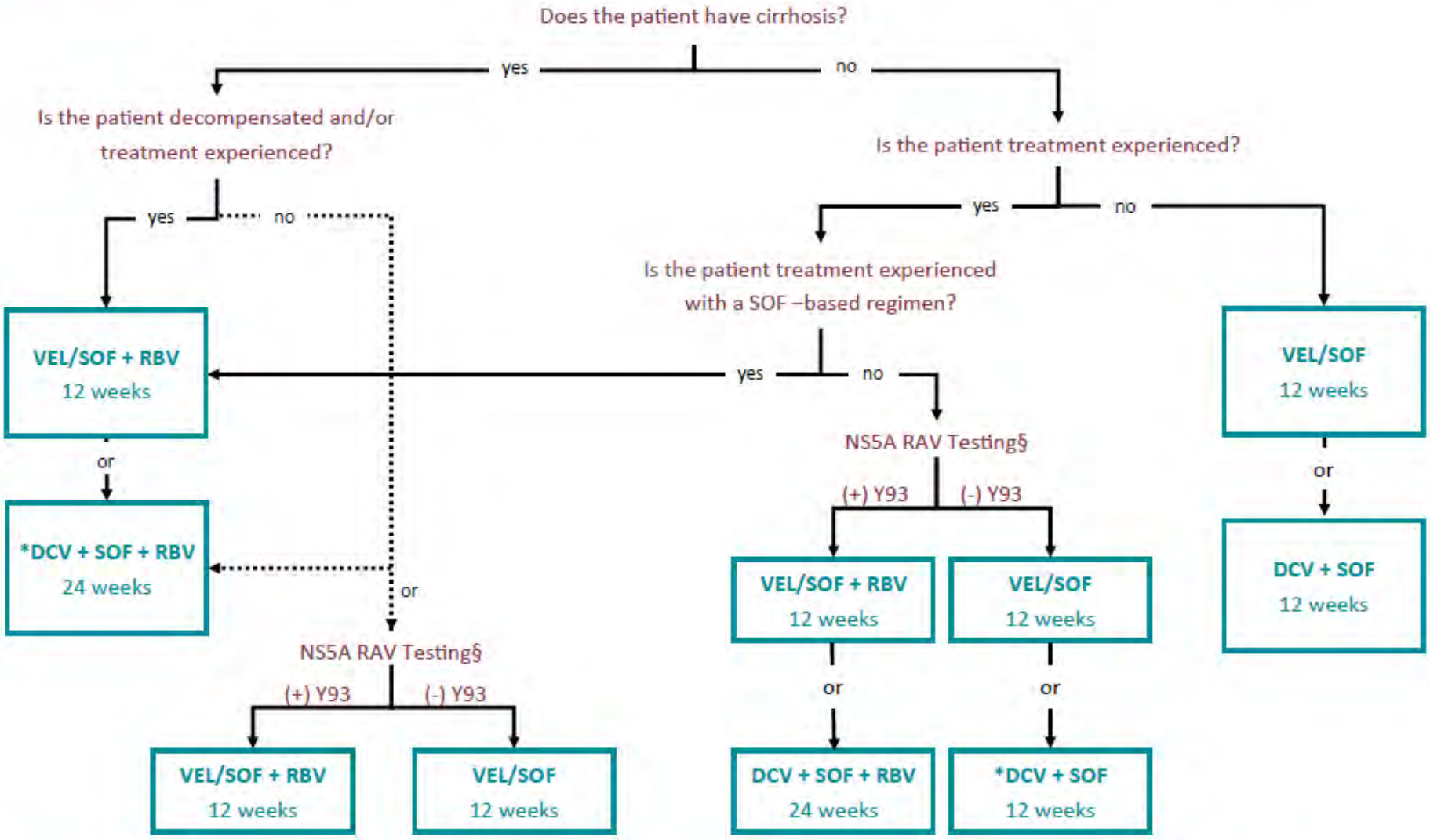
Hepatitis C Genotypes 3 Treatment Regimen Decision Tree

Genotype 3 Patients



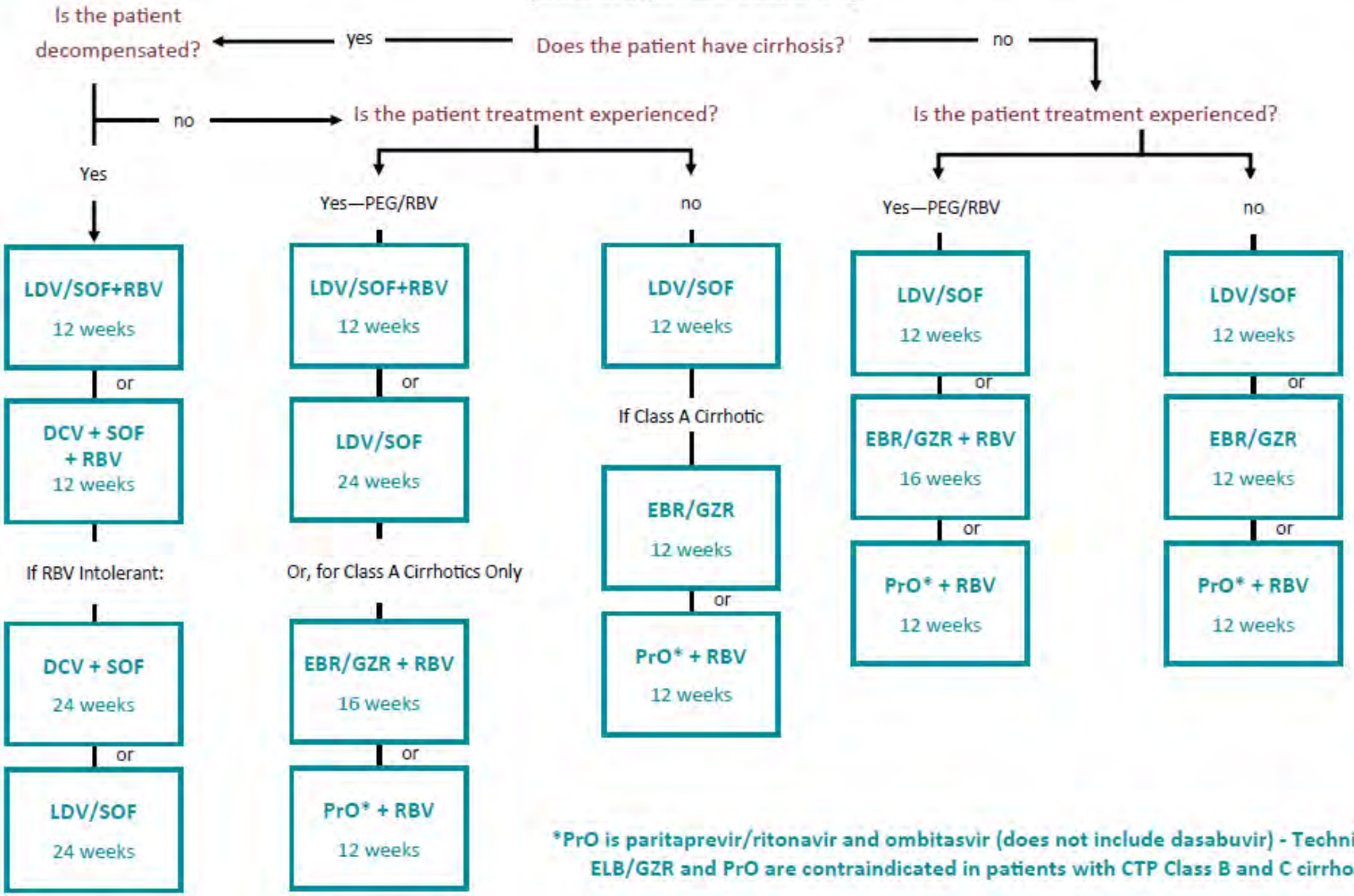
*The optimal duration of therapy for patients with cirrhosis is unknown. The AASLD/ISDA guidelines recommend 24 weeks in patients with compensated cirrhosis and 12 weeks with decompensated cirrhosis. The DCV package insert recommends 12 weeks of therapy in patients with cirrhosis regardless of severity. All patients should receive RBV if they are RBV eligible.

§ If RAV testing is not available, add RBV

Version: 3/3/2016

Hepatitis C Genotypes 4 Treatment Regimen Decision Tree

Genotype 4 Patients



***PrO is paritaprevir/ritonavir and ombitasvir (does not include dasabuvir) - Technivie**
ELB/GZR and PrO are contraindicated in patients with CTP Class B and C cirrhosis.