

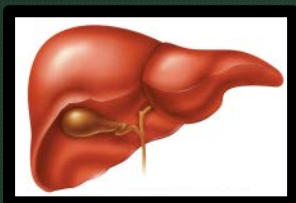
Updates in: Hepatitis C Treatment

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PGY2 Ambulatory Care
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Learning Objectives

1. Discuss the treatment options for each of the hepatitis C genotypes
 2. Identify important considerations to review before using each treatment regimen
 3. Review insurance requirements and preferred treatment regimens
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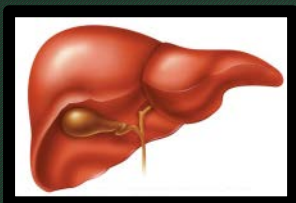
Treatment



Highest Priority

1. Advanced fibrosis (Metavir F3) or compensated cirrhosis (Metavir F4)
2. Organ transplant
3. Type 2/3 mixed cryoglobulinemia with end-organ manifestations
4. Proteinuria, nephrotic syndrome or glomerulonephritis

Treatment



High Priority

1. Fibrosis (Metavir F2)
2. HIV or HBV or other liver co-infection
3. Debilitating fatigue
4. Type 2 diabetes
5. Porphyria cutanea tarda

WHY?

HALT-C

SVR Achieved vs. Not Achieved

**Advanced fibrosis
from HCV infection**

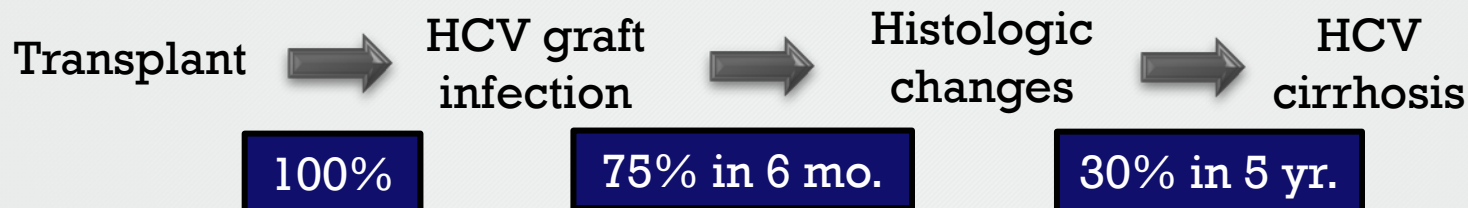
Need for transplant → HR 0.17 (0.06-0.46)

Morbidity/mortality → HR 0.15 (0.06-0.38)

Hepatocellular carcinoma → HR 0.19 (0.04-0.80)

Post-Transplant

HCV Progression



WHY?

Co-Infection

Accelerates disease progression

HIV/HCV ➡ Poor outcomes following transplantation

HBV/HCV ➡ Increased decompensated liver disease
Higher rate of hepatocellular carcinoma

Extrahepatic

Cryoglobulinemia

Arthralgia
Fatigue
Purpura

Renal Disease

Proteinuria
Nephrotic syndrome
Azotemia

Diabetes

Increased insulin
resistance
Progression to
fibrosis and HCC

Insurance Requirements

Sober/Abstaining from drug abuse for a minimum

- **Sobriety date**

Fibrosis Score:

- **F3 or F4**
- **F0-2 with comorbidity**

Liver Biopsy with fibrosis, cirrhosis, vascular changes

Documentation of comorbidities or interactions

Pre-treatment Labs

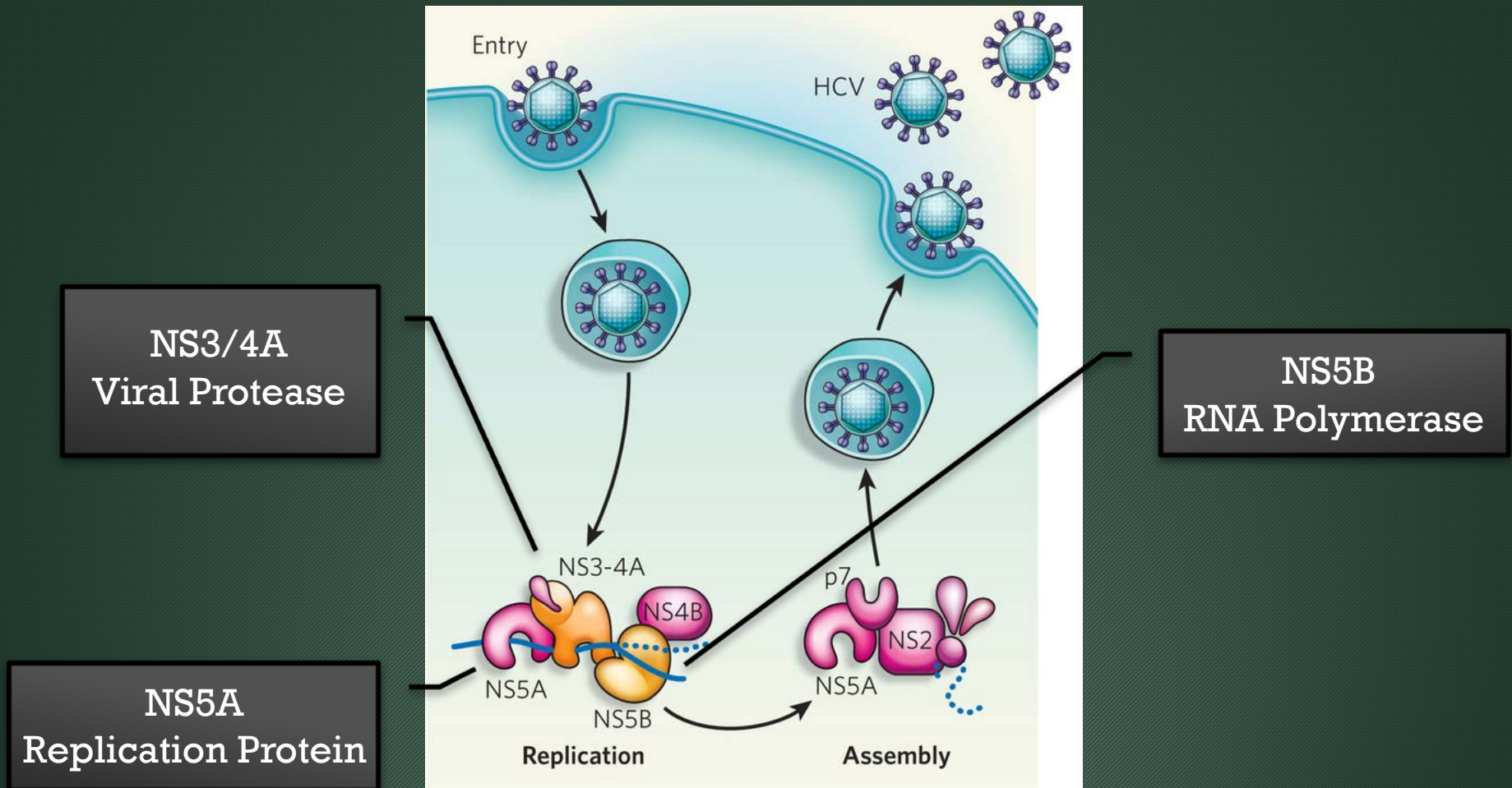
Within
30 days

- CBC
- CMP
- HCV Viral load
- **Drug abuse assay 10 + alcohol**

Anytime
Previously

- HCV Genotype (LIPA)
- Fibrosis score (Fibrosure, biopsy)

HCV Medication Targets



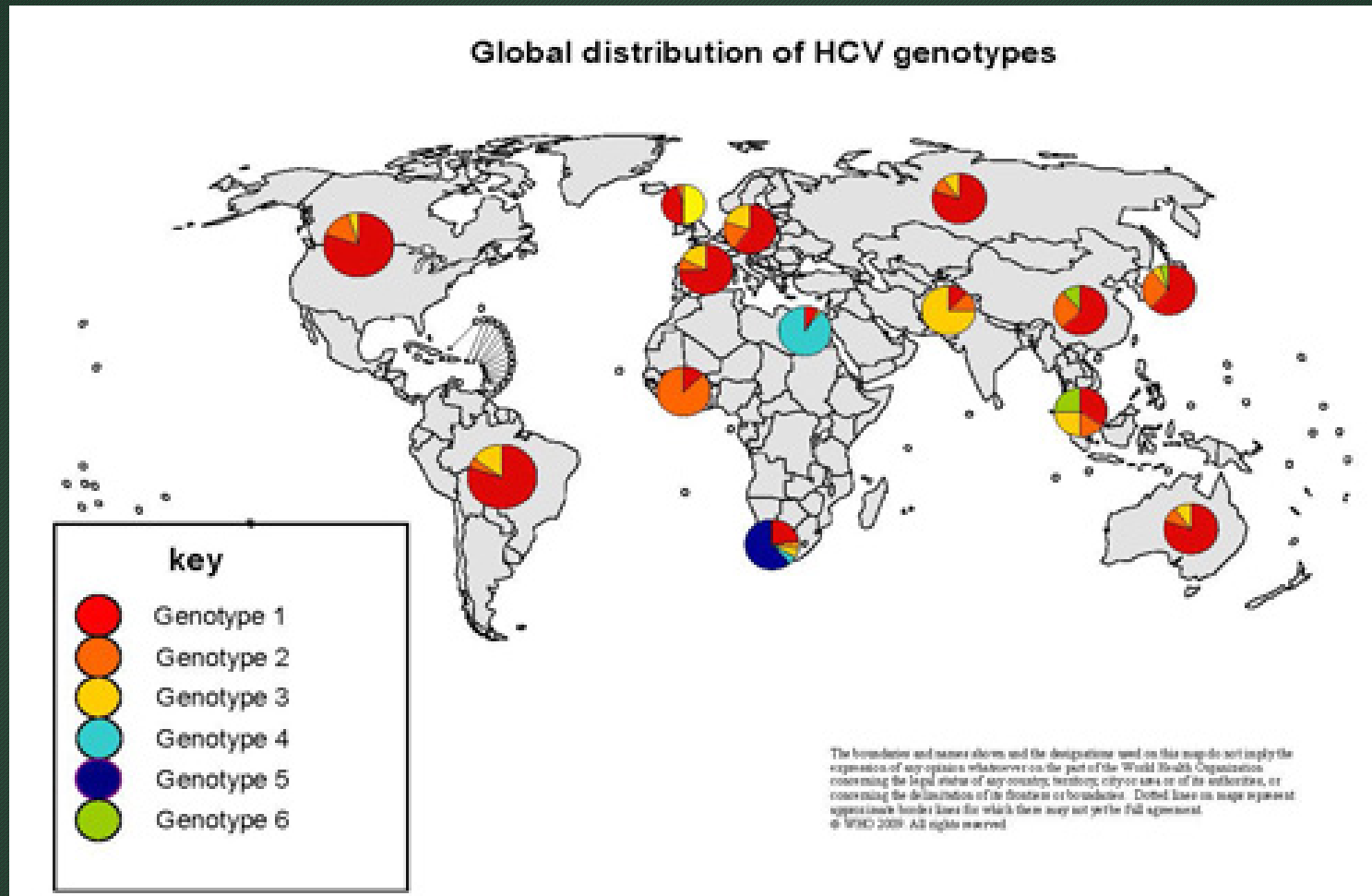
Mechanism

| NS5B | NS3/4A | NS5A | CYP 3A |
|--------------------------|---------------------------------|-------------------------------|----------------------|
| RNA Polymerase inhibitor | Viral protease inhibitor | Replication protein inhibitor | Metabolism inhibitor |
| Dasa bu vir | Parita pre vir | Ombita as vir | Ritonavir |
| Sofos bu vir | Sime pre vir | Ledipa as vir | |
| | | Daclata as vir | |
| *Ribavirin | | | |

Therapy Considerations

1. Genotype
 2. Naive/experienced
 3. Cirrhosis Y/N
 4. Insurance considerations
 5. Co-morbid conditions
 6. Current medications
 7. Adherence
-

HCV Genotypes



Treatment Naïve – Genotype 1a

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|---------------------------|--------------------------|------------|-----------------------|
| NO | Harvoni *VL <6 million | 8* - 12 Weeks | 123/1389 | 98%/98% |
| | Daklinza/Sovaldi | 12 Weeks | 71 | 96% |
| | Viekira + R | 12 Weeks | 305 | 97% |
| | Olysio/Sovaldi | 12 Weeks | 155 | 97% |
| YES | Harvoni | 12 Weeks | 138 | 97% |
| | Daklinza/Sovaldi +/- R | 24 Weeks | 34 | 76% (R) |
| | Viekira + R | 24 Weeks | 261 | 95% |
| | Olysio/Sovaldi +/- R | 24 Weeks | 50 | 88% |

Treatment Naïve – Genotype 1b

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|-----------|---------------------------|-------------------|------------|----------------|
| NO | Harvoni *VL <6 million | 8* - 12 Weeks | 123/1389 | 98%/98% |
| | Daklinza/Sovaldi | 12 Weeks | 71 | 96% |
| | Viekira | 12 Weeks | 419 | 99% |
| | Olysio/Sovaldi | 12 Weeks | 155 | 97% |
| YES | Harvoni | 12 Weeks | 138 | 97% |
| | Daklinza/Sovaldi +/- R | 24 Weeks | 34 | 76% (R) |
| | Viekira | 12 Weeks | 60 | 100% |
| | Olysio/Sovaldi +/- R | 24 Weeks | 50 | 88% |

Treatment Naïve – Genotype 2

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|---|--------------------------|----------|-----------------------|
| NO | Sovaldi + R | 12 Weeks | 214 | 94% |
| | Daklinza/Sovaldi | 12 Weeks | 26 | 92% |
| YES | Sovaldi + R *Includes treatment experienced patients | 16 Weeks | 109 | 78%* |
| | Daklinza/Sovaldi | 16 Weeks | -- | -- |

Treatment Naïve – Genotype 3

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|-----------|---|-------------------|-----|----------------|
| NO | Daklinza/Sovaldi | 12 Weeks | 101 | 97% |
| | Sovaldi + R + PEG | 12 Weeks | 71 | 96% |
| | Sovaldi + R | 24 Weeks | 72 | 90% |
| YES | Daklinza/Sovaldi +/- R *European compassionate use | 24 Weeks | -- | 88%* |
| | Sovaldi + R + PEG | 12 Weeks | 23 | 91% |
| | Sovaldi + R | 24 Weeks | 22 | 82% |

Treatment Naïve – Genotype 4

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|-------------------|--------------------------|----------|-----------------------|
| YES/NO | Harvoni | 12 Weeks | 42 | 95% |
| | Viekira + R | 12 Weeks | 42 | 100% |
| | Sovaldi + R | 24 Weeks | 38 | 95% |
| | Sovaldi + R + PEG | 12 Weeks | 28 | 96% |

Treatment Naïve – Genotype 5/6

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|-----------|-------------------|-------------------|----|----------------|
| YES/NO | Harvoni | 12 Weeks | 41 | 95% |
| | Sovaldi + R + PEG | 12 Weeks | 7 | 100% |

Treatment Naïve Overview

Genotype

1a

1b

2

3

4

5/6

H
V + R
D + S (R)
O + S (R)

H
V
D + S (R)
O + S (R)

D + S
S + R

D + S (R)
S + R + P

H
V + R
S + R

H

H = Harvoni D = Daklinza S = Sovaldi V = Viekira Pak
R = Ribavirin P = PEG Interferon (R) = Add in specific pts

Treatment Experienced – Genotype 1a

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|----------------------|--|--------------------------|------------|-----------------------|
| NO | Harvoni | 12 Weeks | 35 | 94% |
| | Daklinza/Sovaldi | 12 Weeks | 96 | 82-96% |
| | Viekira + R | 12 Weeks | 173 | 96% |
| | Olysio/Sovaldi | 12 Weeks | 40 | 95% |
| YES - Compensated | Harvoni | 24 Weeks | 77 | 97% |
| | Harvoni + R | 12 Weeks | 77 | 96% |
| | Daklinza/Sovaldi +/- R | 24 Weeks | 82 | 82% (R) |
| | Viekira + R | 24 Weeks | 98 | 97% |
| | Olysio/Sovaldi +/- R *Q80K negative | 24 Weeks | 38 | 92% |

Treatment Experienced – Genotype 1b

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|---|--------------------------|----------|-----------------------|
| NO | Harvoni | 12 Weeks | 35 | 94% |
| | Daklinza/Sovaldi | 12 Weeks | 96 | 82-96% |
| | Viekira | 12 Weeks | 91 | 100% |
| | Olysio/Sovaldi | 12 Weeks | 40 | 95% |
| YES | Harvoni | 24 Weeks | 77 | 97% |
| | Harvoni + R | 12 Weeks | 77 | 96% |
| | Daklinza/Sovaldi +/- R | 24 Weeks | 82 | 82% (R) |
| | Viekira | 12 Weeks | 60 | 100% |
| | Olysio/Sovaldi +/- R *Extrapolated from 1a | 24 Weeks | 38 | 92% |

Treatment Experienced – Genotype 2

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|----------------------|--------------------------|-------------------|----|----------------|
| YES/NO | Sovaldi + R | 16-24 Weeks | 32 | 87-100% |
| *Fail PEG/R | Sovaldi + R + PEG | 12 Weeks | 16 | 94% |
| YES/NO | Daklinza + Sovaldi +/- R | 24 Weeks | -- | -- |
| *Fail Sovaldi | Sovaldi + R + PEG | 12 Weeks | 16 | 94% |

Treatment Experienced – Genotype 3

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|----------------------|--------------------------|----------|-----------------------|
| NO | Daklinza/Sovaldi | 12 Weeks | 7 | 84% |
| | Sovaldi + R + PEG | 12 Weeks | 181 | 94% |
| YES | Daklinza/Sovaldi + R | 24 Weeks | -- | --% |
| | Sovaldi + R + PEG | 12 Weeks | 181 | 82% |

Treatment Experienced – Genotype 4

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|------------------|-------------------|--------------------------|----------|-----------------------|
| YES/NO | Harvoni | 12 Weeks | 42 | 95% |
| | Viekira + R | 12 Weeks | 41 | 100% |
| | Sovaldi + R | 24 Weeks | 29 | 87% |
| | Sovaldi + R + PEG | 12 Weeks | 28 | 96% |

Treatment Experienced – Genotype 5/6

| Cirrhosis | Regimen | Length of therapy | n | Efficacy (SVR) |
|-----------|-------------------|-------------------|----|----------------|
| YES/NO | Harvoni | 12 Weeks | -- | --% |
| | Sovaldi + R + PEG | 12 Weeks | 7 | 100% |

Treatment Experienced Overview

Genotype

1a

1b

2

3

4

5/6

H (R)
V + R
D + S (R)
O + S (R)

H (R)
V
D + S (R)
O + S (R)

D + S
S + R
S + R + P

D + S (R)
S + R + P

H
V + R
S + R
S + R + P

H

H = Harvoni D = Daklinza S = Sovaldi V = Viekira Pak
R = Ribavirin P = PEG Interferon (R) = Add in specific pts



Sofosbuvir – Sovaldi

Dosing

400 mg daily

Dosage adjustments

Not studied in $\text{CrCl} \leq 30 \text{ mL/min}$

Administer with or without food

Sofosbuvir – Sovaldi

Adverse effects:

Fatigue
Headache
Fever
Insomnia
Pruritis/rash
Nausea
Diarrhea
Weakness
Myalgia

Interactions:

Amiodarone

Pgp Inhibitors

Ritonavir

Cyclosporine

Verapamil

Azoles

Pgp Inducers: AVOID

Antiepileptics

Rifampin, St John's Wort

Simeprevir– Olysio

Dosing

150 mg daily

Dosage adjustments

Not studied in $\text{CrCl} \leq 30 \text{ mL/min}$

Mutations

NS3 Q80K - Must add ribavirin

Administer with food

Simeprevir – Olysio

Adverse effects:

Fatigue

Headache

Insomnia

Pruritis/rash

Photosensitivity

Nausea

Diarrhea

Myalgia

Interactions:

CYP 3A4

Inducers/Inhibitors

Pgp Inducers/Inhibitors
and Substrates

Digoxin

Contains sulfa moiety

Monitor for signs of
hypersensitivity

Ledipasvir/Sofosbuvir – Harvoni

Dosing

Ledipasvir 90 mg

Sofosbuvir 400 mg

Dosage adjustments

None required

May accumulate in $\text{CrCl} \leq 30 \text{ mL/min}$

Administer with or without food,
tablet contains lactose

Ledipasvir/Sofosbuvir – Harvoni

Adverse effects:

Fatigue
Headache
Fever
Insomnia
Pruritis/rash
Nausea
Diarrhea
Weakness
Myalgia

Interactions:

Amiodarone
Bradycardia
Antacids
Separate by 4 hours
Tenofovir
Increased concentration
Pgp inhibitors, inducers
or substrates

PPIs: Max omeprazole
20 mg daily or equivalent



Daclatasvir – Daklinza

Dosing

60 mg daily

Dosage adjustments: CYP 3A4

Strong inhibitors: 30 mg daily

Moderate inducers: 90 mg daily

Strong inducers: Contraindicated

Administer with or without food

Daclatasvir – Daklinza

Adverse effects:

Fatigue

Headache

Fever

Insomnia

Pruritis/rash

Nausea

Diarrhea

Increased serum
lipase

Interactions:

Amiodarone

Digoxin

Increased concentration

Pgp and 3A4 inhibitors,
inducers

Dose adjust or avoid

Pgp and CYP 3A4
substrates

Increased concentration

Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir: Viekira Pak

Dosing

PRO: 2 tablets qAM

d: 250 mg BID



Dosage adjustments

Not studied in ESRD

Avoid in Child-Pugh class B/C

Administer with food

Ombitasvir, Paritaprevir, Ritonavir and Dasabuvir: Viekira Pak

Adverse effects:

Fatigue

Headache

Fever

Insomnia

Pruritis/dermatitis

Nausea/Diarrhea

Myalgia

Decreased Hgb

Increased bili/ALT

Interactions:

Estrogen products

Digoxin

Increased concentration

Pgp and 3A4 inhibitors,
inducers, substrates

MANY interactions

HIV co-infection

Avoid protease
inhibitors

Ribavirin

Dosing:

- Weight-based

 - <75 kg: 1000 mg daily

 - ≥75 kg: 1200 mg daily

- Daily in 2 divided doses

 - WITH food

Ribavirin

Adverse effects:

Hemolytic Anemia
Fatigue
Headache/Insomnia
Alopecia
Nausea/Anorexia
Myalgia/Arthralgia
Flu-like Symptoms
Bilirubin elevation

Pearls:

Oral

- Tablet
- Capsule
- Solution

Interactions:

PEG or NRTI increase AE

Dose adjust for:

- Renal dysfunction
- Toxicity

Insurance Considerations

| Insurance Type | Insurance Provider | Preferred Regimen | Notes |
|----------------|--------------------|-------------------|--|
| Medicaid | Passport | Harvoni | *Recent switch from Viekira F2 now covered |
| | Coventry | Harvoni | |
| | Wellcare | Harvoni | |
| | Humana | Harvoni | *3 monthly negative tox screens |
| Private | Express Scripts | Viekira Pak | |
| | CVS Caremark | Harvoni | |
| | Envision Rx | Harvoni | |
| | Aetna | Harvoni | |
| | Optimum Rx | Harvoni | |

Target Conditions and Med Rec

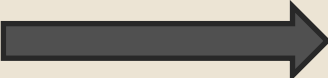
HIV/HBV Co-infection

Cardiovascular Disease

GERD/PUD

HIV/HBV Co-Infection

NRTI

Tenofovir (TDF only)  Caution with Harvoni

NNRTI

Efavirenz
Etravirine  Avoid with Olysio, Viekira
Nevirapine Increase Daklinza dose

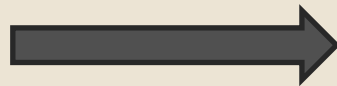
PI

Ritonavir  Avoid with Viekira, Olysio
ANY boosted PI Decrease Daklinza dose

Cardiovascular Disease

Arrhythmia

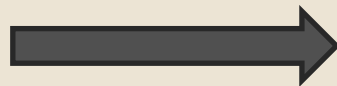
Amiodarone
Digoxin



Bradycardia with Sovaldi
Increased dig with Daklinza

Antihypertensives

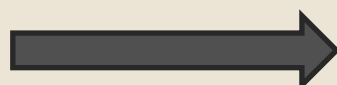
Carvedilol
CCB



Bradycardia with Sovaldi
Increase CCB with Daklinza,
Olysio

Anticoagulants

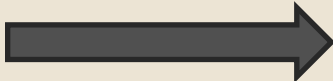
Dabigatran
Anti-Xa Inhib.



Avoid with Daklinza
Avoid with Viekira

HIV Co-Infection

GERD/PUD

Proton Pump Inhibitors  Avoid with Harvoni
Unless = 20mg omeprazole

Therapeutically equivalent PPI doses^a

| PPI | Low dose (mg/d) | Standard dose (mg/d) |
|--------------|-----------------|----------------------|
| Esomeprazole | 20 | 40 |
| Lansoprazole | 15 | 30 |
| Omeprazole | 10-20 | 20-40 |
| Pantoprazole | 20 | 40 |
| Rabeprazole | 10 | 20 |

Target Medications – 3A4, Pgp

Inducers

Antiepileptics

- Phenytoin
- Phenobarbital
- Carbamazepine

Anti-infectives

- Rifampin

Herbals

- St. Johns Wort

Inhibitors

Anti-infectives

- HIV protease inhibitors
- Erythromycin
- Azole antifungals

Cardiovascular

- Diltiazem
- Verapamil
- Amiodarone

Herbals

- Grapefruit

Target Medications – Pgp/3A4

PGP/3A4 Interactions

HMG-COA Reductase Inhibitors

Statins

Daklinza, Viekira

Moderate Inducers

Efavirenz

Etravirine

Dexamethasone

Modafinil

Daklinza, Viekira,
Olysio

Substrates

Fluticasone

Inhaled/Nasal Steroids

Viekira

Adherence

Every pill, every day, at about the same time!

Harvoni: 1 pill once daily

Daklinza/Sovaldi: 2 pills once daily

Viekira Pak: 3 pills qAM, 1 pill qHS

Ribavirin: Always BID with FOOD

Treatment Timeline

Initial workup:
Up to 1-2 months

| Start | Week 2 | Week 4/5 | Week 12/13 | Week 24 | Week 36 |
|-------|---------------------|----------------------|----------------------|----------------------|----------------------|
| | CBC Riba only | CBC CMP HCV VL | CBC CMP HCV VL | CBC CMP HCV VL | CBC CMP HCV VL |
| | | MD Visit | MD Visit | MD Visit | MD Visit |

Recap of Process

Treatment Steps

1. Clean + Sober >6 months
 2. Baseline Labs/MD visit
 3. Full Medication Reconciliation
 4. Initial PA for medication
 5. Appeal Process
 6. Follow Up
 7. HCC Review
-

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