

**New York State
Department of Corrections and Community Supervision
Division of Health Services**

Hepatitis C Primary Care Practice Guideline

INTRODUCTION

These practice guidelines represent an approach to the current management of hepatitis C disease, consistent with community and FDA standards, and appropriate in our correctional setting.

This field of science has been evolving very rapidly. New information and treatment agents have resulted in shorter, safer therapeutic options with high cure rates. As new information becomes available, these guidelines will be periodically reviewed and updated.

Acute Hepatitis C is defined as infection manifesting itself within 6 months of exposure. The average incubation period for acute hepatitis C is 6 to 12 weeks, but may range from 2 to 26 weeks. Persons with acute disease are typically asymptomatic or have a mild clinical illness with a self-limiting course. Fulminant hepatic failure in acute disease is extremely rare.

It is estimated that 15-25% of patients with acute hepatitis C will spontaneously clear the virus within 12 weeks (and no later than 20 weeks) from the onset of symptoms. Those who do not clear the virus go on to develop chronic hepatitis C.

If there is clinical suspicion of acute hepatitis C or a significant exposure has occurred, an HCV RNA assay (BioReference # 3376) along with HCV antibodies must be ordered to make the diagnosis. HCV RNA usually is detected in the serum within 8 weeks post exposure, but can be delayed up to 6 months. It is therefore recommended that HCV RNA be checked at baseline, 4 weeks, 12 weeks and 6 months post exposure.

HCV antibodies are not present in the serum during the acute phase of the disease, and do not become positive until 8 weeks post exposure: usually between 2 and 6 months.

Generally hepatitis C should not be treated in the acute phase in order to allow for spontaneous clearing of the virus. Treatment of acute hepatitis C will only be done after consultation with IFD (infectious disease specialty), and should be deferred for at least 12 weeks from the onset of symptoms.

Chronic Hepatitis C: Of the approximately 75-85% who develop chronic hepatitis C, about 20% will eventually develop cirrhosis over a period of 20 to 30 years. The progression to chronic liver disease in the majority of patients is insidious, advancing without symptoms or physical signs. HIV co-infected and diabetic patients may have an accelerated course. Frequently, chronic hepatitis C is not recognized until symptoms appear with the development of advanced liver disease.

Once cirrhosis has developed, up to 3% per year will develop hepatocellular carcinoma. In the U.S., chronic hepatitis C is the most common cause of end stage liver disease and the leading indication for a liver transplant.

Patients with chronic hepatitis C are at higher risk for morbidity and mortality if they develop either acute hepatitis A or B. Determination of immunity status to both hepatitis A and B is important and lack of immunity should prompt vaccination.

Epidemiology and Pathogenesis

The hepatitis C virus (HCV) was identified in the late 1980s. It is a small, enveloped single stranded RNA virus of the Flaviviridae family. It includes a heterogeneous group of viruses. There are several different genotypes and subtypes. Prevalence of the different genotypes varies worldwide. Genotype 1 is responsible for 70-80% of chronic hepatitis C in the US. Genotypes 2 and 3 are also seen, while other genotypes are rare in the US.

In 1999 the WHO estimated there was a worldwide prevalence of HCV of 170 million people. In the US:

- There are about 3 million people currently infected with chronic hepatitis C.
- The peak prevalence is among those born between 1945 and 1965, accounting for approximately 75% of HCV cases. This prevalence is tied to an increase in IV drug use during the 70s and 80s.
- HCV infection is responsible for 8,000 to 13,000 deaths per year. It is the leading cause of chronic liver disease and hepatocellular cancer, and it accounts for the majority of liver transplants.
- There has been a significant decline in the number of new cases of HCV disease since the 1980s. The decline is mostly due to changes in practices of IV drug users and improved screening of blood products.
- Approximately 30% of the patients with HIV are co-infected with hepatitis C.
- An estimated 10-25% of the adult prison population is infected with chronic hepatitis C.

HCV is transmitted through the percutaneous exposure of infectious blood or blood products, or body fluids contaminated with infectious blood.

Risk factors for acquiring HCV infection are:

- Foremost IV drug abuse and needle sharing
- Receipt of contaminated blood or blood products, or organ transplantation prior to 1992
- Infusion of clotting factor before 1987
- Needle sticks in healthcare workers
- Sharing personal care items like razors or toothbrushes
- Tattoos and body piercings with unsterile equipment

Less commonly:

- Intranasal cocaine use
- Sex with multiple partners

- Transmission between monogamous heterosexual partners and perinatal transmission from mother to child are rare.

The hepatitis C virus is not directly cytopathic to the liver cells, but it is the host's immune response that causes both the hepatic and extra-hepatic manifestations of the disease. In the majority of cases, despite the host's immune response, the virus is not cleared from the body and this leads to chronic hepatitis. Factors that play a role in the outcome of the disease are age, gender, alcohol abuse, viral characteristics and genetic makeup of the host.

Because of its high genetic variability, patients who have recovered from an acute infection or have been cured from a chronic infection can again become infected if re-exposed to the hepatitis C virus.

To date there is no vaccine against HCV, nor is there any pre or post- exposure prophylaxis in the way of medications or immunoglobulins.

SCREENING (Attachment 1)

Inmates that are at risk for hepatitis C should be screened for the presence of antibodies to HCV. **Also, all adults born between 1945 and 1965 should be offered a once in a lifetime screening test for HCV.**

Screening is done with an enzyme immunoassay blood test (EIA).

Inmates with the following risk factors should be screened for HCV:

- Born between 1945 and 1965
- History of IV drug use
- HIV infection
- Intranasal cocaine use
- STD's
- Unprotected sex with multiple sexual partners or known HCV infected sexual partner
- Blood transfusions or solid organ transplant before 1992
- Hemodialysis
- Infusion of clotting factor before 1987
- Tattoos or body piercing with unsterile equipment
- Sharing of personal items like razors or toothbrushes
- Unexplained elevated LFT's or signs/symptoms of hepatitis
- Children of mothers with HCV infection
- Known exposure to HCV
- Needle stick or mucosal exposure to HCV infected blood

DIAGNOSIS

If the screening test for hepatitis C is positive, then a confirmatory test needs to be done. All confirmatory tests directly detect HCV RNA. **Note that a positive hepatitis C antibody screen alone does not indicate hepatitis C disease.**

A positive HCV RNA (viral load- VL) will confirm the diagnosis of chronic hepatitis C. A negative result indicates either a resolved infection with hepatitis C or a false positive screening test.

If the screening test for HCV is positive; but viral RNA is negative and there is a strong suspicion for HCV disease, then the patient can be retested for viral RNA after several months. This test should be repeated only once.

An indeterminate screening test should be worked up as a positive screen.

In immune-compromised patients (including those with HIV, patients on hemodialysis, transplant recipients) and in those recently exposed to HCV, the HCV antibody may not be detected in the screening test. In these patients, if hepatitis C is strongly suspected, then a quantitative HCV RNA needs to be done despite a negative screening test.

The confirmatory quantitative test used in DOCCS is the **COBAS/TaqMan HCV RNA PCR assay** (BioReference # 3376).

Confirmatory testing will be recorded in the FHS1 medical problem list, utilizing the problem codes listed in the next section. The blue "Hepatitis C Data Flow Sheet," Form 3132, can also be utilized for documentation.

HCV education, risk reduction, and treatment options will be discussed with the patient and documented in the ambulatory health record (AHR). (Patient information sheets: [English](#), [Spanish](#)).

REPORTING AND DOCUMENTATION

Persons who have hepatitis C disease must be reported to the county health department using the procedure outlined in Health Services Policy 8.01. In the policy you will find links to the appropriate forms that need to be completed and sent to the local DOH.

DOCCS' Regional Infection Control Nurse will be notified.

Along with regular AHR visit notes, entries will be made on the FHS1 Problem List to document HCV disease and management.

The following FHS1 problem list codes are to be utilized to document test results and hepatitis C management:

- 0701 - Hep C Disease
- 0702 - Hep C Antibody Positive
- 0703 - Hep C Rx Initiated
- 0704 - Hep C Rx Discontinued, Medical
- 0705 - Hep C Rx Discontinued, Other
- 0706 - Hep C Rx Completed
- 0707 - Hep C Rx Refused
- 0708 - Hep C Rx Contraindicated
- 072A - Hep C AB pos, Viral RNA neg
- 072B - Hep C testing refused
- 0725 - Hep C Rx Deferred
- 0726 - Hep C Genotype Known
- 0727 - Hep C Antibody Negative
- 0728 - Hep C Sustained Viral Response
- 0729 - Hep C trt. failure/relapse

Note the following:

- If the screening test is indeterminate, it will be treated as a positive screen and code 0702 will be used (Hepatitis C Antibody Positive); add a notation in the comment section that the screening test was indeterminate.
- Code 0701 (“Hepatitis C Disease”) will be added **only** if the HCV RNA is also positive. If the screening test is positive (or indeterminate), but the confirmatory HCV RNA is negative, then code 072A (“Hep C AB pos, Viral RNA neg”) should be entered.
- When code 0703 is entered (Hepatitis C Rx initiated), add regimen used and length of treatment in the comment section.
- If viral RNA is not detected after treatment, this indicates a Sustained Virologic Response (SVR) and should be coded as such (code # 0728). Code # 072A should not be used after successful treatment.
- Code 0701 (Hepatitis C Disease) should be inactivated once a patient has achieved SVR. Such patients are considered cured and no longer need to be followed for hepatitis C disease unless there are indications of re-infection or relapse. Patients with advanced liver disease need monitoring as outlined in other sections of these guidelines.

EVALUATING HEPATITIS C

Once the diagnosis of chronic hepatitis C and has been confirmed, then the genotype needs to be determined. Identifying the genotype is important for determining both the type and length of treatment. Management of chronic hepatitis C depends on the genotype, stage of disease, the presence or absence of cirrhosis, and whether or not the patient was previously treated.

A liver biopsy is not routinely needed to determine eligibility for treatment. However the presence or absence of cirrhosis needs to be determined in order to decide the course of treatment. Staging of the disease can be done with the use of clinical, laboratory and other non-invasive data. If a liver biopsy has not been performed, patients that are being considered for treatment will have a FibroSure test (BioReference code # 6124) to determine fibrosis stage. Patients with suspected cirrhosis (stage 4 fibrosis) will also undergo an abdominal/liver ultrasound with portal vein doppler to determine the extent of liver disease and/or the presence of portal hypertension. Patients with cirrhosis may require a different regimen than those who do not. Patients with decompensated cirrhosis are not eligible for treatment with many current regimens.

In addition, the APRI (AST to Platelet Ratio Index) score can also be calculated to help determine the stage of fibrosis and presence of cirrhosis. It is based on the AST elevation and the platelet count, and is calculated by the following formula:

$$[(AST/ULN) \div \text{Platelet count in thousands}] \times 100$$

Where ULN stands for the upper limit of normal of the AST value for the lab. Platelet count is reported in thousands.

A score > 0.5 indicates probable fibrosis, a score between 0.5 and 1.5 correlates to a Metavir stage of 1 to 3, and a score > 1.5 indicates cirrhosis.

(See attachments 2, 3 and 4 for scoring systems for hepatic fibrosis, FibroSure conversion table and APRI score).

Initial work up for HCV disease includes:

Any time prior to treatment:

- HCV RNA VL (Ultra-sensitive HCV RNA by PCR, BioReference # 3376)- **if** a regimen lasting less than 12 weeks is considered in GT 1 then an HCV VL must be repeated within 3 months of treatment to determine patient eligibility
- HCV genotype
- HIV screen
- FibroSure assay (BioReference # 6124)
- Liver ultrasound with portal vein Doppler (stage 4 disease only)
- Hepatitis A & B screen
- If screening for hepatitis A or B is negative, the patient will be vaccinated. Treatment can be initiated before the vaccination series is completed.
- Testing for viral resistance **only** in select patients. Resistance testing should be done after approval of the designated RMD. Recommendations as follows:
 - NS5A polymorphism testing in GT 1a if Zepatier regimen considered (BioReference # J242)
 - Q80K polymorphism testing in GT 1a with cirrhosis if SIM/SOF regimen considered (Bioreference # B610)

Within 12 weeks of treatment:

- CBC with differential
- SMA-C
- PT-PTT/INR
- NOTE: a repeat HCV RNA VL should be repeated **ONLY IF** a regimen of Harvoni lasting less than 12 weeks is considered in GT 1

Just prior to initiating treatment:

- HCG in females
- Drug-drug interactions especially in HIV patients

Note: Psychiatric evaluation prior to treatment is no longer routinely required. IFD consult is to be obtained once the work up is complete.

PATIENT SELECTION

Side effects have improved with newer regimens. However, hepatitis C treatment still carries a significant incidence of adverse reactions, some life threatening, especially when ribavirin is used. Treatment regimens have been simplified, but compliance is necessary to achieve a sustained virologic response (SVR) and a committed patient that is highly motivated to adhere to the treatment program is of utmost importance. Patients who have previously exhibited non-adherence to medical care may not be good candidates for HCV treatment.

Patients need to be carefully screened and counseled before therapy is contemplated. The decision of when to treat depends on several factors including genotype, stage and natural history of disease, history of prior treatment, adverse reactions, expected efficacy and ability to tolerate an appropriate regimen.

Newer, safer, more effective drugs are continuously being developed, and patients with earlier stages of fibrosis, based on a risk assessment for progression of hepatitis C, may be given the option to monitor their disease and to defer treatment.

Some of the risk factors predictive of severity and more rapid progression of disease are:

- viral characteristics
- presence of liver fibrosis
- host genetic variations and immune status
- male gender
- age >50 at time of infection
- duration of infection >20 years
- ETOH abuse
- co-infection with HIV or Hepatitis B
- co-morbidities such as diabetes mellitus, steatosis and obesity

Patients not treated at this time will be counseled about disease progression, communicability, and risk reduction. They will be evaluated periodically for progression of fibrosis as outlined in the patient monitoring section below.

All patients with chronic hepatitis C disease should be worked up and evaluated for treatment. In DOCCS priority in treatment will be given to those with more advanced fibrosis (F3 and F4), and to those with either immuno-compromising conditions (e.g. HIV, DM) or severe extra-hepatic manifestations of hepatitis C.

The following criteria will be considered when deciding whom to treat:

- Must be 18 or older
- Eligible patients may be hepatitis C **treatment naïve** or hepatitis C **treatment experienced: relapsers** (achieved an undetectable viral load after treatment, but did not have a SVR after 24 weeks), **partial responders** (achieved a 2-log drop in HCV VL by week 12, but still had a detectable VL at week 24 of treatment), **null-responders** (did not achieve at least a 2-log drop in HCV VL at week 12 of treatment)
- Patients with stage 3 and 4 fibrosis will be treated
- Patients with serious extra-hepatic manifestations of HCV infection, regardless of fibrosis stage, will be treated
- Patients with earlier stages of fibrosis will be evaluated on an individual basis and risk indicators for rapid progression of disease or other compelling reasons to treat will be considered
- Decompensated liver disease- Child-Turcotte-Pugh class B and C (Attachment 5) and candidates for liver transplant will be referred to a transplant center for management of their hepatitis C as most current regimens are contraindicated in this population (Note: Epclusa has been FDA approved for use in patients with decompensated cirrhosis)

- End stage kidney disease, stage IV (GFR<30) and kidney transplant patients should be carefully evaluated on a case-by-case basis with a consultant as only some regimens are approved for use in such patients and careful monitoring is required (Zepatier has been FDA approved for use in patients with end stage renal disease including those on hemodialysis)
- Pregnant females and females that may become pregnant cannot be on treatment. A negative HCG in women of childbearing age is required, and **two methods of effective contraception must be used during treatment and, if Ribavirin used, for six months after completion**
- Male patients, if taking ribavirin, must inform their female partner of childbearing age that **two methods of effective contraception must be used during treatment and for six months after completion**
- Risk of re-infection including using or possessing syringes, tattoo equipment or documented chronic noncompliance with medical care will be considered when making treatment decisions
- Evidence of substance abuse (drug and/or alcohol) in the past 6 months shall not per se serve as exclusion for any care or treatment. Evidence of such substance abuse may only be considered as one factor among all others in assessing and evaluating each individual's needs and suitability for care and treatment. Such evidence may be noted, but shall not in any case be used to prevent any initial work up and/or referral to the IFD specialist. All patients who qualify for hepatitis C treatment, regardless of a drug or alcohol related incident in the past 6 months, will have an initial work up and appropriate testing for HCV disease and will be referred to IFD for an evaluation.
- Psychiatric clearance is no longer needed. It is required **ONLY** if an interferon regimen is considered. However, DOCCS no longer supports using interferon in treating HCV.

Before treatment is initiated the following must be obtained:

- Evaluation and recommendation by IFD
- Approval of Deputy Commissioner/Chief Medical Officer
- Signed consent addressing risks/benefits, and agreeing to comply with treatment regimen
- Male patients on ribavirin considering conjugal visits, must sign a consent to inform their female partner of childbearing age of the teratogenic effects of therapy

OBTAINING APPROVAL & MEDICATIONS FOR TREATMENT

Therapy for Hepatitis C will not be started without an evaluation by an IFD consultant and prior approval by the Deputy Commissioner/Chief Medical Officer.

Steps for obtaining treatment:

1. Referral to IFD through FHS1, screen 4.1 (only patients that have been screened, worked up, and eligible for treatment should be referred to IFD).
2. Treatment approval and medication order via the "Hep C Treatment Request" form found in the Forms and Attachment portion of the Health Exchange shared drive. Indicate at the bottom, in the comment section, what treatment regimen is being requested. This form will automatically go to the CMO for review then forwarded to central pharmacy to obtain requested drugs.

TREATMENT

The field of Hep C therapy has been evolving rapidly. New drugs have recently been approved and others are being developed. All oral regimens, that are highly effective and safe, are now available for all genotypes and more will be approved in the near future.

These treatment guidelines have been drafted mostly following recommendations by the American Association for the Study of Liver Diseases (AASLD) and are in compliance with FDA guidelines. They are meant to establish a standard approach to Hep C treatment in DOCCS in order to improve continuity of care and patient outcomes. The latest AASLD guidelines can be accessed at www.hcvguidelines.org.

It should be noted that the treatment of hepatitis C is not “one size fits all,” and therapy should be individualized on a case-by-case basis in consultation with IFD and prior approval by the DOCCS Deputy Commissioner/Chief Medical Officer.

The FDA has approved new oral medications that are direct acting antivirals (DAA) against the hepatitis C virus. They are used in combination therapy for the treatment of chronic hepatitis C.

Monotherapy with DAAs should never be used for the treatment of hepatitis C.

Dose adjustments of the DAAs should not be made (except for daclatasvir if recommended by consultant). If stopped because of adverse reactions, they should not be restarted. Any modification or discontinuation of therapy must be first discussed with a consultant.

There are currently four classes of DAAs:

1. Nonstructural protein NS3/4A protease inhibitors (PIs)
2. NS5B nucleotide analog polymerase inhibitors (NPIs)
3. NS5B non-nucleotide analog polymerase inhibitors (NNPIs)
4. NS5A protein inhibitors

NONSTRUCTURAL PROTEIN NS3/4A PROTEASE INHIBITORS (PIs)

First Generation PIs

Telaprevir and **Boceprevir** (TVR and BOC) were the first PIs available and were used in combination therapy for the treatment of chronic hepatitis C genotype 1. They are no longer recommended because of their serious adverse reactions, significant drug-drug interactions, high potential for resistance and cumbersome administration schedule.

Second Generation PIs

These are better tolerated compared to the first generation PIs with less adverse reactions, less drug-drug interactions, better efficacy, lower potential for resistance and easier to administer. Most adverse reactions occur in combination therapy especially when ribavirin is used. PIs can cause elevation of liver function tests (LFTs) and worsening liver failure in patients with cirrhosis. Careful monitoring of LFTs in such patients is imperative. Any elevation of ALT or other LFTs will prompt an immediate referral to IFD. A 10-fold elevation requires discontinuation of therapy and immediate IFD evaluation.

Grazoprevir- available as a fixed-dose oral combination with elbasvir (Zepatier). It is FDA approved for use in Genotypes 1 or 4.

Paritaprevir- available as a fixed-dose oral combination tablet with low dose ritonavir and ombitasvir (Technivie, Viekira Pak). It is FDA approved for the treatment of genotype 1 and 4 when used in combination therapy.

Simeprevir (SIM)- dosing is 150 mg daily given by mouth with food. It is used in combination therapy with sofosbuvir +/- ribavirin for the treatment of genotype 1 or 4. When used in genotype 1a, testing for the presence of Q80K mutation may be necessary. Simeprevir is generally well tolerated. Common side effects are fatigue, headache, nausea and skin reactions including photosensitivity especially in the first four weeks. Sun exposure should be avoided and sun protection used. Symptomatic bradycardia requiring pacemaker placement has been reported in patients where simeprevir was co-administered with sofosbuvir and amiodarone. Hepatic decompensation and deaths have occurred in patients with moderate or severe liver disease (Child-Pugh Class B or C) and use in such patients is not recommended. (Prescribing Information – Simeprevir)

NS5B NUCLEOTIDE ANALOG POLYMERASE INHIBITORS (NPIs)

This class of DAAs is active across all genotypes and has a high barrier to resistance.

Sofosbuvir (SOF)- dosing is 400 mg given daily by mouth with or without food. It is used in genotypes 1, 2, 3 and 4 in combination therapy with ledipasvir (Harvoni), velpatasvir (Epclusa), or simeprevir +/- ribavirin. It is well tolerated. Adverse reactions occur mostly in combination with ribavirin. Symptomatic bradycardia requiring pacemaker placement has been reported when sofosbuvir is co-administered with amiodarone and another HCV direct acting antiviral. (Prescribing Information - Sofosbuvir)

NS5B NON-NUCLEOTIDE ANALOG POLYMERASE INHIBITORS (NNPIs)

This class of DAAs is less potent and more genotype specific when compared to the NPIs, they also have a lower barrier to resistance.

Dasabuvir- is used in combination therapy with the fixed-dose combination of paritaprevir, ritonavir and ombitasvir (Viekira Pak). It is given with food as a single 250 mg oral tablet twice a day as part of a regimen for the treatment of genotype 1.

NS5A PROTEIN INHIBITORS

This class of DAAs is highly effective against all genotypes of the hepatitis C virus, but has a low barrier to resistance.

Daclatasvir- dosing is 60 mg given daily by mouth with or without food. It is given in combination therapy with sofosbuvir +/- ribavirin. It is FDA approved for the treatment of genotypes 1 or 3, but effective for other genotypes. Dose of Daclatasvir may need to be modified when co-administered with certain medications; this should be done in consultation with a specialist expert in managing such drug interactions. Symptomatic bradycardia requiring pacemaker placement has been reported in patients where daclatasvir was co-administered with amiodarone and sofosbuvir. (Prescribing Information – Daclatasvir)

Elbasvir- available as a fixed-dose oral combination with grazoprevir (Zepatier).

Ledipasvir- available as a fixed-dose oral combination tablet with sofosbuvir (Harvoni).

Ombitasvir- available as a fixed-dose oral combination tablet with paritaprevir and ritonavir (Technivie, Viekira Pak).

Velpatasvir- available as a fixed-dose oral combination tablet with sofosbuvir (Epclusa).

FIXED-DOSE COMBINATION DRUGS

The following fixed-dose combination drugs are currently FDA approved for use in the treatment of hepatitis C.

Epclusa- contains a fixed dose combination of velpatasvir 100 mg and sofosbuvir 400 mg. It is given orally as a single dose tablet once a day with or without food in the treatment of chronic hepatitis C genotypes 1, 2, 3, 4, 5 or 6. Epclusa may be used in patients with decompensated cirrhosis in combination with ribavirin. It is generally well tolerated, most common side effects are fatigue and headache. Symptomatic bradycardia requiring pacemaker placement has been reported in patients with underlying cardiac disease in whom Epclusa was co-administered with amiodarone. (Prescribing Information – Epclusa)

Harvoni- combination tablet containing ledipasvir 90 mg and sofosbuvir 400 mg. It is given orally as a single dose tablet once a day with or without food.

Harvoni is approved for the treatment of genotype 1 and 4 and is well tolerated. Symptomatic bradycardia requiring pacemaker placement has been reported in patients with underlying cardiac disease in whom Harvoni was co-administered with amiodarone. (Prescribing Information – Harvoni)

Technivie- combination tablet containing paritaprevir 75 mg, ritonavir 50 mg and ombitasvir 12.5 mg. It is used in combination with ribavirin for the treatment of genotype 4. Technivie may cause worsening liver function tests and patients need to be closely monitored. It can result in serious liver injury and death in patients with cirrhosis and use in this population is to be avoided if possible. Any elevation of ALT or other LFTs will prompt an immediate referral to IFD. A 10-fold elevation requires discontinuation of therapy and immediate IFD evaluation. Technivie should not be used in women on ethinyl estradiol. (Prescribing Information - Technivie)

Viekira Pak- contains a fixed-dose oral combination tablet containing paritaprevir 75 mg, ritonavir 50 mg and ombitasvir 12.5 mg plus a tablet containing dasabuvir 250 mg. Recommended dosage is two combination tablets paritaprevir/ritonavir/ombitasvir in the morning and one dasabuvir tablet twice daily. It should be given with food. Viekira is FDA approved for use in GT1 in combination with ribavirin.

Viekira may cause worsening liver function tests and patients need to be closely monitored. It can result in serious liver injury and death in patients with cirrhosis and use in this population is to be avoided if possible. Any elevation of ALT or other LFTs will prompt an immediate referral to IFD. A 10-fold elevation requires discontinuation of therapy and immediate IFD evaluation. Viekira should not be used in women on ethinyl estradiol. (Prescribing Information - Viekira)

Zepatier- fixed-dose oral combination tablet containing elbasvir 50 mg and grazoprevir 100mg. It is FDA approved for the treatment of HCV genotypes 1 and 4. Dosing is one tablet daily, with or without ribavirin. It can be given with or without food. When used in genotype 1a, testing for the presence of NS5A resistance polymorphism is required to determine length of therapy. Zepatier is generally well tolerated. Elevations in ALT have been reported and close monitoring of LFTs is mandatory. Any elevation of ALT or other LFTs will prompt an immediate referral to IFD. A 10-fold elevation requires discontinuation of therapy and immediate IFD evaluation. Zepatier is contraindicated in patients with moderate or severe hepatic impairment (Child-Pugh class B or C). It can be given without dose adjustment to patients with renal impairment, including those on hemodialysis. (Prescribing Information – Zepatier)

NON-DIRECT ACTING DRUGS

Peginterferon and ribavirin are two older drugs used in the treatment of hepatitis C. Their role in the treatment of hepatitis C is through their antiviral, immunomodulatory and anti-inflammatory properties. Although done in past, **dual therapy with PEG/RIBA alone should never be used.**

Pegasys, peginterferon alfa 2a (PEG)- Pegasys was used in the treatment of hepatitis C for many years and was associated with significant adverse reactions including serious infections, anemia, thrombocytopenia, neuropsychiatric decompensation, worsening hepatitis and autoimmune disorders. Because of these serious potentially life-threatening adverse reactions and the availability of safer all oral regimens, DOCCS will no longer recommend using Pegasys in the treatment of hepatitis C. Patients with autoimmune disorders, severe depression, platelet count <50K, decompensated cirrhosis, hepatocellular cancer and solid organ transplant are not eligible to receive Pegasys. (Prescribing Information - Pegasys)

Ribavirin (RIBA) – weight based when used in combination therapy. It is given in a divided BID dose: 1000 mg po daily for patients <75 kg, 400 mg in AM, 600 mg in PM; 1200 mg po daily for patients >75 kg, 600 mg BID. Ribavirin can cause anemia and is highly teratogenic. Dose adjustments of ribavirin may become necessary in managing anemia. The use of erythropoietin has not been FDA approved for the treatment of anemia in patients undergoing Hep C treatment, and it is not recommended as first line therapy. Reduction of RIBA should be done first.

-Ribavirin dose adjustments in anemia (Attachment 6):

- Hgb between 8.5 and 10 (or a drop of 2 gm or more during any 4 week period in patients with cardiac disease)- decrease RIBA to 600 mg daily (200 mg q AM, 400 mg q PM)
- Hgb < 8.5- discontinue RIBA. In patients with cardiac disease, discontinuing RIBA should be considered if Hgb < 12 despite 4 weeks of dose reduction.

Once RIBA has been stopped because of an adverse reaction, it may be restarted at 600 mg daily; if tolerated it can be increased to 800 mg daily, but never to its original dose (1000 or 1200 mg/day).

Ribavirin is highly teratogenic and two forms of effective contraception must be used during treatment, and for six months after treatment has ended, when either males or females are on an HCV regimen containing ribavirin. (Prescribing Information - Ribavirin)

TREATMENT REGIMENS

There are several interferon free, all oral DAA containing regimens available that are both effective and safe. Treatment options for HCV should be reviewed with a consultant and approved by DOCCS' CMO. Regimens are determined by the following factors:

1. HCV genotype
2. Previous treatment experience
3. Presence or absence of cirrhosis
4. Renal function
5. Patient co-morbidities
6. Presence or absence of viral resistance-associated variants (eg. NS5A mutation)
7. Drug- drug interaction
8. HIV co-infection. Many medications used in HIV cannot be used or need dose adjustment when combined with HCV regimens. Therapeutic regimens need to be carefully selected and modified in conjunction with an HIV specialist when treating HIV/HCV co-infected patients. It is not recommended that HIV treatment be interrupted to allow for HCV treatment.
9. Regimen toxicity

Genotype 1

Genotype (GT) 1 is further subdivided into GT 1a and GT 1b. Patients with GT 1 that cannot be subtyped should be treated as GT 1a. In general GT 1a has a higher relapse rate than GT 1b when certain regimens are used. Length of therapy will vary depending on many factors: specific regimen, viral mutations, the presence or absence of cirrhosis, whether or not the patient is treatment naïve or treatment experienced and pretreatment viral load (HCV RNA). For GT 1a only, if Zepatier is being considered for treatment, then testing for NS5A polymorphism must be done to determine regimen and/or length of therapy (BioReference #J242).

The following regimens are used in the treatment of hepatitis C GT1 in order of preference for DOCCS:

Genotype 1a- (Attachment 7)

Treatment Naïve, GT 1a- (test for NS5A polymorphism)

No cirrhosis

No NS5A polymorphism present

- Zepatier for 12 weeks

NS5A polymorphism present

- Harvoni for 8 weeks- this regimen may be considered in selected patients with no co-morbidities **ONLY IF** pre-treatment HCV RNA < 6 million IU/ml and only if recommended by specialist
- Harvoni for 12 weeks if pre-treatment HCV RNA > 6 million IU/ml or comorbid conditions
- Viekira Pak + RIBA for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks

- Daclatasvir + SOF for 12 weeks
- SIM + SOF for 12 weeks

With compensated cirrhosis

No NS5A polymorphism present

- Zepatier for 12 weeks

NS5A polymorphism present

- Harvoni for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance)
- SIM + SOF +/- RIBA for 24 weeks **IF** no Q80K polymorphism present
- Viekira Pak + RIBA for 24 weeks (not recommended; monitor LFTs frequently if used)

Treatment Experienced (Failed PEG/RIBA)- GT 1a (test for NS5A polymorphism)

No cirrhosis

No NS5A polymorphism present

- Zepatier for 12 weeks

NS5A polymorphism present

- Harvoni for 12 weeks
- Viekira Pak + RIBA for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks
- SIM + SOF for 12 weeks

With compensated cirrhosis

No NS5A polymorphism present

- Zepatier for 12 weeks

NS5A polymorphism present

- Harvoni + RIBA for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)

- Harvoni for 24 week
- Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance)
- SIM + SOF +/- RIBA for 24 weeks **IF** no Q80K polymorphism present
- Viekira Pak + RIBA for 24 weeks (not recommended; monitor LFTs frequently if used)

Treatment Experienced (Failed Protease Inhibitor)- GT 1a (test for NS5A polymorphism)

No cirrhosis

No NS5A polymorphism present

- Zepatier + RIBA for 12 weeks

NS5A polymorphism present

- Harvoni for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks

With compensated cirrhosis

No NS5A polymorphism present

- Zepatier + RIBA for 12 weeks

NS5A polymorphism present

- Harvoni + RIBA for 12 weeks
- Zepatier + RIBA for 16 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Harvoni for 24 week
- Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance)

Treatment Experienced (Failed Sofosbuvir/RIBA)- GT 1a

No cirrhosis

- Harvoni + RIBA for 12 weeks

With compensated cirrhosis

- Harvoni + RIBA for 24 weeks

Genotype 1b- (Attachment 8)

Treatment Naïve- GT 1b

No cirrhosis

- Harvoni for 8 weeks- this regimen may be considered in selected patients with no co-morbidities **ONLY IF** pre-treatment HCV RNA < 6 million IU/ml and only if recommended by specialist
- Zepatier for 12 weeks
- Harvoni for 12 weeks if pre-treatment HCV RNA > 6 million IU/ml or comorbid conditions
- Viekira Pak for 12 weeks
- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks
- SIM + SOF for 12 weeks

With compensated cirrhosis

- Zepatier for 12 weeks
- Harvoni for 12 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Daclatasvir + SOF +/- RIBA for 24 weeks
- SIM + SOF +/- RIBA for 24 weeks
- Viekira Pak for 12 weeks (not recommended; monitor LFTs frequently if used)

Treatment Experienced (Failed PEG/RIBA)- GT 1b

No cirrhosis

- Zepatier for 12 weeks
- Harvoni for 12 weeks
- Viekira Pak for 12 weeks
- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks
- SIM + SOF for 12 weeks

With compensated cirrhosis

- Zepatier for 12 weeks
- Harvoni + RIBA for 12 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Harvoni for 24 weeks
- Daclatasvir + SOF +/- RIBA for 24 weeks
- SIM + SOF +/- RIBA for 24 weeks

- Viekira Pak for 12 weeks (not recommended; monitor LFTs frequently if used)

Treatment Experienced (Failed Protease Inhibitor)- GT 1b

No cirrhosis

- Zepatier + RIBA for 12 weeks
- Harvoni for 12 weeks
- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks

With compensated cirrhosis

- Zepatier + RIBA for 12 weeks
- Harvoni + RIBA for 12 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Harvoni for 24 week
- Daclatasvir + SOF +/- RIBA for 24 weeks

Treatment Experienced (Failed Sofosbuvir/RIBA)- GT 1b

No cirrhosis

- Harvoni + RIBA for 12 weeks

With compensated cirrhosis

- Harvoni + RIBA for 24 weeks

Treatment Experienced (Failed regimens that include an NS5A inhibitor) GT 1a and 1b

Clinical and scientific data is very limited on retreatting HCV patients that have failed regimens containing an NS5A polymerase inhibitor (Harvoni, Viekira, Zepatier, Epclusa) and studies are ongoing. As such DOCCS recommends deferring treatment until more data or newer agents become available. Patients with cirrhosis, that cannot wait to be retreated, will be considered for retreatment on an individual basis under the recommendations of a consultant. Prior to treatment these patients will need to be tested for resistance-associated variants for NS5A inhibitor and for Q80k as per direction of a consultant and RMD approval. Therapy will then be tailored according to drug resistance patterns.

Genotype 2- (Attachment 9)

Treatment Naïve GT 2

No cirrhosis

- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks (not FDA approved)

With compensated cirrhosis

- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Daclatasvir + SOF for 16-24 weeks (not FDA approved)

Treatment Experienced (Failed Peg/RIBA)- GT 2

No cirrhosis

- Epclusa for 12 weeks

With compensated cirrhosis

- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)

Treatment Experienced (Failed Sofosbuvir/RIBA)- GT 2

No cirrhosis or with compensated cirrhosis

- Epclusa + RIBA for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Daclatasvir + SOF +/- RIBA for 24 weeks (limited data, not FDA approved; consider only if cannot take RIBA)

Genotype 3- (Attachment 10)

Treatment Naïve – GT 3

No cirrhosis

- Epclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks

With compensated cirrhosis

- Epclusa for 12 weeks (studies are ongoing looking into resistance patterns and the need to add RIBA; can be used in decompensated cirrhosis)
- Daclatasvir + SOF +/- RIBA for 24 weeks (latest data no longer supports the FDA approved 12 week regimen)

Treatment Experienced (Failed Peg/RIBA)- GT3

No cirrhosis

- Eplclusa for 12 weeks
- Daclatasvir + SOF for 12 weeks

With compensated cirrhosis

- Eplclusa for 12 weeks (AASLD recommends adding RIBA in this population based on preliminary data; can be used in decompensated cirrhosis)
- Daclatasvir + SOF + RIBA for 24 weeks (latest data no longer supports the FDA approved 12 week regimen)

Treatment Experienced (Failed Sofosbuvir/RIBA)- GT3

No cirrhosis or with compensated cirrhosis

- Eplclusa + RIBA for 12 weeks (recommended by AASLD, but no data available)
- Daclatasvir + SOF + RIBA for 24 weeks (limited data, not FDA approved)

Studies are ongoing and better options may be available soon for GT 3 treatment experienced patients. It may be beneficial for those with earlier stages of fibrosis to defer treatment at this time.

There are no retreatment recommendations at this time for patients with GT 3 who have failed an NS5A inhibitor regimen. Unless urgent treatment is necessary, treatment of these patients should also be deferred.

Genotype 4- (Attachment 11)

Studies are still ongoing for the treatment of HCV GT 4 and some of the regimens used are off label and not FDA approved. Limited data is available especially in retreatment treatment experienced patients with GT 4.

Treatment Naïve- GT 4

No cirrhosis

- Zepatier for 12 weeks
- Harvoni for 12 weeks
- Technivie + RIBA for 12 weeks
- Eplclusa for 12 weeks

With compensated cirrhosis

- Zepatier for 12 weeks
- Harvoni for 12 weeks
- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Technivie + RIBA for 12 weeks (not recommended; monitor LFTs frequently if used)

Treatment Experienced (Failed PEG/RIBA)- GT 4

No cirrhosis

- Technivie + RIBA for 12 weeks
- Epclusa for 12 weeks
- Harvoni for 12 weeks
- Zepatier for 12 weeks (Preliminary studies indicate treatment with Zepatier should be extended to 16 weeks and RIBA added if there was prior virologic failure on treatment)

With compensated cirrhosis

- Epclusa for 12 weeks (Note: Epclusa may also be used in patients with decompensated cirrhosis)
- Harvoni + RIBA for 12 weeks
- Zepatier for 12 weeks (Preliminary studies indicate treatment with Zepatier should be extended to 16 weeks and RIBA added if there was prior virologic failure on treatment)
- Harvoni for 24 weeks
- Technivie + RIBA for 12 weeks (not recommended; monitor LFTs frequently if used)

DRUG INTERACTIONS

Prior to initiating treatment for hepatitis C, a careful review of DRUG-DRUG interactions should be conducted, especially in HIV co-infection.

Many drugs co-administered with HCV treatment may require dose modification and/or specific timing of administration around HCV medications. It is recommended that each drug given during HCV treatment be individually researched and medical necessity established prior to initiating treatment. Dose modification of HCV drugs (other than daclatasvir, if recommended by consultant) should not be done.

HIV co-infected patients may require drug dose modification or regimen change when treated for HCV. HIV therapy should not be suspended when treating HCV.

Refer to the links and lists provided below as a guide on drug interactions.

However, remember that new interactions present themselves regularly and such lists may not be complete. A detailed individual search for drug-drug interaction should be done just before therapy is initiated.

Daclatasvir (Daklinza)- (Daclatasvir Drug Interactions)

Is a substrate of CYP3A and an inhibitor of P-glycoprotein transporter (P-gp). Drugs that are inducers of CYP3A may decrease plasma levels of daclatasvir; inhibitors of CYP3A may increase plasma levels of daclatasvir. Also daclatasvir may increase plasma levels of drugs that are substrates of P-gp. Dosage modification of daclatasvir may be required when using such drugs.

Daclatasvir is contraindicated for use with the following:

- **Alpha 1-adrenoreceptor antagonists:** silodosin
- **Antiarrhythmics:** amiodarone (co-administration of amiodarone with daclatasvir in combination with sofosbuvir may cause life-threatening symptomatic bradycardia)
- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antigout agents:** colchicine
- **Antimicrobials:** rifampin
- **Antineoplastic agents:** topotecan, vincristine (liposomal)
- **HCV Drugs:** grazoprevir
- **Herbal Supplements:** St. John's Wort

Epclusa (sofosbuvir/velpatasvir)- (Epclusa Drug interactions)

Sofosbuvir and velpatasvir are both substrates of the drug transporter systems P-gp and breast cancer resistance protein (BCRP). Velpatasvir also of CYP. Epclusa is not recommended for use with drugs that are P-gp inducers or moderate to strong CYP inducers as they may decrease efficacy of sofosbuvir and/or velpatasvir. Epclusa may be co-administered with P-gp, BCRP and CYP inhibitors. Velpatasvir is an inhibitor P-gp and BCRP. Co-administration of Epclusa with drugs that are substrates to these transporters may increase the therapeutic levels of these drugs, and dose adjustments of such drugs may be necessary.

Epclusa is contraindicated with the following:

- **Acid reducing agents:** antacids, H2 blockers, PPIs may reduce plasma levels of velpatasvir. PPIs should not be used. If other acid reducing drugs given, these will need to be given at a lower dose and timing of administration carefully established
- **Alpha 1-adrenoreceptor antagonists:** silodosin
- **Antiarrhythmics:** amiodarone (co-administration of amiodarone with Epclusa may cause life-threatening symptomatic bradycardia); digoxin (if medically necessary digoxin levels should be carefully monitored and dose adjustment may be necessary)
- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- **Antigout agents:** colchicine
- **Antimicrobials:** rifampin, rifabutin, rifapentine
- **Antineoplastic agents:** doxorubicin (conventional), topotecan, vincristine (liposomal)
- **CNS stimulators:** modafinil
- **HCV Drugs:** simeprevir, grazoprevir
- **Herbal Supplements:** St. John's Wort
- **HIV Antiretrovirals:** (IFD input is mandatory when modifying HIV regimens)
 - efavirenz (Sustiva)
 - lopinavir/ritonavir (Kaletra)
 - tipranavir/ritonavir (Aptivus)
 - HIV regimens containing tenofovir DF combinations
- **Statins:** rosuvastatin, atorvastatin; other statins may be used if necessary, but need dose reduction and careful monitoring for signs of myopathy. Pravastatin may be used.

Harvoni (sofosbuvir/ledipasvir)- (Harvoni Drug Interactions)

Sofosbuvir and ledipasvir are substrates of the drug transporter system P-gp and BCRP. P-gp inducers may decrease plasma levels of both sofosbuvir and ledipasvir leading to a reduced therapeutic effect of Harvoni. Harvoni cannot be co-administered with strong P-gp inducers. Ledipasvir is an inhibitor of P-gp and BCRP and may increase intestinal absorption of drugs that are substrates for these transporters.

Harvoni is contraindicated for use with the following:

- **Acid reducing agents:** antacids, H2 blockers, PPIs may reduce plasma levels of ledipasvir. If acid reducing drugs given, these will need to be given at a lower dose and timing of administration carefully established.
- **Alpha 1-adrenoreceptor antagonists:** silodosin
- **Antiarrhythmics:** amiodarone (co-administration of amiodarone with Harvoni may cause life-threatening symptomatic bradycardia); digoxin (if medically necessary digoxin levels should be carefully monitored and dose adjustment may be necessary)
- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- **Antigout agents:** colchicine
- **Antimicrobials:** rifampin, rifabutin, rifapentine
- **Antineoplastic agents:** bosutinib, doxorubicin (conventional), topotecan, vincristine (liposomal)
- **CNS stimulators:** modafinil
- **HCV Drugs:** simeprevir
- **Herbal Supplements:** St. John's Wort
- **HIV Antiretrovirals** (note: some of these HIV drugs may be used individually, but not the combinations listed. IFD input is mandatory):
 - elvitegravir/cobicistat/emtricitabine/tenofovir DF (Stribild)
 - tipranavir/ritonavir (Aptivus)
 - efavirenz/emtricitabine/tenofovir DF (Atripla)
 - HIV regimens containing a protease inhibitor/ritonavir or cobicistat and tenofovir DF combinations:
 - atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF (Reyataz or Evotaz + Truvada)
 - darunavir/ritonavir or cobicistat + emtricitabine/ tenofovir DF (Prezista or Prezcofix + Truvada)
 - lopinavir/ritonavir + emtricitabine/tenofovir DF (Kaletra + Truvada);
- **Statins:** rosuvastatin; other statins may be used if necessary, but need dose reduction and careful monitoring for signs of myopathy. Pravastatin may be used.

Pegasys cannot be co-administered with clozapine, telbivudine and tizanidine.

Ribavirin cannot be co-administered with didanosine and zidovudine.

Simeprevir (Olysio) - (Simeprevir Drug Interactions)

Is metabolized through the hepatic CYP3A system; it inhibits the P-gp transporters and is a mild inhibitor of CYP1A2 and CYP3A4 intestinal activity. Drugs that are moderate to strong inhibitors or inducers of CYP3A may significantly affect the plasma level of simeprevir impacting its therapeutic effect and such combination is not recommended.

Co-administration with drugs that are substrates for P-gp transport may result in increased concentration of such drugs, and careful monitoring is needed.

Simeprevir is contraindicated for use with the following:

- **Antiarrhythmics:** amiodarone (co-administration of amiodarone with simeprevir in combination with sofosbuvir may cause life-threatening symptomatic bradycardia)
- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- **Antibiotics:** clarithromycin, erythromycin, telithromycin
- **Antifungals:** fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole
- **Antigout agents:** colchicine
- **Antimicrobials:** rifampin, rifabutin, rifapentine
- **Antineoplastic agents:** bosutinib, doxorubicin (conventional), topotecan, vincristine (liposomal)
- **Corticosteroids:** dexamethasone
- **GI:** cisapride
- **HCV Drugs:** grazoprevir
- **Herbal supplements:** Milk Thistle, St. John's Wort
- **HIV drugs:** cobicistat
- **HIV Integrase Strand Transfer Inhibitors:** elvitegravir
- **HIV Non-Nucleoside Reverse Transcriptase Inhibitors:** delavirdine, efavirenz, etravirine, nevirapine,
- **HIV Protease Inhibitors:** atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
- **Immunosuppressants :** cyclosporine
- **Statins:** atorvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin- if medically necessary statins should be given at the lowest possible dose and careful monitoring is needed

Sofosbuvir (Sovaldi) - (Sofosbuvir Drug Interactions)

Is a substrate for the drug transport system P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Drugs that are potent intestinal P-gp inducers will decrease sofosbuvir plasma levels and may result in its decreased therapeutic effect. P-gp inducers may not be co-administered with sofosbuvir. On the contrary sofosbuvir may be given with P-gp inhibitors without altering its therapeutic effect.

Sofosbuvir is contraindicated for use with the following:

- **Antiarrhythmics:** amiodarone (co-administration of amiodarone with sofosbuvir in combination with another DAA may cause life-threatening symptomatic bradycardia)
- **Anticonvulsants:** carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- **Antimicrobials:** rifampin, rifabutin, rifapentine
- **CNS stimulators:** modafinil
- **Herbal Supplements:** St. John's Wort
- **HIV Protease Inhibitors:** tipranavir/ritonavir

Technivie (ombitasvir/paritaprevir/ritonavir) - (Technivie Drug Interactions)

Many drug interactions exist with Technivie and a careful review of drug-drug interactions should be done before treatment is initiated.

Technivie cannot be co-administered with drugs that are highly dependent on the CYP3A system for clearance, or drugs that are moderate or strong inducers or strong inhibitors of CYP3A and CYP2C8. Drug interactions are also present when Technivie is co-administered with drugs that are substrates or inhibitors of P-gp and BRCP.

Technivie is contraindicated for use with the following:

- **Alpha 1-adrenoreceptor antagonists:** alfuzosin, silodosin, tamsulosin
- **Angiotensin II Receptor Blockers:** losartan, valsartan
- **Anti-angina:** ranolazine
- **Antiarrhythmics:** digoxin
- **Antibiotics:** clarithromycin, erythromycin, telithromycin
- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antifungals:** ketoconazole (systemic)
- **Anti-gout:** colchicine
- **Anti-hyperlipedemics:** gemfibrozil
- **Antimicrobials:** rifampin
- **Antineoplastic agents:** bosutinib, doxorubicin (conventional), topotecan, vincristine (liposomal)
- **Antiplatelet agents:** ticagrelor
- **Beta agonists:** salmeterol
- **Calcium Channel Blockers:** amlodipine, nimodipine
- **Corticosteroids:** systemic budesonide, fluticasone inhaler
- **Ergot derivatives:** bromocriptine, dihydro-ergotamine, ergonovine, ergotamine, methyl-ergonovine
- **Estrogens:** ethinyl estradiol
- **GI:** cisapride
- **HCV Drugs:** daclatasvir, grazoprevir, simeprevir
- **Herbal Supplements:** St. John's Wort
- **HIV Non-Nucleoside Reverse Transcriptase Inhibitors:** efavirenz, rilpivirine
- **HIV Protease Inhibitors:** atazanavir, darunavir, lopinavir
- **Immunosuppressants:** tacrolimus
- **Narcotics:** oxycodone, fentanyl
- **Neuroleptics:** pimozide
- **Phosphodiesterase-5 inhibitors:** sildenafil, tadalafil when used in doses for pulmonary arterial hypertension
- **Sedatives/hypnotics:** oral midazolam, triazolam
- **Statins:** lovastatin, pravastatin, simvastatin; statins should be avoided with Technivie; but if medically necessary, other statins may be given at the lowest possible dose and careful monitoring for signs of myopathy is needed.

Viekira Pak(ombitasvir/paritaprevir/ritonavir + dasabuvir)-(Viekira Drug Interactions)

Many drug interactions exist with Viekira and a careful review of drug-drug interactions should be done before treatment is initiated.

Viekira cannot be co-administered with drugs that are highly dependent on the CYP3A system for clearance, or drugs that are moderate or strong inducers or strong inhibitors of CYP3A and CYP2C8. Drug interactions are also present when Viekira is co-administered with drugs that are substrates or inhibitors of P-gp and BRCP.

Viekira Pak is contraindicated for use with the following:

- **Alpha 1-adrenoreceptor antagonists:** alfuzosin, silodosin, tamsulosin
- **Anti-angina:** ranolazine
- **Antibiotics:** clarithromycin, erythromycin, telithromycin
- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antifungals:** ketoconazole (systemic)
- **Angiotensin II Receptor Blockers:** losartan, valsartan
- **Anti-gout:** colchicine
- **Anti-hyperlipedemics:** gemfibrozil
- **Antimicrobials:** rifampin
- **Antineoplastic agents:** bosutinib, doxorubicin (conventional), topotecan, vincristine (liposomal)
- **Antiplatelet agents:** ticagrelor
- **Beta agonists:** salmeterol
- **Calcium Channel Blockers:** amlodipine, nimodipine
- **Corticosteroids:** systemic budesonide, fluticasone inhaler
- **Ergot derivatives:** bromocriptine, dihydro-ergotamine, ergonovine, ergotamine, methyl-ergonovine
- **Estrogens:** ethinyl estradiol
- **GI:** cisapride
- **HCV Drugs:** daclatasvir, grazoprevir, simeprevir
- **Herbal Supplements:** St. John's Wort
- **HIV Non-Nucleoside Reverse Transcriptase Inhibitors:** efavirenz, rilpivirine
- **HIV Protease Inhibitors:** atazanavir, darunavir, lopinavir
- **Immunosuppressants:** tacrolimus
- **Narcotics:** oxycodone, fentanyl
- **Neuroleptics:** pimozide
- **Phosphodiesterase-5 inhibitors:** sildenafil, tadalafil when used in doses for pulmonary arterial hypertension
- **Sedatives/hypnotics:** oral midazolam, triazolam
- **Statins:** atorvastatin, lovastatin, simvastatin; statins should be avoided with Viekira, but if medically necessary other statins may be given at the lowest possible dose and careful monitoring for signs of myopathy is needed.

Zepatier (elbasvir/grazoprevir) - (Zepatier Drug Interactions)

Zepatier is not recommended for use with drugs that are moderate to strong CYP3A inducers or strong CYP3A or OATP1B1/3 inhibitors.

Zepatier is contraindicated for use with the following:

- **Antibiotics:** nafcillin
- **Anticonvulsants:** carbamazepine, phenobarbital, phenytoin
- **Antifungals:** ketoconazole (systemic)
- **Antimicrobials:** rifampin
- **Antineoplastic agents:** topotecan
- **Herbal Supplements:** St. John's Wort

- **HIV drugs:** cobicistat containing regimens
- **HIV Non-Nucleoside Reverse Transcriptase Inhibitors:** efavirenz, etravirine, nevirapine
- **HIV Protease Inhibitors:** atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir, tipranavir
- **Immunosuppressants :** cyclosporine
- **Neuroleptics:** pimozide
- **Statins:** atorvastatin, rosuvastatin. If medically necessary other statins can be used at a reduced dose and patient closely monitored for signs of myopathy. Pravastatin may be used.

MONITORING PATIENTS ON TREATMENT (Attachment 12)

- A monthly evaluation will be done by the facility physician/PA/NP and be recorded in the AHR.
- Specialty IFD consultation will be mandatory prior to starting HCV therapy, then as clinically indicated. Routine IFD follow up after treatment is initiated and at the end of treatment is not needed.
- Periodic laboratory testing while on treatment will be done as follows:
 - CBC with diff. at week 2, 4 then monthly
 - SMA-C at week 2, 4 then monthly. Patients on a PI containing regimen may need more careful monitoring of LFTs; any elevation of ALT or other LFTs will prompt an immediate referral to IFD. A 10-fold elevation requires discontinuation of all therapy and immediate IFD evaluation.
 - HCV RNA VL should **NOT** be checked during treatment, since there is limited data at this time to support stopping rules for futility
 - HCG monthly in females of childbearing age; if ribavirin used, HCG should also be checked monthly for 6 months after Rx ended
- End of treatment and 12 week post-treatment testing:
 - CBC with diff.
 - SMA-C
 - HCG in females of childbearing age; if ribavirin used, HCG should be checked monthly for 6 months after Rx ended
 - PT-PTT/INR
 - HCV RNA VL (Bioreference # 3376). Patients who have an undetectable VL at 12 weeks post-treatment have achieved a Sustained Virologic Response (SVR) and are considered cured. In such patients HCV RNA monitoring is not necessary after 12 week post treatment and it should not be ordered unless there is clinical suspicion of re-infection with HCV.
 - Clinic evaluation by DOCCS' physician, NP or PA. IFD consultation is not routinely needed during nor at the end of treatment.
 - In patients with an SVR, problem code 0728 (Hep C SVR) is to be added to the problem list and problem code 0701 (Hep C disease) inactivated.
 - Patients who have achieved SVR are considered cured and should be followed as though they were never infected with HCV. Those with advanced liver disease need monitoring as outlined in the section below.

MONITORING PATIENTS NOT TREATED & TREATMENT FAILURES

Patients who are not being treated (treatment contraindicated, refused or deferred) and those who failed to achieve SVR after treatment will be re-evaluated periodically as they have ongoing HCV infection and are at risk of progression of liver disease and disease transmission.

Patient assessment will be done as follows:

- Clinic evaluation by a physician/PA/NP every 6 months at minimum for mild disease, more frequently if clinical decompensation occurs.
- Laboratory testing every 6 months for mild disease, more frequently if needed:
 - CBC with diff
 - SMA-C
 - PT-PTT/INR
- FibroSure assay (BioReference # 6124) will be done annually in patients not treated to determine the progression of fibrosis, earlier if LFTs become elevated or if indicators for rapid fibrosis are present.
- Serial HCV RNA viral load (VL) should **NOT** be done since the VL does not have prognostic value.
- **Patients with cirrhosis need periodic surveillance for hepatocellular carcinoma (HCC).** According to the AASLD guidelines, these patients should be monitored every 6 months with an ultrasound of the liver. A baseline endoscopic evaluation should be done to screen for the presence of esophageal varices and surveillance done as indicated. If the ultrasound is abnormal or there is a palpable abdominal mass or change in clinical condition, a Triple Phase CT scan of the abdomen or contrast MRI should be ordered to screen for HCC. Patients with decompensated cirrhosis should be followed more closely in collaboration with a gastroenterologist or hepatologist. Liver transplantation may need to be considered in end stage cirrhosis.

SPECIAL CONSIDERATIONS- TREATMENT ISSUES

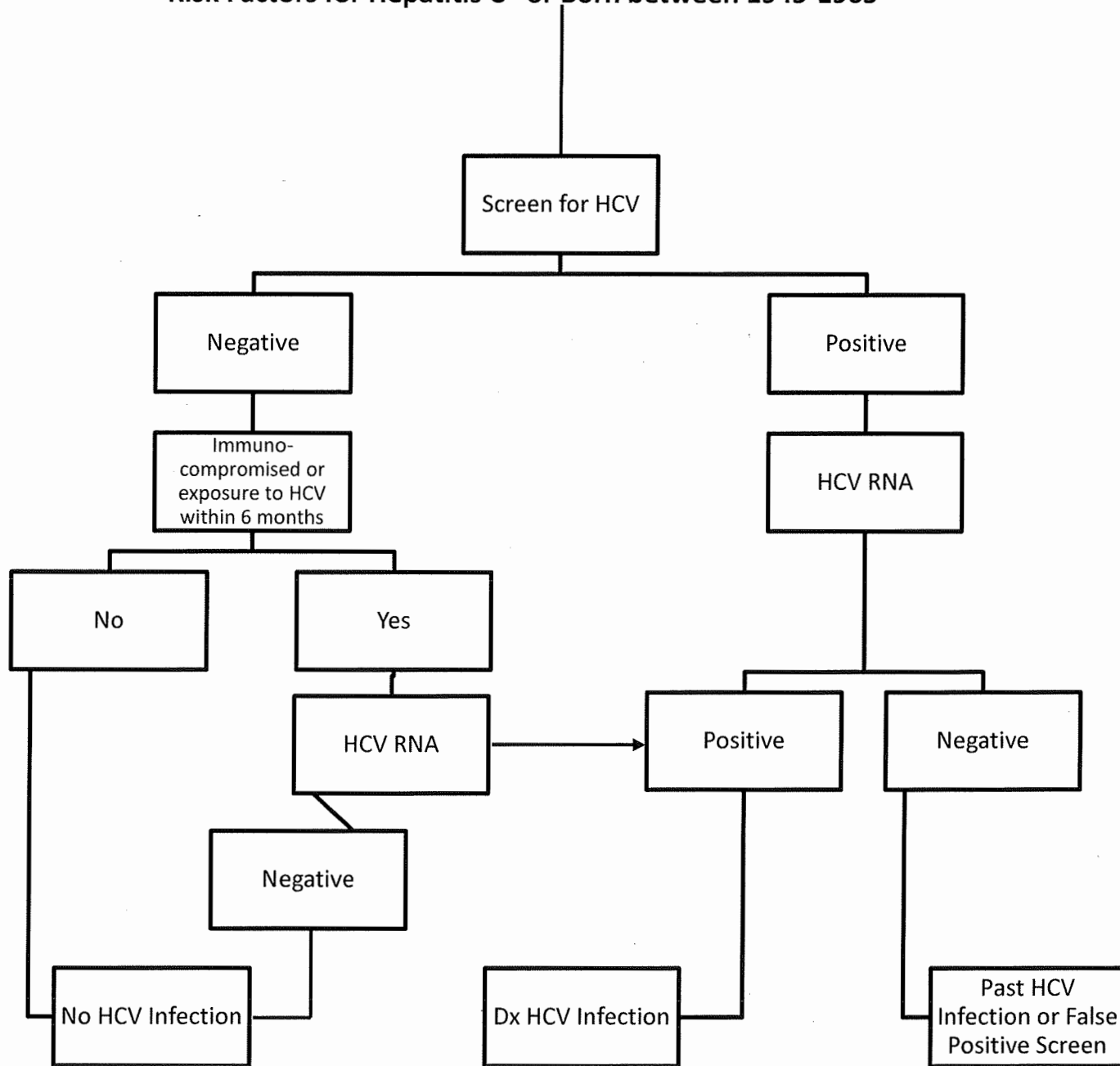
1. Before starting treatment for Hepatitis C, the patient will be counseled about the risks/benefits of therapy. **A signed consent will be obtained** stating the patient has read and understands the risks of therapy and that he/she agrees to the treatment regimen and will comply with all medical follow up (Form #3139/Form #3139SP). **Strict adherence to the regimen is imperative. Three refusals by the patient of either medication, lab work, primary or specialty clinic follow up will be considered criteria for stopping all treatment.**
2. Because of the serious side effect profile of some these drugs and the importance of adherence to therapy, all hepatitis C medications will be administered 1:1 by a nurse, and should not be "self carry."
3. **Ribavirin (RIBA) is highly teratogenic. It is contraindicated in pregnant females and in men whose female partners are, or may become, pregnant.** Pregnancy must be avoided in female patients and female partners of male patients during treatment and up to 6 months after treatment has ended. Female patients must have a negative HCG prior to starting therapy, monthly during therapy, and for 6 months thereafter.

Two forms of effective contraception will be required if conjugal visits are being considered.

Male patients on ribavirin, who wish to engage in conjugal visits, must inform their female partners of the serious risk for birth defects and fetal death should they become pregnant, and must ensure that two effective methods of birth control are being used. Patients who will participate in the family reunion program must agree to inform their spouse they are on treatment for hepatitis C (Family Reunion Letter – for further information refer to directive 4500; Ribavirin Patient Information – Ribavirin Warning Sheet).

4. **Dose adjustments:** When managing adverse reactions or drug interactions, dose adjustment of the DAAs or other HCV drugs should **NOT** be done without specialty consultation. Dose modification of daclatasvir may be necessary when daclatasvir is co-administered with certain other medications. Dose reduction of RIBA or discontinuing therapy may be necessary because of adverse reactions. If RIBA is permanently discontinued the entire regimen should also be stopped.
All dose adjustments and discontinuation of treatment must always be done after consultation with a specialist.
5. Patients on treatment for Hepatitis C should **not be routinely admitted to the infirmary** or any other special designated housing for the purpose of administering medications. Infirmary admissions should be based solely on medical conditions as the need arises.
6. Patients undergoing treatment for Hepatitis C will remain on Facility Hold during the first month of therapy. After that, stable patients may be transferred only after review of laboratory tests and facility primary care evaluation. All transfers and any overnight outside trip (court trips) must be coordinated with the RMD and the medical services of the receiving facility to insure consistent medication availability for the duration of the trip.
7. If there is a possibility that the patient will be released prior to completion of treatment, he/she will have to sign the "Hepatitis C Continuity Program Acceptance," Form #3138/ Form #3138SP. The Regional Infection Control Nurse needs to be contacted to initiate the enrollment process into the continuity program, Form #3131.
8. **The only quantitative HCV RNA assay that will be used in DOCCS for confirming the diagnosis and to monitor response to Hep C treatment is the COBAS/TaqMan HCV RNA PCR assay (BioReference # 3376).**
Viral detection and quantification for this test is as follows: the lower limit of quantification (LLOQ) is 15 IU/ml, the upper limit of quantification (ULOQ) is 50 million IU/ml. Reports will be reported with a numerical value between the two or > 50 million IU/ml if HCV RNA above the ULOQ. When the HCV RNA is below the LLOQ then it will be reported as < 15 ND (not detected) if no virus is detected at all, and < 15 D (detected) if virus is detected but less than 15 IU/ml.

Risk Factors for Hepatitis C* or Born between 1945-1965



*HIV, Hx of IV drug abuse, receipt of contaminated blood/blood products or organ transplant prior to 1992, infusion of clotting factor before 1987, needle sticks in health care workers, sharing of razors or toothbrushes, tattoos, intranasal cocaine use, multiple sex partners, hx of STDs, signs of hepatitis, mother with HCV, exposure to HCV, hemodialysis

Scoring System for Hepatic Fibrosis*

Attachment 2

Score	IASL	Metavir	Ishak	Batts & Ludwig
0	No fibrosis	No fibrosis	No fibrosis	No fibrosis
1	Mild fibrosis	Periportal fibrotic expansion	Fibrous expansion of some portal areas, with or w/o short fibrous septa	Fibrous portal expansion
2	Moderate fibrosis	Periportal septa (>1 septum)	Fibrous expansion of most portal area, with or w/o short fibrous septa	Rare bridges or septa
3	Severe fibrosis	Portal-central septa	Fibrous expansion of most portal areas, with occasional portal-portal bridging	Numerous bridges or septa
4	Cirrhosis	Cirrhosis	Fibrous expansion of most area, with marked bridging (portal-portal and portal-central)	Cirrhosis
5			Marked bridging (portal-portal and portal-central) with occasional nodules (incomplete cirrhosis)	
6			Cirrhosis, probable or definite	

APRI Score

APRI score = $[(AST/ULN) \div \text{Platelet count in thousands}] \times 100$

ULN = Upper Limit of Normal of the AST value for the lab.

Platelet count is reported in thousands.

A score > 0.5 indicates probable fibrosis, a score between 0.5 and 1.5 correlates to a Metavir stage of 1 to 3, and a score > 1.5 indicates cirrhosis.

Example: AST 76, Upper Limit of Normal for the lab 35, platelets 120,000

APRI score = $[76/35 \div 120] \times 100 = 1.8$ (consistent with cirrhosis)

*Reference:

Ghany et al.; AASLD Practice Guidelines; Diagnosis, Management and Treatment of Hepatitis C: an Update. Hepatology 2009; 49: 1339

Knodell score (HAI score) of liver biopsy specimens¹

I. Periportal \pm bridging necrosis	Score	II. Intralobular degeneration and focal necrosis ²	Score	III. Portal inflammation	Score	IV. Fibrosis	Score
None	0	None	0	No portal inflammation	0	No fibrosis	0
Mild piecemeal necrosis	1	Mild (acidophilic bodies, ballooning degeneration and/or scattered foci of hepatocellular necrosis in < 1/3 of lobules or nodules)	1	Mild (sprinkling of inflammatory cells in <1/3 of portal tracts)	1	Fibrous portal expansion	1
Moderate piecemeal necrosis (involves less than 50 percent of the circumference of most portal tracts)	3	Moderate (involvement of 1/3 to 2/3 of lobules or nodules)	3	Moderate (increased inflammatory cells in 1/3 to 2/3 of portal tracts)	3	Bridging fibrosis (portal-portal or portal-central linkage)	3
Marked piecemeal necrosis (involves more than 50 percent of the circumference of most portal tracts)	4	Marked (involvement of >2/3 of lobules or nodules)	4	Marked (dense packing of inflammatory cells in >2/3 of portal tracts)	4	Cirrhosis ³	4
Moderate piecemeal necrosis plus bridging necrosis ⁴	5						
Marked piecemeal necrosis plus bridging necrosis	6						
Multilobular necrosis ⁵	10						

¹ HAI score is the combined scores for necrosis, inflammation, and fibrosis.

² Degeneration-acidophilic bodies, ballooning; focal necrosis-scattered foci of hepatocellular necrosis.

³ Loss of normal hepatic lobular architecture with fibrous septae separating and surrounding nodules.

⁴ Bridging is defined as ≥ 2 bridges in the liver biopsy specimen; no distinction is made between portal-portal and portal-central linkage.

⁵ Two or more contiguous lobules with panlobular necrosis.

Adapted from Knodell, RG, et al. Hepatology 1981; 1:431.

Conversion of FibroSure Score Into Stages According to Histologic Classification

Fibrosure	Metavir	Knodell/HAI	Ishak
0 – 0.21	F 0	F 0	F 0
0.22 – 0.27	F 0 – F 1	F 0- F 1	F 1
0.28 – 0.31	F 1	F 1	F 2
0.32 – 0.48	F 1- F 2	F 1- F 3	F 2 – F 3
0.49 – 0.58	F 2	F 1 – F 3	F 3
0.59 – 0.72	F 3	F 3	F 4
0.73 – 0.74	F 3 – F 4	F 3 – F 4	F 5
0.75 – 1.0	F 4	F 4	F 6

0 – 0.31: Minimal or absent fibrosis
0.32 – 0.58: Moderate Fibrosis
0.59 – 1.0: Significant fibrosis

References:

BioPredictive website: Fibrotest/Fibrosure

<http://www.biopredictive.com/intl/physician/fibrotest-for-hcv/>

Modified Child-Turcotte-Pugh Severity of Liver Disease Worksheet

Clinical and Biochemical Measurements	Points Scored for Increasing Abnormality			
	1	2	3	Score
Encephalopathy (grade)	None	1 or 2 (or precipitant induced)	3 or 4 (or chronic)	
Ascites	Absent	Mild/Moderate (diuretic-responsive)	Moderate/Severe (diuretic-refractory)	
Bilirubin (mg per 100 mL)	<2	2-3	>3	
Albumin (g per 100 mL)	>3.5	2.8-3.5	<2.8	
Prothombin Time (seconds prolonged) or INR	<4 <1.7	4-6 1.7 to 2.3	>6 >2.3	

Total _____

- Grade A: Total score of 5 or 6 compensated
- Grade B: Total score of 7 to 9 decompensated
- Grade C: Total score of 10-15 decompensated

Reference:

Ghany et al.; AASLD Practice Guidelines; Diagnosis, Management and Treatment of Hepatitis C: an Update. Hepatology 2009; 49: 1356

Ribavirin Treatment Dosing Modifications

Dose adjustments of ribavirin may become necessary during hepatitis C treatment if significant anemia occurs.

Dose reduction of any DAA (direct acting antiviral) or the use of erythropoietin should not be done. Dose adjustment of ribavirin should be done as follows:

Ribavirin dose modification*

Laboratory Values	Reduce Ribavirin Dose to 600 mg/day	Discontinue Ribavirin
Hgb in patients with no cardiac disease	< 10 g/dl	< 8.5 g/dl
Hgb in patients with hx of stable cardiac disease	≥ 2 g/dl decrease in Hgb during any 4 week treatment period	< 12 g/dl despite 4 weeks at reduced dose

*Once Ribavirin has been stopped because of an adverse reaction, it may be restarted at 600 mg daily. If tolerated, it can be increased to 800 mg daily, but never to its original dose.

**TREATMENT OF CHRONIC HEPATITIC C
Genotype 1a**

Patient Groups (including both HCV mono- infected and HCV/HIV co-infected individuals)	Treatment Regimens in order of preference	
	No NS5A polymorphism present:	NS5A polymorphism present:
Rx naïve w/o cirrhosis	-Zepatier for 12 weeks	-Harvoni for 12 weeks (<i>a regimen of Harvoni for 8 weeks may be considered in select patients IF pre-treatment HCV RNA <6 million IU/ml, only if recommended by specialist</i>) -Viekira Pak + RIBA for 12 weeks -Zepatier + RIBA for 16 weeks -Eplclusa for 12 weeks -Daclatasvir + SOF for 12 weeks -SIM + SOF for 12 weeks
Rx naïve with compensated cirrhosis	-Zepatier for 12 weeks	-Harvoni for 12 weeks -Zepatier + RIBA for 16 weeks -Eplclusa for 12 weeks (can also be used in decompensated cirrhosis) -Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance) -SIM + SOF +/- RIBA for 24 weeks IF no Q80K polymorphism present -Viekira Pak + RIBA for 24 weeks (monitor LFT's frequently)
Failed PEG/RIBA w/o cirrhosis	-Zepatier for 12 weeks	-Harvoni for 12 weeks -Viekira Pak + RIBA for 12 weeks -Zepatier + RIBA for 16 weeks -Eplclusa for 12 weeks -Daclatasvir + SOF for 12 weeks -SIM + SOF for 12 weeks
Failed PEG/RIBA with compensated cirrhosis	-Zepatier for 12 weeks	-Harvoni + RIBA for 12 weeks -Zepatier + RIBA for 16 weeks Eplclusa for 12 weeks (can also be used in decompensated cirrhosis) -Harvoni for 24 weeks -Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance) -SIM + SOF +/- RIBA for 24 weeks IF no Q80K polymorphism present -Viekira Pak + RIBA for 24 weeks (monitor LFTs frequently)
Failed Protease Inhibitor w/o cirrhosis	-Zepatier + RIBA for 12 weeks	-Harvoni for 12 weeks -Zepatier + RIBA for 16 weeks - Eplclusa for 12 weeks -Daclatasvir + SOF for 12 weeks
Failed Protease Inhibitor with compensated cirrhosis	-Zepatier + RIBA for 12 weeks	-Harvoni + RIBA for 12 weeks -Zepatier + RIBA for 16 weeks Eplclusa for 12 weeks (can also be used in decompensated cirrhosis) -Harvoni for 24 weeks -Daclatasvir + SOF +/- RIBA for 24 weeks (consider NS5A resistance)
Failed SOF/RIBA w/o cirrhosis	Harvoni + RIBA for 12 weeks	
Failed SOF/RIBA with compensated cirrhosis	Harvoni + Riba for 24 weeks	
Failed NS5A inhibitor regimens	Limited data- defer treatment if possible; refer to consultant	

**TREATMENT OF CHRONIC HEPATITIS C
Genotype 1b**

Attachment 8

Patient Groups (including both HCV mono-infected and HCV/HIV co-infected individuals)	Treatment Regimens in order of preference
Rx naïve w/o cirrhosis	<ul style="list-style-type: none"> -Zepatier for 12 weeks -Harvoni for 12 weeks (<i>a regimen of Harvoni for 8 weeks may be considered in selected patients IF pre-treatment HCV RNA <6 million IU/ml, only if recommended by specialist</i>) -Viekira Pak for 12 weeks -Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks -SIM + SOF for 12 weeks
Rx naïve with compensated cirrhosis	<ul style="list-style-type: none"> -Zepatier for 12 weeks -Harvoni for 12 weeks -Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Daclatasvir + SOF +/- RIBA for 24 weeks -SIM + SOF +/- RIBA for 24 weeks -Viekira Pak for 12 weeks (monitor LFTs frequently)
Failed PEG/RIBA w/o cirrhosis	<ul style="list-style-type: none"> -Zepatier for 12 weeks -Harvoni for 12 weeks -Viekira Pak for 12 weeks -Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks -SIM + SOF for 12 weeks
Failed PEG/RIBA with compensated cirrhosis	<ul style="list-style-type: none"> -Zepatier for 12 weeks -Harvoni + RIBA for 12 weeks -Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Harvoni for 24 weeks -Daclatasvir + SOF +/- RIBA for 24 weeks -SIM + SOF +/- RIBA for 24 weeks -Viekira Pak for 12 weeks (monitor LFTs frequently)
Failed Protease Inhibitor w/o cirrhosis	<ul style="list-style-type: none"> -Zepatier + RIBA for 12 weeks -Harvoni for 12 weeks -Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks
Failed Protease Inhibitor with compensated cirrhosis	<ul style="list-style-type: none"> -Zepatier + RIBA for 12 weeks -Harvoni + RIBA for 12 weeks -Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Harvoni for 24 weeks -Daclatasvir + SOF +/- RIBA for 24 weeks
Failed SOF/RIBA w/o cirrhosis	<ul style="list-style-type: none"> -Harvoni + RIBA for 12 weeks
Failed SOF/RIBA with compensated cirrhosis	<ul style="list-style-type: none"> -Harvoni + RIBA for 24 weeks
Failed NS5A inhibitor regimens	<ul style="list-style-type: none"> Limited data- defer treatment if possible; refer to consultant

**TREATMENT OF CHRONIC HEPATITIS C
Genotype 1b**

Attachment 8

**TREATMENT OF CHRONIC HEPATITIS C
Genotype 2**

Patient Groups (including both HCV mono-infected and HCV/HIV co-infected individuals)	Treatment Regimens in order of preference
Rx naïve w/o cirrhosis	-Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks (not FDA approved)
Rx naïve with compensated cirrhosis	-Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Daclatasvir + SOF for 16-24 weeks (not FDA approved)
Failed PEG/RIBA w/o cirrhosis	-Epclusa for 12 weeks
Failed PEG/RIBA with compensated cirrhosis	-Epclusa for 12 weeks (can also be used in decompensated cirrhosis)
Failed SOF/RIBA with or w/o compensated cirrhosis	-Epclusa for 12 weeks (can also be used in decompensated cirrhosis)- Daclatasvir + SOF +/- RIBA for 24 weeks (limited data, not FDA approved)

**TREATMENT OF CHRONIC HEPATITIS C
Genotype 3**

Patient Groups (including both HCV mono-infected and HCV/HIV co-infected individuals)	Treatment Regimens in order of preference
Rx naïve w/o cirrhosis	-Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks
Rx naïve with compensated cirrhosis	-Epclusa for 12 weeks (studies ongoing into resistance patterns and need to add RIBA; can be used in decompensated cirrhosis) -Daclatasvir + SOF +/- RIBA for 24 weeks (latest data no longer supports 12 week regimen)
Failed PEG/RIBA w/o cirrhosis	-Epclusa for 12 weeks -Daclatasvir + SOF for 12 weeks
Failed PEG/RIBA with compensated cirrhosis	-Epclusa for 12 weeks (AASLD recommends adding RIBA based on preliminary studies; can be used in decompensated cirrhosis) -Daclatasvir + SOF +RIBA for 24 weeks (latest data no longer supports 12 week regimen)
Failed SOF/RIBA with or w/o compensated cirrhosis	-Epclusa + RIBA for 12 weeks (recommended by AASLD, but limited data; can be used in decompensated cirrhosis) -Daclatasvir + SOF + RIBA for 24 weeks (limited data, not FDA approved)

**TREATMENT OF CHRONIC HEPATITIS C
Genotype 4**

Patient Groups (including both HCV mono-infected and HCV/HIV co-infected individuals)	Treatment Regimens in order of preference
Rx naïve w/o cirrhosis	-Zepatier for 12 weeks -Harvoni for 12 weeks -Technivie + RIBA for 12 weeks -Epclusa for 12 weeks
Rx naïve with compensated cirrhosis	-Zepatier for 12 weeks -Harvoni for 12 weeks -Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Technivie + RIBA for 12 weeks (monitor LFTs frequently)
Failed PEG/RIBA w/o cirrhosis	-Technivie + RIBA for 12 weeks -Epclusa for 12 weeks -Harvoni for 12 weeks -Zepatier for 12 weeks (preliminary studies indicate treatment should be for 16 weeks and RIBA added if prior virologic failure on treatment)
Failed PEG/RIBA with compensated cirrhosis	-Epclusa for 12 weeks (can also be used in decompensated cirrhosis) -Harvoni + RIBA for 12 weeks -Zepatier for 12 weeks (preliminary studies indicate treatment should be for 16 weeks and RIBA added if prior virologic failure on treatment) -Harvoni for 24 weeks -Technivie + RIBA for 12 weeks (monitor LFTs frequently)

MONITORING TREATMENT

Initial Workup	Week 2	Week 4 then monthly until end of treatment	End of treatment & 12 week follow up
Any time prior to treatment: <ul style="list-style-type: none"> • HCV RNA¹ • HCV genotype • HIV Screen • Fibrosure assay • Liver US Doppler (for cirrhosis only) • Hep A & B screen • NS5A polymorphism in GT1a only if Zepatier considered • Q80K polymorphism in GT1a with cirrhosis only if SIM/SOF considered Within 12 weeks prior to treatment: <ul style="list-style-type: none"> • CBC w/diff • SMA-C • PT/INR • IFD consult² Just prior to initiating treatment <ul style="list-style-type: none"> • HCG in females • Facility clinic visit • Drug-drug interactions 	CBC w/diff SMA-C	CBC w/diff SMA-C HCG Facility clinic visit ³	CBC w/diff SMA-C HCG ⁴ HCV RNA PT/INR Facility clinic visit

¹ HCV RNA (VL) should NOT be monitored during therapy as there are no stopping rules. If a treatment regimen lasting less than 12 weeks is considered, then HCV VL must be repeated within 3 months of starting therapy.

² IFD consult is mandatory prior to starting therapy, to be requested after w/u is complete. Subsequent evaluations are as needed.

³ Monthly clinic evaluations are to be done by a physician, NP, or PA. More frequent evaluations are to be done as needed.

⁴ HCG to be checked monthly up to 6 months post treatment if RIBA used.