

CHRONIC HCV HEPATITIS (cHCV) EVALUATION AND TREATMENT: 2016 CLINICAL PRACTICE GUIDELINES FOR THE OREGON DEPARTMENT OF CORRECTIONS (ODOC)

Medical care standards evolve as knowledge and treatment options expand. ODOC treatment guidelines change accordingly, in keeping with the mandates and mission of medicine in a correctional environment. Since their initiation in ODOC in 1999, medical guidelines for cHCV have been updated multiple times, notably: in 2004 in cooperation with a court appointed expert panel; in 2010 to reflect AASLD Guidelines; in 2012 to incorporate the first generation protease inhibitor drugs; and in now in 2016 to analyze and provide the correctional perspective complementary to the evidence-based scientific and advocacy driven advice presented in the AASLD/IDSA website www.hcvguidelines.org. This ODOC clinical guideline will direct the present use of the rapidly expanding group of direct-acting antiviral agents and help patients plan for their future.

BACKGROUND: HCV hepatitis continues to be a common health problem in Oregon prisons, as in all U.S. correctional institutions, and is primarily associated with substance abuse (usually injection drug use [IDU] prior to incarceration). Of those exposed to HCV, approximately 80% develop chronic infection, as evidenced by sustained HCV-RNA viremia; however, of these patients only about 1/5 will progress to have cirrhosis or life-limiting disease (see section below on Natural History and Progression of HCV). The course of cHCV and the likelihood of progression to advanced liver disease vary greatly among individuals over time and is difficult to predict in its early stages. The goal of HCV evaluation within the ODOC is to identify and prioritize treatment to the patients who need it soonest and will benefit the most.

In the new and expanding world of the direct-acting antiviral agents (DAAs), exponentially increased drug acquisition costs (of which correctional institutions routinely pay more than community averages [ref: www.hcvguidelines.org]) require sound resource allocation management. The American College of Correctional Physicians has stated in a 2014 position statement: “...*The treatment of hepatitis C is advancing rapidly with new treatments utilizing medications that are more efficacious but also more expensive. It is the obligation of the correctional physician to use evidence-based criteria to identify those patients who would benefit most from these new medications and to advocate for their treatment. Correctional systems must not prohibit the new medications based solely on price. They must balance the available resources to treat hepatitis C without compromising the delivery of care for other medical conditions.*” (<http://societyofcorrectionalphysicians.org/resources/position-statements/hepatitis-c-position-statement>.)

The positive outcomes of increased survival and improved quality of life associated with successful viral eradication and a sustained viral response (SVR) are also dependent upon sobriety and positive lifestyle change.¹ Patients have a responsibility to learn from past

¹ A long term Danish study demonstrated 18.2 fold increased mortality risk among younger patients with chronic HCV, not due to liver disease but due to unnatural death: i.e., mortality associated with untreated mental illness and substance abuse associated suicide, homicide, and trauma. Liver related mortality becomes more prevalent as the population ages. Sobriety is key to overall harms reduction. *Clin Gastro and Hepatology* 2011; 9:71-78.

behaviors and interact with society positively. Evaluation and treatment of chronic health problems such as cHCV and substance abuse play a crucial role in establishing trust and developing healthy behaviors, thereby reducing rates of substance abuse relapse and correctional recidivism. This supports the Oregon Accountability Model², the ultimate goal of which is to improve public safety, by recognizing and supporting these positive behaviors in a multi-component approach. Successful cHCV treatment also reduces risk of transmission after release. Thus, the benefits of evaluation and treatment of cHCV go beyond the immediate goal of viral eradication in the individual. cHCV treatment is one part of a multi-part strategy to promote healthy lifestyles, which in turn benefits the individual, his/her family, and society.

Any patient interested in cHCV evaluation should understand that further laboratory testing, liver biopsy, imaging, or another method for staging hepatic fibrosis may be required prior to and during therapy. The risk and side effects of evaluation, the proposed treatment regimen and the need for monitoring must be fully discussed with patients. If there is reasonable documented concern about a patient's ability to adhere to and benefit from a standardized treatment regimen, and these concerns are not able to be resolved through a cooperative treatment plan, treatment should not be initiated.

Identifying patients who need treatment soonest and would benefit most is a complex task requiring evaluation of multiple and diverse factors. These guidelines have been developed to keep ODOC recommendations consistent statewide and to help physicians evaluate patients, consider treatment options and determine both eligibility and priority for treatment.

NATURAL HISTORY AND PROGRESSION OF HCV CHRONIC INFECTION (cHCV) AND ESTIMATION OF HEPATIC FIBROSIS

The figure below, based on the most up to date natural history data, shows that about 30% of cHCV patients progress rapidly to cirrhosis. Alternately, a large proportion (up to 70%) of the 50-80% of patients infected with HCV who develop cHCV are clinically stable. They either do not demonstrate progressive hepatic fibrosis **OR** if progression is noted it is very slow and natural history studies have not been able to document significant progression to end-stage hepatic fibrosis as yet (published data reflect ~20 yrs of prospective follow-up, consistent with the identification of HCV in 1989 and the availability of widespread testing for HCV-Ab in 1992).

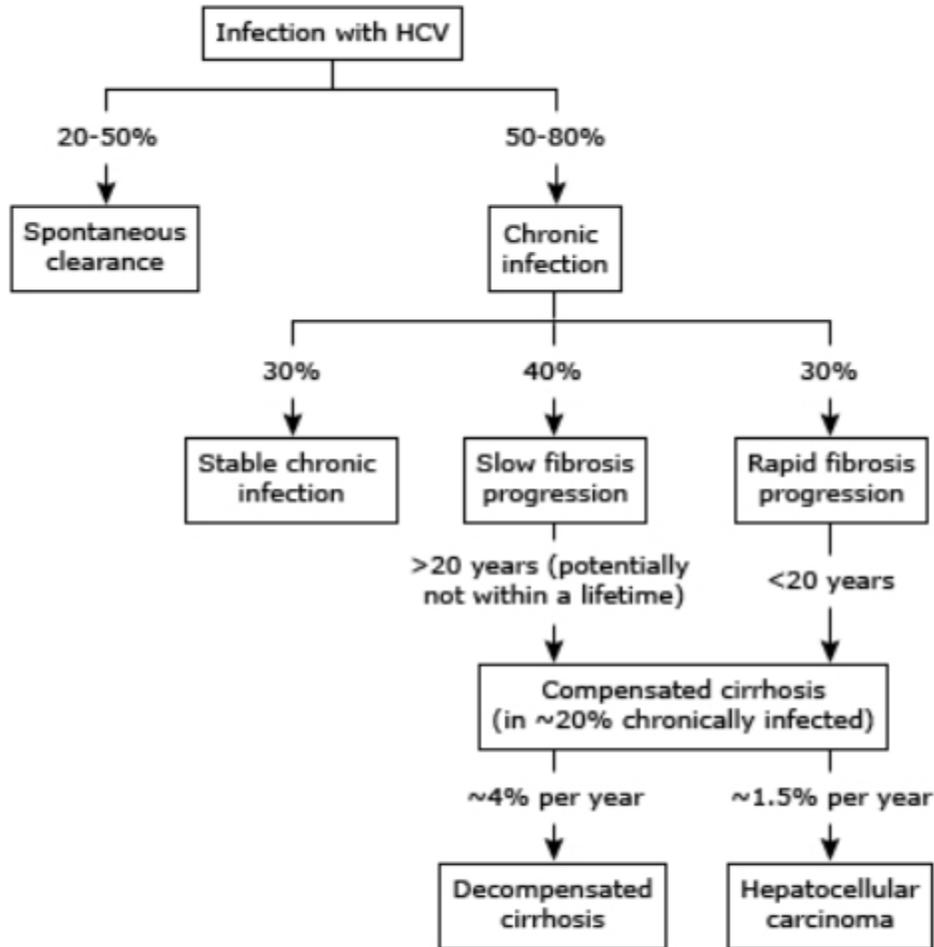
Estimation of Progression of Hepatic Fibrosis: Factors associated with rapid progression or death (<20yrs to cirrhosis) are many, including but not limited to, ALT elevation (especially if ALT>200, or “ALT flare”), active alcohol and drug abuse, grade 3 inflammation (Batts and Ludwig classification) on liver biopsy, presence of bridging fibrosis (Batts and Ludwig S3+/Metavir F3+) on liver biopsy, genotype 3 infection, HIV co-infection, HBV co-infection (with HIV+HBV +HCV co-infection and detectable viremia of both HIV+HBV at highest risk), hepatic steatosis and NASH, diabetes and insulin resistance, obesity, daily use of marijuana, and uncontrolled underlying liver disease. HCV risk behaviors >10yr prior to diagnosis, male sex, age >40yrs are also associated, but are less significant in multivariate analysis. Generally, it is

² http://www.oregon.gov/doc/OC/Pages/oam_welcome.aspx.

wise to assume that patients with more risk factors for progression also have higher risk for more rapid progression.

FIGURE 1
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Natural history of hepatitis C virus



The likelihood of chronic infection following acquisition of HCV and the rate of fibrosis progression depend on various host and viral factors. As examples, young women and children are more likely to spontaneously clear HCV infection, and if chronically infected, have relatively slow fibrosis progression rates. Refer to the UpToDate topic on the natural history of HCV infection for further details.

Graphic 99947 Version 1.0

Estimation of Hepatic Fibrosis: Factors associated with non-progression of hepatic fibrosis are not fully understood at this time, and may be less well studied due to treatment bias. Non-progression is more likely in patients with the following characteristics: female sex, age <40yrs, BMI<30, Batts and Ludwig inflammation Grade 0-1, Batts and Ludwig S0-1/Metavir F0-1, IL28B genotype (with C/C and C/T genotypes less likely to be associated with advanced hepatic fibrosis), and normal ALT ($\geq 75\%$ do not have advanced hepatic fibrosis). African-American race (slower progression/histology less severe in black patients), patients whose HCV risk behaviors have happened in the recent past (usually <5-10yrs), and those without an alcohol abuse history also have less risk. The contribution of sobriety/cessation of IDU to slowing the progression of hepatic fibrosis is poorly quantitated but highly significant in terms of positive lifestyle behaviors associated with improved quality and length of life. Additionally, statin use has been associated with a lower progression rate, and coffee (caffeinated only) consumption has been demonstrated in both retrospective and prospective trials to be associated with reduced hepatic fibrosis.

Estimation of Hepatic Fibrosis by Predictive Scoring: Use of predictive scoring uses laboratory surrogate markers to predict the stage of hepatic fibrosis and may help inform the patient's decision as to whether to proceed. An APRI score (see Definition of Terms in Addenda section) >0.5 or FIB-4 score of >1.45 identify $\geq 75\%$ of patients with advanced hepatic fibrosis (Lin, *et al*; *Hepatology*, March 2011). Likewise, patients with APRI <0.5 or FIB-4 <1.45 have corresponding lower risk. Proprietary indices that predict hepatic fibrosis stage such as FibroSure™ or Hepascore™ are also available at an increased price, with the caveat that they may over-predict hepatic fibrosis in the presence of increased hepatic inflammation. Conversely, they may do a better job of predicting which patients don't have significant fibrosis (Metavir F0-1, Batts and Ludwig S0-1) than the APRI or FIB-4.

Estimation of Hepatic Fibrosis by Liver Biopsy, and by Elastography Methods (using either U/S or MRI) are also critical in the staging process, and are discussed further in later sections of the guideline. Imaging studies may also identify cirrhosis, and not require further staging.

Extrahepatic complications independent of hepatic fibrosis: Regardless of the stage of hepatic fibrosis, HCV-associated complications such as DM2, cryoglobulinemia associated kidney disease, B-cell lymphoma, porphyria cutanea tarda, lichen planus, and other diseases may necessitate earlier evaluation and/or treatment of cHCV. These extrahepatic manifestations of cHCV may also cause morbidity and mortality in patients with Batts and Ludwig S0-2, or Metavir F0-2 hepatic fibrosis, but at a very low rate if recognized and treated promptly.

Although an imprecise science, usually patients benefit from a thorough discussion of risk for progressive hepatic fibrosis, resulting in an improved therapeutic relationship as they have their choices informed. Helping them understand their options for medical care after release also assists in this process.

BENCHMARK TIMELINESS STANDARDS FOR EVALUATION AND TREATMENT:

1. As established in accordance with court decrees, in order to consider treatment for cHCV an individual's total time within ODOC needs to be ≥ 18 months. This allows for the establishment of sobriety, initial development of healthy lifestyles reinforced by

consistent living, full treatment within the variable treatment regimen timelines currently established, and post-treatment follow-up (including SVR assessment), and medical and mental health stabilization post-treatment (especially for patients who received regimens containing RIBAVIRIN or alpha-interferon [aIFN]). This may be an exceedingly short window of time for a patient to assimilate healthy lifestyle change, sobriety, and become fully ready for treatment. In the community this evolution usually occurs over years. Providers should make the patient aware of this fact even while encouraging the patient along his accelerated timeline of change. Present data indicate the patient benefits from this process, even in the limited duration of an incarceration.

2. Initiation of evaluation after a minimum of 3 months within ODOC. This allows reasonable time for the individual to stabilize within the incarcerated environment medically, mentally, and socially. As an example, transaminase levels may continue to decline 3-6 months after establishment of sobriety.
3. The individual needs 6 months without evidence of continuing HCV risk behaviors, or uncontrolled mental health problems which would affect adherence. This may include time prior to ODOC in county jails.
4. If previously unevaluated, the patient should have ≥ 15 months before the earliest release date. However, many have already had much of the evaluation completed prior to incarceration and this may be obtained from previous ODOC records or community medical records.
5. At biopsy consideration by TLC the patient should have ≥ 12 months.
6. Post-treatment should have at least 3-6 months. Females who receive RIBAVIRIN (RBV) treatment should usually have at least 6 months after treatment completion in order to reduce teratogenicity risk were the patient to become pregnant immediately after release.

INCLUSION/EXCLUSION CRITERIA FOR cHCV TREATMENT:

Prior authorization by the TLC (Therapeutic Level of Care Committee) is required for treatment initiation. The decision to treat will be made on an individual, case by case basis, with evidence-based treatment efficacy, application of the appropriate timeliness standard, and population risk given comprehensive consideration. Exceptions to criteria such as timeliness, inclusion and exclusion criteria, etc., may be warranted due to individual circumstances; these should be brought to TLC, discussed and resolved prior to the treatment decision.

Inclusion/exclusion criteria as follows:

1. Patient has had testing for HCV genotype, and has cHCV verified by a detectable viral load within 12 months of starting treatment.
2. Treatment experience documented (either no prior treatment or treatment experienced with the specific regimen recorded in chart)
3. No evidence of HCV risk behavior for at least 6 months prior to treatment initiation
4. The patient agrees to illicit drug screening at the provider's discretion before and during treatment. Screening positive for illicit substances prior to or during cHCV usually will delay treatment, and may be grounds for stopping treatment.

5. Patient adherence issues have been addressed and resolved to the satisfaction of the TLC committee. Examples of issues which will delay inclusion would be unstable medical or mental health conditions, recent poorly controlled behavior, or disciplinary issues indicating the patient is not fully capable of treatment adherence.
6. The patient can be expected to attain reasonable benefit from treatment as evidenced by improvement in quality of life (QOL) or lifespan.
7. Highest priority will be given to patients with advanced hepatic fibrosis (bridging fibrosis) corresponding to a Batts and Ludwig Stage of 3-4, or Metavir score of 3 or greater fibrosis as confirmed by liver biopsy **OR** transient elastography (Fibroscan™) score ≥ 9.5 kPa. At this time we will, in general, not recommend treatment of patients with fibrosis/staging scores of ≤ 2 .
8. Alternatively, the following groups of patients will also qualify:
 - a. Patients with any fibrosis score who are at highest risk of cHCV complications, including cryoglobulinemia with end-organ manifestations (vasculitis, decreased eGFR, proteinuria, nephritic syndrome, or membranoproliferative glomerulonephritis), or co-infection with HIV or HBV or other underlying liver disease where rapid progression of hepatic fibrosis can be reasonably predicted.
 - b. Concordance between laboratory, imaging, or predictive scoring using APRI, FIB-4 or proprietary lab battery combinations consistent with advanced hepatic fibrosis or cirrhosis. In this instance, concordance must exist between at least two of the four modalities listed (e.g., laboratory AND imaging evidence of cirrhosis, or imaging AND predictive scoring consistent with cirrhosis).
 - c. If decompensated cirrhosis is noted clinically or by laboratory parameters then treatment may still be considered after further special TLC review using an evolving evidence-based approach.
9. Treatment of major medical and underlying liver conditions is optimized and not impeded by patient non-adherence. Examples of these conditions may include, but are not limited to:
 - a. Uncontrolled hypertension, BP>160/110.
 - b. Symptomatic CHF, COPD or asthma with frequent exacerbations (indications of either end-stage disease or patient non-adherence).
 - c. ASCAD with active angina
 - d. Poorly controlled diabetes, A1c>8.0
 - e. Untreated thyroid disease
10. For patients who will be taking a regimen containing RIBAVIRIN:
 - a. Patient is not pregnant
 - b. Women of childbearing potential and within 6 months of treatment conclusion agree to use of two forms of effective birth control post-release with male partners. This should usually be accomplished by treatment initiation within 12 months prior to release.
11. For patients who will be taking a regimen containing ALPHA-INTERFERON (Pegasys®), patients must NOT have the following:
 - a. Platelet count <100k a relative contraindication, and <75k is an absolute contraindication for aIFN due to acute hepatic failure during treatment with increased mortality. Risk for acute hepatic failure during IFN treatment is usually ~2% but with these levels has been observed to be ~4%.

- b. Major uncontrolled depressive illness
 - c. Solid organ transplant (renal, heart or lung)
 - d. Autoimmune hepatitis or other autoimmune condition known to be exacerbated by aIFN-based therapies, e.g., inflammatory bowel disease, rheumatoid arthritis, ITP, SLE, severe psoriasis
 - e. CHF, LVEF<40%
 - f. COPD, FEV1<1.0
12. For patients who will be taking a regimen containing VIEKIRA PAK® with concurrent cirrhosis, the cirrhosis class must be Class A only. Class B/C cirrhosis patients are excluded due to the potential of drug related hepatotoxicity.
13. Pharmacy and prescribing provider have determined that no significant drug-drug interactions exist with the HCV regimen and the patient's other medical/psychiatric therapies.

Indications and contraindications Follow-Up: Routine follow up to re-assess indications for treatment should occur at appropriate intervals. As monitoring reveals either compliance with treatment indications or new contraindications the patient should be re-evaluated for treatment accordingly. During each evaluation the patient should receive a summary of testing done, reason for treatment contraindication if present, and education regarding the next step to resolve the contraindication if possible.

Uncorrected HCV behavioral risk factors as contraindications for cHCV treatment: Drug or alcohol use/abuse (self report, positive drug screen, possession, rule violation) or a new tattoo (DOC specific) within the prior 6 months is a contraindication to medication treatment for Hepatitis C, but is not a contraindication for work up or evaluation.

HCV Treatment Contract: The patient and provider will review the "Hepatitis C Treatment Contract"; and the patient must agree to terms of treatment, which may include any/all of the following:

1. Inmate may be subject to random alcohol and drug testing at ODOC discretion
2. Evidence of use of alcohol or non-prescribed drugs or a positive random alcohol or drug testing or fresh tattoos or equipment possession should usually result in removal from therapy.

Special considerations of patients undergoing liver biopsy: Usually, liver biopsies should be performed only on patients who will be potential candidates for treatment. Liver biopsies remain the best medical evaluation to determine the stage of hepatic fibrosis, which yields information vital to deciding whether to treat and the urgency of treatment. However, liver biopsies may underestimate (never overestimate) the level of hepatic fibrosis. This sampling error may result in 1 stage differences between the right lobe (usually sampled due to safety concerns) and the left lobe in ~1/3 of biopsies, and in ~1/6 of patients this is the difference between fibrosis stage 3 and cirrhosis. Other disadvantages of biopsy include invasiveness with potential for peri-operative events (usually bleeding or vasovagal reactions), and variability of pathologist's interpretation.

If the liver biopsy shows severely advanced fibrosis (cirrhosis, Metavir F4 or Batts-Ludwig S4), patients should be referred for EGD to assess for the presence of esophageal varices, and regular

abdominal imaging with U/S q6-12 months for hepatocellular carcinoma (HCCa) screening will be initiated. EGD referral may also be indicated if the platelet/spleen diameter ratio is $< 900^3$.

If there are no contraindications to a liver biopsy, the provider will hold a PARQ (**P**rocedure, **A**lternatives, **R**isks, and **Q**uestions) conference with the patient about the risks and difficulty of liver biopsy as well as treatment.

Interpretation of Liver Biopsy Results: Liver biopsy pathology reports will be submitted to the TLC and final eligibility for therapy will be established by consent of the committee. In general the following guidelines apply:

1. Advanced hepatic fibrosis is defined as Metavir F3-4, or Batts and Ludwig stage 3-4.
2. Re-evaluation by means of repeat biopsy within 4-5 years may be recommended for any patient in whom hepatic fibrosis is not advanced in order to establish progression. Per AASLD guidelines: “progression to cirrhosis may be accelerated in persons who are of older age, who are obese, [and] who are immunosuppressed (e.g., HIV co-infected).”
3. Consideration should be given to biopsy sampling error, i.e., up to 15% of patients biopsied may show a score less than the actual extent of fibrosis, and this may affect treatment decisions.
4. If cirrhosis is present, which is a disease in and of itself, it needs to be managed in accordance with separately established chronic cirrhosis care guidelines and the patient enrolled in the cirrhosis care SNR clinic.

Use of concordance in diagnostic modalities to establish eligibility for treatment: As discussed above, in some cases the liver biopsy may not be the definitive answer for eligibility. Some experts presently believe that there is no “gold standard” of hepatic fibrosis staging, and prefer instead to establish the presence of advanced hepatic fibrosis (Metavir F3+, or Batts-Ludwig S3+) through concordance between laboratory, imaging, and predictive scoring (APRI, FIB-4, or proprietary indices). ODOC protocols allow for the presence of advanced hepatic fibrosis to be established by non-biopsy methods; however, liver biopsy is still preferred as it gives the most complete picture of hepatic fibrosis and associated hepatic parenchymal pathology.

HCV TREATMENT PROTOCOLS: Although treatment regimens are changing rapidly as new agents become available, consensus has developed around several available treatment regimens. Usually 8-12wk regimens are preferred due to improved adherence, lower toxicity, and cost-effectiveness:

cHCV-1a:

- a. HARVONI® 1tab PO QD 8 wks (56 doses) if no previous treatment experience, VL $<$ 6million copies, and no evidence of cirrhosis by abdominal U/S.
- b. HARVONI® 1tab PO QD 12 wks (84 doses) if no previous treatment experience and VL \geq 6million copies.

³ Gianni EG, Zaman A, Kreil A, et al; Am J Gastroenterol 2006 Nov; 101:2511-9;
<http://www.ncbi.nlm.nih.gov/pubmed/17029607>.

- c. HARVONI® + RBV (weight based dosing) 12 wks in patients with Class A cirrhosis and/or previous treatment experience.

cHCV-1b: as above; except patients with Class A cirrhosis or previous treatment experience do not generally need RBV.

cHCV-2 (all subtypes):

- a. SOFOSBUVIR (SOF) + RBV (weight based) 12 wks if not cirrhotic
- b. SOF + RBV (weight based) 16wks if Class A cirrhosis is present.
- c. Alternatively, in patients who do NOT have underlying medical conditions such as respiratory disease which would preclude the use of aIFN + RBV (PR), the patient may enter a 4 week PR lead-in, then if a Rapid Viral Response (RVR: VL not detected at end of 4 wks PR) is present patient completes 24wks total PR. In patients who do NOT experience RVR, default to guideline recommended SOF+RBV 12wks.

cHCV-3 (all subtypes):

- a. PR + SOF 12wks remains the only presently available regimen with demonstrated SVR \geq 90% in patients with or without cirrhosis. Platelet count $<$ 100k a relative contraindication, and $<$ 75k is an absolute contraindication for aIFN due to acute hepatic failure during treatment with increased mortality.

Clear orders must be written or entered into the computerized order entry system in order to facilitate best management of medication delivery to the patient. An example of a SOFOSBUVIR order would be: "SOFOSBUVIR (or SOLVADI®) 1T PO DAILY x 84 doses, concurrent with (other drugs in regimen)." In the box for "Days Supply" we presently advise typing "120" in order for delays in treatment initiation to not interrupt the consistent and consecutive delivery of the required 84 doses.

All other genotypes or unusual combinations of treatment experience and/or cirrhosis should undergo specialty evaluation for treatment recommendations. Guidelines will be revised as new drugs become available and can be used efficiently within the correctional environment; i.e., the arrival of VELPATASVIR in 2016 may change recommendations for cHCV-3 treatment for patients who are ineligible for aIFN.

TELAPREVIR or BOCEPREVIR are no longer considered in treatment regimens due to excessive toxicity.

MAJOR DRUG-DRUG INTERACTIONS WITH THE DIRECT-ACTING ANTIVIRALS:

Pharmacy input on the patient's current drug profile should be reviewed prior to dispensing to patient, and appropriate patient education should be given.

SOFOSBUVIR: Mechanism of action-inhibits HCV NS5B RNA-dependent RNA polymerase, essential for viral replication, and acts as a chain terminator. Selected important interactions common to ODOC patients may include (not a comprehensive list):

Amiodarone: SOF may enhance the bradycardic effect of Amiodarone.

OXcarbazepine: May decrease the serum concentration of SOF.

Rifapentine: May decrease the serum concentration of Sofosbuvir. Do not use concurrently.

HARVONI® (SOFOSBUVIR-LEDIPASVIR): Ledipasvir mechanism of action-inhibition of the HCV NS5A protein necessary for viral replication (see above for SOFOSBUVIR information). Additional important interactions:

H2-Antagonists: May decrease the serum concentration of Ledipasvir. *Risk D: Consider therapy modification*

Proton Pump Inhibitors: May decrease the serum concentration of Ledipasvir. Management: Avoid the use of PPIs at doses greater than the equivalent of omeprazole 20 mg, avoid administration of PPIs within 2 hours prior to ledipasvir dosing, and avoid use of PPIs in combination with food.

Both classes should be avoided during treatment; use temporary supportive measures for reflux instead, then reinstitute H2 or PPI after cHCV treatment completed.

VIEKIRA Pak®, ELBASVIR-GRAZOPREVIR (Zepatier®): Not used commonly in ODOC at the present time due to multiple drug-drug interactions and concerns for hepatotoxicity. If these drugs are used, extreme caution for drug-drug interactions will be required, and Childs-Pugh Class A cirrhosis must be recently verified and checked throughout treatment. Additionally, use of RIBAVIRIN is probably necessary for all S3-4 (F3-4) patients due to resistance concerns with **ELBASVIR-GRAZOPREVIR (Zepatier®)**

DACLATASVIR, SIMEPREVIR (Olysio®): Used only in specialty consultation at this time.

TREATMENT GUIDELINE ADDENDA (AS APPLICABLE):

RATIONALE FOR PATIENT EDUCATION: WHO CAN SAFELY WAIT FOR TREATMENT? Or, how do we talk to patients about treatment delays in the present day? (The following discussion is provided to help providers assimilate critical concepts prior to discussing with the patient):

Because www.hcvguidelines.org advocates nearly universal treatment, i.e., viral eradication, of patients with cHCV, some patients will believe that he/she is being discriminated against and not offered what he/she believes they are entitled to. This belief may be reinforced by media and advocacy messages without the filter of individual patient responsibility and a more realistic view of the future.

In a majority of cases at this time the patient will not have advanced hepatic fibrosis or otherwise meet present criteria for treatment. This should be presented positively to patients without removing hope for the future, i.e., “not having bad scarring of the liver is a very good thing!” Many factors are expected to increase the availability of antiviral drugs to a larger segment of the cHCV population in the next several years, including market competition lowering the price of medications, expanding state and federal support of Medicaid programs, and expanded funding of public health initiatives supporting treatment of patients with lower fibrosis scores during incarceration. If the patient remains clean and sober and lives a healthy lifestyle it is highly likely that these changes will occur prior to significant progression of their cHCV.

Accordingly, patients should be educated that many factors influence progression of hepatic fibrosis, not just the presence of a VL. They should understand that the height of the VL does NOT impact positively or negatively on fibrosis progression. Also, if their ALT/AST levels have normalized in their clean and sober state, the rate of progression will be very slow, and the large majority of patients may never progress to advanced fibrotic states. So the outlook for the clean and sober patient is bright even before viral eradication.

This positive prognosis is not possible if they experience substance abuse relapse, and those who do are also at an higher risk of death. Substance abuse relapse is, was, and continues to be lethal. It also makes it very difficult for the patient to participate in post-release medical care and keep eligible for treatment when it becomes available.

Decreased mortality has been seen in patients who obtain an SVR from treatment at all stages of hepatic fibrosis (www.hcvguidelines.org). Decreased mortality has also been seen in patients who become clean and sober at all ages. SVR is associated with increased probability of sobriety and decreased rates of substance abuse relapse (www.hcvguidelines.org); therefore, sobriety is an as yet unquantified but highly significant component of decreased mortality rates in patients who obtain SVR (in fact, all cHCV drug treatment studies to date have required sobriety prior to study entry). These positive outcomes, i.e., improved survival, sobriety, and

SVR, are inextricably inter-related, and correctional treatment programs should assist the patient to understand the inter-relationship and continue to “own” their sobriety as they await cHCV treatment availability. As previously stated, the benefits of evaluation and treatment of cHCV go beyond the immediate goal of viral eradication in the individual. cHCV treatment is one part of a multi-component strategy to promote healthy lifestyles, which in turn benefit the individual, his/her family, and society.

Patients and providers have also heard a lot about re-infection in patients who relapse into substance abuse. The following facts regarding re-infection may be discussed for patient consideration: The primary incidence of HCV re-infection in a community meta-analysis population was 6-30/100 person.yrs. (Aspinal, et al; *Clin Infect Diseases* 2013; 57:S80-S89); although may be higher among previously incarcerated persons. Expert interpretation of the available data indicates that chances for re-infection are relatively low but present, and “...engaging with healthcare and going through the treatment process often has very positive outcomes among injectors, as far as reduction in risk behavior and increasing access to healthcare after treatment.”

Regardless of viral eradication status, patients should be thinking positively about sobriety and establishing care with a medical provider post-release. Further resource allocation within the ODOC will likely assist the process of post-release medical follow-up in the future.

The treatment of cHCV is multifactorial, and should include a major emphasis on healthy lifestyle. The maintenance of a healthy weight will prevent or delay the onset of HCV-associated DM2, and early use of statins in patients with cardiovascular risk also has the potential of moderating the effect of hepatic steatosis. Even concurrent control of hypertension, especially with ARBs, has the potential of decreasing hepatic inflammation. Although studies of and interventions for the reduction of hepatic inflammation are still ongoing, “getting the fat out of your liver” is always a healthy goal. To this end, aerobic exercise and conditioning, with a decreased emphasis on weight training, is very appropriate.

Chronic HCV Hepatitis Evaluation Worksheet

<i>SECTION 1 Initial Screening Information</i>			Date
HCV-Ab positive? _____; HCV-VL _____ (<1yr old titer needed for Rx)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Hepatitis C Genotype _____ ALT _____; AST _____; PLT _____; TBIL _____; ALB _____; INR _____ Other pertinent lab: _____ (ferritin, ANA, TSH, sCr if abnormal)			
APRI and/or FIB-4 (http://www.hepatitisc.uw.edu/page/clinical-calculators/apri.)			
Hepatitis B surface Ag positive? (If yes, consider specialty consult/TLC.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
HIV positive? (If yes, refer for specialty consult/TLC.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Prior HCV treatment? When/What	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Has been in ODOC > 3 months and has greater than 12 months left ? Admit date _____ Release date _____			
TLC request for LIVER BX? If patient has been previously staged and/or has cirrhosis, are we referring to TLC for Rx?	<input type="checkbox"/> BX request	<input type="checkbox"/> RX request	

<i>SECTION 2 Further Medical Evaluation</i>			Date
Evidence of cirrhosis or decompensated liver disease, e.g., ascites, history of hepatic encephalopathy, history of esophageal varices with bleed, etc; or HCV-associated disease (rashes, arthritis) ?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If evidence of cirrhosis: refer to Cirrhosis Chronic Disease Monitoring/Cirrhosis SNR (EGD referral, ABD U/S for HCCa surveillance, etc.)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Major Medical Illness poorly controlled, e.g. Diabetes, ASCVD, Angina, COPD, Mental Health Issues, Cancer, Autoimmune Disorder, etc. Explain.	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Age of patient at first IDU or other risk behavior: _____ Hx alcohol abuse: _____; if YES: have patient estimate years of alcohol abuse _____	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Medications causing possible Drug-Drug interactions with HCV Rx? (e.g., PPI for DAAs)	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
<i>SECTION 3 Mental Health Considerations</i>			Date
Unstable MH conditions which could affect adherence or completion of a treatment program?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If clean/sober, how long? _____; If sobriety occurred at entry into incarceration, what steps have they taken to show motivation for ongoing sobriety?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

<u>SECTION 4 Other Concerns</u>			Date
Evidence of ongoing HCV risk behaviors?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Evidence of non-compliance with other treatments or evaluations?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Patient refused to sign contract?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
If female, pregnancy ruled out? Is patient willing to use 2 methods of contraception if released within 6 months after completion of RIBAVIRIN containing regimens?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Other Concerns? Explain.	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

<u>SECTION 5 Clinical Decision making</u>			Date
Is patient an appropriate candidate for possible liver biopsy? <i>(If YES, proceed to Section 6—Biopsy and Treatment)</i>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Is patient an appropriate candidate for treatment for viral eradication by ODOC guidelines? <i>(If YES, proceed to Section 6—Biopsy and Treatment)</i>			
If patient is not an appropriate candidate at this time for liver biopsy and treatment, give reason:			
<i>Proceed to "Hepatitis C Monitoring"</i>			

<u>SECTION 6 Biopsy and Treatment</u>			Date
Liver biopsy approved?	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Liver biopsy results? Grade _____ Stage _____			
Liver biopsy results to TLC	<input type="checkbox"/> Yes	<input type="checkbox"/> No	
Treatment approved by TLC? If yes, proceed to treatment. <i>If no, proceed to "Hepatitis C Monitoring"</i>	<input type="checkbox"/> Yes	<input type="checkbox"/> No	

Signature _____

Date _____

Name _____
SID# _____

USING THE GUIDELINE DURING DIRECT PATIENT CARE ENCOUNTERS.

Translating the clinical guideline into what to actually say and do during the patient visit can be challenging. Patient education and developing and maintaining a therapeutic relationship is beneficial at all stage of the process. Usually this process evolves over time and occurs in stages. Using the guide below may help the clinician to develop a treatment plan tailored to individual patient needs. Common patient scenarios are presented.

INITIATION OF EVALUATION AND DECIDING WHETHER TO PROCEED WITH STAGING: In the initial patient visit(s), the patient is informed of their HCV-Ab and HCV-VL status, and patient education and discussion helps inform the patient's choice as to whether to proceed further. HCV risk behavior discussion helps establish a likely period of infection (with longer periods of infection giving higher risk for advanced stages of hepatic fibrosis). Discussion of other liver injury risk behavior such as alcohol abuse gives additional information about likelihood of underlying liver scarring. Use of the simple APRI score or FIB-4 score gives further information about likelihood. Further lab work may help guide the patient's decision. Also, education regarding timeliness standards is given. It is appropriate to give the patient time to decide and then discuss again at a future clinical visit.

PATIENT CARE EXAMPLE #1: A 44 y.o. patient has a HCV-Ab+ and HCV-VL is not detected. This patient does not have cHCV and does not need further F/U for HCV after education that re-infection is likely if risky behavior continues. If the AST and ALT are abnormal, further evaluation should focus on non-HCV differential diagnosis such as NASH/NAFLD, use of hepatotoxic substances or misuse of NSAIDs/APAP, etc.

PATIENT CARE EXAMPLE #2: A 23 yr old African-American female states she has participated in IDU since age 18. She abused alcohol in the past 2 yrs prior to incarceration. She has cHCV-1a, and her AST and ALT have normalized within the first 6 months of incarceration. Her APRI score is <0.5, and her FIB-4 <1.45. This patient's risk for advanced hepatic fibrosis is very low and is not likely to progress if she maintains sobriety. Long term management of cHCV is instituted if the patient decides against staging at this time. Options for further care using medical insurance upon release are explained and she decides to prioritize sobriety and continue medical F/U after release.

PATIENT CARE EXAMPLE #3: The same patient now decides she wishes to pursue evaluation. She has an adequate time to expected release date. Further evaluation including staging with liver biopsy or non-invasive elastography is advised and patient information is gathered and organized using the Chronic HCV Evaluation Worksheet in order to present for further staging. In the future, when elastography becomes more widely available, this will probably reduce the need for biopsy.

PATIENT CARE EXAMPLE #4: A 57 y.o. male with cHCV-3a has a 30 yr hx of HCV risk behavior and intermittent alcohol abuse. His AST and ALT remain elevated despite >6months of sobriety during incarceration. He wishes to pursue evaluation and treatment, and so now the Chronic HCV Evaluation Worksheet can be used to ready the patient for presentation to TLC for liver biopsy.

AT COMPLETION OF STAGING: Further patient education regarding treatment and further evaluation is directed by the results of staging. Specialty consultation for HCV viral eradication treatment recommendations may be indicated. Further evaluation and management of cirrhosis, if present, is initiated at this time. The patient is concerned about his/her prognosis and should be given adequate time and resources for education and anxiety reduction.

PATIENT EXAMPLE #5: The patient in example #4 has a liver biopsy showing Grade 2 inflammation and Stage 2 fibrosis, with the presence of hepatic steatosis and without the presence of iron. The patient is informed of good news of biopsy, informed that he is not presently a candidate for treatment, and long-term management of HCV with CBC, CMP q6-12 months and careful clinical observation is instituted. If the clinician suspects more hepatic fibrosis than indicated by the biopsy, further information via abdominal U/S, elastography when available, or other labs such as ANA or serum ferritin may help clarify the clinical picture and reassure the patient. Sobriety is encouraged.

PATIENT EXAMPLE #6: The patient in example #4 has an abdominal U/S while waiting for liver biopsy in order to evaluate RUQ pain. The U/S shows liver nodularity, an enlarged portal vein with flow away from the liver, and splenomegaly (15.8cm). His platelet count was 138, an APRI score was >2.0 and FIB-4 score was >3.25. He now has multiple diagnostic domains indicating advanced hepatic fibrosis/cirrhosis. Using the Worksheet, further planning for the patient is instituted. The patient is referred to the Cirrhosis Chronic Care Clinic/SNR. EGD for varices surveillance is indicated. Annual U/S screening for hepatocellular carcinoma is planned. A treatment decision for viral eradication is made at TLC.

LONG-TERM MANAGEMENT OF cHCV: Regular clinical observation of the patient who is not yet eligible for treatment is instituted, and re-referral to the TLC is indicated if the clinical picture changes.

PATIENT EXAMPLE #7: The patient in example #5 experiences an ALT flare with ALT>200 for >6 months. Careful history regarding use of supplements, NSAIDS, APAP, potentially hepatotoxic medications is discussed and further patient education provided. Random drug screening may be appropriate, or a review of the patient's disciplinary record may be indicated. Staging earlier than the usually recommended 4-5 yr interval is considered. Abdominal imaging may be helpful to rule out a mass lesion or other abnormality of the liver. If BMI>30 then discussion of weight loss should take place as treatment trial for possible NASH/NAFLD.

DEFINITION OF TERMS:

HCV-RNA: HCV viral load, or **HCV-VL**, or **VL**

PR: Pegylated alfa-interferon and Ribavirin

TW: Treatment Week

SVR: sustained viral response

HCV-1, HCV-2, HCV-3, HCV-4: HCV genotypes presented numerically.

PEGaIFN2a/PEGASYS®: fixed dose aIFN, 180mcg/wk (ODOC formulary choice)

APRI score: AST/PLT ratio index

(<http://www.hepatitisc.uw.edu/page/clinical-calculators/apri>.)

FIB-4 score: (<http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4>.)

ADVERSE EVENTS DURING TREATMENT CAUSED BY aIFN: The course of aIFN-based therapy is usually very difficult and stressful for patients, almost all of whom experience adverse events at some point. This burden of treatment has been significantly relieved by shortened treatment times (12 wks). However, the following symptom/signs remain common:

1. **Influenza-like symptoms**, which tend to occur immediately following or soon after PEGASYS® injections, including headache, fatigue, fevers and chills (incidence >50%). These symptoms tend to be self-limited and can be treated with rest, fluids, acetaminophen (<1.5gm/day total dose) and/or NSAIDs.
2. **Psychiatric symptoms:** depression, irritability, insomnia (22-31% incidence per AASLD review, which included >12wk regimens); especially exacerbation of symptoms of pre-existing disorders, e.g., major depression progressing to frank suicidality, or anger management dysfunction progressing to physical aggression. Depression specific symptoms (mood, anxiety, and cognitive symptoms) are responsive to serotonergic antidepressants. Neurovegetative symptoms (fatigue, anorexia, pain, psychomotor slowing) do not respond to serotonergic medications but may be partially alleviated by catecholaminergic antidepressants in consultation with mental health. See footnote to table 3 for exam intervals*.
3. **Neutropenia;** although serious infectious complications are unusual, dose reduction is recommended: 50% reduction in PEGASYS® for ANC<750, and discontinuation of therapy if ANC<500 repeatedly (see table 3).
4. **Anemia;** usually reaching a nadir within the first 8wks. Dose modification is recommended for Hgb <10 (see table 3). The use of erythroid cell line growth factors has not been shown to improve SVR rates (AASLD, 2009).
5. **Thrombocytopenia**, especially common (~25%) in patients with compensated cirrhosis. As yet, administration of growth factor treatments have not yet shown improved SVR rates.
6. **Hypothyroidism** due to autoimmune thyroiditis (induced by aIFN).
7. **Autoimmune disorders** Exacerbation of pre-existing conditions including autoimmune hepatitis (AIH). In AIH, persistently elevated ALT is noted even as the serum HCV-RNA becomes undetectable. Specialty consultation is usually needed to co-manage patients in this category.
8. **Respiratory complications:** Rarely, aIFN-based therapy may cause respiratory complications. These are predominately autoimmune-mediated, causing interstitial

pneumonitis, which is usually reversible and of only mild-moderate intensity, requiring only cessation of the drug and supportive care. However, because progression to severe bronchiolitis obliterans and/or ARDS has been reported, any new pulmonary symptom such as new onset of dyspnea or progressive dyspnea should be recognized early and a high index of suspicion maintained for hypoxemia and oxygen desaturation. Oxygen desaturation as measured by SpO₂ monitoring (see footnote to Table 3) will help differentiate between the universally prevalent dyspnea caused by anemia and the hypoxemia caused by diffuse parenchymal lung disease.

ADVERSE EVENTS DURING TREATMENT CAUSED BY RBV:

1. **Hemolytic anemia**; especially in patients who have reduced GFR due to renal disease.
2. **Hyperuricemia** induced by RBV is usually asymptomatic, but may induce exacerbation of pre-existing gouty arthritis.
3. **Pruritis**: alleviated with usual symptomatic therapy.
4. **Cough**, nasal stuffiness; unknown mechanism
5. **Tetratogenicity**: up to 6 months post therapy.
6. **Hyperbilirubinemia**: seen usually in patients with decompensated cirrhosis or moderate to severe hemolytic anemia.

MONITORING: Regular laboratory and clinical evaluation must take place after initiation of aIFN or RBV therapy, and should be guided by the “Hepatitis C Viral Eradication Treatment Monitoring” worksheet (see attached). At a minimum, this should include a CBC and ALT @ 2 and 4wks, and q monthly thereafter until 1 month after end of treatment. An hTSH assay prior to 3m of treatment, and at end of treatment is also indicated.

Sustained Viral Response (SVR; i.e. “cure”) is established if the viral load is not detectable at the end of 12 weeks post-treatment. All patients should have the 12wk post treatment HCV-VL to document SVR.

TABLE 3: Laboratory Monitoring when applicable in patients receiving aIFN and/or RBV

LAB TEST	Indications for Monitoring	Recommended Monitoring Intervals	Recommended Actions
CBC, CMP	Rx-induced anemia, thrombocytopenia, ALT elevations or reductions, etc.	CBC and CMP q2wks for 4 weeks then monthly if stable. Recommend blood draw ≤ 24 hours before weekly aIFN dose.	<p>ALT: If over 2 times baseline, consider aIFN-induced autoimmune hepatitis* and stopping aIFN therapy.</p> <p>Hgb >10: No intervention</p> <p>Hgb 8.5-9.9: decrease RBV by 200 mg/day or add EPO*</p> <p>Hgb <8.0: stop RBV +/-</p>

			<p>EPO</p> <p>ANC >500: No intervention</p> <p>ANC <500: Consider aIFN dose reduction or add G-CSF (Neupogen®)*</p> <p>ANC <250: Stop aIFN; administer G-CSF until ANC>1000</p> <p>PLT >50K: No intervention</p> <p>PLT 25-50K: aIFN dose reduction</p> <p>PLT <25K: Hold aIFN until >50K, then resume at 50% dose*</p>
TSH	Rx-induced thyroid inflammation causing hyper/hypo-thyroidism	Baseline, 12 wks	

EXAM: Do a directed physical exam at each visit. If SOB/DOE present, consider SpO2 monitoring*;

Mental Health: Evaluate for depression, aggression, drug abuse at each visit and consult CTS as needed.*

cHCV Hepatitis Treatment Guidelines: Patient Lab Result Summary Sheet*

FOR USE WITH PEGASYS AND RIBAVIRIN ONLY; OPTIONAL

GENOTYPE _____

LIVER BIOPSY RESULT (Date, Grade, Stage, ?Fe, ?Steatosis)

Therapy Start Date: _____

Target End Date: _____

	Base-line	TW1	TW2	TW4	TW6	TW8	TW12	TW16	TW20	TW24
DATE										
HCV-RNA										
ANC#										
HGB										
HCT										
PLT										
ALT										
AST										
INR										
ALB										
TBILI										
TSH										
Preg. Test										

(*When applicable. This is for convenience only, not all labs need to be trended unless indicated for that patient. For example, trending HGB is a good idea, but HCT does not need to be trended also but is listed for clinicians who are more comfortable with HCT indices)

ANC=WBC x (% NEUTROPHILS + % BANDS + % MYELOCYTES); ANC >500: No intervention; **ANC <500:** Consider aIFN dose reduction or add G-CSF (Neupogen®); **ANC <250:** Stop aIFN; administer G-CSF until ANC>1000

ALT: If over 2 times baseline, consider aIFN-induced autoimmune hepatitis* and stopping aIFN therapy.

Hgb >10: No intervention; **Hgb 8.5-9.9:** decrease RBV by 200 mg/day or add EPO; **Hgb <8.0:** stop RBV +/- EPO

PLT >50K: No intervention; **PLT 25-50K:** aIFN dose reduction; **PLT <25K:** Hold aIFN until >50K, then resume at 50% dose

TSH: measure at baseline and 12 wks; continue monitoring if indicated (rising trend, above ULN, etc.)