

HIV and Hepatitis Co-infections:

Management and Treatment Guidelines

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1. INTRODUCTION

A quarter of a century into the HIV epidemic the spectrum of illness confronting HIV care providers has changed significantly. Today end stage liver disease (ESLD) and hepatocellular cancer (HCC) due to co-infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) cause more morbidity and mortality in co-infected individuals than PCP, toxoplasmosis, CMV, and disseminated MAC combined. Adjusting to this new post-HAART reality is an important aspect of providing medical care for the millions of individuals living with HIV.

It is estimated that there are roughly 300,000 HCV/HIV and 60,000 HBV/HIV co-infected individuals living in the U.S. Meeting the medical care needs of this large diverse population may require blurring of traditional medical care boundaries. Ideally the assessment and treatment of co-infected patients would be a cooperative effort between HIV care providers and liver specialists. However, the complexity of HAART regimens and the potential for adverse drug interactions can pose major challenges for referral-based HCV and HBV care. In many communities, the best care model for treating co-infected patients may be liver specialists with enhanced knowledge of HIV therapy, or HIV care providers educated in treating HBV and HCV co-infections.

The goal of this handbook is to outline the rationale for treating hepatitis virus co-infections in HIV positive individuals, and to provide the practical details for delivering that care safely and efficiently to patients who need it. The overall management approach presented here is intended as a starting point for providers with appropriate qualifications but limited experience in treating co-infected patients.

2. DEFINITIONS & VOCABULARY

GENERAL TERMS:

- *International Units (IU)* – a standardized measure of HCV or HBV viral loads that allows comparison of viral load results obtained using different quantitative assays.
- *Cryoglobulins* – Immune complexes composed of antibodies, complement, and viral particles that can embed in blood vessel walls causing inflammation and end organ damage.
- *Transaminitis* – Elevations in ALT & AST that reflect immune-mediated elimination of infected hepatocytes; correlates with degree of inflammation in the liver.
- *Hepatic flare* – Episode of transaminitis, potentially severe, related to hepatitis therapy. Hepatic flares are more common with HBV therapy than HCV therapy.
- *Fibrosis* – Scar formation within the liver. Bands of collagen fibers begin in the portal triads and progress to disrupt the architecture of the liver lobule, ultimately disrupting the visible appearance of the liver itself (cirrhosis). Staging of fibrosis is a critical factor in deciding whether to initiate hepatitis treatment.
- *Alpha fetoprotein (AFP)* – a marker of abnormal proliferation of hepatocytes within the liver. Used as a screen for hepatocellular cancer (HCC). Normal values are < 20 ng/ml. Values > 400 ng/ml have a strong correlation with HCC.¹

HEPATITIS C VIRUS (HCV) VOCABULARY:

- *Genotype* – HCV has nine subspecies, referred to as genotypes, associated with important biological and clinical consequences. In the United States and Europe, genotypes 1-4 predominate. Genotype 1 is the most common in the U.S.

- *Very Early Treatment Response (VETR)* – determined by an HCV viral load after four weeks of therapy. Patients with an HCV viral load < 50 IU/ml after 4 weeks of therapy are known as super responders.
- *Early Treatment Response (ETR)* – determined by an HCV viral load after twelve weeks of therapy. Patients with HCV viral loads < 50 IU/ml, or decreased 100-fold (2 logs) from initial values, are considered early treatment responders.
- *End of Treatment Response* – the HCV viral load after 48 weeks of HCV therapy. Patients with HCV viral loads of < 50 IU/ml are considered end of treatment responders.
- *Sustained Virologic Response (SVR)* – An HCV viral load < 50 IU/ml 6 months after completing HCV therapy. An SVR is the functional equivalent of a *cure*. Relapses of HCV in co-infected or mono-infected patients after an SVR are rare (~1% per year with 5 year follow-up).

3. HEPATITIS C VIRUS

HCV is a positive strand RNA virus, which means that the genetic material in the virus particle can be translated directly into protein by ribosomes of the infected cell. The HCV replication process occurs entirely in the cytoplasm and does not kill the infected hepatocyte. The virus genome encodes a viral capsid protein, two envelope glycoproteins, a protease/helicase, an RNA-dependent polymerase, and several proteins of unknown function. The protease and RNA-dependent RNA polymerase are promising targets for future anti-HCV therapeutics. Similar to HIV, the positive strand HCV RNA is translated into a polyprotein that undergoes autocleavage to generate the viral subunits. HCV is a stealth pathogen that evades immune recognition, at least in part, by dampening hepatocyte responses to being infected. Mammalian cells have sensors for invading viruses, including a sensor for double-stranded RNA virus replication intermediates in the cytoplasm called RIG-I. HCV ‘wisely’ blocks hepatocyte production of interferon- α/β by disabling the RIG-I signaling pathway.² One can view pegylated interferon therapy as overcoming HCV’s stealth strategy by providing the interferon that HCV had suppressed. Infected hepatocytes exposed to interferon α become better targets for the cellular immune response, resulting in their elimination.

THE RATIONALE FOR TREATING HCV

While ‘quoting the literature’ is not a prerequisite to providing medical care to co-infected patients, it is useful to be familiar with the two major studies that address treatment of HCV in HIV co-infected individuals. Two large randomized prospective clinical trials have been performed evaluating pegylated interferons plus ribavirin for treating HCV in co-infected patients. The pegylated interferon- α 2a trial is known as the APRICOT trial; a large randomized prospective clinical trial comparing pegylated interferon- α 2a (Roche Pharmaceuticals, Pegasys) as monotherapy, pegylated interferon- α 2a combined with ribavirin (800 mg per day), and standard interferon- α 2a plus ribavirin (800 mg per day).³ The pegylated interferon- α 2b trial was RIBAVIC; a similar large randomized prospective trial comparing pegylated interferon- α 2b (Schering Pharmaceuticals, Peg-Intron) combined with ribavirin (800 mg per day) with standard interferon- α 2b plus ribavirin (800 mg per day).⁴ The treatment algorithms and sustained virologic responses for each regimen by genotype are summarized in Table 1. At this time, only pegylated interferon- α 2a plus ribavirin (Roche Pharmaceuticals Pegasys and Copegus) is approved for treating HCV in HIV co-infected individuals in the United States.

TABLE 1- MAJOR CLINICAL TRIALS ADDRESSING HCV TREATMENT IN HIV CO-INFECTED INDIVIDUALS*

CLINICAL TRIAL ENDPOINTS	Interferon- α 2a (Pegasys) 180 mcg SC weekly Plus ribavirin 800 mg qday (Copegus) x 48 weeks (APRICOT)	Interferon- α 2b (Peg-Intron) 1.5 mcg/kg SC weekly Plus ribavirin 800 mg qday (Rebetrol) x 48 weeks (RIBAVIC)
12 week response	71%	<i>Different criteria</i>
End of Treatment Response	47%	35%
Overall SVR	40%	27%
SVR genotype 1, 4	29%	17%
SVR genotype 2, 3	62%	44%
Histologic Response	<i>Not done</i>	Stable or Improved: 85% Worsened: 15%
Treatment discontinuation due to side effects	15%	17%

* Superiority or inferiority cannot be legitimately assigned as the two alternative interferon treatments were not compared head-to-head.

4. EVALUATING HIV/HCV CO-INFECTED PATIENTS FOR TREATMENT

Current HIV treatment guidelines recommend screening all HIV positive individuals for HCV antibodies. All individuals with a positive HCV EIA should have follow-up HCV viral load testing to determine whether the positive result represents chronic infection or resolution of a prior HCV infection. Approximately 85% of individuals acutely infected with HCV develop chronic HCV infections, while 15% resolve the acute HCV infection. Patients with positive EIAs and negative HCV viral loads (< 50 IU/ml, usually done twice 3-6 months apart) have resolved a prior HCV infection, or have a false positive HCV EIA, and require no further investigation or treatment. The false positive EIA *versus* resolved infection issue can be settled by an HCV western blot known as a RIBA, but this is rarely necessary. Care providers for HIV patients should be aware that false negative HCV tests can occur in patients with advanced HIV (CD4 counts < 100), but at a frequency < 5%.⁵ Patients with advanced HIV and an unexplained transaminitis or hepatotoxicity on HAART therapy, with negative hepatitis serologies, should have an HCV viral load to rule out occult HCV infection.

TABLE 2- HCV DIAGNOSTIC TESTING			
Test	Measures	Results	Interpretation
HCV antibody/EIA	Antibodies to HCV	pos/neg	Positive result = current or prior HCV infection
RIBA (recombinant immunoblot assay) – not commonly used	Antibodies to four specific HCV proteins	pos/neg	Positive result = current or prior HCV infection. Negative does not absolutely r/o HCV infection. (Send an HCV viral load).
<i>HCV viral load testing:</i>			
-Standard PCR (ROCHE AMPLICOR HCV MONITOR® Test, v2.0)	HCV RNA	600-850,000 IU/ml	Quantitative: For initial HCV viral load and monitoring response to therapy. <i>Not sensitive enough to evaluate SVR</i>
-Standard PCR (Roche AMPLICOR® HCV Test, v2.0)	HCV RNA	pos/neg	Qualitative: Sensitive to ≤ 50 IU/ml. <i>Ok for 72 week SVR HCV viral load.</i>
-Standard PCR [National Genetics Institute (Lab Corp) HCV NGI QuantaSure™]	HCV RNA	2-2x10 ⁶ IU/ml	Quantitative: For initial HCV viral load and monitoring response to therapy. <i>Also ok for 72 week SVR HCV viral load.</i>
-Real time PCR (Roche HCV Taqman®)	HCV RNA	75-1x10 ⁸ IU/ml	Quantitative: For initial HCV viral load and monitoring response to therapy. <i>Not sensitive enough for 72 week SVR HCV viral load.</i>
-Transcription-mediated amplification (TMA) (Bayer VERSANT® HCV RNA Assay)	HCV RNA	pos/neg	Qualitative: Sensitive to ≤ 6 IU/ml. <i>Ok for 72 week SVR HCV viral load.</i>
-Branched DNA (Bayer VERSANT® HCV RNA 3.0 Assay)	HCV RNA	615 to 7,690,000 IU/ml	Quantitative: For initial HCV viral load and monitoring response to therapy. <i>Not sensitive enough to evaluate SVR</i>

*HCV PCR and TMA testing is available through ARUP, Covance, and Quest Diagnostics commercial laboratories, also available locally within larger medical centers' laboratories. QuantaSure™ HCV PCR available from LabCorp.

There are two major reasons to initiate HCV therapy in co-infected individuals; significant scarring of the liver and symptomatic HCV disease. Scarring within the liver is not evident by physical exam until it is very advanced. Therefore the physical exam is limited to identifying features of end-stage liver disease (ESLD) such as jaundice, lower extremity edema, ascites, hemorrhoids, spider angiomas, and palmar erythema, or end organ damage from cryoglobulinemia such as necrotizing cutaneous dermatitis, polyarteritis, and peripheral neuropathy. Similarly, biochemical evidence of liver dysfunction including elevated protimes, thrombocytopenia, hypoalbuminemia, and elevated bilirubin are late manifestations of HCV liver disease. Levels of transaminitis in HCV patients do not correlate well with the degree of fibrosis. Fibrosis progresses faster in HIV/HCV patients than in HCV mono-infected patients.⁶

Liver biopsy remains the most useful piece of clinical data for making a decision about whether to initiate HCV therapy. The simplest system for scoring the liver biopsy is the METAVIR fibrosis score (Figure 1). Other complicated scoring systems exist, however they are more useful in assessing therapies in clinical trials. The inflammatory scores in any pathology scoring system add little to the pretreatment evaluation that is not provided by an ALT (SGPT). The METAVIR fibrosis score has the advantage of being visual and readily understandable by patients trying to decide whether to start HCV treatment. The process of explaining the liver biopsy and its interpretation provides patients with the rationale for doing a liver biopsy, and facilitates the discussion of the result:

- **Stage 0 & 1** – No fibrosis (0), or fibrosis limited to the portal tract (1). “You don’t need treatment; repeat the biopsy in 3-5 years to make sure that the fibrosis is not progressing. You can get treated if that is your preference (genotype 2 & 3) or you are symptomatic from HCV.”

- **Stage 2** – Fibrotic septae that extend beyond the portal triads without bridging adjacent portal tracts. “We recommend treatment, but it is reasonable to wait and repeat biopsy in three years”; especially if there are relative contraindications to HCV therapy.

- **Stage 3 & 4** – Bridging fibrosis (3), or bridging fibrosis with disruption of lobular architecture [cirrhosis] (4). “HCV is potentially your greatest risk for failing health or death. We strongly recommend treatment, and will make arrangements to work around any relative contraindications for initiating HCV therapy.” Implicit in the discussion is “Why wouldn’t you want to be treated?” For HAART-adherent patients with stage 3 or 4 fibrosis, HCV likely exceeds the risk of HIV for future morbidity and mortality.

There are noninvasive alternatives to the liver biopsy based on algorithms utilizing serum markers that correlate with severity of liver disease. In the U.S., the Fibrotest-Fibrosure serum test is available (LabCorp). This test carries with it some intrinsic uncertainty as it misses significant fibrosis (METAVIR stage 2-4) in roughly 1/10-1/20 patients (negative predictive value 90-95%), and over diagnoses significant fibrosis in roughly half of patients with positive tests (positive predictive value ~50%). For this reason, many care providers remain uncertain where non-invasive testing fits into the pretreatment evaluation. One possible application would be in patients with relative contraindications to receiving HCV therapy, such as ongoing substance abuse or moderate-severe psychiatric issues. The noninvasive Fibrotest-Fibrosure test could be used to rule out a high probability of significant liver scarring,

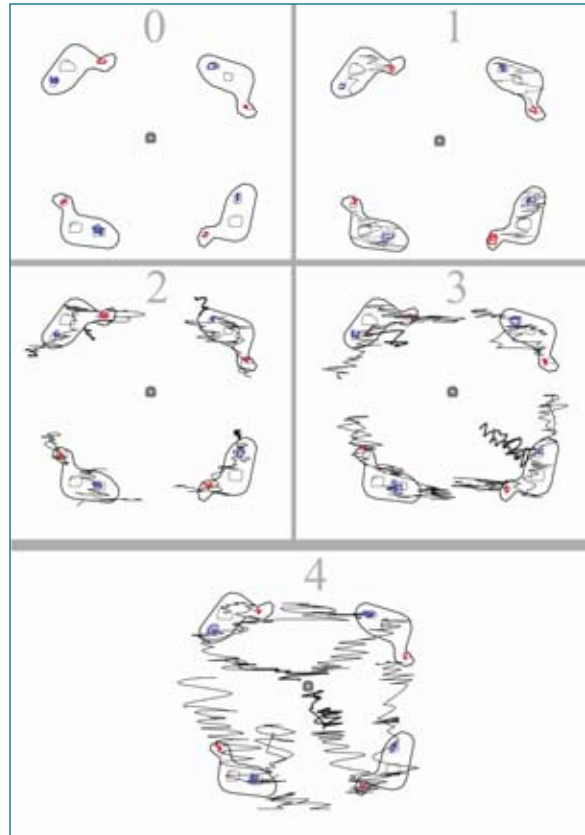


Figure 1- Schematic of a liver lobule, and the changes that correlate with the METAVIR fibrosis scoring system stages.

thereby validating focusing on other issues prior to addressing HCV therapy. The significant false positive rate would require liver biopsies in patients with positive test results. Caution is advised in using Fibrotest-Fibrosure in HIV patients on indinavir or atazanavir as total bilirubin level is a component of the algorithm. In addition to the serum marker algorithms, there is a noninvasive liver elasticity scanning device (Fibroscan). Early evaluation of this technology suggests that it has a sensitivity/specificity similar to the serum marker algorithms, possibly better in patients with normal ALT. However, currently there is not enough data to know where liver elasticity scanning fits in co-infection clinical practice.

Unlike the noninvasive testing alternatives a liver biopsy also rules out non-HCV liver pathology. In addition, liver biopsies pre and post treatment provide data regarding histologic responses to HCV therapy. In patients with significant fibrosis who do not achieve SVRs, assessment of histologic responses will likely become important as the role of maintenance interferon therapy for partial responders is resolved by ongoing clinical trials in HCV co-infected (SLAM-C) and HCV mono-infected patients (HALT-C). At this point in time, the best practice approach for initial evaluation of HCV co-infected patients includes a liver biopsy. This may change in the future if/when noninvasive testing is validated for assessing ‘histological’ responses to HCV therapy.

The majority of liver biopsies are performed with ultrasound guidance by GI radiologists who accept referrals from multiple medical specialties. In most settings, this procedure is done as an outpatient with a 3-4 hour post-biopsy observation period prior to discharging the patient to home with a friend, family member, or cab ride. Typical pre-biopsy labs include a CBC with platelets and a PT/INR. For patients with abnormal laboratories that suggest an increased risk of bleeding (*e.g.*, hemophiliacs), a transjugular liver biopsy can be performed through interventional radiology to minimize the risk of bleeding. In general, ultrasound guided liver biopsies are safe and well-tolerated, though there is some operator-dependent variability in patient satisfaction. It is reasonable for care providers to request METAVIR scoring of the liver biopsy specimens to simplify interpretation of the result:

Pathology Form: Patient hx: “HIV/HCV positive patient. Liver biopsy to stage fibrosis. Please use METAVIR scoring system for fibrosis.”

Patients without significant fibrosis are candidates for therapy if they have extrahepatic manifestations of HCV. Extrahepatic manifestations of HCV are numerous and likely underdiagnosed. Renal insufficiency due to mixed cryoglobulinemia is a well-known complication of HCV disease, and should be considered for all co-infected patients with renal insufficiency and proteinuria. Ideally co-infected patients with elevated Scr and proteinuria would have a kidney biopsy to distinguish HCV-related kidney disease from HIVAN (HIV-associated nephropathy) and other glomerulonephritides. Treatments for the different forms of renal dysfunction are different and potentially antagonistic; *e.g.*, steroids for HIVAN *versus* interferon/ribavirin for HCV. HCV-associated vasculitis (cryoglobulin positive or negative) can affect multiple organ systems including skin (cutaneous necrotizing vasculitis), nerves (peripheral neuropathy), joints (chronic arthralgia syndromes), lungs (microscopic polyarteritis nodosa), and medium-size arteries (polyarteritis nodosa syndromes). Nonhealing extremity ulcers, recurrent antibiotic-unresponsive swelling/cellulitis, peripheral nerve palsies, chronic arthralgias, and unexplained interstitial lung disease should prompt further investigation for possible relationship to HCV. Patients with possible extrahepatic HCV manifestations should have additional laboratory evaluations including cryoglobulins and rheumatoid factor (a specific cryoglobulin). Accurate testing for cryoglobulins requires keeping blood samples at 37° Celsius until the test can be performed, which may be problematic in some laboratory settings. Rheumatoid factor is a useful additional test that is less finicky. Absence of cryoglobulins does not rule out vasculitis, and should not end the evaluation. Tissue biopsy, angiography, and nerve conduction studies can be important components of the workup when extrahepatic manifestations of HCV are being considered.

The majority of patients with HCV are fatigued beyond the level associated with work, middle age, children, stress, etc. After addressing possible co-existing depression, unexplained fatigue that interferes with activities

of daily living is a reason to consider HCV therapy. This HCV treatment scenario is analogous to initiating HAART therapy in HIV patients with symptomatic early stage HIV [high CD4 counts (> 350 cells/ml) and low HIV viral loads (< 100,000 copies/ml)].

5. PROGNOSTIC FACTORS AFFECTING RESPONSE TO HCV THERAPY

The single most important prognostic factor for achieving an SVR is the HCV genotype. HCV genotypes 1 & 4 are much less responsive to therapy than genotypes 2 & 3 in HCV mono-infected or HIV/HCV co-infected individuals. In the APRICOT HIV/HCV trial the SVR rate for genotype 1 & 4 virus was 29%, while the SVR rate for genotypes 2 & 3 was 62%. In the RIBAVIC HIV/HCV trial the SVR rate for genotype 1 & 4 virus was 17%, while the SVR rate for genotypes 2 & 3 was 44%.

High HCV viral loads, > 800,000 IU/ml (2 million copies/ml), in genotype 1 patients (not genotype 2 & 3 patients), are associated with lower SVR rates; HCV genotype 1 \leq 800,000 IU/ml SVR = 61%, while > 800,000 IU/ml SVR = 18%. Other factors associated with reduced SVR rates that have been identified in HCV mono-infected clinical trials include normal ALT, age > 40, African American race, male gender, increased weight, and steatosis on liver biopsy. It should be noted that, of all these prognostic factors, the only one that can be modified prior to initiating HCV therapy is weight. Intuitively, reasonable physical conditioning and weight loss prior to initiating HCV therapy makes sense for patients who are overweight or obese, though there are no prospective data supporting that practice. It is unclear whether prognostic indicators other than HCV genotype and viral load play a major role deciding whether to start HCV therapy.

African American patients with HCV have been reported to have lower SVR rates than Caucasians, and providers may experience increased skepticism regarding HCV therapy among African American patients. Close examination of those clinical trials reveals that African American subjects were twice as likely as Caucasians (40% versus 20%) to develop severe neutropenia (ANC < 500) requiring discontinuation of therapy.⁷ It's well known that African Americans run lower Absolute Neutrophil Counts (ANC) than Caucasians. In that context, it is not surprising that African Americans had a higher incidence of severe neutropenia during pegylated interferon therapy. It is clear that dose reductions or discontinuations of pegylated interferon or ribavirin early in the course of HCV treatment are detrimental to achieving SVRs.⁸ Treatment-associated neutropenia should be addressed with filgrastim (Neupogen®; G-CSF) to prevent disruption of therapy (*see upcoming treatment management section*). It is important to note that race was not a predictor of response to therapy in the APRICOT HIV/HCV trial.

PRE-TREATMENT LABORATORY EVALUATION (FOR HCV & HBV)

- *CD4 T cell count* – Patients with absolute CD4 counts < 100 are not typically considered for HCV treatment. Patients in this category may become treatment candidates once their HIV care is optimized, or their current HAART facilitates immune reconstitution. Patients with a CD4 >200, or >100<200 with a HIV viral load < 5000 copies/ml, are candidates for HCV therapy. Patients on HAART should be on stable therapy, *i.e.*, no plans to change/optimize therapy during next 12 weeks (standard HIV monitoring interval).

- *HIV viral load* – Baseline HIV viral loads prior to starting therapy are necessary for decisions about initiating HCV therapy and subsequent safety monitoring.

- *CBC with platelets* – Patients with significant anemia (Hb < 12) need to be evaluated for reversible causes

(Fe deficiency, occult GI bleeding, folate/B12 deficiency). Underlying deficiencies should be corrected prior to starting HCV therapy. Patients without documented Fe deficiency should not be placed on Fe supplementation (detrimental to liver scarring). Workup-negative anemia-of-chronic-disease patients are candidates for HCV therapy. Patients on AZT-based HAART should be switched to an alternative HAART regimen unless there are no available options based on HIV genotyping or prior adverse drug reactions. Patients with irreversible causes for anemia, such as sickle cell anemia or thalassemias, are not candidates for standard HCV therapy. Thrombocytopenia is common in HIV/HCV patients. Most HIV/HCV care providers are comfortable starting HCV therapy as long as the platelet count is $\geq 50,000$. Prior to the availability of HAART, HIV-associated ITP was treated with standard interferon α .⁹

- *Comprehensive metabolic panel* – baseline electrolytes, serum creatinine, albumin, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT). For patients on tenofovir, a baseline phosphate and a urinalysis should be included.

- *PT/INR* – indicator of liver synthetic function. Elevated PT/INR should be treated with Vitamin K (10 mg po qday for 3 days) to establish whether the elevation in INR is due to synthetic dysfunction or vitamin K deficiency. The PT value affects the Child-Pugh scoring for patients with cirrhosis on liver biopsy.

- *TSH* – Autoimmune thyroiditis is a potential complication of HCV therapy. Baseline TSH is obtained for future monitoring. Patients with previously diagnosed hypothyroidism, on supplemental therapy, should have a TSH within normal limits prior to starting HCV therapy.

- *Hepatitis A Virus IgG* – Screen for HAV and vaccinate seronegative individuals, or skip the screen and simply vaccinate for HAV in regions with low HAV endemicity.

- *HBsAb, HBcAb total, HBsAg, HBeAg* – Screen for HBV co-infection. Seronegative patients should be vaccinated against HBV. HBcAb total seropositive patients should have a Hepatitis B virus DNA level (viral load) to rule out occult HBV co-infection.

- *HCV antibody EIA* – Screen for HCV co-infection.

- *Alpha fetoprotein* – screen for hepatocellular cancer.

- *Hepatitis viral loads* – HCV viral load for HCV co-infections; HBV DNA (viral loads) for HBV co-infections; HCV and HBV viral loads for HIV/HCV/HBV patients.

- *Genotypes* – All HCV co-infected patients require an HCV genotype (subspecies identification). HBV co-infected patients with prior exposures to lamivudine (Epivir; 3TC), emtricitabine (Emtriva), tenofovir (Viread or Truvada), or famciclovir (Famvir, e.g., HSV suppression) should have HBV resistance testing. Ordering an HBV ‘genotype’ can mean two different things to commercial laboratories (see HBV co-infection section for details on ordering HBV genotypes).

- *Liver ultrasound* – screening for hepatocellular cancer. Abnormal liver ultrasounds should be followed up with a dual-phase liver CT scan or liver MRI to rule out hepatocellular cancer. Patients with lesions suspicious for hepatocellular cancer should be referred to a liver transplant center for further evaluation.

- *Urine beta HCG* – for women of childbearing age. Ribavirin is a major teratogen!

• *EKG* – for patients over 50 years old to rule out pre-existing coronary artery disease. Patients with EKG changes consistent with ischemia or prior infarction require a cardiac evaluation, and revascularization if indicated, before being treated for HCV.

Clinical staging using the Child-Pugh classification scheme (*below*) should be performed for patients with cirrhosis on their liver biopsy:

Table 3- Child-Pugh Classification Scheme						
Scoring Value	Bilirubin (mg/dl)	Albumin (gm/dl)	Protime (increase in seconds)	Hepatic Encephalopathy (grade)	Ascites (grade)	
1	< 2	≥ 3.5	1-4	0 (normal)	None	
2	2-3	2.8-3.5	4-6	1-2 (altered sensorum)	Mild	
3	> 3	< 2.8	> 6	3-4 (gross confusion to coma)	Severe	
Value for each column	—	—	—	—	—	
			Total of column values = Child-Pugh score →			—
Child-Pugh Class by Score						
Class A: 5-6		Class B: 7-9		Class C: >9		

Patients on atazanavir or indinavir can have elevated bilirubin levels that do not reflect the functional status of the liver. Ideally, these patients would switch to alternative HAART therapy and have repeat labs prior to calculating their Child-Pugh score. Cirrhotic patients with a Child-Pugh score > 6 (Child-Pugh class B-C) should be referred to a liver transplant center for further evaluation. Some experienced HIV/HCV providers treat selected Child-Pugh class B patients; however this is not standard practice, and should not be attempted by providers without relevant expertise and appropriate transplant support.

Other exclusion criteria:

Patients with:

- autoimmune hepatitis
- other autoimmune diseases (SLE, RA, etc.)
- active opportunistic or non-opportunistic infection
- women unwilling to utilize effective birth control methods (typically oral contraception or DepoProvera, plus a barrier method, e.g., condoms)
- men with pregnant partners
- severe psychiatric disease
- severe co-morbid medical conditions

6. ISSUES RELATED TO HIV THERAPY

Warning

Patients on DDI (Didanosine; DDI EC; Videx®; Videx EC®) should not be placed on HCV therapy that includes ribavirin

The intracellular active metabolite of didanosine is increased by ribavirin therapy leading to increased toxicity. Co-administration of didanosine (DDI) and ribavirin is associated with a markedly increased risk for hepatic decompensation and death. The combination of DDI plus D4T (stavudine; Zerit®) with ribavirin may be especially dangerous. Patients on DDI-based HAART regimens are not candidates for HCV therapy until their antiretroviral therapy has been changed. When changing the HAART regimen, it is not advisable to switch DDI to D4T. Patients on chronic D4T therapy (> 6 months) without side effects can initiate ribavirin-containing HCV therapy if there is no reasonable alternative HAART regimen. Lactic acidosis syndromes and hepatotoxicity related to D4T generally present 3-6 months after initiation of D4T. Changing antiretroviral therapy to include D4T shortly before initiating HCV therapy should be avoided.

Zidovudine (AZT; Retrovir®; also in combination pills Combivir® and Trizivir®) is a suboptimal medication in the context HCV therapy because of its bone marrow suppressive effects. Bone marrow suppression is also a side effect of pegylated interferon. Dual marrow suppression resulting from combining pegylated interferon with AZT-based HAART, in the setting of increased RBC turnover due to ribavirin-induced hemolysis, increases the incidence of anemia and neutropenia compared with alternative non-AZT-based HAART. If there are no good alternatives to AZT, then HCV therapy can go forward anticipating increased episodes of anemia and neutropenia. For patients on AZT-based HAART, it makes sense to investigate access to growth factors (pre-approval for G-CSF and erythropoietin) prior to initiating HCV therapy (*see: example insurance letter text in appendix A*).

Hepatotoxicity is an issue with most HIV protease inhibitors, and the NNRTI medication nevirapine (Viramune®). In general, ritonavir-boosted regimens containing saquinavir (Inverase®, Fortovase®), tipranavir (Aptivus®), atazanavir (Reyataz®), or indinavir (Crixivan®), and NNRTI regimens based on nevirapine, should be avoided if a patient has good alternatives.

Table 4 - HIV Medications in the Context of HCV Therapy containing Ribavirin

<i>Prohibited HIV Medications</i>	Didanosine (DDI, DDI EC)
<i>Relatively Contraindicated HIV Medications</i>	Stavudine (D4T), Zidovudine (AZT)
<i>Less Desirable HIV Medications</i>	Rit/Saquinavir, Rit/Tripranavir, Rit/Atazanavir, Nevirapine

<i>Optimal HIV Medications</i>	<p><u>NRTIs:</u> lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF), abacavir (ABC)</p> <p><u>NNRTIs:</u> efavirenz (EFV), delaviridine (DLV)</p> <p><u>Protease Inhibitors:</u> lopinavir/ritonavir, nelfinavir, fosamprenavir, darunavir</p> <p><u>Others:</u> T20 (Fuseon)</p>
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Patients on tenofovir containing regimens may experience transient hypophosphatemia early in HCV therapy. If serum creatinine is stable, and urinalysis does not show new glucosuria, treat with Neutra-Phos 1 cap bid with meals for seven days. Recheck next routine lab draw and repeat replacement therapy as needed, as long as the Scr remains stable. The hypophosphatemia tends to resolve while on HCV therapy without evidence of significant renal injury.

Patients should be advised that their absolute CD4 T cell counts are likely to drop significantly during HCV therapy, but that CD4% remains stable or increases. In general, the absolute CD4 count returns to pre-treatment values once HCV therapy has been discontinued or completed. HIV viral loads typically remain undetectable in patients in whom the virus is undetectable when HCV therapy is initiated. In patients with detectable HIV viral loads, the HIV viral load typically drops ~0.7 logs with HCV therapy. Pegylated interferon is a reasonably good antiretroviral drug (more potent than D4T), though not approved for HIV therapy.³ The net effect of HCV therapy on patients' HIV clinical status is felt to be neutral.

During the course of HCV therapy, patients whose CD4 counts drop below 200 or CD4% drops below 14% should be placed on PCP prophylaxis. Patients with CD4 counts below 100 should have eye exams, and those with counts less than 50 should begin MAC prophylaxis as per standard HIV care. Management of HAART therapy during HCV therapy is as per usual care except for avoiding DDI and AZT.

7. ISSUES RELATED TO IVDA

Patients on stable methadone therapy are candidates for HCV therapy. Methadone levels are modestly increased with HCV therapy (ribavirin), and patients should be monitored for methadone related toxicity (constipation, water retention, drowsiness, skin rash, excessive sweating, and changes in libido). Most care providers are not willing to consider therapy for individuals with an ongoing substance abuse problem. Patients with active substance abuse issues should be referred to rehabilitation programs and reconsidered after their successful completion.

8. HCV TREATMENT

The primary goal of treatment is to achieve a sustained virologic response (SVR) which is defined as an HCV viral load < 50 IU/ml six months after completion of HCV therapy. The secondary goal of therapy is to slow the progression of liver fibrosis to prevent ESLD and HCC. HCV therapy that improves or stabilizes liver fibrosis may allow patients to remain healthy long enough to benefit from future HCV therapies.

The large majority of HIV/HCV patients requiring HCV therapy should be treated with pegylated interferon- α 2a plus ribavirin. The only exceptions are patients with renal insufficiency who must be treated with pegylated interferon- α 2a monotherapy (addressed below). The dose of ribavirin that should be given with pegylated inter-

feron α 2a therapy is controversial.

The FDA-approved dose for treating HCV in HIV co-infected patients is 800 mg total per day (400 mg po bid). This is a reduced dose compared with the FDA-approved dose of ribavirin given to HCV mono-infected patients treated with pegylated interferon- α 2a (1000 mg total qday for weight <75 kg; 1200 mg total qday for weight >75 kg). Many providers treating HCV with pegylated interferon- α 2b (Peg-Intron) use weight-based ribavirin (1000 mg total qday for weight <75 kg / 1200 mg total qday for weight >75 kg / 1400 mg total qday for weight >105 kg) rather than the FDA-approved dose of 800 mg total per day because of data showing improved efficacy.¹⁰ An ongoing HIV/HCV clinical trial, SLAM-C, uses the 1000/1200 mg total per day weight-based dosing of ribavirin. That trial is nearing completion without any safety concerns identified by the Data Safety Monitoring Board.

Weight-based dosing of ribavirin for treating HCV in co-infected patients does not adversely affect the rate of anemia¹¹

In *HCV mono-infected patients* there are genotype-specific durations of therapy and genotype-specific dosing for ribavirin. The duration of therapy for HCV genotype 1 & 4 is 12 months, while genotypes 2 & 3 are treated for 6 months. For HCV genotypes 2 & 3, the FDA-approved dosing of ribavirin with pegylated interferon- α 2a or pegylated interferon- α 2b is 800 mg per day; while the dosing of ribavirin for genotype 1 & 4 is 800 mg/day when combined with pegylated interferon- α 2b, and weight-based 1000/1200 mg/day when combined with pegylated interferon- α 2a. HCV genotype 1 mono-infected patients with undetectable HCV viral loads after 4 weeks of therapy are known as ‘super responders’ and may be able to shorten HCV therapy from 12 months to 6 months without negatively affecting their rate of SVR.¹² However, data from HCV-mono-infected clinical trials should not be extrapolated to co-infected patients.

The current duration of therapy in HIV/HCV co-infected patients is 12 months regardless of HCV genotype or HCV virologic response at 4 weeks. It is unclear whether the appropriate dose of ribavirin in HIV/HCV co-infected patients is 800 mg per day or weight-based 1000/1200 mg per day. Until a post-approval clinical trial shows otherwise, most HIV/HCV providers use weight-based 1000/1200 mg per day of ribavirin regardless of genotype. The existing data shows that the higher weight-based dosing of ribavirin is safe as long as appropriate safety monitoring is being performed.

Twelve weeks into therapy an HCV viral load is drawn to assess the early treatment response (ETR). Patients with an HCV viral load > 50 IU/ml, and less than a 100-fold drop in HCV viral load from baseline, have a 2% chance of an SVR if they complete a year of HCV therapy. At this time it is not clear what these patients should do. If they have fibrosis scores of 2 or less, they can reasonably stop therapy and repeat a liver biopsy in three years. For patients with fibrosis scores > 2, many providers would advocate treating for at least 24 weeks with a follow-up liver biopsy (on therapy) to determine whether there is a histologic response to therapy. Patients with stable or improved histology should be considered for maintenance interferon therapy. Maintenance therapy consists of dropping ribavirin and continuing pegylated interferon (90-180 mcg/wk). One approach is to start with 180 mcg/wk of pegylated interferon and taper to an interferon dose (minimum 90 mcg/week) that maintains normal ALT (or stable HCV viral load). Patients in APRICOT (predominantly genotype 1) who were early treatment responders had a 56% chance of an SVR with completion of 48 weeks of HCV therapy.

HCV viral loads are drawn at 24 & 36 weeks. Patients with HCV viral loads <50 IU/ml continue HCV therapy out to 48 weeks (12 months). Patients with relapsed or continued HCV viremia should have a follow-up liver biopsy while on HCV therapy. If they have a stable or improved fibrosis with pretreatment fibrosis F>2, then maintenance interferon therapy should be considered. If no histologic response or pretreatment fibrosis stage was \leq 2, patients should discontinue HCV therapy and plan on having a follow-up biopsy in three years.

An HCV viral load is drawn at 48 weeks to assess end-of-treatment responders; and an HCV viral load is drawn 6 months later (72 weeks), while off therapy, to identify patients who have achieved an SVR (HCV viral load < 50 IU/ml). HIV/HCV care providers should be sure to order an HCV RNA assay sensitive to at least 50 IU/ml.

The FDA-approved pegylated interferon treatment regimen for HCV in co-infected patients with estimated CrCl > 50 ml/min is:

$$[\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight in kg} \times 0.85 \text{ for women}}{72 \times \text{Scr}}]$$

Pegylated Interferon- α 2a (Pegasys) 180 mcg injection once a week plus non-FDA approved weight-based ribavirin (Copegus):

400 mg po qAM / 600 mg po qPM for weight < 75 kg (1000 mg total daily) or 600 mg po bid for weight > 75 kg (1200 mg total daily)

Treatment duration is 12 months regardless of HCV genotype

9. HCV TREATMENT IN PATIENTS WITH RENAL INSUFFICIENCY

Co-infected patients with renal insufficiency are candidates for HCV therapy; especially if they have stage 3 or 4 fibrosis or end organ damage from mixed cryoglobulinemia; including renal insufficiency. Patients with CrCl < 50 ml/min cannot take ribavirin, and should be treated with pegylated interferon- α 2a monotherapy. Pegylated interferon monotherapy is compatible with all HAART regimens except those based on AZT. In the APRICOT trial pegylated interferon α 2a monotherapy for 1 year had an SVR rate of 14% for genotype 1, and 36% for genotypes 2 & 3. While the decreased rates for SVR may dampen patients' and providers' enthusiasm for pursuing treatment, it is important to remember that the duration and quality of life for patients with ESLD and renal failure is short and poor, and that renal damage due to cryoglobulins may be stabilized even without achieving an SVR. Maintenance interferon therapy should be considered for patients who fail to achieve an SVR if there is evidence of histologic improvement on the post treatment liver biopsy or a halt in end organ damage, e.g., stabilization of renal function after initiation of interferon therapy.

The FDA-approved pegylated interferon treatment regimen for HCV in co-infected patients with estimated CrCl < 50 ml/min (no ribavirin) is:

*Pegylated Interferon- α 2a (Pegasys) 180 mcg injection once a week
Treatment duration is 1 year regardless of genotype.*

THE MEDICATIONS:

Pegylated interferon- α 2a (Pegasys®) comes in packages of four preloaded syringes containing 180 mcg of medication (1 month supply). Prefilled syringes have gradations for delivering 135 mcg and 90 mcg of pegylated interferon- α 2a. Ribavirin (Copegus®) comes as 200 mg tablets. Typical initial prescriptions would be:

- 1) Pegylated interferon- α 2a (Pegasys) 180 mcg/ 0.5cc in prefilled syringes with supplies.
Sig: inject 180 mcg once weekly for four weeks #1 convenience pack / Refills: 5
- 2) Ribavirin (Copegus) 200 mg tablets
Sig: three po twice a day #180 / Refills: 5

10. MANAGING HCV TREATMENT

The two critical components of adherence to HCV therapy are patient ‘buy-in’ and provider management of medication-related side effects.

Investing time with HIV/HCV patients prior to starting therapy is very helpful in shaping expectations and alleviating anxiety. After confirming chronic HCV infection with HCV viral load testing, the remaining educational process can flow naturally out of the pretreatment evaluation.

Patients are advised that they have a chronic HCV infection; that HCV exists as several different subtypes (genotypes); and that the subtype (genotype) is an important prognostic factor for responding to HCV treatment. The need for treating HCV is determined by the likelihood of success (HCV genotype) and the degree of liver fibrosis (risk for progression to ESLD or HCC). “Reliable determination of the amount of scarring in your liver can only be determined by liver biopsy.” [Explaining METAVIR staging for fibrosis with a visual aide (Figure 1) is quick and educational.] *E.g.*, “Your liver is made of millions of individual filter units (lobules). Blood enters at the edge of the filter, called the portal triad, and is cleansed as it flows toward the central vein. Scarring disrupts the function of these small filters. When you lose too many filtering units, you turn yellow (jaundice), develop swelling in your legs, fluid in your abdomen, problems with your brain (encephalopathy), hemorrhoids, large varicose veins in stomach and esophagus that can rupture causing death in some cases. In HIV positive patients with HCV, the risk of death is about 50% per year once these symptoms develop. Once you have symptoms, it is too late to be treated. If your liver biopsy shows stage 2 fibrosis, we recommend that you get treated but it is reasonable to wait and repeat the biopsy in three years. If it shows stage 3 or 4 fibrosis, HCV may be your greatest risk for declining health or death. In that case, I would strongly encourage you to get treated, and badger you if you were reluctant because it is unlikely that any new treatment for HCV will be available in the next three years. It is possible that your liver could decompensate prior to a follow-up biopsy in three years. Once the genotype and liver biopsy results are back, you can make an informed decision about treatment.” Most patients familiar with the rationale for the liver biopsy base their treatment decision on its result. The discussion about whether to treat during the post biopsy clinic visit can be surprisingly short, and the focus can shift to the medications and their side effects.

Pegylated interferon and ribavirin have side effects. That may seem like an understatement, but the magnitude of HCV treatment side effects is commonly overstated, which contributes to the reluctance of many health care providers to get involved in treating HCV (and HBV). *Pegylated interferon and ribavirin have side effects, but they can be managed.* Time spent with patients discussing the medications and their side effects before starting therapy is critical. Patients who experience a side effect ‘out-of-the-blue’ are more anxious because they have no way to assess their risk. Anticipated side effects are more readily accepted and dealt with. Common side effects of HCV therapy that should be mentioned to patients before initiating therapy are listed in Table 5.

Table 5- HCV Treatment Side Effects with a Frequency > 10%

<i>Side Effect</i>	<i>Frequency</i>	
	<i>Mono-infected</i>	<i>Co-infected (APRICOT)</i>
Fatigue	65%	44%
Headache	43%	39%
Fever	41%	44%
Myalgia	40%	36%
Irritability/anxiety	33%	-
Insomnia	30%	26%

Alopecia (mild, not like chemotherapy)	28%	-
Nausea/vomiting	25%	30%
Rigors	25%	-
Anorexia	24%	-
Arthralgia	22%	-
Depression	20%	26%
Pruritis	19%	-
Dizziness	14%	-
Dyspnea	13%	-
Diarrhea (mild & transient)	11%	28%

While an individual patient has less than a 50% chance of any one side effect, overall the incidence of one or more side effects in an individual patient is ~ 97%. The side effects above are intimidating; but they tend to be most pronounced during the first two to four weeks of therapy and dissipate thereafter. The clinical trials from which these statistics are drawn did not standardize the treatment of side effects. Many patients likely received supportive medications after the side effect had already occurred, while others may have received no supportive medications at all.

Oncologists routinely premedicate patients for side effects associated with chemotherapy. The same practice can be applied to HCV therapy. Patients who are working should be encouraged to continue working. Non-working patients should be encouraged to maintain their daily activities and social contacts. Patients should have the expectation that any side effects they experience can be treated so that HCV therapy will not be debilitating. HCV side effects can be broken down into three basic types; inflammatory, central nervous system (CNS), and gastrointestinal.

Inflammation-related side effects can be tempered with NSAIDS or acetaminophen (Tylenol®). Premedicating patients with ibuprofen for each interferon injection can prevent or greatly diminish headache, fever, myalgia, rigors, and arthralgias. Acetaminophen can be substituted for ibuprofen in patients with contraindications to NSAIDS or with ibuprofen intolerance. Non-cirrhotic or cirrhotic patients with Child-Pugh scores < 7 using ibuprofen are not taking a significant risk. Typical premedication schedules are presented below:

- 1) Ibuprofen: Pegylated interferon injection given mid day once a week
 - i. Ibuprofen 600 mg po at time of injection, at dinner, at bedtime, and upon awakening (with food). After these four scheduled doses, ibuprofen can be continued as needed at 400-600 mg po tid for the remainder of the week. Most patients do not require more than the four scheduled doses.
 - ii. After the third or fourth interferon injection, patients can adjust the ibuprofen premedication to suit their individual needs. Many patients take only one or two doses with each pegylated interferon injection.

- 2) Acetaminophen: Pegylated interferon shots given in the early evening once a week
 - i. Acetaminophen 500-650 mg po at the time of injection, at bedtime, and upon awakening. After these three scheduled doses, acetaminophen can be continued at 500-650 mg po tid for the remainder of the week as needed.
 - ii. After the third or fourth interferon injection, patients can adjust this premedication to suit their individual needs. Many patients take only one or two doses with each pegylated interferon injection.

All patients should be encouraged to take up a light exercise program prior to starting HCV therapy to help with fatigue, arthralgias and myalgias associated with therapy. In general, narcotic analgesics are not indicated and should be avoided. Tramadol (Ultram®) carries an increased risk of seizure in patients on HAART regimens and generally should be avoided.

CNS side effects include insomnia (→ fatigue), irritability, and depression. Depression will be dealt with in greater detail below. A quick glance would suggest that these are likely interrelated side effects. Patients on HCV therapy may spend 7-10 hours in bed every night, but they are not necessarily sleeping soundly. Mood disorders are aggravated by sleep deprivation. It is very important that patients on HCV therapy get to sleep. Patients should be advised about good sleep hygiene (no naps) and light exercise. Insomnia should be addressed proactively with pre medication, at least during the first couple weeks of therapy:

- 1) Diphenhydramine (Benadryl®; generic) (25 mg tablets):
 - i. Diphenhydramine 25-50 mg po QHS beginning with the first injection of pegylated interferon.
 - ii. After the first three or four injections, patients can adjust this medication to their individual needs. Patients who oversleep or are excessively groggy in the morning simply discontinue this premedication.
 - iii. Patients who continue to have insomnia move on to doxepin.
- 2) Doxepin (Senaquin®; generic) (10 mg tablets):
 - i. Doxepin 10-50 mg po QHS with each dose of pegylated interferon. Patients should start with 10-20 mg and increase the dose as needed up to 50 mg po QHS over one week (give 50 tabs).
 - ii. Patients who oversleep or are excessively groggy in the morning simply discontinue this premedication.
 - iii. For patients not sleeping well with 50 mg of doxepin QHS, the dose can be increased up to 150 mg QHS in 25 mg increments. (tablets come as 10, 25, 50, 75, 100, 150 mg) Very few patients with insomnia fail to respond to doxepin.

Doxepin is safe with HAART therapy and is particularly suited to treating “anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry” (FDA prescribing information). While doxepin does not work for everyone, its therapeutic affect matches up very well with the side effect profile of HCV therapy. Uncommon patients who fail doxepin therapy will need alternative sleep medications. It is very important to check whether prescribed alternative medications are compatible with a patient’s HAART therapy. Benzodiazepines are potentially dangerous in patients on HAART and generally should be avoided. Zaleplon (Sonata®) and zolpidem (Ambien®) are reasonable alternative medications for patients unresponsive to doxepin. Eszopiclone (Lunesta®) should be limited to 1 mg po QHS. Ramelteon (Rozerem™) levels are potentially significantly increased by HAART therapy and probably should be avoided in the absence of clinical data.

Depression is the most worrisome side effect associated with HCV therapy, and a common cause for treatment discontinuation. Treatment-related suicides have occurred during HCV clinical trials. Patients with recent suicide attempts or gestures are not candidates for HCV therapy. When possible, it is helpful for the patient to assemble his/her own support group; family members or friends who will commit to monitoring the patient’s mood, and ensuring that the patient is gets out \geq once a week for social events (walks, biking, dinner, movies, religious services, etc). A light exercise program is helpful for preventing mood disorders, especially when it involves being outside (sunlight). All patients should be screened for depression prior to initiating HCV therapy. A simple screen for depression is the Patient Health Questionnaire-2 (PHQ-2),¹³ a 2 question screening tool (Table 6).

Table 6- Patient Health Questionnaire-2 (PHQ-2) ©

During the past <i>two weeks</i> how often have you been bothered by any of the following problems?	Not at all 0 points	Several Days 1 point	More than half the days 2 points	Nearly every day 3 points	
A) little interest or pleasure in doing things	—	—	—	—	
B) feeling down, depressed, or hopeless	—	—	—	—	
				Score =	—

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Scores ≥ 3 correlate with depression and merit intervention.¹³ Patients already on HCV therapy who score ≥ 3 on PHQ-2, or become sad, apathetic or emotionally labile, should be treated for depression with an SSRI with close follow-up (weekly in clinic or by phone). Patients with progressive symptoms or suicidal ideation in spite of initiating SSRI therapy with close follow-up must discontinue HCV treatment and receive psychiatric care.

Patients with well-controlled depression on antidepressant therapy are ready to start HCV therapy. It is helpful to contact patients' mental health providers to alert them about upcoming HCV therapy and ask their assistance in managing the patient. Addressing insomnia proactively with premedication, and asking patients to report any problems between clinic visits, is important. For patients with past episodes of depression or borderline scores on depression screening tools, prophylactic initiation of SSRI therapy is warranted. Citalopram (Celexa™) has been shown to be effective for this purpose and is compatible with HAART regimens. Other SSRIs that are useful include paroxetine (Paxil®) generally, and fluoxetine (Prozac®, Sarafem®) and sertraline (Zoloft®) in patients without insomnia. Bupropion (Wellbutrin®) and venlafaxine (Effexor®) can cause anxiety and insomnia. Mirtazapine (Remeron®) and duloxetine (Cymbalta®) should generally be avoided because of limited clinical experience and potential drug interactions with HAART.

Gastrointestinal side effects tend to be mild with the exception of ribavirin-associated nausea when it occurs. Diarrhea (loose stools) is generally minimal and self-limiting. *C. difficile* colitis can occur in patients on HCV therapy, and should be considered in patients with diarrhea that includes peritoneal irritation, fevers, or bloody diarrhea. Diarrhea that occurs after the first month of therapy is likely to be related to enteric pathogens rather than medication intolerance, and should be worked up accordingly. Decreased appetite and weight loss are very common in co-infected patients on HCV therapy. Excessive weight loss due to decreased appetite is rarely a treatment limiting issue. Prior to beginning therapy, patients should be advised that they can expect to lose 5-25 lbs depending on body habitus. During the course of therapy, reassurance that the weight will return once treatment is completed is usually sufficient intervention. Patients who lose too much weight can try Marinol® therapy and nutritional supplements (Boost®, Ensure®, etc).

The most vexing gastrointestinal side effect is ribavirin-induced nausea. Few patients with persistent nausea can make it through a year of HCV therapy. Premedication with 12.5-25 mg of promethazine (Phenergan®) or 5-10 mg of prochlorperazine (Compazine®) before taking ribavirin is generally not very effective, probably because of the long half-life of ribavirin (120 hours). The most effective medication tends to be dronabinol (Marinol®) initiated at 2.5 mg po bid and titrated up to 10 mg po bid as needed to get the nausea under control. A summary of supportive medications is presented in Table 7.

Table 7- Medications for Treating HCV Therapy Side Effects		
<u>Medication</u>	<u>Dosing</u>	<u>Pill size</u>
<u>Inflammation</u>		
Ibuprofen	400-600 mg po tid-qid	200, 400, 600 mg
Acetaminophen	500-650 mg po tid	325, 500 mg
<u>CNS</u>		
<i>Insomnia:</i>		
Diphenhydramine	25-50 mg po QHS	25 mg
Doxepin (Sinequan®)	10-150 mg po QHS	10, 25, 50, 75, 100, 150 mg
<i>Depression:</i>		
Citalopram (Celexa™)	20-40 mg po qd	10, 20, 40 mg
Escitalopram (Lexapro™)	10-20 mg po qd	5, 10, 20 mg
Fluoxetine (Prozac®, Sarafem®)	20-40 mg po qd	10, 20, 40 mg
Sertraline (Zoloft®)	50-200 mg po qd	25, 50, 100 mg
Paroxetine (Paxil®)	10-50 mg po qd	10, 20, 30, 40 mg
<u>Gastrointestinal</u>		
Dronabinol (Marinol®)	2.5-10 mg po bid	2.5, 5, 10 mg

There are a several less frequent side effects of HCV therapy that providers should be aware of:

Gout – Ribavirin commonly causes hyperuricemia, but infrequently causes gout. Monitoring uric acid levels is not recommended during HCV therapy. Patients who develop gout require individualized assessment to decide whether to continue HCV therapy.

Phototoxicity – Ribavirin combined with sun tanning or prolonged unprotected sun exposure can cause a significant phototoxicity reaction (sun burn limited to sun exposed areas). Patients on HCV therapy should be advised to avoid prolonged unprotected sun exposure and tanning booths.

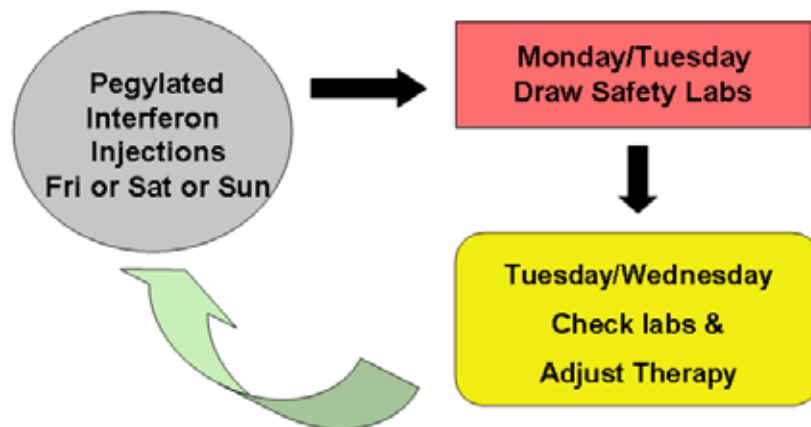
Dry Mouth – patients on HCV therapy subjectively have less saliva than at baseline. This alteration in normal oropharyngeal physiology may account for some of the cases of thrush. This problem rarely causes discontinuation of therapy. Patients can try sugar free gum, hard candies etc.

Sarcoid-like syndromes – Patients on HCV therapy can develop fevers of unknown origin or changes in vision. After ruling out opportunistic infections and routine bacterial infections, further diagnostic workup often reveals noncaseating granulmata in tissue biopsies (lung, bone marrow). Sarcoid-like syndromes due to pegylated interferon should be considered in patients on HCV therapy with an FUO and a negative initial workup. Discontinuation of HCV therapy typically results in resolution of the FUO and any associated symptoms (e.g., mild dry cough). Patients with sarcoid-like syndromes cannot restart HCV treatment.

11. SAFETY MONITORING DURING THERAPY

Safely providing HCV therapy is largely a matter of bookkeeping. Potential lab safety issues include neutropenia, anemia, and thrombocytopenia. *Appendix B* contains a spreadsheet with recommended laboratories during the course of HCV therapy; 12 months of medications plus 6 months post-treatment follow-up. It is very helpful to schedule all co-infected patients' safety labs on the same day, and to set aside 15-30 minutes the next day to review their results. This eliminates the stress of randomly timed alert values, and greatly simplifies providing care:

WORK FLOW DIAGRAM

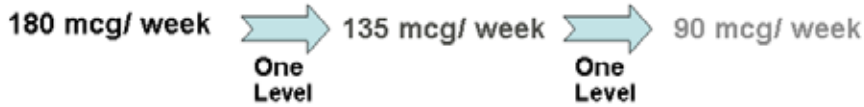


Neutropenia due to pegylated interferon is the most common safety lab abnormality associated with HCV therapy (27%), and generates the most anxiety among health care providers. Bacterial infections during HCV therapy are uncommon, and do not resemble the fatal septicemia seen with cytotoxic chemotherapy for malignancies. The most common infection seen in HIV patients during HCV therapy in the APRICOT and RIBAVIC trials was thrush. Bacterial infections were uncommon; 0.5% in APRICOT and 5% in RIBAVIC. Pneumonia was the most common bacterial infection. No deaths in either study were directly attributable to infection. Neutropenia is readily reversible with G-CSF or interferon dose reductions. Dose reductions in pegylated interferon, especially early in the course of therapy, are associated with reduced rates of SVR. Neutropenia should be treated with G-CSF rather than dose reduction unless there is no mechanism for the patient to receive G-CSF. Access to G-CSF is especially important for African American patients who have higher rates of neutropenia.

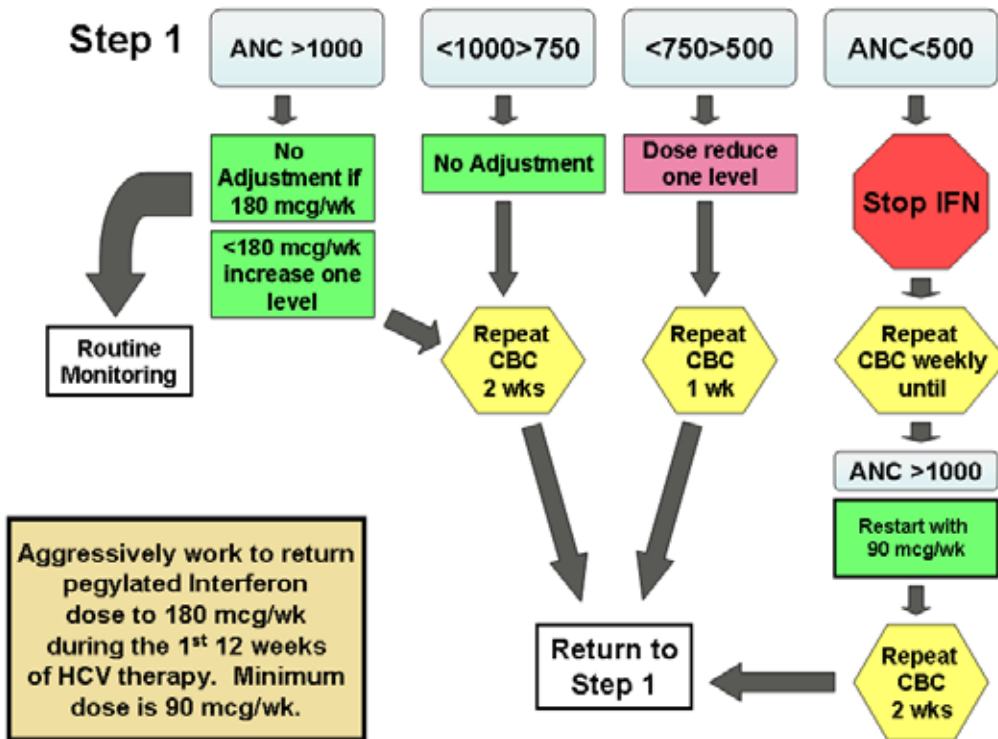
Initial G-CSF dosing is once a week given subcutaneously, usually two days before each pegylated interferon- α 2a injection. If additional G-CSF is needed the frequency is increased to twice a week, and maximal G-CSF therapy is given three times a week (very rare). G-CSF (filgrastim; Neupogen®) should be dosed as 300 mcg for weight <60 kg; 480 mcg for weight \geq 60 kg. There is little experience in HCV patients with pegylated

filgrastim (Neulasta®), and therefore it is not recommended.

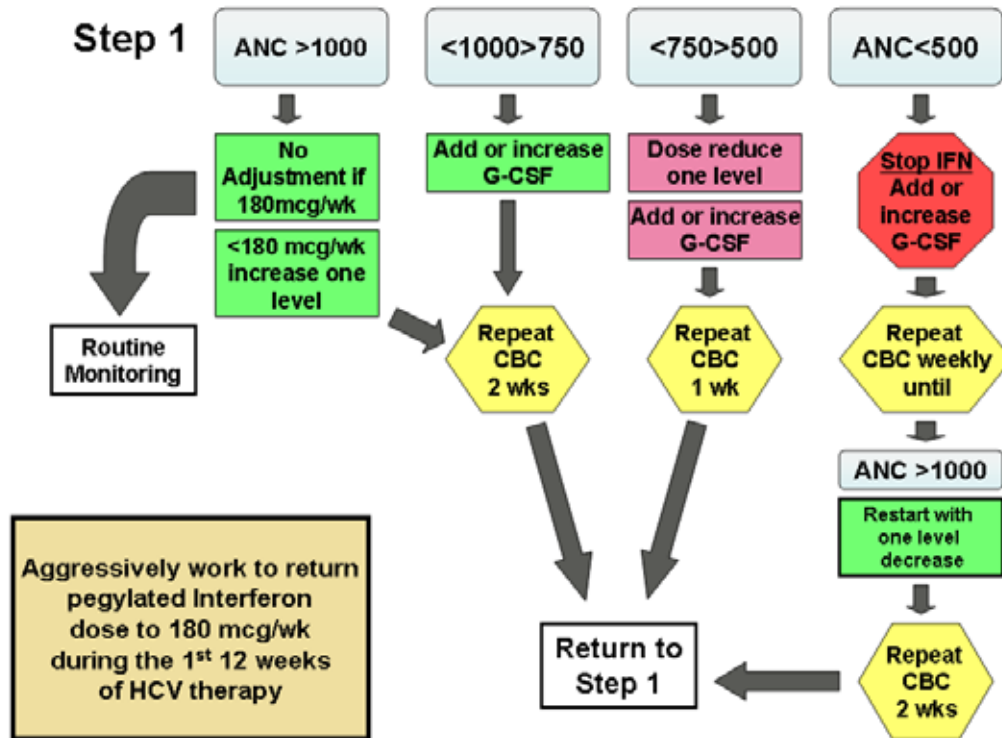
Dose Reducing Pegylated Interferon



Neutropenia Adjustments without G-CSF



Neutropenia Adjustments when G-CSF Available

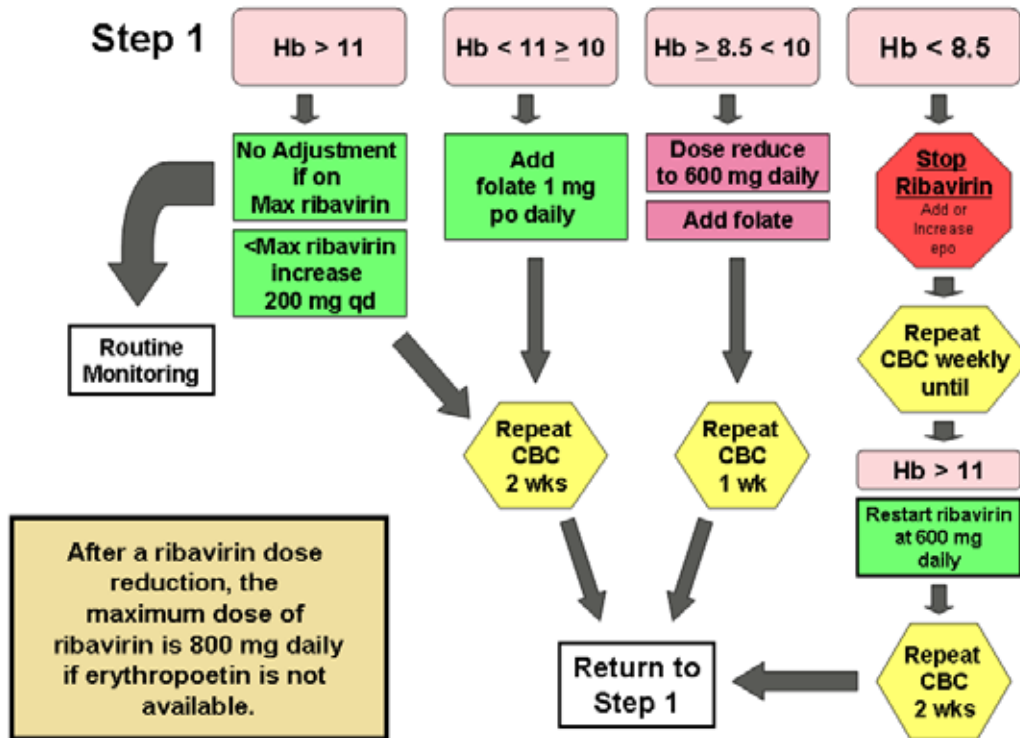


Anemia due to ribavirin is the second most common safety lab abnormality associated with HCV therapy in co-infected patients (16%). Ribavirin concentrates within RBCs causing a low grade hemolysis. This complication of therapy can be remedied by increasing the rate of RBC production using erythropoietin or darbepoetin. Folate is inexpensive and anecdotally helpful in some patients. Anemia is much more common if the patient is on AZT because of its bone marrow suppression. If possible, patients on AZT should be switched to non-AZT HAART regimens to avoid problematic anemias.

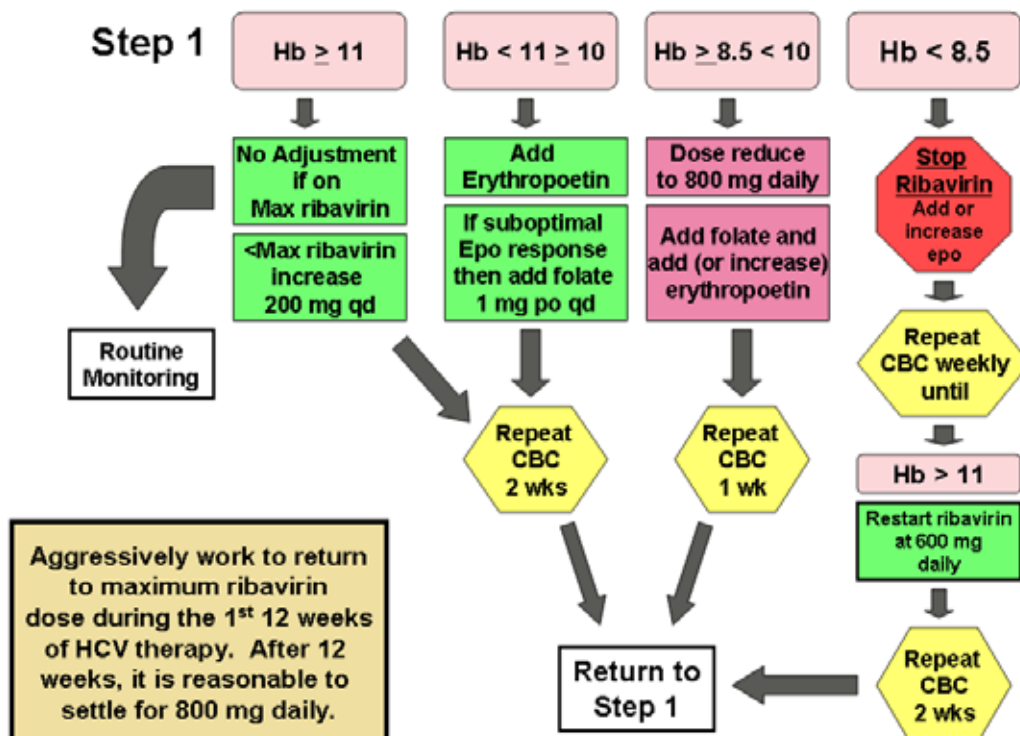
Erythropoietin or darbepoetin are typically given once a week subcutaneously. Initial doses are 10,000 units of erythropoietin or 25 mcg of darbepoetin, usually two days before each pegylated interferon injection. Dosing should be adjusted to keep Hb levels <12 g/dL as excessive supplementation increases the risk for thrombotic events including pulmonary emboli, strokes, and myocardial infarctions. Medications for treating lab abnormalities are summarized in Table 8.

Table 8- Medications for Treating Anemia		
Medication	Dosing	Supplied as
Erythropoietin (Procrit®)	10,000 units → 40,000 units SC q week	10,000 & 40,000 unit single dose vials
Darbepoetin (Aranesp®)	25→40→60→100 mcg SC q week	25, 40, 60, 100 mcg single dose vials
Folate	1 mg po q day	1 mg tabs by prescription

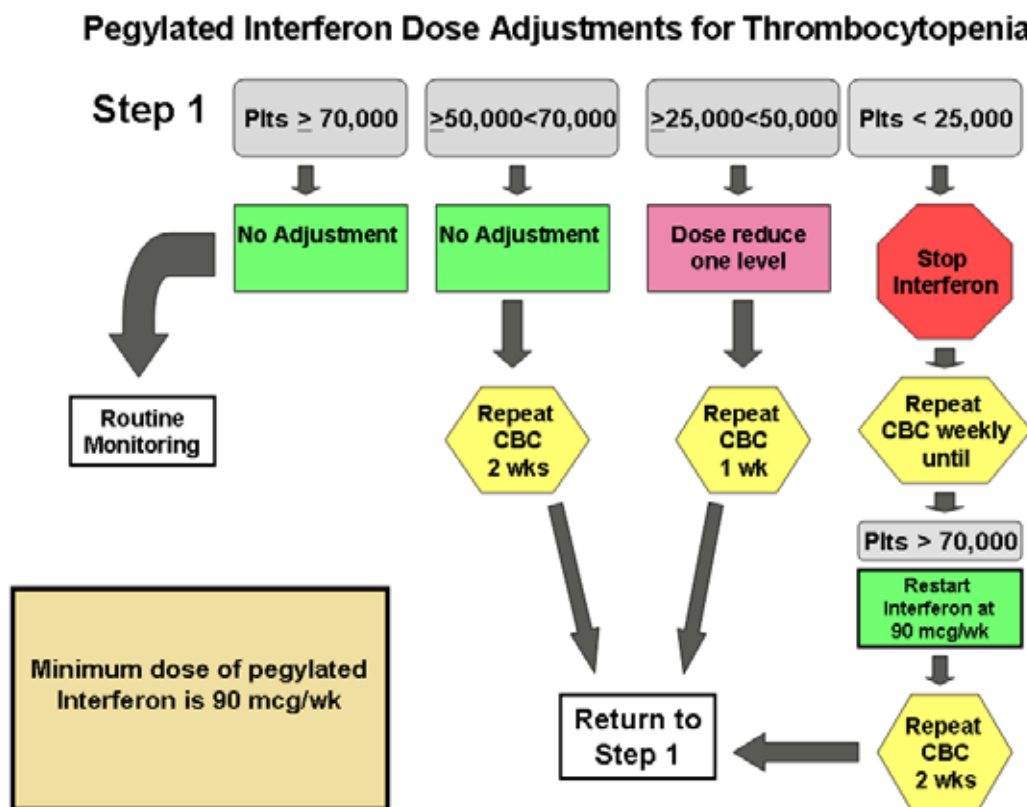
Ribavirin Dose Adjustments for Anemia without Erythropoietin



Ribavirin Dose Adjustments for Anemia with Erythropoietin



Thrombocytopenia is a side effect of pegylated interferon. Thrombocytopenia that limited HCV therapy was relatively uncommon in the APRICOT clinical trial (6%). However, patients with platelet counts $< 70,000$ per ml were excluded from participation. HIV/HCV care providers initiating HCV therapy in patients with lower platelets can anticipate increased incidents of thrombocytopenia requiring pegylated interferon dose adjustments.



12. POST HCV THERAPY DECISION MAKING

The risk of relapse after documented SVR is very low, including co-infected patients. No further HCV viral load testing is indicated unless a patient has an unexplained bump in their LFTs. HCV patients with SVR do not have a significant ongoing risk for HCC, and the biannual serum AFP levels can be discontinued. Patients placed on doxepin or antidepressant therapy during HCV treatment can be tapered off those medications (doxepin and SSRIs should not be discontinued abruptly).

Nonresponders and patients who fail treatment with detectable HCV viral loads at 24, 48, or 72 weeks should have a repeat liver biopsy to determine whether there was a histologic response to therapy, and determine their current stage of fibrosis. Patients who relapse at 72 weeks have a significant response to retreatment (at least in HCV mono-infected patients). For patients with current METAVIR fibrosis stage > 2 , potential retreatment options include high dose (360 mcg qweek) pegylated interferon induction for 12 weeks supported by erythropoietin/G-CSF, or standard dose HCV therapy extended beyond 48 weeks (*e.g.*, 72 weeks). In retreatment, optimal management, including growth factors to avoid dose reductions, is essential. These non-approved HCV treatment strategies should only be utilized by providers with relevant expertise. Patients without SVR and cirrhosis on liver biopsy should continue HCC screening (biannual AFP plus annual liver ultrasound).

New HCV therapies focusing on inhibiting the HCV polymerase (*e.g.*, valopicitabine; Idenix Pharmaceuticals) and HCV protease (*e.g.*, VX-950; Vertex Pharmaceuticals) are in development. Patients without indications for immediate retreatment should be assured that HCV pharmaceutical research is ongoing, and they will likely have better retreatment options in the future.

13. HBV CO-INFECTIONS

HEPATITIS B VIRUS (HBV) VOCABULARY:

- *Hepatitis B core antigen (HBcAg)* – the core antigen is the viral capsid, which contains the viral genome. HBcAg is contained within a viral envelope, and therefore cannot be directly measured in serum.
- *Hepatitis B core antibody (HBcAb)* – antibody (IgG or IgM) specific for the HBcAg. IgM is a marker for acute infection or recurrent flares of HBV. IgG is a marker of prior resolved or current chronic infection with HBV.
- *Hepatitis B e antigen (HBeAg)* – a unique viral polypeptide that initiated from a promoter upstream of the core antigen that generates a secreted protein including the proximal portion of the core antigen. HBeAg is not incorporated into the virus, and therefore antibodies generated to it have no ability to neutralize virus. HBeAg is detectable in serum. HBeAg is a marker for infectivity.
- *Hepatitis B e antibody (HBeAb)* – antibody specific for HBeAg. Detection of HBeAb in serum is referred to as an “HBeAg seroconversion event.” This is the primary endpoint of most clinical trials addressing treatment of HBV because HBeAg seroconversion generally heralds decreases in HBV viral loads and improvement in liver inflammation (normalization of ALT). However only about 20% of HBeAg seroconvertors go on to develop HBsAb, the true marker of stable resolution.
- *Hepatitis B surface antigen (HBsAg)* – the viral envelope glycoprotein complex made up of three related proteins. The envelope glycoproteins are made in great excess and are readily detectable in serum.
- *Hepatitis B surface antibody (HBsAb)* – antibody specific for HBsAg. Detection of HBsAb in serum is referred to as an “HBsAg seroconversion event.” HBsAg seroconversion events represent stable immune-mediated control of HBV infections. HBsAg seroconversion can occur several years after HBeAg seroconversion making it an inconvenient endpoint for HBV clinical trials. HBsAb recognizing the viral envelope glycoproteins are neutralizing antibodies that contribute directly to host defense.
- *Chronic HBV infection* – HBsAg+ six months after acute infection.
- *HBeAg+ HBV* – Acute or chronic HBV with detectable HBeAg in serum. HBV viral loads tend to be high, and these patients can transmit HBV infections to others.
- *HBeAg-negative HBV* – a form of chronic HBV lacking detectable HBeAg in serum, usually because the viral promoter driving HBeAg transcription has been mutated (pre-core mutant). Patients are HBsAg positive and HBV DNA positive. HBeAg- HBV represents a chronic infection state after a failed host immune-mediated attempt to clear the virus, in which HBV viral loads are relatively low, but inflammation and scarring can continue. HBeAg negative HBV infections are typically associated with long-standing HBV infections (maternal-fetal acquisition) and are relatively uncommon in the U.S.; definitively identified by directed HBV genome sequencing.

14. HEPATITIS B VIRUS

Hepatitis B virus (HBV) exists as seven subspecies referred to as genotypes A-G. HBV is a DNA virus with an RNA intermediate replication step. Within the virion, the HBV genome is a partially doubled stranded relaxed open plasmid. Upon entering the hepatocyte, the viral nucleocapsid is transported to the nucleus where the HBV genome is converted into a covalently closed circular double stranded plasmid (cccDNA) that is maintained as a minichromosome within the nucleus of the infected cell. The cccDNA serves as a template for viral protein transcription. Viral transcripts are translated into protein, and viral assembly occurs, in the cytoplasm. RNA copies of the viral genome are *reverse transcribed* into DNA by the virus RNA-dependent DNA polymerase. This replication step makes HBV susceptible to reverse transcriptase inhibitors including drugs that were originally developed to treat HIV. Superinfection (repeat infection) of hepatocytes leads to an increase in the number of cccDNA copies within each cell. The HBV genome encodes the viral capsid (core antigen, HBcAg), three related envelope glycoproteins (surface antigen, HBsAg), the viral polymerase, and a mysterious protein that is not incorporated into the virion call the E antigen (HBeAg). The HBeAg is the initial portion of the capsid (HBcAg) modified with a signal peptide that targets it for secretion from the hepatocyte into the blood. Generation of antibodies to the HBeAg is the first sign of immune resolution of acute HBV infections, but the role of HBeAg in the viral life cycle is likely related to immune evasion. HBV is a stealth pathogen that does not kill the infected hepatocyte. Prior to the invention of the syringe, and the phenomenon of IV drug use, HBV was a sexually transmitted pathogen that was commonly transmitted vertically from mother to neonate. Some experimental data suggests that the role of HBeAg is to cross the placenta into the fetus where it tolerizes the nascent immune system to T cell targets (epitopes) on the HBcAg. Because the exposed neonate recognizes a major component of HBV as ‘self,’ neonates are compromised in their ability to clear acute HBV infections, and more likely than adolescents and adults to become chronically infected by HBV.

THE RATIONALE FOR TREATING HBV

The treatment of HBV in co-infected patients is not ‘settled’ clinical science. Unlike HCV there are no large randomized clinical trials in co-infected patients that have established a standard-of-care, and there is no FDA-approved HBV treatment for HIV co-infected patients. The primary goal of HBV therapy is to preserve liver function and prevent HCC. HBV cannot be ‘cured.’ Even individuals who resolve acute HBV infections carry HBV genomes (cccDNA) in their hepatocytes, and in rare instances can relapse. The best response to any HBV therapy in HBV mono-infected patients is an HBeAg seroconversion rate of 32% for pegylated interferon- α 2a monotherapy.¹⁴ The highest HBeAg seroconversion rate in HBV mono-infected patients for nucleoside or nucleotide monotherapy is 21% for entecavir.¹⁵ The majority of HBV-infected patients, mono-infected or co-infected, require durable HBV suppression to achieve the primary treatment goals of preserving liver function and preventing HCC.

In spite of some therapeutic uncertainty, the majority of HBV co-infected patients should have their HBV treated. Unlike HCV, HBV infected patients without significant liver fibrosis can develop HCC. In mono-infected patients, HBV viral loads $\geq 10,000$ copies/ml are associated with increased risk of HCC independent of the stage of liver fibrosis.¹⁶ This major difference in HCC risk between HCV and HBV may relate to the cccDNA HBV genomes residing in the nucleus of infected hepatocytes. Co-infected patients with HBV appear to be at greater risk for HCC than co-infected patients with HCV.¹⁷ Until there is data to the contrary, co-infected patients with HBV viral loads $\geq 10,000$ copies/ml should be treated for HBV.

Similar to HCV, fibrosis in HBV coinfecting patients progresses faster than in HBV mono-infected patients, and stage of fibrosis does not correlate with ALT elevations. The majority of HBV co-infected patients have METAVIR fibrosis scores >1 .¹⁸ Although there fewer HBV co-infected patients, the individual risk of future morbidity and mortality is probably greater for an untreated HBV co-infected patient than an untreated HCV co-infected patient.

PRETREATMENT LABORATORY EVALUATION

Pretreatment evaluation is essentially the same as for HCV except for the HBV serologies, HBV viral load, and HBV genotyping. The term HBV genotyping is confusing as it can mean either identifying the subspecies (as in the HCV vernacular) or identifying HBV promoter and polymerase mutations (as in the HIV vernacular). As in HCV, liver biopsies should be performed to stage fibrosis. Knowing the fibrosis stage influences the how strongly treatment should be recommended, and how aggressively to push through side effects of therapy. Diagnostic tests for HBV are shown in Table 9.

As part of the pretreatment evaluation, patients should have HIV labs (CD4 count, HIV viral load), CBC with platelets, LFTs, PT/INR, AFP, Liver Ultrasound, HBsAg, HBeAg, HBsAb, HBeAb, HBV DNA level (viral load), and an HBV genotype (meaning genome sequencing for drug resistance) for patients with prior exposure to, or viremia while on, lamivudine, emtricitabine, tenofovir, or famciclovir. Roughly half of untreated HBV coinfecting patients will have an HBV DNA level higher than the upper limit of detection of commercial assays. A Child-Pugh calculation, β -HCG, an EKG, and a TSH are necessary if considering interferon therapy.

Table 9- HBV Diagnostic Testing

Test	Measures	Results	Interpretation
HBsAb	Antibodies to viral envelope glycoprotein (surface antigen)	pos/neg by titer	Positive result correlates with immunologic control of HBV infection – marker of resolution of acute HBV infection & goal of HBV therapy.
HBcAb	Antibody to viral capsid (core antigen)	pos/neg	Positive tests correlate with chronic or resolved infections. Can be positive in HBsAg – occult HBV infections.
HBeAb	Antibody to E antigen	pos/neg	Positive result correlates with initial step toward immune control of HBV- however viral relapse can occur. In the setting of nucleoside/ nucleotide therapy only 20% go on to develop HbsAb.
HBsAg	HBV surface antigen	pos/neg	Positive result = HBV infection
HBeAg	HBV E antigen	pos/neg	Positive result correlates with infectivity. Identifies HBV infections largely unaffected by the host immune response.
<i>HBV DNA(viral load)*:</i>			
-Standard PCR (ROCHE AMPLICOR HBV MONITOR® Test, v2.0)	HBV DNA	1000-4x10 ⁷ copies/ml	HBV viremia
-Real time PCR (ROCHE HBVTAQMAN, LABCORP HBV TAQMAN)	HBV DNA	~200-1x10 ⁹ copies/ml	HBV viremia

-bDNA (Bayer VERSANT® HBV DNA 3.0 Assay)	HBV DNA	2000-1x10 ⁸ copies/ml	HBV viremia
HBV genotype (subspecies)	a) identifies subspecies	Genotype A-G	Clinically relevant biology still being established. Genotype G may cause more fibrosis.
HBV genotype (genome sequencing for polymerase mutations) Currently available from Quest Diagnostics – test #10529N & LapCorp – test#551840 -> 1.5 mL frozen plasma (PPT white-top tube); Plasma should be separated and frozen within 2 hours of collection. -Alternatively, submit > 1.5 mL (EDTA purple top) frozen serum in a sterile, plastic, screw-capped, aliquot tube.	b) sequence of viral promoter and polymerase mutations	Specific mutations	Lamivudine/Emtricitabine resistance mutations: L180M, A181T/V, M204V Adefovir resistance mutations: A181V, N236T Telbivudine resistance mutations: L180M, M204I/V, A181V Entecavir resistance mutations: M250V, T184G, S202I, I169T, V173L Famciclovir resistance mutations: L180M, V207I **Tenofovir resistance mutations: A194T, ¹⁹ N236T?, A181V?

*HBV PCR and bDNA testing is available through ARUP, Covance, LabCorp, and Quest Diagnostics commercial laboratories, also available locally within larger medical centers' laboratories.

** Tenofovir is not FDA-approved for treating HBV and there currently is no consensus on tenofovir resistance mutations. LabCorp and Quest do not report out the A194T mutation. To know whether patients are resistant to tenofovir based on an A194T mutation the commercial laboratories must be contacted with a query for a specific patient.

15. HBV TREATMENT

The goal of HBV nucleotide/nucleoside therapy is durable suppression with HBV viral load < 200 copies/ml (lower limit of detection), or at least < 10,000 copies/ml (HCC risk cutoff). For all patients, especially those with liver biopsy fibrosis scores > 2, it makes sense to aggressively pursue complete HBV suppression to minimize the risk of developing drug resistance.

An International HIV-HBV panel²⁰ and the International AIDS Society-USA panel²¹ recommended tenofovir combined with either emtricitabine or lamivudine as two components of three drug HAART therapy for patients requiring HIV treatment. The International AIDS Society-USA panel recommended adding entecavir to tenofovir-based HAART therapy in patients with lamivudine/emtricitabine resistant HBV. For patients that do not require HIV therapy, the International HIV-HBV panel recommended considering adefovir monotherapy, entecavir monotherapy, or interferon therapy, while the International AIDS Society-USA panel recommended adefovir or entecavir monotherapy. Both panels recommended against lamivudine (or emtricitabine) monotherapy because of the high annual rate of resistance and risk of severe hepatic flares. At the 2007 Retrovirus Meeting entecavir was shown to select for the HIV reverse transcriptase mutation M184V and therefore cannot be used without simultaneous HAART therapy. Table 10

summarizes the available anti-HBV medications.

Providers uncomfortable with adefovir monotherapy in HBV co-infected patients who do not require HAART can rationally, but without data, combine adefovir-telbivudine. Adefovir (at 10 mg/day) does not have activity against HIV and does not select for HIV reverse transcriptase mutants. Telbivudine is reported to lack activity against HIV. Telbivudine is not likely to be effective against lamivudine-resistant HBV based on its resistance profile.

Table 10- Medications for Treating HBV		
<u>Medication</u>	<u>Dosing</u>	<u>Pill size</u>
Nucleotides:		
Adefovir (Hepsera®)	10 mg po qd	10 mg
Tenofovir (Viread®)*	300 mg po qd	300 mg
Nucleosides:		
Lamivudine (Epivir®)	150 mg po bid, or 300mg po qd	150 mg
Emtricitabine (Emtriva®)*	200 mg po qd	200 mg
Entecavir (Baraclude™)	1 mg po qd‡	0.5, 1 mg
Telbivudine (Tyzeka™)	600 mg po qd	600 mg
Interferons:		
Pegylated interferon-α2a (Pegasys®)	180 mcg SC qwk x 1 year	180 mcg prefilled syringes
Standard interferon-α2b (Intron A®)	5 million IU SC qd, or 10 million IU SC TIW x 16 weeks	Multidose pens for qd or TIW, 10 million IU vials

* Not FDA-approved for HBV therapy

‡ In HBV mono-infected patients without lamivudine resistance used at 0.5 mg po qd

The HBV co-infection treatment guidelines are not based on large randomized prospective clinical trials. Both major guidelines recommend using tenofovir for a non-FDA approved indication (HBV treatment), and dual HBV nucleotide/nucleoside therapy in the absence of definitive clinical trial data. The guidelines are reasonable based on the available data. In a small co-infection study, failure to completely suppress HBV replication with tenofovir monotherapy was only seen with pretreatment HBV viral loads >1x10⁷ copies/ml.²² HBV monotherapy with tenofovir with an HBV viral load > 1x10⁷ copies/ml risks incomplete HBV suppression, and carries a risk for development of tenofovir resistance. Analogous to combination therapy for HIV, dual therapy for HBV should decrease the risk of developing drug resistant HBV. Dual HBV therapy combining tenofovir with either emtricitabine or lamivudine as two components of a three drug HAART regimen is a reasonable approach for all treatment-naive HBV co-infected patients requiring HIV therapy.

Unfortunately the majority of HAART-experienced HBV co-infected patients have received HIV therapy containing lamivudine (Epivir, or Combivir) without a second anti-HBV drug. Co-infected patients on lamivudine HBV monotherapy have an annual lamivudine resistance rate of 20-40%, and a four year cumulative resis-

tance rate of 90%. The majority of HAART-experienced co-infected patients have lamivudine-resistant HBV. Lamivudine-resistant HBV is also emtricitabine-resistant and telbivudine-resistant.

The long term resistance rates for nucleoside/nucleotide HBV therapies other than lamivudine in HIV co-infected patients are not known. In HBV treatment-naïve mono-infected patients, adefovir monotherapy has a four year resistance rate of 15%; entecavir has a three year resistance rate of <1%. In the setting of pre-existing HBV lamivudine mutations, entecavir’s three year resistance rate is 15%. Resistance is a potentially more significant problem in HIV co-infected patients because they have higher pre-treatment HBV viral loads, which translate into larger pre-treatment pools of HBV virus with random polymerase mutations. Though there are no guidelines, HIV co-infected patients initiating entecavir therapy should probably start with 1 mg daily, rather than 0.5 mg daily, regardless of their status with respect to lamivudine exposure or resistance.

Whenever possible, HIV/HBV patients being treated for HBV with nucleoside/nucleotide therapy should be on two active HBV drugs, taking into account their HIV therapy requirements. For HBV therapy, lamivudine-emtricitabine and adefovir-tenofovir should not be used because these pairs represent closely related drugs with similar HBV resistance profiles. Lamivudine or emtricitabine combined with telbivudine is unlikely to be useful dual therapy because of shared resistance mutations. Co-infected patients can only be treated with entecavir, tenofovir, lamivudine, or emtricitabine as part of (or in addition to) effective HAART therapy. Without simultaneous HAART therapy these medications will select for drug-resistant HIV and complicate future HIV treatment. Adefovir and the recently approved telbivudine are the only nucleotide/nucleoside therapies that can be given in the absence of simultaneous HAART therapy. HIV/HBV care providers need to be aware that Truvada® is an HIV combination pill containing tenofovir and emtricitabine; Atripla™ is an HIV combination pill containing tenofovir, emtricitabine and efavirenz; Epzicom™ is an HIV combination pill containing lamivudine and abacavir; Combivir® is an HIV combination pill containing lamivudine and AZT. Nucleotide/nucleoside therapies should continue indefinitely in co-infected patients; even those who develop HBeAb+ as this does not appear to correlate well with HBV viral load suppression in co-infected patients, and discontinuing nucleotide/nucleoside HBV therapy carries risk for severe hepatic flares that can be fatal. Table 11 presents a summary of HBV dual therapy treatment options in co-infected patients.

Table 11- HBV Dual Therapies†		
<i>No HAART</i>	<i>HAART without prior 3TC/FTC‡ exposure</i>	<i>HAART + 3TC/FTC exposure & detectable HBV DNA* (Check HBV resistance genotype)</i>
Adefovir + telbivudine	Tenofovir + emtricitabine with 3 rd antiretroviral drug for HAART or	Pegylated Interferon-α2a followed by Tenofovir + entecavir or
Pegylated Interferon-α2a followed by Adefovir + telbivudine	Tenofovir + lamivudine with 3 rd antiretroviral drug for HAART	Tenofovir + entecavir
Entecavir + telbivudine		Need additional 2-3 antiretroviral drugs for effective HAART

‡3TC = lamivudine; FTC = emtricitabine

†No definitive efficacy data for dual therapies.

*For patients on lamivudine HBV monotherapy with undetectable HBV DNA due to coincident HAART, consider adding entecavir.

An alternative to nucleotide/nucleoside ('nuc') HBV therapy in co-infected patients is interferon therapy. Pegylated interferon- α 2a (Pegasys®) and standard interferon- α 2b (Intron-A®) are FDA-approved for treating HBV in mono-infected patients. For practical reasons related to convenience and tolerability, pegylated interferon- α 2a is more commonly used for HBV therapy. Interferon therapy is not affected by pre-existing nucleotide/nucleoside mutations, and does not generate polymerase mutations. Pegylated interferon should be considered for treating HBV in co-infected patients harboring HBV resistant to lamivudine/emtricitabine or adefovir/tenofovir, or in co-infected patients who are intolerant of tenofovir. With the current HBV drug armamentarium these patients are running out of treatment options, and a single additional HBV resistance event or medication intolerance potentially leaves them with HBV monotherapy or no therapy. In that setting, the increased commitment required to take and supervise interferon therapy for HBV makes sense. Providers may also want to consider interferon therapy for patients with fibrosis stage > 2 , though there is no data supporting superiority of interferon over 'nuc' therapy or *visa versa*.

The goal of interferon therapy is seroconversion; *i.e.*, development of HBeAb+ with subsequent development of HBsAb+. HBeAg seroconversions (HBeAb+) occur in 32% of HBV mono-infected patients treated with pegylated interferon- α 2a therapy for 1 year.¹⁴ There are no data for HIV/HBV co-infected patients, but it is likely that seroconversion events will be less frequent. The secondary goal for the majority of patients who do not seroconvert is to lower HBV viral loads before beginning 'nuc' therapy in order to increase the fraction of patients who achieve HBV DNA < 200 copies/ml; an endpoint that likely correlates with durable HBV suppression. Patients who do not have seroconversion events with interferon therapy should proceed on to a dual 'nuc' HBV regimen.

Patients on pegylated interferon monotherapy are monitored with q3 month HBV viral load testing. Nucleotides/nucleosides should not be started simultaneously with pegylated interferon therapy. Clinical trial data show that this approach does not improve the seroconversion rate and may actually decrease it. Patients who have virologic failure (defined as rebound or plateau in HBV viral load) on two consecutive monitoring HBV viral loads should start dual HBV 'nuc' therapy and discontinue pegylated interferon after an arbitrary overlap of 3-6 months. While co-administration of interferon with 'nuc' therapy does not help seroconversion, it does decrease the development of drug resistance. Treatment-responsive patients who have not seroconverted after 12 months of pegylated interferon would similarly start HBV 'nuc' therapy with an arbitrary 3-6 month overlap. Patients who have an HBsAg seroconversion event (HBeAb- \rightarrow HBeAb+) after 12 months of therapy go off all HBV therapy with follow-up monitoring (HBV viral loads q3-6 months). HBeAb+ patients with HBV viral loads $< 10,000$ copies/ml would not necessarily require HBV suppression with nucleoside/nucleotide therapy. Annual testing for HBsAg seroconversion (HBsAb- \rightarrow HBsAb+) is reasonable. Patients who develop HBsAb+ will still require ongoing routine HBV-related monitoring (HBV viral loads and HBsAb testing twice a year) as an HBV relapse has been reported in a co-infected patient with an adefovir-interferon induced HBsAg seroconversion (HBsAb+).

Famciclovir is a weak anti-HBV drug and its role in HBV therapy, if any, is unclear. Abacavir also has weak anti-HBV activity. It is unclear whether that activity is important with respect to treatment or development of resistance. Ribavirin is not active against HBV.

16. SAFETY MONITORING AND MANAGING HBV TREATMENT

Managing nucleoside/nucleotide HBV therapy is relatively easy. HBV viral loads and LFTs should be monitored q3 months (like HIV viral loads) until the HBV viral load goes to < 200 copies/ml. At that point HBV viral

load monitoring can decrease to twice a year; drawn with the biannual AFP screen for HCC. Patients whose HBV viral loads do not drop below 200 copies/ml should continue q3 month HBV viral load monitoring. In the setting of incomplete suppression, an HBV resistance genotype should be sent for significant increases in HBV viral loads (10-fold), and HBV therapy adjusted taking concomitant HIV therapy into account. AFP testing should continue twice a year, with an annual liver ultrasound if the HBV viral load is > 9,999 copies/ml (increased risk of HCC). Increasing AFP values should be followed up with a dual phase liver CT scan or a liver MRI. Patients with lesions suspicious for HCC should be referred to transplantation centers. Monitoring for seroconversion events once a year is sufficient because therapy continues indefinitely for safety reasons regardless of the serology results.

Managing pegylated interferon monotherapy for HBV is easier than managing HCV therapy because nausea, insomnia, and depression are much less of a problem without the ribavirin (Table 12). In addition, all HAART regimens are compatible with pegylated interferon monotherapy with the exception that AZT should be avoided if possible. Similar to HCV management, safety labs are drawn once a month. Appendix C contains a spreadsheet for following safety laboratories while on interferon therapy for HBV.

Hepatic flares are more common with interferon treatment of HBV than HCV. Patients generally notice mild anorexia and fatigue. If ALT is > 250 units/L, then monitoring of alkaline phosphatase, total bilirubin, ALT and protime should increase to once a week until flare abates. If ALT goes over 500, then pegylated interferon should be dose reduced one or two levels with continued weekly monitoring. Persistent elevations in ALT above 500 units/L, or significant increases in protime or alkaline phosphatase/bilirubin, require discontinuation of interferon therapy. Patients should be warned about the possibility of hepatic flares, but also informed that hepatic flares generally reflect favorable responses to interferon therapy.

Table 12- Pegylated Interferon- α 2a HBV Treatment Side Effects with a Frequency > 10%

<i>Side Effect (listed by relative frequency during HCV therapy)</i>	<i>Frequency in HBV Mono-infected Trial ¹⁴/ (Frequency in APRICOT HCV/HIV Trial)</i>
Fatigue	40% / (44%)
Headache	28% / (39%)
Fever	49% / (44%)
Myalgia	26% / (36%)
Insomnia	Uncommon / (26%)
Alopecia (mild, not like chemotherapy)	20% / (Not scored)
Nausea/vomiting	9 % / (30%)
Depression	5% / (26%)
Diarrhea	9% / (28%)

17. POST HBV THERAPY DECISION MAKING

HBV therapy continues indefinitely except for patients who seroconvert on interferon therapy. Co-infected patients who seroconvert on ‘nuc’ therapy stay on it, and patients who do not seroconvert on interferon therapy are treated with indefinite ‘nuc’ suppression. In this setting, follow-up liver biopsies do not have major implications for adjusting therapy and are not routinely performed. One exception may be patients with initial fibrosis scores > 2 who run out of treatment options due to drug resistance or intolerance, and are considering initiating

interferon therapy or continuing interferon as ‘maintenance therapy’ for chronic HBV infection.

Patients with multidrug resistant HBV should be assured that pharmaceutical research is ongoing. However, the two HBV drugs furthest along in development, clevudine and telbivudine (recently FDA-approved), are not likely effective against lamivudine-resistant HBV.

18. HIV/HCV/HBV – THE ‘TRIPLE THREAT’

It can’t get much more complicated than this! In general, a reasonable approach is to combine the pretreatment evaluations for HCV and HBV therapy. Treat the HCV, and address the HBV as you would an HBV co-infected patient on pegylated interferon monotherapy, checking HBV viral loads q3 months. If the HBV viral load rebounds or plateaus during monitoring, then start dual ‘nuc’ HBV therapy while completing the 12 months of interferon/ribavirin for HCV. If the patient is not HBeAb+ after 12 months of HCV therapy, then start dual HBV ‘nuc’ therapy with a 3-6 month interferon overlap (taking into account the patients HAART status). If the patient has an HBV seroconversion event (HBeAb+) documented at the end of 12 months of HCV therapy, then the patient goes off all hepatitis virus therapy and is monitored for HBV relapse and HCV SVR. Witnessing a treatment-induced HBsAg seroconversion event (HBeAg+/HBeAb- → HBeAg-/HBeAb+ → HBsAg-/HBsAb+) with a simultaneous HCV SVR would be an enormously rewarding outcome and a *tour de force* in clinical care.

19. REFERENCES

1. Gebo KA, Chander G, Jenckes MW, et al. Screening tests for hepatocellular carcinoma in patients with chronic hepatitis C: a systematic review. *Hepatology*. Nov 2002;36(5 Suppl 1):S84-92.
2. Johnson CL, Gale M, Jr. CARD games between virus and host get a new player. *Trends Immunol*. Jan 2006;27(1):1-4.
3. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med*. Jul 29 2004;351(5):438-450.
4. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *Jama*. Dec 15 2004;292(23):2839-2848.
5. Bonacini M, Lin HJ, Hollinger FB. Effect of coexisting HIV-1 infection on the diagnosis and evaluation of hepatitis C virus. *J Acquir Immune Defic Syndr*. Apr 1 2001;26(4):340-344.
6. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology*. Oct 1999;30(4):1054-1058.
7. Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. *Hepatology*. Jun 2004;39(6):1702-1708.
8. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. Oct 2002;123(4):1061-1069.
9. Northfelt DW, Charlebois ED, Mirda MI, Child C, Kaplan LD, Abrams DI. Continuous low-dose interferon-alpha therapy for HIV-related immune thrombocytopenic purpura. *J Acquir Immune Defic Syndr Hum Retrovirol*. Jan 1 1995;8(1):45-50.
10. Hadziyannis SJ, Sette H, Jr., Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med*.

- Mar 2 2004;140(5):346-355.
11. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat.* Oct 2006;13(10):683-689.
 12. Yu ML, Chuang WL, Dai CY, et al. Different viral kinetics between hepatitis C virus genotype 1 and 2 as on-treatment predictors of response to a 24-week course of high-dose interferon-alpha plus ribavirin combination therapy. *Transl Res.* Sep 2006;148(3):120-127.
 13. Lowe B, Kroenke K, Grafe K. Detecting and monitoring depression with a two-item questionnaire (PHQ-2). *J Psychosom Res.* Feb 2005;58(2):163-171.
 14. Lau GK, Piratvisuth T, Luo KX, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med.* Jun 30 2005;352(26):2682-2695.
 15. Chang TT, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med.* Mar 9 2006;354(10):1001-1010.
 16. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *Jama.* Jan 4 2006;295(1):65-73.
 17. Bonacini M, Louie S, Bzowej N, Wohl AR. Survival in patients with HIV infection and viral hepatitis B or C: a cohort study. *Aids.* Oct 21 2004;18(15):2039-2045.
 18. Lacombe K, Massari V, Girard PM, et al. Major role of hepatitis B genotypes in liver fibrosis during Co-infection with HIV. *Aids.* Feb 14 2006;20(3):419-427.
 19. Sheldon J, Camino N, Rodes B, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. *Antivir Ther.* 2005;10(6):727-734.
 20. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *Aids.* Feb 18 2005;19(3):221-240.
 21. Hammer SM, Saag MS, Schechter M, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society-USA panel. *Jama.* Aug 16 2006;296(7):827-843.
 22. Lacombe K, Gozlan J, Boelle PY, et al. Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate. *Aids.* Jun 10 2005;19(9):907-915.

APPENDIX A: SAMPLE INSURANCE LETTER

X Insurance Provider

Re: Growth factors to support HCV therapy

To Whom It May Concern:

Your client Mr./Ms. Smith has HIV with a significant HCV co-infection. His/her liver biopsy shows stage ___ fibrosis and on that basis it is recommended that his/her HCV be treated, consistent with the current standard-of-care for co-infected patients. Because Mr/Ms Smith is _____ I anticipate that he/she will have more problems with neutropenia/anemia than other patients, and I would like to confirm that he/she will have access to filgrastim and erythropoietin to support his/her HCV therapy. Treatment interruptions or dose reductions in ribavirin or pegylated interferon due to anemia or neutropenia are detrimental to sustained virologic responses (HCV cures).¹

African American² or on AZT as part of HAART therapy³

1. McHutchison JG, Manns M, Patel K, et al. Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology*. Oct 2002;123(4):1061-1069.
2. Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. Peginterferon alfa-2a (40 kd) and ribavirin for black American patients with chronic HCV genotype 1. *Hepatology*. Jun 2004;39(6):1702-1708.
3. Alvarez D, Dieterich DT, Brau N, Moorehead L, Ball L, Sulkowski MS. Zidovudine use but not weight-based ribavirin dosing impacts anaemia during HCV treatment in HIV-infected persons. *J Viral Hepat*. Oct 2006;13(10):683-689.

APPENDIX C - HBV INTERFERON SAFETY MONITORING

		HIV HAART: Avoid AZT (Retrovir, Combivir, Trizivir)											
		HAART #1: HAART #2: HAART #3: Other Meds 1: Other Meds 2: Base line CD4:											
		Date of Birth: Baseline Total Bil: Baseline Alk Phos: Baseline ALT: Baseline Albumin: Baseline Protine: Liver ultrasound date: #2											
		Baseline weight (kg): Baseline Hb: Baseline platelets: Baseline ANC: Baseline Scr: Baseline TSH: Baseline AFP: Hep A Vaccine Dates: #1											
		Routine Labs											
		Week 2											
		1 month	2 months	3 months	4 months	5 months	6 months	7 months	8 months	9 months	10 months	11 months	12 months
Patient Name:		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Baseline HBV vi:		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Liver Biopsy (metavir fibrosis stage):		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
History of 3TC, FTC, Tenofovir, Famciclovir exposure:		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
HBV genotype/resistance mutations:		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Child-Pugh score (if cirrhosis):		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
HBsAg:	HBsAb; HBeAg; HBeAb	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Treatment Start Date:		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
12 month HBeAb+:	YES or NO	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Laboratory													
CBC:	Hb	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	platelets	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	ANC	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	Hb f/u												
	plat f/u												
	ANC f/u												
Absolute CD4		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
CD4%		X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Liver functions:	total bili	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	Alk phos	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	AST	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	ALT	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	Albumin	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	Protine	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Renal:	Scr	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HCO3	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Endocrine	TSH	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	Weight	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	AFP	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Virology	HIV vi	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HBV vi	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HBeAg	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HBeAb	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HBsAg	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
	HBsAb	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=	X=
Medications (dose/frequency)													
	Pegylated IFN-α 2a												
	erythropoietin												
	darbopoetin												
	folate												
	G-CSF												