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Dear Provider,

Management of patients co-infected with HIV and hepatitis C (HCV) remains a challenge for providers seeking to stem the tide of morbidity and mortality caused by liver disease. It is estimated that HIV infection is present in about 30% of HCV-infected individuals, representing approximately 300,000 individuals nationwide. More research into the treatment and management of HIV/HCV co-infection is urgently needed since co-infection is associated with higher HCV RNA levels and more rapid progression to cirrhosis, decompensated liver disease, hepatocellular carcinoma and death^[1]. Indeed, the success of HAART (highly active antiretroviral therapy) in the treatment of HIV has allowed HCV to emerge as the most significant cause of morbidity and mortality in HIV/HCV co-infected patients.

Who are the co-infected?

HCV can be transmitted through a variety of parenteral routes, but most patients with HIV/HCV co-infection have a history of illicit injection drug use (IDUs). Although a challenging population to manage, recent experience has demonstrated the feasibility and effectiveness of treating HCV in people who use illicit injection drugs. This is important from a public health perspective because IDUs comprise the largest group of hepatitis patients in the US, and successful management may reduce

transmission. Consequently, healthcare providers must know if a patient has a history of or is currently using alcohol or illicit drugs. These issues should therefore be part of every intake history and should be addressed as part of routine primary care. A good discussion tool to facilitate the screening and diagnosis of alcoholism and substance abuse is in the recently published (2003) *Clinical Guide to Supportive and Palliative Care for HIV/AIDS*, Chapter 11^[2].

What makes treatment in this population challenging?

Sometimes the perceived intransigence of active substance abusers can put a barrier between patient and provider. Can an active IDU or alcoholic be trusted to adhere to HIV therapies or complete difficult HCV treatment regimens? In order to give patients the best opportunity for successful treatment, active substance abuse must be addressed before beginning HIV or HCV therapy. The NIH Consensus Statement (Management of Hepatitis C: 2002) cautioned that candidates should not be active intravenous drug or alcohol users, and that enrollment into alcohol and drug treatment programs should be encouraged strongly. Also, HIV-positive patients can do well on HIV treatment, but it is important to be aware of drug-drug interactions. Patients on methadone programs are good candidates for HCV treatment, but it has also been successful even when the patients have not been abstinent from continued drug use or on methadone^[3]. This is important because it dispels the somewhat common belief that active users cannot follow a treatment plan. Although few data are available in HCV treatment in active IDUs who are not in drug treatment programs, it is known that progression to a new AIDS-defining clinical event or to death was independently associated with HCV seropositivity (hazard ratio 1.7 [95% CI 1.26-2.30]), and with active intravenous drug use (1.38 [1.02-1.88])^[4].

Alcohol is an important co-factor in the progression of HCV liver disease to cirrhosis and HCC, but a history of alcohol abuse is not an absolute contraindication to HIV or HCV therapy. However, continued alcohol use during therapy adversely affects response to treatment and there are drug-drug interactions to consider. For example, it is recommended that didanosine (ddI), a nucleoside reverse transcriptase inhibitor (NRTI) used in some HIV treatment regimens, should not be used by active HIV/HCV co-infected alcohol drinkers, since risk of pancreatitis seems to rise with higher doses of ddI and more advanced HIV disease.

Since the main barriers to treatment in this population are missed clinic visits, active psychiatric illness, drug and alcohol use, liver disease or other medical illnesses, it is very important to link IDUs and alcoholics to drug treatment programs and case management, and for providers to collaborate on some level with these service providers when possible. And as mentioned above, to do this effectively, providers must implement preliminary screening and diagnostic processes. Providing easy access to 12-Step meetings by obtaining 12-Step meeting schedules (for locales within 30 miles of your practice) and making them available to patients is an often helpful first step.

HCV Testing

Key diagnostic tests in patient management include serologic testing, qualitative/quantitative HCV-RNA testing, HCV genotyping, and in most cases, liver biopsy. The gold standard for assessing the stage of fibrosis remains the liver biopsy, which may not be

available or readily accepted by the patient. Nevertheless, the level or "stage" of liver fibrosis is important when deciding whether to initiate or modify treatment for HCV, as is determining genotype. Predicting liver fibrosis using non-invasive biochem-

ical markers and liver ultrasound can be used to provide information about the possible stage of liver fibrosis when biopsy is not appropriate or possible^[6].

It should also be noted that HCV infection may not always be detected by standard HCV antibody testing. In one recent, prospective study, whole blood testing for hepatitis C virus (HCV) RNA in HIV-infected, HCV antibody-negative patients yielded an inci-

dence of 20%. The patients with HCV antibodies also had higher ALT values than the antibody-negative patients ($p=0.002$)^[7]. Consequently, it is sensible to consider HCV infection in HIV-positive persons who test negative for HCV antibody, especially those with elevations in liver-associated enzymes, and the use of quantitative PCR testing is recommended in these cases.

Factors in HIV and HCV treatment sequencing

Historically, HIV treatment was always the first priority. With so many now dying of liver disease rather than AIDS-related illness, those priorities are being reassessed. In a study presented at the 53rd AASLD, it was shown that the estimated time from HCV infection to established cirrhosis in HIV/HCV co-infected patients was 20 years compared to 32 years in HCV mono-infected persons. The rate of HCV progression in 6 patients who had paired liver biopsies was 0.29 fibrosis unit/year, with an estimated time to cirrhosis of 13.8 years. In addition, co-infected patients had significantly higher inflammatory grade ($p=0.006$) despite lower alcohol consumption. HIV/HCV co-infected patients therefore appear to have a more rapid rate of fibrosis

progression and higher inflammatory grades compared to HCV mono-infected patients. Interestingly, an ALT > 80 emerged as an independent marker for more aggressive disease in this patient cohort^[8].

HIV/HCV co-infected patients show a significantly higher HCV load, more-advanced fibrosis, and a higher liver fibrosis progression rate (FPR) than do non-HIV-infected patients. A high HCV viral load and a low CD4+ T-Cell count are also associated with a higher FPR. The immune response induced by treating HIV with HAART does not appear to influence this progression. The accelerated progression of liver fibrosis and cirrhosis support a more aggressive approach to the treatment of HCV infection in these patients.

HIV treatment in HCV-positive patients

HAART-induced hepatotoxicity is common in patients co-infected with HCV. CD4 values below 250 and higher ALT at baseline are associated with hepatotoxicity^[9]. Hepatotoxicity, which is defined as a 3–5 times increase in serum transaminases (e.g., aspartate aminotransferase, alanine aminotransferase) with or without clinical hepatitis, has been reported among patients receiving HAART. Increased risk for hepatotoxicity has been reported in some studies with the use of ritonavir, stavudine, and nevirapine. However, ritonavir has also been associated with improved outcomes. All marketed nonnucleosides (NNRTIs) and protease inhibitors (PIs) have been associated with serum transaminase elevation. The majority of patients are asymptomatic, and certain cases resolve spontaneously without therapy interruption or modification^[10]. Hepatic steatosis in the presence of lactic acidosis is a rare but serious adverse effect associated with NRTIs. The most offending NRTIs are those with the most inhibitory interaction with DNA polymerase gamma, specifically the “d” drugs ddC, ddI, and d4T. Patients might experience nonspecific gastrointestinal and flu-like symptoms with or without liver enzyme abnormalities. The syndrome can progress rapidly to hepatomegaly, jaundice, and hepatic failure within days^[11]. Results from an ongoing trial in 868 HIV/HCV co-infected patients, APRICOT, that compares the potential benefits of adding anti-HCV combination therapy to HIV HAART are eagerly anticipated for 2003. Until more evidence is available, it is safe to conclude that treatment of HCV may need to take precedence over HIV in these patients, and during HCV therapy, avoiding the more hepatotoxic HIV agents may be prudent.

NNRTIs: Because of the potential severity of clinical hepatitis, certain clinicians advise close monitoring of liver enzymes and clinical symptoms if initiating HIV

treatment including the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (e.g., every 2 weeks for the first month; then monthly for first 12 weeks, and every 1–3 months thereafter). A two-week lead-in dosing with 200mg once daily before dose escalation to twice daily might reduce the incidence of hepatotoxicity.

Protease Inhibitors: Unlike the early onset hepatotoxicity observed with nevirapine, protease inhibitor-associated liver enzyme abnormalities can occur any time during the treatment course, but may be less prevalent with the use of nelfinavir^[12]. HAART-induced immune reconstitution rather than direct liver toxic effects of the PIs have been implicated as the cause of liver decompensation among hepatitis C or hepatitis B co-infected patients. Other potential risk factors for hepatotoxicity include hepatitis B infection, alcohol abuse, baseline elevated liver enzymes, stavudine use^[13], and concomitant use of other hepatotoxic agents.

Recently, the FDA Adverse Event Reporting System was searched for reports of any adverse events associated with concomitant use of ribavirin (RBV), an NRTI used in combination with interferon in the treatment of HCV, and didanosine (ddI), an NRTI used in HIV, or any other NRTI, and the results were presented at the 10th Conference on Retroviruses and Opportunistic Infections (10th CROI). In the data set examined, concomitant use of ddI and RBV appeared to be associated with an approximately 5-fold increased likelihood of events suggestive of mitochondrial toxicity (MT) compared to use of RBV with other NRTIs^[14]. In response to cumulative data, the FDA required the manufacturer to add black box warnings to labels for its ddI products (Videx®/VidexEC®). Consequently, RBV and ddI should not be co-administered, and selection of other NRTIs should be considered.

HCV treatment in HIV-positive patients

It has been suggested by experts in the field that consideration be given to treating (and thus potentially eradicating) HCV before initiating HAART to reduce the hepatotoxic effects patients are likely to experience when taking HAART and because HCV can be eradicated in many patients (unlike HIV). Some suggested criteria for treating HCV in HIV-positive patients:

CRITERIA	GOAL
CD4+ cell counts > 200 cells/mm ³ regardless of HIV viral load or serum transaminase levels	Eradicate HCV
CD4+ cell counts of 100-200 cells/mm ³ , HIV viral loads below 10,000 copies/mL, and any elevation in transaminase level	Limit liver disease progression and perhaps eradicate HCV
Compensated cirrhosis with any elevation in transaminase level and CD4+ cell count	Limit or reverse fibrosis and prevent decompensation
Recurrent antiretroviral-related hepatotoxicity	Increase tolerability of HAART

Torriani F. , 1st IAS Conference on HIV Pathogenesis and Treatment; July 8-11, 2001; Buenos Aires, Argentina. Abstract 40.

But modifying these broad treatment recommendations, a new study suggests many patients co-infected with HIV and HCV have barriers to overcome before HCV treatment is possible. Any attempts to overcome these will involve earlier evaluation by specialized multidisciplinary teams. Successful treatment of HCV in this population involves overcoming these barriers^[15]. Once again, this emphasizes the importance of linking IDUs and alcoholics to drug treatment programs and case management, and of provider collaboration on some level with such providers when possible.

Standard of care (HCV)

The previous standard was a six-month course of standard interferon administered subcutaneously three times weekly with oral ribavirin twice daily, but pegylated interferon has a longer half-life than standard interferon, allowing once-weekly administration. Two preparations are FDA approved: interferon alpha-2a (*Pegasys*[®], Hoffman-LaRoche) and interferon alpha-2b (*PegIntron*[®], Schering-Plough) and duration of treatment is 24-48 weeks based on genotype. These products differ from nonpegylated interferon in certain pharmacologic properties. In non-HIV-infected populations, pegylated interferon has been shown to provide a higher response rate and better tolerance than nonpegylated interferon. In HIV-positive patients, pegylated interferon therapies are also found to be superior to standard interferon and are the current standard of care, although HIV/HCV co-infected patients have lower response rates than HCV mono-infected patients, and patients with HCV genotypes 1 and 4, have lower response rates than those of genotype 2-3. According to the package inserts for the pegylated interferon plus ribavirin combos, in patients with genotype 1 virus (the most common in the US and the most difficult to treat), the difference in sustained responses were in a similar range, 41% (*Peg-Intron*[®] + *Rebetol*[®]) to 44% (*Pegasys*[®] + *Copegus*[™]), respectively. The dosing of the approved ribavirin products (*Rebetol*[®], *Copegus*[™]) are also determined by genotype (800mg-1200mg range) and may be reduced in response to toxicity^[9]. The weight of the patient may also influence dose selection in that heavier patients may need dosing in the higher range.

Recently, results from a multi-center, randomized, open-label study comparing daily vs three-times weekly interferon alpha-2b plus ribavirin (RBV) for the treatment of

hepatitis C infection in HIV-infected persons were presented. The study's objective was to assess the efficacy and safety of RBV with daily (QD) or three times weekly (TIW) IFN for chronic HCV in HIV-infected patients. Patient characteristics and discontinuation for adverse events (AEs) across both groups (QD/TIW) were similar, and a total of 162 (79 QD/83 TIW) were eligible for the intent-to-treat (ITT) analysis. Even though adverse event rates were similar in both groups, more patients taking QD IFN completed 48 weeks of treatment (30.0% QD vs 12.0% TIW, $p = 0.0003$), since 43.4% of patients taking TIW IFN stopped due to virologic failure compared to only 20.2% of those taking QD IFN ($p = 0.0003$).

HCV RNA response (undetectable < 600 IU/mL) was assessed at week 12, early virologic response (EVR), and week 24 post-treatment (sustained virologic response/SVR). On-treatment results: EVR QD 44.3%/TIW 17.1% ($p = 0.004$); SVR: QD 42.9%/TIW 28.8% ($p = 0.03$). Intention to treat results: EVR: QD 32.9%/TIW 13.3%; SVR: QD 9.3%/TIW 4.3% (note: missing data = failure). No significant effect was seen on HIV RNA levels; absolute CD4 fell in both groups (QD > TIW), but no decrease in CD4% was observed. EVR was a strong predictor of SVR (90.9% sensitivity, NPV 93.9%). Both EVR and SVR were significantly greater in HIV-infected patients taking QD IFN/RBV than in those taking TIW IFN/RBV. However, the attrition rate for both arms was substantial, and the intention-to-treat SVR rates observed were low^[16]. So while response to HCV treatment in HIV-positive patients may be higher with daily injections of standard INF, this option might best be saved for when other more convenient options have failed.

12-week plan

In HCV mono-infected patients, the treatment response at 12 weeks or early virological response predicts which patients will not benefit from continued therapy with pegylated interferon/ribavirin. **A reduction in HCV RNA > 2 logs at 12 weeks predicts a benefit of continued therapy.** In a current study, investigators evaluated 89 HIV/HCV co-infected patients who completed a course of anti-HCV therapy. Pegylated interferon was adminis-

tered to 63 and standard interferon to the remaining patients, all at standard doses. All received ribavirin 400 mg twice daily. Overall, sustained virological response (SVR) occurred in 29 patients. End-of-treatment response with further relapse was seen in 15. The remaining 45 were non-responders. A drop in HCV RNA > 2 logs occurred in 38 (43%) and 52 (58%) of patients at 4 and 12 weeks, respectively. Of those subjects, only 18

(48%) and 29 (56%), respectively, reached SVR. In contrast, SVR occurred in 11 (38%) and 0 patients who did not show a > 2 log drop in HCV RNA at weeks 4 and 12, respectively. *Thus the negative predictive value (NPV) was 100% at week 12.* There were no significant differences between HCV genotypes, baseline HCV RNA and use of either pegylated or regular interferon.

In patients with HCV genotype 2-3, a high rate of relapse in early responders was noted, which suggests

that extending treatment beyond six months might have provided a higher SVR rate for them. The investigators concluded that the use of an early time decision point at 12 weeks to identify which subjects will not benefit from continuing anti-HCV treatment is valid for HIV-positive patients. However, a delayed clearance of HCV RNA in early responders with HIV might account for a higher relapse rate when treatment is stopped prematurely -e.g., six months in genotypes 2-3^[17].

In conclusion

If we are to answer the challenges presented to us by HIV/HCV co-infection, it is recommended that providers:

- **Develop relationships with case managers at drug treatment centers and AIDS Service Organizations (ASOs) to help those who are more vulnerable but less easy to treat than many patient groups**
- **Discover clinical relevance of HCV treatment in HIV-positive patients and apply standards of care in a team setting**
- **Continue to monitor emerging research**
- **Be careful in the selection and monitoring of patients on potentially hepatotoxic HIV treatment, avoiding those that are most toxic when other choices are available, and monitoring closely when other options are not viable**

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