HIV/Viral Hepatitis Coinfection: The Immunology Center Experience

Lynn E. Taylor, MD

Chronic hepatitis C virus (HCV) infection is a significant public health concern among HIV-infected populations and a leading cause of morbidity and mortality in the **highly active antiretroviral therapy (HAART)** era.[1] Due to shared transmission routes, HIV/HCV coinfection impacts 30% of HIV-infected persons in the US and 4-5 million worldwide.[2,3] HIV accelerates HCV disease course, with more rapid progression to cirrhosis, liver failure and **hepatocellular carcinoma (HCC)** in coinfection. While coinfected individuals face greater risk of HAART-related hepatotoxicity than HIV-monoinfected persons, liver disease progression is slower in patients receiving HAART, and benefits outweigh risk. Early HAART introduction is recommended to reduce the rate of progression of hepatic disease.[4]

Anti-viral HCV medications offer the potential for viral eradication, termed **Sustained Virologic Response (SVR,** undetectable serum HCV RNA six months post-treatment). SVR can lead to regression of fibrosis; limit progression to cirrhosis, end-stage liver disease and HCC; and reduce liver-related mortality.[5,6] Based on results of five randomized clinical trials, therapy with pegylated interferon (pegIFN) plus **weight-based ribavirin (RBV)** is deemed effective for coinfected patients, although SVR rates are 10-15% lower than in HCV-monoinfection, and twelve month treatment duration irrespective of HCV genotype is typically indicated.[6,7] Therapy for coinfected patients is considered safe with close monitoring, although adverse events are more common and severe than in HCV-monoinfection. National and international guidelines endorse considering all coinfected patients for pegIFN/RBV.[8,9] Implementation of these guidelines is limited. Low treatment eligibility rates are due primarily to concomitant drug use and psychiatric illness, a common comorbidity.[10,11] Coinfection is distinguished by many social and medical needs, stigma and system-level problems with access. Referral of HIV-infected patients to off-site subspecialty HCV care yields low treatment rates (1-4%), while integrated care improves access and health outcomes.[12, 16]

Worldwide, 10% of HIV-infected persons are coinfected with chronic **hepatitis B virus (HBV)**. [17] HIV hastens HBV disease course, accelerating fibrosis progression, and increasing risk of HCC and liver-related death in HIV/HBV coinfection. The advent of well-tolerated, potent antiviral agents with a high barrier to resistance is beginning to mitigate these effects.

One-third of Immunology Center patients are coinfected with chronic HCV...

Miriam Hospital Immunology Center HIV/Viral Hepatitis Coinfection Clinic

Established in 2001, the Coinfection Clinic is an integral part of the Immunology Center.

All patients are screened for HCV, HBV and **hepatitis A virus (HAV)** upon their initial Immunology Center visit, with annual HCV antibody testing for antibody-negative patients thereafter. One-third of Immunology Center patients are coinfected with chronic HCV, and 3% with chronic HBV. Immunology Center physicians refer HCV-infected patients to Coinfection Clinic, and HBV-infected patients on an as-needed basis. Referrals are welcomed from outside physicians and come from Rhode Island, Massachusetts and Connecticut. Clinic is held weekly in the same suite where patients receive HIV and primary care. Forty patients have been seen monthly since the Clinic's inception. A coinfection physician and nurse staff the Clinic, with rotating Brown University gastroenterology and infectious disease fellows, residents and medical students.

Goals of the Coinfection Clinic include: patient education; evaluation of disease stage and other etiologies of liver disease; determining sequencing of HIV and HCV therapy; HAV/HBV vaccination if susceptible; HCV treatment; evaluation and treatment of drug dependence, psychiatric disease and other potential relative contraindications that may hinder successful HCV therapy; consultation to optimize HBV care; HCC screening; and care of cirrhosis. Approximately 30% of co-infected patients have cirrhosis, and as our cohort ages, HCC rates are rising. Many patients undergo subcutaneous liver biopsy, performed by Miriam Hospital interventional radiologists, to gauge the extent of fibrosis. If HCV therapy is deferred, biopsy is repeated in three years.[18] In a prospective study of coinfected patients in Baltimore, a population similar to our own, almost 30% of patients with minimal scarring at first biopsy had a substantial increase in fibrosis three years later.[20] Normal ALT levels do not guide decisions about biopsy or treatment because ALT does not reliably indicate the extent of fibrosis in coinfection. Steatosis, which may advance fibrosis and diminish SVR rates, may be exacerbated by didanosine and stavudine;[19] these medications are now contraindicated in coinfected patients.

To deliver HCV therapy to patients with active drug use and/or psychiatric illness, weekly visits for directly administered pegIFN injections are offered to optimize safety, tolerability, adherence and thus efficacy—and minimize treatment discontinuations—through aggressive management of adverse events. Phlebotomy is coordinated with nursing visits and a peer-based support group. Consideration for pegIFN/RBV is based on review of all assessments in accordance with current standards. However, our goal is to move beyond conventional criteria for treatment of patients with drug dependence and psychiatric illness. Whether an

individual wants and is able to follow through with evaluation is a more important consideration than whether drug use or psychiatric symptoms or history exist. There are no exclusion criteria based on addiction or psychiatric diagnoses.[20] We address addiction as a chronic, relapsing disease to be treated along with HIV and HCV. We prescribe a wide range of medications to stabilize psychiatric symptoms prior to HCV therapy, as well as buprenorphine, an opioid agonist/antagonist approved for office-based treatment of opiate dependence. A community-based organization, Family Service of RI, provides coordinated psychiatric care, counseling and case management for a subset of patients. For patients with pre-existing relationships with a psychiatrist, methadone program, therapist or case manager, a team including these providers is assembled. For others, we facilitate new linkages to needed services. Patients who are unstable for HCV therapy or who are homeless may reside at Sunrise House assisted living to undergo treatment, in collaboration with AIDS Care Ocean State.

To date 85 patients have undergone HCV therapy in the Immunology Center. Many report current drug use at initial visit. Approximately 75% have a history of non-substance-based psychiatric diagnosis, including major depression, anxiety, post-traumatic stress disorder, schizophrenia, bipolar disease and personality disorders. Overall, SVR rate is 24%. Thus three-quarters of treated patients remain HCV-viremic and may progress to end-stage liver disease. Only one coinfected patient has received a liver transplant via the Immunology Center, although several are currently wait-listed for transplantation.

Emerging Epidemic of Acute HCV (AHCV)

Recent reports demonstrate an alarming rise in AHCV (the initial 6-month period of newly acquired HCV infection, defined by HCV viremia, ALT rise and HCV antibody seroconversion), among HIV-seropositive men who have sex with men in association with traumatic sexual practices and sexually transmitted infections in the absence of IDU.[21-24] AHCV natural history is especially aggressive if acquired after HIV infection, while early treatment results in SVR rates of up to 91% with condensed therapy course.[25, 26] Diagnosis of AHCV is rare because most individuals are asymptomatic, or symptoms are mild and non-specific, yet diagnosis provides an opportunity for preventive intervention and effective treatment. Evaluating patients with unexplained ALT elevations for AHCV also establishes that hepatotoxicity is not caused by medications and prevents unwarranted HAART interruptions.[27] At Coinfection Clinic we routinely identify and treat AHCV. Patients with a negative HCV antibody and unexplained ALT elevation are tested for serum HCV RNA.[28]

ALT does not reliably indicate the extent of fibrosis in coinfection

Future Directions

Newer anti-HBV agents may lessen the burden of liver disease for HIV/HBV coinfected individuals, while HBV vaccine provides hope for stemming pandemic HBV. While individual viral kinetics and on-treatment virologic responses permit tailored HCV therapy to improve outcomes for coinfected patients, treatment initiation and SVR rates remain low, and the global HIV/HCV coinfection epidemic continues to grow. The most promising drugs in development, HCV protein-specific inhibitors, are intended to supplement RBV; non-IFN-based therapies will not be available in the near future.[29] Currently early phase trials of novel medications exclude HIV-seropositive persons. Their inclusion is a critical next step, along with lifting the federal ban on funding for needle exchange to help curtail new HCV infections.

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Lynn E. Taylor, MD, is Assistant Professor of Medicine, The Warren Alpert Medical School of Brown University.

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Correspondence

Lynn E. Taylor, MD
The Miriam Hospital
153 Summit Ave.
Providence, RI 02906
Phone: (401) 793-4705
e-mail: LTaylor@lifespan.org