

Medical Writers' Circle

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a series of articles
written by medical
professionals about
the management
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hepatitis C

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HIV-HCV Coinfection Update

Background

Human Immunodeficiency Virus (HIV) and chronic hepatitis C virus (HCV) coinfection is a growing public health concern, with an estimated 4-5 million persons coinfecting worldwide.¹ In the United States, of the approximately one million people living with HIV/AIDS (PLWHA), 30% are also infected with HCV. What has ignited and sustained this dual epidemic is the shared routes of viral transmission, primarily injection drug use with contaminated injection equipment.²⁻⁴ As many as 90% of PLWHA who inject drugs or have injected drugs are coinfecting with HCV.⁵ Parenteral transmission of both infections also has occurred via transfusion of contaminated blood and blood products.

In the late 1990s, with the introduction of potent medication combinations against HIV (highly active antiretroviral therapy, HAART) and improved prophylaxis and treatments for opportunistic infections, death rates due to AIDS declined dramatically. PLWHA started to live

much longer. Other medical problems emerged, namely liver disease due to chronic HCV. This is because HIV affects the natural course of HCV by accelerating the rate of fibrosis (scarring) progression. Coinfected persons may develop cirrhosis (full scarring of the liver) and end-stage liver disease (signs that the scarred liver is leading to damage to other parts of the body) more quickly than individuals infected with only HCV,^{6,7} especially when CD4 cell counts are lower than 200/ μ L and alcohol is consumed.⁸ As a result, liver disease due to chronic HCV has become a leading cause of death and illness amongst PLWHA with well-controlled HIV.^{9,10} It is therefore important to acknowledge coinfection as a condition distinct from either HCV or HIV infection alone (mono-infection).

Diagnosis

According to the National Institutes of Health (NIH) and the American Association for the Study of Liver Diseases (AASLD), all PLWHA should be screened for HCV with the most sensitive blood test

available for HCV antibodies. Positive results should be confirmed by testing for the HCV virus itself with a test for HCV RNA by PCR (polymerase chain reaction). HIV-seropositive persons can have a negative HCV antibody but still be infected with HCV (false negative test). Therefore, a person with a negative HCV antibody who has elevated ALT (alanine aminotransferase, a blood liver enzyme that indicates liver cell function), unexplained liver disease, risk factors for HCV, or CD4 cell count less than <200/ μ L should undergo testing for the HCV virus itself with HCV RNA.

There is controversy regarding the role of liver biopsy in HIV-HCV coinfection. Many experts recommend a liver biopsy if it can be obtained to determine the stage of liver disease (amount of scarring) to help guide whether or not to initiate HCV treatment at a particular time and rule out other causes of liver disease. However, liver biopsy is not a perfect test. It is associated with risks, can give inaccurate results, and is not

always accessible. Additionally, many other types of liver disease can be diagnosed through less invasive means. Thus, lack of a liver biopsy should not prevent treatment. Some experts agree that if a person has a high likelihood of achieving a sustained virologic response

with minimal scarring at their first biopsy had a substantial increase in fibrosis three years later.¹¹ Some experts thus now recommend that a biopsy be repeated in two to three years in the setting of HIV. It is important to note that ALT levels in the blood do not always reliably indicate

cations) due to HIV therapies may take the HCV medications to calm down their livers and allow reintroduction of vital HIV medications. After all, suppressing HIV and elevating CD4 cell counts to provide a stronger immune system is the foundation for caring for HCV.

tion, particularly in patients with genotype 1 and a high baseline HCV RNA.¹⁴⁻¹⁷ Even when SVR does not occur, fibrosis in the liver can improve or stabilize. Data from these studies showed that adherence to pegylated interferon and ribavirin is critical to successful therapy; coinfecting individuals need to take at least 80% of their ribavirin and 80% of their pegylated interferon doses for at least 80% of the course of therapy in order to get the maximum benefit. Pegylated interferon alpha 2a and ribavirin were approved in March 2005 for treatment of chronic HCV in HIV-HCV coinfecting individuals.

The APRICOT trial has provided important data regarding EVR (early virologic response, at least 2-log decline from baseline of HCV RNA or undetectable levels at week 12). The negative predictive value (NPV) at week 12 was the best predictor of non-response, which means that participants who did not achieve an EVR at week 12 were much less likely to achieve SVR with continued treatment. In the ACTG study, of those participants who did not have an EVR, none went on to have a SVR (NPV, 100%). When EVR is not achieved on HCV-monoinfecting patients, treatment is often discontinued.²² The lack of EVR in the setting of HIV should not be considered an absolute reason to stop treatment but instead an op-

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(SVR, absence of HCV in the blood six months after treatment) and/or if she/he is a candidate for pegylated interferon/ribavirin therapy, that she/he should receive HCV treatment without a liver biopsy. Furthermore, if coinfecting patients show signs of cirrhosis clinically or by radiologic imaging, a liver biopsy is not necessary. What about coinfecting individuals who do get a liver biopsy and decide to defer HCV therapy because the biopsy shows none or minimal scarring? When should a repeat biopsy be performed? For people with HCV alone, the standard is to repeat a biopsy in three to five years. However, recent data from Mark Sulkowski, MD, suggest that waiting three to five years may not be advisable for coinfecting persons. In his study, almost 30% of the sixty-one coinfecting persons

the extent of liver disease in HIV-HCV coinfecting individuals. Therefore, ALT should not be used to guide decisions on biopsy or treatment.¹²

Evaluation and Treatment

Every HIV-HCV coinfecting person with compensated chronic HCV (which means no history of ascites/fluid in the belly, encephalopathy/toxins in the bloodstream due to the liver's inability to filter, or variceal bleeding/bleeding from swollen veins around the liver) should be considered for HCV antiviral therapy.¹³ The goals of treating HCV in HIV-seropositive persons are to eliminate the virus and to stabilize, improve or decrease the progression of liver disease to cirrhosis (which may lead to liver cancer). Some people with hepatotoxicity (liver inflammation caused by medi-

The good news is that recent studies have explored the potential benefits and adverse consequences of different HCV treatment plans for coinfecting persons. As a result, there is more data available now about the use of pegylated interferon and ribavirin combination therapy in HIV-HCV coinfection. Four studies published in 2004 indicated that the optimal first-line treatment for chronic HCV in HIV-seropositive individuals never before treated for HCV is pegylated interferon plus ribavirin. Overall, SVR rates were 26-44%; higher SVRs were achieved in participants with genotypes 2 and 3 (43-73%), indicating that a substantial proportion of coinfecting individuals can achieve virologic response. However, overall treatment responses were lower than previously reported in the HCV-monoinfecting popula-

portunity to contemplate the benefits and disadvantages of discontinuing therapy. Continuation might be more important if scarring is more advanced, for example. APRICOT demonstrated that the positive predictive value was highest at week 4 for all genotypes. This means that if a study participant achieved a virologic response at 4 weeks then she/he was most likely to achieve SVR. Information from these early time points can help an individual decide to continue or stop treatment before a year.

As most HIV-HCV coinfecting persons in the U.S. have genotype 1 infection and high HCV viral loads, investigators are considering strategies to boost treatment efficacy. The best dose of ribavirin and optimal length of treatment are not yet established. Most large studies have used lower doses (e.g. 800 mg daily) of ribavirin rather than the weight-based higher doses used in the HCV-monoinfection (participants did not have HIV) trials due to concerns about side effects, especially anemia (a drop in red blood cells, cells that carry oxygen). In the recent PRESCO trial, the impact of higher ribavirin doses and a longer duration of therapy with pegylated interferon and ribavirin was evaluated in a multi-center, prospective study across 25 HIV clinics in Spain. Although almost half of study participants (46%) stopped treatment early, 49%

achieved SVR in an intent-to-treat analysis. No significant differences in SVR were observed when comparing short and extended treatment arms. The investigators therefore concluded that the use of higher ribavirin doses rather than extended duration of ribavirin therapy seems to account for the high SVRs.¹⁸ There were many differences in the abovementioned studies, so it is difficult to compare them side-by-side. Participants' baseline characteristics varied, different brands of interferon were used, and the doses of ribavirin were different. It is also important to note that patients who had major depression, active drug use, autoimmune disease or a CD4 count < 100/uL were not included.¹⁹ Future studies therefore need to explore HCV treatment for coinfecting people with these common conditions. The present understanding based on care of people with HCV alone is that many individuals contending with drug addiction and/or mental health problems can be treated for HCV with multidisciplinary care and appropriate supports.

In terms of CD4 cell counts, there have been questions about treating individuals with lower counts. In the APRICOT study, investigators analyzed a subset of 17 patients who had CD4 counts < 200/uL. The study showed that low baseline CD4 counts had no impact on outcome in the context of SVR.²⁰ Although

the number of participants in this subset was too small to make strong conclusions, pegylated interferon alpha 2a was approved for persons with CD4 cell counts as low as 100 with well-controlled HIV virus. This is not to suggest that a person with advanced AIDS should be treated with medications for HCV. However, HCV medications do not need to be withheld for individuals with HIV who, despite being on optimal HAART, have lower CD4 counts and advanced liver fibrosis.

Current Recommendations

There are many sets of practice guidelines available regarding HIV-HCV coinfection. The AASLD, NIH, Centers for Disease Control (CDC) and the Veterans' Administration (VA) have established these guidelines to help ensure proper screening, diagnosis, and treatment. Each person with both HIV and HCV should be evaluated to determine the extent of liver disease, whether she/he needs treatment for HCV, and whether it is safe to treat at a particular time. The only contraindication to HCV medications specific to HIV-seropositive persons is an active opportunistic infection. Liver enzymes should be monitored after starting HIV medications. Individuals should be screened for hepatitis A and B and given vaccines for these liver viruses if they are susceptible.

Counseling and education is an important part of care to reduce transmission to others and diminish further liver damage. All coinfecting individuals should be advised to avoid alcohol since it is known to worsen liver disease. Alcohol also can have a negative influence on treatment response.²¹ Condom use is recommended to prevent both hepatitis virus and HIV transmission. Of recent concern are reports of outbreaks of acute (new) HCV among HIV-positive men who have sex with men, likely due to unprotected anal sex, potentially facilitated by co-occurring sexually transmitted infections.

The regimen of choice for the initial treatment of HCV in HIV-positive persons is pegylated interferon in combination with ribavirin for 48 weeks irrespective of genotype. Treating an individual for HCV at a given time depends on three main factors: 1) weighing the relative stages of HIV and HCV; 2) determining whether there are contraindications to therapy (health issues that make HCV medications unsafe); and 3) defining the primary objective of treating HCV for that individual. Deciding whether to start treatment first for HIV or HCV is done on a case-by-case basis. Controlling HIV infection should be given top priority. If the individual has advanced liver disease, then HCV should be treated first.

Treatment for both conditions should not be initiated at the same time because if side effects develop it will be difficult to determine which medication was responsible. If a coinfecting individual does not need HAART or if the HIV is well controlled with HAART, then she/he may take pegylated IFN with ribavirin on top of HIV medications. There are many contraindications

Special Considerations

A few studies have shown a higher rate of treatment discontinuation in people with both HIV and HCV. This may be due to an increased susceptibility to developing certain adverse effects of antiviral therapy, such as cytopenias (lowering of blood cells, including red cells, white cells and platelets).

lactic acidosis and serious complications.²³ In addition, zidovudine (AZT/Retrovir) can increase the risk of anemia in combination with HCV medications, primarily due to the fact that AZT can cause anemia on top of a ribavirin-induced anemia. Substitution of AZT may be considered; alternatives include lowering the ribavirin dose or adding erythropoietin (red blood cell growth factor), which may

starting weights are higher, so people may not get down to dangerously low weights. Most people gain back any weight they lose once therapy is over. A recent study led by Barbara McGovern, MD, showed that steatosis (fatty liver) is associated with the severity of liver disease, may play a role in fibrosis progression in HIV-positive persons, and may be due in part to certain HIV medicines including ddI and stavudine (Zerit, d4T).²⁷

It is crucial that future research focus on strategies to safely treat coinfecting persons with co-existing mental health and addiction problems.



to pegylated interferon/ribavirin, including uncontrolled seizures, serious heart disease, pregnancy and autoimmune disease. Since a substantial proportion of coinfecting persons may not achieve SVR, the objective of HCV therapy can also include slowing down disease progression. For example, a person with genotype 2, a low blood level of HCV and mild scarring has a higher potential for SVR than a person with genotype 1, an elevated blood level of HCV and cirrhosis, and could be treated with the goal of SVR. The person with cirrhosis would more realistically be treated with the goal of reducing the progression of liver disease.

Another contributing factor is the inexperience of health care providers. Sometimes liver specialists do not know enough about HIV, and HIV doctors do not know enough about HCV. To remedy this, we need broader collaboration between specialists, and/or more doctors with specific coinfection expertise. This can lead to better management of adverse effects. The side effects are predictable and can be promptly and aggressively treated to permit treatment completion.

Before starting treatment for HCV, coinfecting patients need to have their HAART regimen reviewed. Didanosine (ddI/Videx) should not be used with ribavirin because of the increased risk of

improve adherence and quality of life.²⁴

A small study performed on HIV-HCV co-infected individuals receiving pegylated interferon and ribavirin therapy for at least 3 months showed that some of the coinfecting individuals developed ophthalmic complications (eye disease). The researchers attributed these adverse effects to the use of pegylated interferon and suggest close monitoring to prevent ophthalmic disease.²⁵ Another study of coinfecting individuals in Europe showed severe weight loss in those being treated with pegylated interferon and ribavirin therapy.²⁶ This may be less of a problem in the U.S. where even among people with HIV the

Future Directions

Over the last few years much progress has been made in understanding HIV-HCV coinfection. However, an enormous need for further research remains. Studies are in progress to evaluate new agents (potential medications) to target the HCV virus. As the population of coinfecting individuals ages, there will be a greater prevalence of advanced liver disease over time.

Barriers to treating HCV in HIV-HCV coinfecting individuals are plentiful and have been identified in recent studies. In one study, only 2 of the 300 coinfecting individuals were treated for HCV.²⁸ Drug dependence is among the main reasons that coinfecting persons are not being treated for HCV infection. This does not need to be the case and makes little sense given that the reservoir of HCV infection in the U.S. is among persons who inject

drugs. If we want to have an impact on the HCV epidemic, we must extend delivery of care to this population. An increasing body of literature demonstrates that drug-involved persons may be successfully treated for HCV with appropriate supports.²⁹⁻³⁰ At our Ryan White –Funded HIV clinic for example, we deliver HCV care to coinfecting persons contending with substance use using multidisciplinary care, adherence assistance and peer support.³¹⁻³² The 2002 NIH Consensus Statement on the management of HCV states that active drug use in itself is not a contraindication to HCV treatment.³³ According to the AASLD, patients with ongoing drug use should be considered for treatment with continued support from addiction care programs.¹³ Mental health disorders can present another barrier to HCV therapy for coinfecting individuals. Patients need to be carefully screened and treated for depression, bipolar disease and other psychiatric diagnoses and symptoms since interferon can worsen psychiatric symptoms such as depression and anxiety and even induce these symptoms in persons who have not experienced these problems before. Patients should be monitored closely for the development of psychiatric events and treated promptly. It is crucial that future research focus on strategies to safely treat coinfecting persons with co-existing mental health and

addiction problems.

Finally, prevention efforts are vital to stem the overlapping epidemics of HIV, HCV and opioid addiction, and to limit the burden of liver disease among PLWHA. These include expanded access to: HCV and HIV testing and care; sterile syringes via needle exchange programs and over-the-counter syringe sales; substance abuse treatment such as the recently approved buprenorphine; and integrated, cross-disciplinary HIV, HCV and addiction care. This can only occur with additional resources. It is a public health imperative to prevent further HIV-HCV coinfection and to expand access to high quality HCV care for PLWHA.



References

1. Tossing G. Management of chronic hepatitis C in HIV-coinfecting patients – results from the First International Workshop on HIV and Hepatitis Co-Infection, December 2-4, 2004, Amsterdam, Netherlands. *Eur J Med Res.* 2005;10(1):43-5.
2. Sherman KE, Rouster SD, Chung RT, et al. Hepatitis C virus prevalence among patients infected with human immunodeficiency virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *CID.* 2002;34:831-7.

3. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected person. *Ann Intern Med.* 2003;138(3):197-207.
4. Thomas DL. Hepatitis C and human immunodeficiency virus infection. *Hepatology.* 2002;36(5 suppl 1):S201-9.
5. Verruchi G, Calza L, Manfredi R, et al. Human immunodeficiency virus and hepatitis c virus coinfection: Epidemiology, natural history, therapeutic options and clinical management. *Infection.* 2004; 33: 33-46.
6. Martin-Carbonero L, Benhamou Y, Puoti M, et al. Incidence and predictors of severe liver fibrosis in human immunodeficiency virus-infected patients with chronic hepatitis C: a European collaborative study. *Clin Infect Dis.* 2004;38:128-33.
7. Ragni MV, Belle SH. Impact of human immunodeficiency virus infection on progression to end-stage liver disease in individuals with hemophilia and hepatitis C virus infection. *J Infect Dis.* 2001;183:1112-5.
8. 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.* 1999;30(4):1054-1058.
9. Bica I, McGovern B, Dhar R, et al. Increasing mortality due to end-stage liver disease in patients with human immunodeficiency virus infection. *CID* 2001;32:492-497.
10. Monga HK, Rodriguez-Barradas MC, Breaux K, et al. Hepatitis c virus infection-related morbidity and mortality among patients with human immunodeficiency virus infection. *CID.* 2001;22:240-247.

11. Sulkowski M, Mehta S, Torbenson M, et al. Unexpected significant liver disease among HIV/HCV-coinfecting persons with minimal fibrosis on initial liver biopsy. Program and abstracts of the 12th Conference on Retrovirus and Opportunistic Infections; February 22-25, 2005; Boston, Massachusetts. Abstract 121.
12. Clinical Consensus Update in Infectious Disease: The Complex Clinical Challenges Presented by Patients with HIV-HCV Coinfection. Editor in Chief Gideon Bosker, MD. Pharmatecure, LLC. May 1, 2006.
13. Strader DB, Wright T, Thomas DL, Seeff LB. American Association for the Study of Liver Diseases. Diagnosis, Management, and Treatment of Hepatitis C. *Hepatology* 2004;39:1147-1171.
14. Torriani FJ, Roriguez-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* 2004;351; 438-450.
15. Chung RT, Anderson J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon for chronic hepatitis C in HIV-coinfecting persons *N Engl J Med* 2004;351: 451-459.
16. Carrat F, Bani-Sadr F, Pol S, et al. Pegylated interferon alpha-2b vs standard interferon alpha-2b plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial
17. Laguno M, Murillas J, Blanco JL, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for treatment of HIV-HCV co-infected patients. *Acquir*

Immune Defic Syndr 2004; 18: F27-F36.

18. Nunez M, Maida I, Berden MA, et al. Efficacy and safety of pegylated interferon alfa2a plus ribavirin for the treatment of hepatitis C in the HIV-infected patient: the PRESCO trial. Presented at the 44th Interscience Conference on Antimicrobial Agents and Chemotherapy 2004; Washington, D.C. Abstract V-1148

19. Arends JE, Boucher CA, Hoepelman AI. Hepatitis c virus and human immunodeficiency virus coinfection: where do we stand? *Neth J Med.* 2005; 63(5): 156-63.

20. Opravil M, Sasadeusz J, Cooper D, et al. Effect of baseline CD4 count on efficacy and safety of pegylated interferon-alfa-2a (PEGASYS) plus ribavirin in HIV? HCV co-infection: the AIDS PEGASYS ribavirin international co-infection trial (APRICOT). Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005; Boston, Massachusetts. Abstract 926.

21. Fishbein DA, Lo Y, Netski D, et al. Predictors of Hepatitis C Virus RNA Levels in a Prospective Cohort Study of Drug Users. *J Acquir Immune Defic Syndr* 2006; 41:471

22. Thomas DL. Options for treatment of hepatitis C in HIV-infected persons. *J Hepatol* 2006; 44 Suppl 1:S40.

23. Kakuda TN, Brinkman K. Mitochondrial toxic effects and ribavirin. *Lancet* 2001; 357: 1802-1803.

24. Sulkowski MS, Dieterich DT, Bini, EJ, et al. Epoetin Alfa once weekly improves anemia in

HIV/hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial. *J Acquir Immune Defic Syndr* 2005; 39:504.

25. Farel C, Suzman DL, McLaughlin M, et al. Serious ophthalmic pathology compromising vision in HIV-HCV co-infected patients treated with peginterferon alpha-2b and ribavirin. *AIDS.* 2004 Sep 3; 18 (13): 1805-9.

26. Perez-Olmeda M, Nunez M, Romero M, et al. Pegylated IFN-alpha 2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS* May 2; 17 (7): 1023-28.

27. McGovern BH, Ditelberg JS, Taylor LE, et al. Hepatic steatosis is associated with fibrosis, nucleoside analogue use, and hepatitis C virus genotype 3 infection in HIV-seropositive patients. *Clin Infect Dis* 2006; 43(3):373-376.

28. Fultz SL, Butt AA, Rabeneck L, et al. Testing, referral, and treatment patterns for hepatitis C virus coinfection in a cohort of veterans with human immunodeficiency virus infection. *Clin Infect Dis.* 2003;36(8):1039-46.

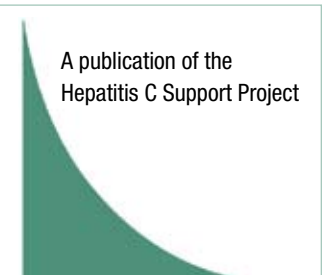
29. Sylvestre, D. Hepatitis C treatment in drug users: perception versus evidence. *Eur J Gastroenterol Hepatol.* 2006 Feb;18(2):129-30.

30. Sylvestre D. Approaching treatment for hepatitis C virus infection in substance users. *Clin Infect Dis.* 2005 Jul 1;41 Suppl 1:S79-82.

31. Taylor LE . Delivering care to injection drug users coinfecting with HIV and Hepatitis C virus. *CID* 15:40 Suppl 5: S346-8, 2005.

32. Taylor LE , Gholam PM, Schwartzapfel B, et al. Hepatitis C Treatment in an HIV/HCV Coinfected Patient with Drug Addiction and Psychiatric Illness: A Case Report. *The AIDS Reader.* Nov; 5(11):629-31, 2005.

33. NIH Consensus Statement on Management of Hepatitis C: 2002. NIH Consensus State Sci Statements. 2002 Jun 10-12;19(3):1-46.



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