

Viral Hepatitis Screening in HIV and Aging

- Due to frequent overlap of risk factors for HIV and viral hepatitis, all HIV-seropositive individuals should be screened for hepatitis A, hepatitis B, and hepatitis C upon entry into care.
- Older age may be a risk factor for liver disease progression and complications in those individuals who are coinfecting with HIV and viral hepatitis.
- HIV-infected persons who are non-immune to hepatitis A should receive vaccination.
- HIV-infected persons who are non-immune to hepatitis B should receive vaccination with a recheck of the hepatitis B surface antibody following the vaccine series to assess for immunologic response.
- Persons with HIV who have ongoing risk for hepatitis C infection should undergo repeat screening at least annually; more frequent screening is indicated if risk is significant, such as ongoing injection drug use or diagnosis of a sexually transmitted infection (STI).
- Individuals with risk for hepatitis C and elevated transaminases should be screened for hepatitis C with both an antibody and an RNA (viral load) test, given the possibility of seronegative hepatitis C infection.
- HIV infection accelerates the progression of liver disease in those who are coinfecting with viral hepatitis; counseling about avoidance of alcohol is paramount because alcohol also hastens the progression to end-stage liver disease and liver-related complications.
- Screening for hepatocellular carcinoma in those with chronic HBV and HCV is discussed in the section on cancers. (See Cancer in HIV and Aging Section)

Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV) Rates and Clinical Course Among U.S. HIV-Seropositive Individuals

The rate of HBV and HCV among HIV-infected individuals in the United States and other Western countries is up as much as tenfold higher than that among HIV-uninfected individuals [1, 2].

A prevalence study of active and occult HBV infection in a geographically representative HIV-infected U.S. population identified chronic HBV infection in 7.1% of the cohort overall and 10% of those with isolated HBV core antibody positivity [3]. By comparison, occult HBV infection has been reported in 0.1–2.4% of HIV-uninfected blood donors with isolated HBV core antibody

positivity in Western countries [4]; the rate is increased more than twofold in those with chronic HCV [5].

In a representative cohort of HIV-infected individuals from two large clinical studies of the U.S. Adult AIDS Clinical Trials Group, the overall estimate of HCV prevalence was 16.1%, with significant variability based on risk factors and HIV RNA levels [1]. In that study, among patients defined as “at risk” (e.g., parenteral exposure) a staggering 72.7% were HCV seropositive, whereas among low-risk individuals, the seropositivity rate was only 3.5%.

In some cohorts, as many as 85% of HIV-infected individuals with high-risk behaviors like injection drug use are coinfecting with HCV [6]. Given the frequent overlap of HIV and viral hepatitis, baseline screening and repeat testing for those with ongoing risk are critical.

Clinical Course Among HIV-Infected Individuals

Hepatitis B and hepatitis C infections generally have a more virulent course in HIV-infected individuals as compared to that in HIV-uninfected individuals. These infections affect HIV disease progression and/or response to antiretroviral therapy (ART), while HIV infection appears to alter the clinical course of these chronic infections negatively, causing accelerated progression of liver disease and more frequent complications.

Hepatitis B

While most HIV-uninfected individuals spontaneously clear HBV infection, and most with chronic HBV do not progress to hepatic complications, the risk of developing chronic HBV infection, HBV-associated end-stage liver disease, and mortality are increased in the setting of HIV coinfection [2, 7, 8].

In the Multicenter AIDS Cohort Study (MACS) cohort, an eightfold increased risk of liver-related mortality was seen among HBV-HIV coinfecting, compared with HIV-monoinfected individuals [9]. HBV-HIV coinfection also increases the risk of progression to chronic HBV infection and reduces the rate of spontaneous HBsAg and HBeAg seroconversion [10]. Hepatocellular carcinoma (HCC) may develop at a younger age and be more aggressive in HBV-HIV coinfecting individuals [11]. The availability of anti-HBV medications has improved these poor outcomes to some degree.

Hepatitis C

Some reports suggest that HCV infection has an effect on HIV disease. These studies indicate that increased HCV RNA levels are associated with clinical progression to AIDS [12], that HCV seropositivity is associated with progression to a new AIDS-defining illness or death [13], and that HCV seropositivity is associated with reduced

CD4 cell recovery during antiretroviral therapy [14].

With respect to HCV infection, HIV coinfection has been associated with faster progression to liver fibrosis and cirrhosis [15-17], higher rates of morbidity and mortality [18, 19], more rapid progression to HCC, and more aggressive HCC [11]. Traditionally, HIV infection has correlated with poorer response to HCV treatment [20, 21]; however, in the era of directly acting antiviral (DAA) therapy for HCV infection, rates of sustained virologic response (SVR) in HIV-infected individuals approach those of HIV-uninfected individuals, and HIV infection is no longer a marker for low cure rates with HCV therapy [22].

Hepatitis in the Elderly HIV-Infected Population

Older individuals coinfecting with HIV and hepatitis B or C may be at higher risk for liver-related complications than younger coinfecting individuals.

Older age is a predictor of liver-related complications in HIV-infected individuals. In the D:A:D Study, predictors of liver-related deaths included latest CD4 cell count, *older age*, intravenous drug use, HCV infection, active HBV infection, HIV RNA level, and ART duration [23].

In addition, age greater than 50 years has been associated with increased rates of hospitalization for liver-related disease among HIV-infected individuals, compared with younger HIV-seropositive individuals [24]. Among those with HIV-HCV coinfection, an individual's age at time of HCV-infection is independently associated with higher liver fibrosis progression rates [17].

Current Recommendations on Viral Hepatitis Screening for HIV-Seropositive Patients

Hepatitis B

The Infectious Disease Society of America (IDSA) HIV primary care guidelines recommend that:

- (i) HIV-infected patients should be screened for evidence of HBV infection upon initiation of care by detection of hepatitis B surface antigen (HBsAg), antibody to hepatitis B surface antigen (HBsAb) and antibody to hepatitis B total core antigen (HBcAb or anti-HBc);
- (ii) those who are susceptible to infection should be vaccinated against HBV; and
- (iii) sexual partners of persons who are positive for HBsAg should also be offered vaccination [25].

Some clinicians wait to vaccinate for hepatitis B until the patient is on antiretroviral therapy with a suppressed HIV RNA and improved CD4 count given data for higher response rates to the vaccine [26, 27].

Hepatitis B surface antibody (HBsAb) should be repeated one to two months after the third dose of vaccine to assess for immunogenic response, and those without an adequate response should be considered for a repeat series of vaccination [25]. Some data suggest benefit from using double-dose vaccine, and some clinicians use double-dose for either initial vaccine series or for repeat vaccine series in those who did not respond to a series with the standard dose [28-30].

Isolated hepatitis B core antibody positivity (positive anti-HBc antibody, negative HBsAg and negative HBsAb) is a common clinical scenario among HIV-infected individuals. Possible reasons for this pattern of results include:

- (i) remote past infection with subsequent loss of HbsAb;
- (ii) occult hepatitis B infection with loss or low level of HbsAg; or
- (iii) a false-positive anti-HBc antibody result.

Most guidelines agree that individuals with isolated HBV core antibody positivity should be vaccinated for hepatitis B, because of low rates of anamnestic response and data that these individuals remain susceptible to infection.

Some guidelines suggest that those patients who are negative for HBsAg and antibody to HBsAg but positive for hepatitis B total core antigen antibody should be screened for chronic occult HBV infection by determination of HBV load by HBV DNA PCR [25]. Certainly in the setting of isolated HBcAb positivity clinicians should have a low threshold to screen for occult hepatitis B infection, especially if there are specific risk factors or if transaminitis is present.

Hepatitis C

In terms of HCV screening for the general population, the Centers for Disease Control and Prevention (CDC) recommends routine testing for HCV in patients at increased risk for infection. Of note, this now includes so called “baby boomer” screening, or testing for HCV in all individuals born between 1945 and 1965.

The United States Preventive Services Task Force (USPSTF) has come out in agreement about routine testing for this cohort of individuals because of higher rates of seropositivity. Additional at-risk groups who should be screened for HCV include:

- (i) those who have injected illicit drugs in the past (even once);
- (ii) those with conditions associated with a high prevalence of HCV, including HIV infection, hemophilia, receipt of clotting products before 1987, persons who were ever on hemodialysis, and those with unexplained abnormal aminotransferase levels;
- (iii) prior recipients of transfusions or organ transplants (before July

1992), including those who were notified that they received blood from a donor who later tested positive for HCV infection, those who received a transfusion of blood/blood products, those who received an organ transplant; (iv) children born to HCV-infected mothers; (iv) healthcare, emergency and public safety workers after a needle stick injury or mucosal exposure to HCV-positive blood; and (v) current sexual partners of HCV-infected persons [31].

For initial screening in HIV-infected individuals, guidelines agree that all should be screened at entry into care [25, 32]. The Infectious Disease Society of America (IDSA) HIV primary care guidelines recommend that:

- (i) HIV-infected patients should be screened for HCV infection upon initiation of care by a test for HCV antibody
- (ii) positive HCV antibody test results should be confirmed by measurement of HCV RNA levels by PCR and
- (iii) infants born to HCV-positive women should be tested for HCV transmission [25].

For repeat HCV screening among HIV-infected individuals, guidelines suggest that those who remain at risk should undergo repeat screening at least yearly. European guidelines, however, suggest that those individuals with ongoing injection drug use or those diagnosed with a sexually transmitted infection (STI) should be screened three months after last use or diagnosis, respectively [32].

Furthermore, because around 6% of HIV-infected individuals may have seronegative HCV infection (chronic infection with detectable HCV RNA but negative HCV antibody), all those with risk factors and elevated transaminases

should be screened with HCV RNA (viral load) testing in conjunction with HCV antibody testing [25].

The European guidelines also suggest that, in addition to yearly antibody testing, all HIV-infected MSM be screened with liver function panel every six months[32]. In addition, some have suggested that all HIV-infected men who have sex with men (MSM) and who have unexplained elevated transaminase values should be evaluated for acute HCV infection. This recommendation is based on the increasing detection of sexually transmitted acute HCV infection in HIV-infected MSM, particularly in association with concurrent sexually transmitted diseases [33, 34].

Patients with HBV and/or HCV should receive HAV vaccination unless they have documented immunity (and patients with HCV should also receive HBV vaccination, if susceptible). All persons with chronic viral hepatitis should be instructed on the importance of avoiding alcohol and of limiting acetaminophen use.

References

1. Sherman KE, Rouster SD, Chung RT, Rajicic N. Hepatitis C Virus prevalence among patients infected with Human Immunodeficiency Virus: a cross-sectional analysis of the US adult AIDS Clinical Trials Group. *Clin Infect Dis* 2002,**34**:831-837.
2. Soriano V, Puoti M, Peters M, Benhamou Y, Sulkowski M, Zoulim F, et al. Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel. *AIDS* 2008,**22**:1399-1410.
3. Shire NJ, Rouster SD, Rajicic N, Sherman KE. Occult hepatitis B in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004,**36**:869-875.
4. Hollinger FB. Hepatitis B virus infection and transfusion medicine: science and the occult. *Transfusion* 2008,**48**:1001-1026.
5. Cacciola I, Pollicino T, Squadrito G, Cerenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. *N Engl J Med* 1999,**341**:22-26.
6. Sulkowski MS, Thomas DL. Hepatitis C in the HIV-infected patient. *Clin Liver Dis* 2003,**7**:179-194.
7. Konopnicki D, Mocroft A, de Wit S, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005,**19**:593-601.
8. Puoti M, Airoldi M, Bruno R, Zanini B, Spinetti A, Pezzoli C, et al. Hepatitis B virus co-infection in human immunodeficiency virus-infected subjects. *AIDS Rev* 2002,**4**:27-35.
9. Thio CL, Seaberg EC, Skolasky R, Jr., Phair J, Visscher B, Munoz A, et al. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet* 2002,**360**:1921-1926.
10. Hadler SC, Judson FN, O'Malley PM, Altman NL, Penley K, Buchbinder S, et al. Outcome of hepatitis B virus infection in homosexual men and its relation to prior human immunodeficiency virus infection. *J Infect Dis* 1991,**163**:454-459.
11. Brau N, Fox RK, Xiao P, Marks K, Naqvi Z, Taylor LE, et al. Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a U.S.-Canadian multicenter study. *J Hepatol* 2007,**47**:527-537.
12. Daar ES, Lynn H, Donfield S, Gomperts E, O'Brien SJ, Hilgartner MW, et al. Hepatitis C virus load is associated with human immunodeficiency virus type 1 disease progression in hemophiliacs. *J Infect Dis* 2001,**183**:589-595.
13. Greub G, Ledergerber B, Battegay M, Grob P, Perrin L, Furrer H, et al. Clinical progression, survival, and immune recovery during antiretroviral therapy in patients with HIV-1 and hepatitis C virus coinfection: the Swiss HIV Cohort Study. *Lancet* 2000,**356**:1800-1805.
14. Macias J, Pineda JA, Lozano F, Corzo JE, Ramos A, Leon E, et al. Impaired recovery of CD4+ cell counts following highly active antiretroviral therapy in drug-naive patients coinfecting with human immunodeficiency virus and hepatitis C virus. *Eur J Clin Microbiol Infect Dis* 2003,**22**:675-680.
15. Martinez-Sierra C, Arizcorreta A, Diaz F, Roldan R, Martin-Herrera L, Perez-Guzman E, et al. Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfecting with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2003,**36**:491-498.
16. Soto B, Sanchez-Quijano A, Rodrigo L, del Olmo JA, Garcia-Bengoechea M, Hernandez-Quero J, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* 1997,**26**:1-5.
17. Benhamou Y, Bochet M, Di Martino V, Charlotte F, Azria F, Coutellier A, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfecting patients. The Multivirc Group. *Hepatology* 1999,**30**:1054-1058.
18. Bica I, McGovern B, Rakesh D, Stone D, McGowan K, Scheib R, et al. Increasing Mortality Due to End-Stage Liver Disease in Patients with Human Immunodeficiency Virus Infection. *Clinical Infectious Diseases* 2001,**32**:492-497.
19. Tedaldi EM, Baker RK, Moorman AC, Alzola CF, Furhrer J, McCabe RE, et al. Influence of coinfection with hepatitis C virus on morbidity and mortality due to human immunodeficiency virus infection in

- the era of highly active antiretroviral therapy. *Clin Infect Dis* 2003,**36**:363-367.
20. Chung RT, Andersen J, Volberding P, Robbins GK, Liu T, Sherman KE, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004,**351**:451-459.
 21. Perez-Olmeda M, Nunez M, Romero M, Gonzalez J, Castro A, Arribas JR, et al. Pegylated IFN-alpha2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS* 2003,**17**:1023-1028.
 22. Sulkowski MS. Interferon-containing and interferon-free HCV therapy for HIV-infected patients. *Semin Liver Dis* 2014,**34**:72-78.
 23. Weber R, Sabin CA, Friis-Moller N, Reiss P, El-Sadr WM, Kirk O, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Arch Intern Med* 2006,**166**:1632-1641.
 24. Gebo KA, Fleishman JA, Moore RD. Hospitalizations for metabolic conditions, opportunistic infections, and injection drug use among HIV patients: trends between 1996 and 2000 in 12 states. *J Acquir Immune Defic Syndr* 2005,**40**:609-616.
 25. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA, et al. Primary care guidelines for the management of persons infected with HIV: 2013 update by the HIV medicine association of the Infectious Diseases Society of America. *Clin Infect Dis* 2014,**58**:e1-34.
 26. Landrum ML, Huppler Hullsiek K, Ganesan A, Weintrob AC, Crum-Cianflone NF, Barthel RV, et al. Hepatitis B vaccine responses in a large U.S. military cohort of HIV-infected individuals: another benefit of HAART in those with preserved CD4 count. *Vaccine* 2009,**27**:4731-4738.
 27. O'Bryan T, Rini E, Okulicz J, Messner O, Ganesan A, Lalani T, et al. HIV viraemia during hepatitis B vaccination shortens the duration of protective antibody levels. *HIV Med* 2015.
 28. Chaiklang K, Wipasa J, Chaiwarith R, Preparattananan J, Supparatpinyo K. Comparison of immunogenicity and safety of four doses and four double doses vs. standard doses of hepatitis B vaccination in HIV-infected adults: a randomized, controlled trial. *PLoS One* 2013,**8**:e80409.
 29. Launay O, van der Vliet D, Rosenberg AR, Michel ML, Piroth L, Rey D, et al. Safety and immunogenicity of 4 intramuscular double doses and 4 intradermal low doses vs standard hepatitis B vaccine regimen in adults with HIV-1: a randomized controlled trial. *JAMA* 2011,**305**:1432-1440.
 30. Potsch DV, Camacho LA, Tuboi S, Villar LM, Miguel JC, Ginuino C, et al. Vaccination against hepatitis B with 4-double doses increases response rates and antibodies titers in HIV-infected adults. *Vaccine* 2012,**30**:5973-5977.
 31. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology* 2009,**49**:1335-1374.
 32. European ATNAHCICP. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. *AIDS* 2011,**25**:399-409.
 33. Luetkemeyer A, Hare CB, Stansell J, Tien PC, Charlesbois E, Lum P, et al. Clinical presentation and course of acute hepatitis C infection in HIV-infected patients. *J Acquir Immune Defic Syndr* 2006,**41**:31-36.
 34. Browne R, Asboe D, Gilleece Y, Atkins M, Mandalia S, Gazzard B, et al. Increased numbers of acute hepatitis C infections in HIV positive homosexual men; is sexual transmission feeding the increase? *Sex Transm Infect* 2004,**80**:326-327.