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Review

Viral hepatitis and HIV coinfection☆

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Persons at high risk for human immunodeficiency virus (HIV) infection are also likely to be at risk for other infectious pathogens, including hepatitis B virus (HBV) or hepatitis C virus (HCV). These are bloodborne pathogens transmitted through similar routes; for example, via injection drug use (IDU), sexual contact, or from mother to child during pregnancy or birth. In some settings, the prevalence of coinfection with HBV and/or HCV is high. In the context of effective antiretroviral therapy (ART), liver disease has emerged as a major cause of morbidity and mortality in HIV-infected persons. Further, coinfection with viral hepatitis may complicate the delivery of ART by increasing the risk of drug-related hepatoxicity and impacting the selection of specific agents (e.g., those dually active against HIV and HBV). Expert guidelines developed in the United States and Europe recommend screening of all HIV-infected persons for infection with HCV and HBV and appropriate management of those found to be chronically infected. Treatment strategies for HBV infection include the use of nucleos(t)ide analogues with or without anti-HIV activity and/or peginterferon alfa (PegIFN) whereas HCV treatment is limited to the combination of PegIFN and ribavirin (RBV). Current approaches to management of HIV-infected persons coinfected with HBV or HCV are discussed in this review.

***Keywords*: HIV; HCV; HBV; Liver**

1. Introduction

Persons at high risk for human immunodeficiency virus (HIV) infection are also likely to be at risk for other infectious pathogens, including hepatitis B virus (HBV) or hepatitis C virus (HCV). These are bloodborne pathogens transmitted through similar routes; for example, via injection drug use (IDU), sexual contact, or from mother to child during pregnancy or birth [1]. In some settings, the prevalence of coinfection with HBV and/or HCV is high [2,3]. In the context of effective antiretroviral therapy (ART), liver disease has emerged as a major cause of morbidity and mortality in HIV-infected persons [4–6]. Further, coinfection with viral hepatitis may complicate the delivery of ART by increasing the risk of drug-related hepatoxicity and impacting the selection of specific agents (e.g., those dually active against HIV and HBV) [7]. Expert guidelines developed in the United States and Europe recommend screening of all HIV-infected persons for infection with HCV and HBV and appropriate management of those found to be chronically infected [8–11]. Treatment strategies for HBV infection include the use of nucleos(t)ide analogues with or without anti-HIV activity and/or peginterferon alfa (PegIFN) whereas HCV treatment is limited to the combination of PegIFN and ribavirin (RBV). Current approaches to management of HIIV-infected persons coinfected with HBV or HCV are discussed in this review.

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2. Hepatitis C virus infection

2.1. Epidemiology and natural history

HCV and HIV have similar modes of transmission but the transmission efficiency of each virus differs. HCV is most efficiently spread through exposure to contaminated blood or blood products, particularly injection drug use (IDU). Rates of vertical and perinatal transmission are relatively low (3–6%), although increased ~2-fold when the mother is HIV-infected [12,13]. Sexual transmission of HCV is inefficient and the exact risk related to different types of sexual activity is unknown. However, there is increasing evidence of sexually transmitted HCV in HIV-infected men who have sex with men (MSM). For example, in one cohort, the incidence of HCV infection among HIV seropositive MSMs increased 10-fold after 2000 [14]. Sexually acquired HCV infection has been associated with sexually transmitted diseases and traumatic anal receptive intercourse [15]. Based on the relative efficiency of transmission, the prevalence of HCV coinfection varies depending on the route of HIV transmission, ranging from 10% to 14% among persons reporting high-risk sexual exposure to approximately 85–90% among those reporting IDU [16]. In the United States and Europe, ~33% of all HIV-infected persons are HCV infected [2,17,18].

HIV infection exacerbates the natural history of HCV infection [19–22]. HIV-infected patients are less likely to clear hepatitis C viremia following acute infection, have higher HCV RNA loads, and experience more rapid progression of HCV-related liver disease than those without HIV infection [23]. As early as 1993, Eyster and colleagues reported that HCV RNA levels were higher in people with hemophilia who became HIV infected than in those who remained HIV negative, and liver failure occurred exclusively in coinfected patients [19]. Among HCV-positive patients with hemophilia who were prospectively monitored, Goedert and colleagues estimated the 16-year cumulative incidence of end-stage liver disease (ESLD) among men with and without HIV to be 14.0% and 2.6%, respectively [24]. Among those men with coinfection, the ESLD risk increased 8.1-fold with HBV surface antigenemia, 2.1-fold with CD4 cell counts below 200 cells/mm^3, and 1.04-fold per additional year of age. Finally, the effect of HIV on HCV was summarized in a meta-analysis of multiple studies that assessed the correlation between HIV coinfection and the progression of HCV-related liver disease [6]. HIV coinfection was associated with a relative risk of ESLD of 6.14 and a relative risk of cirrhosis of 2.07 when compared with HCV monoinfection (Fig. 1).

Studies on the effect of ART on the natural history of chronic HCV disease have been contradictory [25–28].

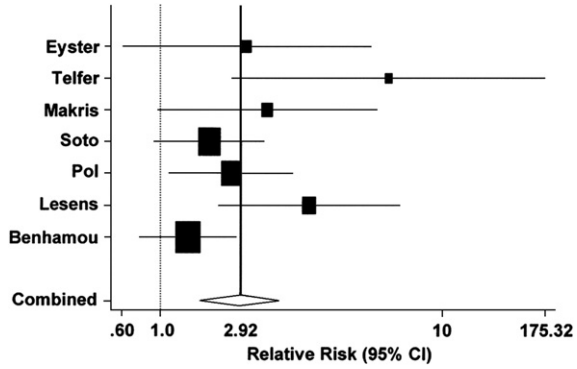

Fig. 1. Adjusted relative risk of decompensated liver disease or histological cirrhosis in patients with HIV/HCV coinfection compared with patients who have HCV infection alone (adapted from meta-analysis published by Graham and colleagues) [6].

Qurishi et al. reported a lower risk of liver mortality in persons who lived long enough to receive effective ART [29]. However, several prospective studies have not detected a beneficial effect of ART on HCV disease [4,30,31]. In other studies, ART has been associated with hepatic injury (e.g., hepatocellular necrosis and steatosis) [7,32,33]. Indeed, in a cohort of 23,441 HIV-infected patients, Weber et al. observed an increased risk of liver-related mortality with longer ART exposure [4]. Additional research is needed to determine the long-term effect of ART on HCV disease progression.

Nonetheless, as a consequence of the high HCV prevalence and accelerated disease progression, HCV-related morbidity and mortality is substantial in HIV-infected persons. In one study, Gebo and coworkers evaluated rates of admission at an urban hospital from 1995 to 2000 among HIV-infected patients and found that admissions for liver-related complications among HCV-positive patients increased nearly 5-fold from 5.4 to 26.7 admissions per 100 person-years during that time [5]. Similarly, among 23,441 HIV-infected North American and European patients followed in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, liver disease was the second leading cause of death, with an incidence of 0.23 cases per 100 person-years follow-up behind HIV/AIDS (0.59 cases per 100 person-years) and ahead of cardiovascular disease (0.14 cases per 100 person-years) (Fig. 2) [4]. These data suggest that HCV-related liver disease will continue to be a major cause of hospital admissions and deaths among HIV-infected persons.

The effect of HCV infection on HIV disease progression is less clear. Some studies report impaired immune reconstitution in patients with HIV/HCV co-infection treated with ART compared to those with HIV alone [34]; however, this effect has not been observed in other studies [2,35] and is not likely to be clinically relevant [36]. Patients with underlying viral hepatitis are more likely to experience hepatotoxicity on ART [37]. How-