Opinions

Antiretroviral Therapies for Human Immunodeficiency Virus and Liver Disease: Challenges and opportunities

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SUMMARY

The post antiretroviral therapy (ART) era for human immunodeficiency virus (HIV) infection resulted in a dramatically increased proportion of deaths attributed to liver-related causes in patients with HIV treated with ART. Additionally, as patients become older as a result of effective ART, liver-related conditions and application of safe therapies are now major concerns in the setting of HIV infection.

1. Introduction

Human immunodeficiency virus (HIV)-related liver disease has become one of the most common causes of mortality in patients infected with HIV. In addition to the role of the liver in HIV clearance from blood, it may concentrate infectious virus, and it is accepted that HIV itself induces liver disease [1]. Major comorbidities, including coinfections with hepatotropic viruses as well as antiretroviral therapy (ART), drive liver disease progression. Moreover, nonalcoholic fatty liver disease (NAFLD) is highly prevalent in individuals infected with HIV, and ART seems to play a role in NAFLD pathogenesis that in turn may progress to nonalcoholic steatohepatitis (NASH). Therefore, the design of therapeutic strategies to reduce HIV-mediated liver disease could ultimately prevent the development of end-stage liver damage.

2. HIV and the liver

During infection, HIV induces hepatocyte apoptosis and infects Kupffer cells; these cells are responsible for clearing translocated products. This explains why viral infection affects the gut microbiome, promoting microbial translocation and ultimately accelerating chronic inflammation. In addition, the function of activated hepatic stellate cells, the main source of collagen in the liver, is dysregulated by the modification of the hepatic cytokine profile as a result of CD4+ T cell depletion. This allows for an exacerbated proinflammatory environment and collagen overproduction by hepatic stellate cells, resulting in liver inflammation and fibrosis. Moreover, studies *in vitro* and *ex vivo* have demonstrated that hepatocytes play a role as both viral reservoirs and a source of infective viral particles [2,3]. This strongly suggests that the liver constitutes a replication organ for HIV. Globally, it is accepted that liver disease in patients infected with HIV can be induced by a dysregulation of immune function, by a direct effect of the virus on lipogenesis or by metabolic dysfunction related to the infection. Additionally, long-term ART plays a major role in liver injury during infection [4,5].

3. ART and liver function

More than 60% of the prescribed drugs are cleared in the liver, and hepatic injury is the most frequent cause of drug discontinuation in clinical trials. Thus, it is not surprising that all ART drugs have some risk of hepatotoxicity, which varies depending on the specific characteristics of the drugs.

During HIV infection, in addition to viral reverse transcriptase inhibition, nucleoside reverse transcriptase inhibitors (NRTIs) can also inhibit the enzyme responsible for the replication of mitochondrial DNA; this can induce a defective liver fatty acid oxidation and the production of lactates, and these conditions may lead to

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liver injury [6]. Additionally, it has been proposed that autophagy inhibition due to NRTIs increases apoptosis, intracellular lipid accumulation and reactive oxygen species (ROS) production, and decreases proliferation [7]. Thus, it is accepted that NRTI-related liver disease resembles steatohepatitis. Given that most patients with HIV are commonly exposed to more than one NRTI, the role of specific drugs in the development of liver steatosis has often been difficult to determine. Zalcitabine, didanosine, stavudine and zidovudine dideoxynucleosides are more likely to inhibit mitochondrial DNA synthesis. On the other hand, a biopsy study of patients infected with HIV and coinfected with HCV suggests that the use of efavirenz might be associated with an increased risk of progressive liver steatosis [8]. This is in agreement with one study of patients infected with HIV with NAFLD who were switched from an efavirenz treatment to a treatment containing raltegravir (an ART that has a safe metabolic profile and does not induce mitochondrial toxicity) that revealed a subsequent decrease in the degree of hepatic steatosis in comparison with patients continuing an efavirenz treatment [9]. Finally, metabolic abnormalities, including fat accumulation, dyslipidemia, hyperglycemia, and insulin resistance, are frequently observed in patients receiving protease inhibitors (PIs). Consequently, the occurrence of liver steatosis among patients infected with HIV may also be attributable to these abnormalities. In general, it is accepted that although new PIs have little impact on lipid levels, they still have a less favorable lipid profile than integrase inhibitors [10]. Thus, considerable attention should be paid to the hepatotoxic properties of preexisting and newly designed ART.

4. HIV: ART and comorbidities in liver disease

Coinfection with HCV or HBV in patients with HIV is common. Of the 170 million people chronically infected with HCV, 4-5 million individuals are coinfected with HIV worldwide, and approximately 10% of people infected with HIV are also chronically infected with HBV. Overall, patients with HIV/HCV or HIV/HBV coinfection have a higher risk of developing accelerated fibrosis progression, cirrhosis and increased decompensated cirrhosis compared with those who are HCV or HBV monoinfected.

In general, opposite effects of ART in mitigating or worsening liver disease in coinfection have been reported. Although ART does not directly inhibit HCV replication, a reduction in the progression of liver disease by HIV replication inhibition in the setting of HIV/HCV coinfection has been reported. Furthermore, given that ART enhances HCV-specific T cell responses, it results in a decrease in HCV RNA levels, and liver-related mortality and hepatic decompensation have been reported to be reduced in ART-treated patients who are HIV positive with chronic viral hepatitis. Moreover, numerous authors accept that the progression to fibrosis in patients with HIV/HCV coinfection is reduced by ART. In HIV/HBV coinfection, early initiation of ART is recommended. The therapy used for coinfection includes adefovir tenofovir, emtricitabine, entecavir and lamivudine. As described for HIV/HCV, reports provide evidence of the benefits of ART on virologic and clinical outcomes in HIV/HBV coinfection. However, other authors reported that liver fibrosis decreases only in a small number of patients with HIV/HBV coinfection during the tenofovir disoproxil fumarate therapy. Additionally, it has been reported that acute and long-term ART-associated hepatotoxicity occurs more frequently in individuals with HIV/HCV coinfection [4]. Thus, the vigilance of the effect of distinct ARTs on liver disease, should be taken into consideration in the setting of HIV/HCV or HIV/HBV coinfection.

On the other hand, the burden of NAFLD in patients with HIV infection is poorly characterized and has varied over time in a manner that reflects the various eras of HIV treatment. In the pre-ART era, it was 85%, but at the beginning of the ART era, it was reduced to 60%. Despite the move away from the most hepatotoxic agents in the modern ART era, the prevalence of NAFLD among patients with HIV remains high, with a prevalence varying between 28% and 48% [11]. This is agreement with reports suggesting that the control of HIV replication by ART plays an indirect role in the development of liver steatosis in patients with HIV monoinfection. Taking into account that the epidemiology of NAFLD/NASH has been increasing in recent years, larger cross-sectional studies on the basis of the role of ART regulating NAFLD in patients with HIV are needed.

5. Remarks

Early detection of liver disease during HIV infection is key to allow for improved outcomes. Research is needed to identify safe and effective treatments in the setting of HIV/HCV and HIV/HBV coinfection, and screening for fatty liver should become standard of care in ART-treated patients with HIV. Further studies to uncover the common and unique mechanisms of liver disease during HIV infection with and without ART should be conducted. Likewise, a better understanding of the virus-host interactions leading to liver disease will allow us to open avenues for the advancement of the design of new ART.

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