Human Immunodeficiency Virus Infection, Antiretroviral Therapy, and Liver Pathology

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KEYWORDS

• HIV • Drug-induced liver injury • Coinfections • Obesity
• Low/high-income countries

KEY POINTS

- Antiretroviral therapy has resulted in a dramatic decrease in death in human immunodeficiency virus infection.
- Hepatitis B and C coinfection alters the natural history of viral hepatitis.
- Drug-induced liver injuries cause mortality and morbidity, so early diagnosis is crucial.

INTRODUCTION

The 25-year global human immunodeficiency virus (HIV)/AIDS pandemic has resulted in more than 35 million deaths and currently 37 million people living with HIV.[1] More than 70% live in sub-Saharan Africa with Southern Africa an epicenter with more than half of the global disease burden concentrated in this area.[2] Developments in antiretroviral therapy (ART) with sustained viral suppression has resulted in HIV infection becoming a treatable chronic lifelong disease with a life expectancy significantly prolonged.[3] Coinfections and coexistent diseases are now the target of therapy, as they are increasingly responsible for liver-related morbidity and mortality.[4]

Low-income and middle-income countries disproportionately carry the HIV/AIDS burden with South Africa, as an example, having 6.4 million people living with HIV representing an adult population prevalence of 12%.[5] Its public ART program now has 3.4

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million people receiving ART.[2,5] Apart from HIV, sub-Saharan Africa, Eastern Europe, and India shoulder a tuberculosis (TB) burden with the associated problem of drug-resistant TB.[6] In South Africa, TB-HIV coinfection is frequent, with up to 65% of new sputum-positive TB cases HIV positive.[7] Sub-Saharan Africa is endemic for hepatitis B (HBV), mostly acquired in childhood with HIV acquisition in adulthood.[8] This differs from high-income or developed countries where HBV and HIV are acquired through similar transmission routes, invariably in adulthood. Globally, HIV-HBV coinfection rates are between 5% and 20%, with approximately 4 to 6 million people HIV-HBV coinfected, rates being highest in Western and Southern Africa.[9] Hepatitis C (HCV) and HIV share similar transmission routes, with HIV adversely impacting the natural history of hepatitis C, with accelerated liver disease and elevated hepatocellular carcinoma risk.[10] Viral hepatitis coinfection significantly contributes to liver-related mortality in the ART era of HIV management, most notably with HIV-HBV coinfected patients in whom incident risk rate is doubled.[11]

With the obesity epidemic and the long-term metabolic consequences of ART, nonalcoholic fatty liver disease (NAFLD) is an additional burden in HIV. In a high HIV burden area, such as sub-Saharan Africa, obesity rates are increasing. In South Africa, 13.5% of men and 42.0% of women are obese.[12] Additional comorbidities include alcohol, drug use, and hepatotoxic traditional/herbal remedies.

Liver disease manifests though clinical symptoms, jaundice, hepatomegaly, abnormal liver function tests or imaging, and biopsy forms part of this assessment in HIV. With careful clinic-pathological assessment, biopsy has significant clinical value. Pathology findings have changed over the 3 decades of the HIV pandemic, and can appropriately be differentiated into the pre-ART and ART era of HIV/AIDS.

PRE-ANTIRETROVIRAL THERAPY

Most liver pathology data were published in the pre-ART era, with fewer data from the ART era. Findings on biopsy invariably differed between the developed and developing world and influenced by local prevalence of infectious diseases.

The largest series published was of 501 biopsies in HIV-infected patients from New York, biopsied for investigation of abnormal liver enzymes, persistent fever, or hepatomegaly.[13] Biopsy yielded a histologic diagnosis in 64%, whereas in 46% it was treatable. *Mycobacterium avium intracellulare* (MAC) was present in 17.6%, TB in 2.6%, and chronic viral hepatitis in 12%. Other opportunistic infection accounted for 2.8% and the commonest neoplasm was lymphoma in 2.6%. *Mycobacterium tuberculosis* (MTB) was an infrequent finding. Another series from Boston of 36 patients biopsied for unexplained fever (83%) and abnormal liver profiles (89%), provided a diagnosis in 75% with a low CD_4 as compared with 25% of those with more preserved immunity. Opportunistic infections included mycobacteria, cytomegalovirus (CMV), and schistosomiasis. Noninfective observations included granulomas of unknown etiology, cirrhosis, and "chronic persistent hepatitis."[14] An Irish study of 39 biopsies revealed pathologic change in 86% of cases. Findings included nonspecific changes, chronic viral hepatitis, acute hepatitis, and cirrhosis. Granulomatous change was an infrequent finding and liver biopsy in this study was deemed very useful in diagnosing hepatic pathology. In several instances, it provided the source of a "pyrexia of unknown origin" but was less useful for detecting opportunistic infection.[15] A 58-case Spanish study found liver biopsy to be diagnostic/suggestive of a specific diagnosis in 63% of cases. Here, MTB was present in 50% and Leishmaniasis in 20%.[16]