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The Changing Epidemiology of Liver Disease in HIV Patients

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Abstract

Liver disease continues to be one of the leading causes of hospitalization and death in HIV-infected individuals. Important etiologies include both alcoholic and non-alcoholic steatohepatitis, and coinfection with hepatitis viruses B and C. While non-alcoholic fatty liver disease is increasingly diagnosed in this population, most cases of chronic hepatitis B can be well controlled with tenofovir-based regimens, and hepatitis C has entered a revolutionary era in which most patients may be cured with direct-acting antivirals. However, important gaps remain unaddressed. Hepatitis delta is a neglected disease, despite 15 million people being infected worldwide, and represents the most severe form of viral hepatitis. Hepatitis E is largely unrecognized, despite being the major cause of acute viral hepatitis worldwide and occasionally leading to chronicity in immunosuppressed individuals. **(AIDS Rev. 2013;15:25-31)**

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Key words

Hepatitis C. HIV. Hepatitis B. Hepatitis delta. Hepatitis E. Antiviral therapy.

Introduction

During the last decade, liver-related complications have become a leading cause of hospitalization and death in HIV-infected patients living in Western countries[1,2], representing 9% of deaths in HIV-positive persons in the latest D:A:D survey. This largely reflects the high prevalence of viral hepatitis in the HIV population, in which successful antiretroviral therapy has halted the development of opportunistic complications. Figure 1 represents the estimated burden of infections with HIV and hepatitis viruses worldwide. Coinfection with hepatitis B (HBV) and C (HCV) viruses occurs in 10 and 25%, respectively, of HIV-positive individuals[3,4]. In the absence of treatment for viral hepatitis, coinfected patients are at increased risk for developing end-stage liver disease, including hepatocellular carcinoma[5].

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Since the beginning of the HIV epidemic, different hepatitis viruses have played a major role as cause of liver-related complications in HIV individuals (Fig. 2). Outbreaks of severe and fulminant hepatitis delta were reported in the 1980s among intravenous drug users in Europe[6]. In the 1990s, symptomatic acute and chronic hepatitis B episodes were frequent, and only began to decline following the widespread use of lamivudine (and tenofovir after 2002) and expanded HBV vaccination campaigns[7]. During the last decade, end-stage hepatic events and drug-induced liver injury in patients with chronic hepatitis C have been the major determinants of hepatic complications in HIV patients[4,8-10]. Hopefully, the use of direct-acting antivirals (DAA) will reverse the growing impact of HCV in coinfected individuals[11]. Even so, the horizon is clouded by growing reports of new acute HCV and HEV infections, and by hepatic injury associated with fatty liver infiltration and the long-term consequences of use of antiretroviral agents[12-15].

Hepatitis C

The efficient parenteral transmission of HCV explains why coinfection is so common (often > 75%) in individuals that have acquired HIV using drugs intravenously

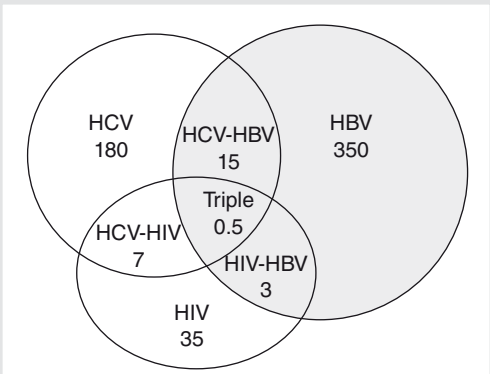

Figure 1. *Estimated number of persons infected with HIV and hepatitis viruses B and C worldwide (in millions). HBV: hepatitis B virus; HCV: hepatitis C virus.*

or after receiving contaminated blood products[3]. While intravenous drug use has declined dramatically in Western Europe, after peaking in the 1980s[16], it is still ongoing in some urban cities in North America, and is currently expanding in Eastern Europe and South East Asia[17]. With respect to the risk of blood transfusions, universal screening for both HIV and HCV has blunted this route of transmission in developed countries. However, it continues to be an important source of contagion in resource-poor regions[18]. Finally, during the last decade, rising incidence[19] and outbreaks of acute hepatitis C among homosexual men (Fig. 3) have highlighted that the virus can also be transmitted efficiently in this population, with HIV acting as a positive cofactor[11].

Despite well-established evidence of faster liver disease progression in HIV/HCV-coinfected patients, only

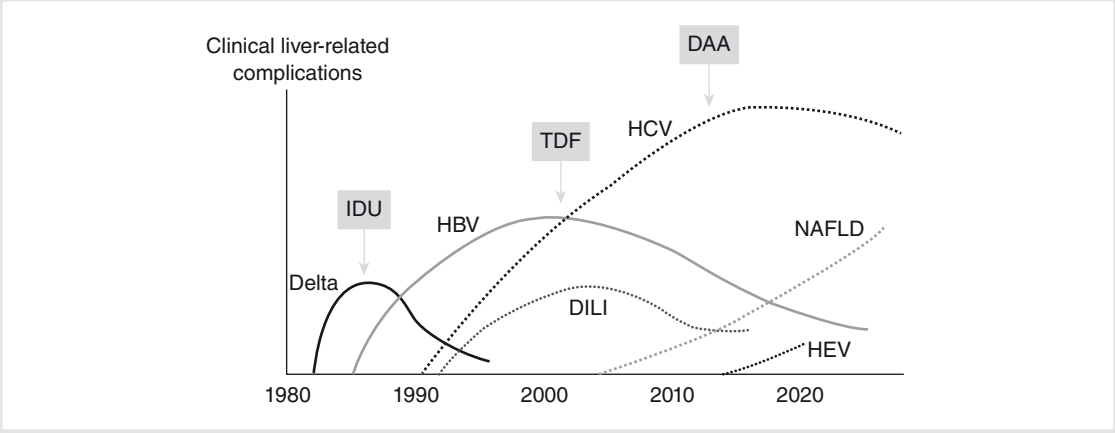

Figure 2. *Time trends in liver disease etiologies in HIV patients. DAA: direct-acting antivirals; TDF: tenofovir; IDU: intravenous drug users; NAFLD: non-alcoholic fatty liver disease; DILI: drug-induced liver injury; HEV: hepatitis E virus.*

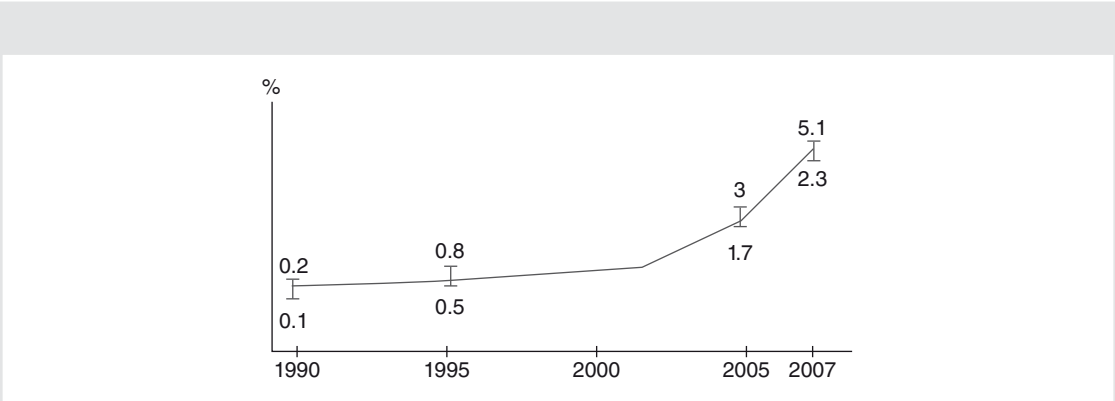

Figure 3. *Annual incidence of acute hepatitis C in HIV-positive men who have sex with men.*

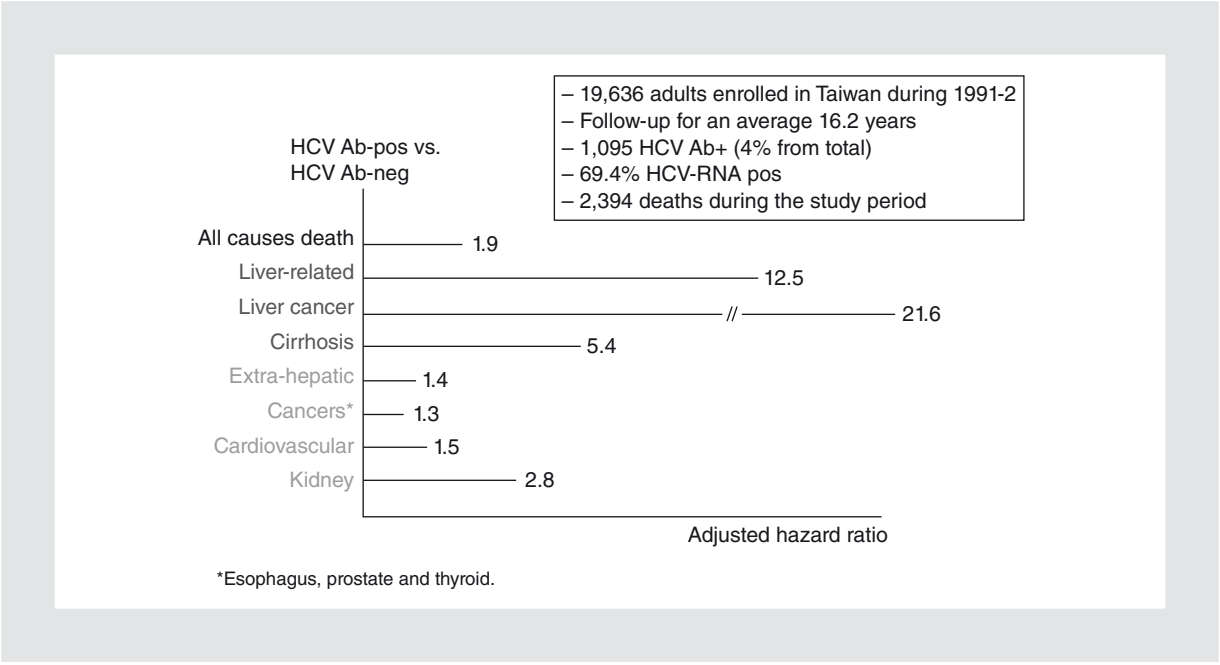

Figure 4. *Risk and causes of death in the REVEAL-HCV study. HCV Ab: hepatitis C antibody.*

a small fraction of these individuals has been treated with peginterferon/ribavirin[20]. Low response rates and poor tolerance of the medication has discouraged its use. However, the recent appreciation of the huge and growing impact of HCV-associated complications in HIV patients has revived the need for treating hepatitis C in this population. The recognition that chronic HCV infection, through unclear mechanisms of persistent immune activation and inflammation, may contribute to extrahepatic manifestations and mortality has further increased the interest for treating hepatitis C. In this regard, the results of the REVEAL-HCV study are an important hallmark[21]. Kidney disease, cardiovascular events, and some cancers are increased in chronic hepatitis C patients compared to controls (Fig. 4). More importantly, this effect is driven by persistent HCV replication and vanishes in subjects who had cleared the virus spontaneously.

Together, this information provides a rationale to treat chronic HCV infection as soon as possible, similar to what has occurred in the HIV field, once less toxic and easy to take medications have become available[22,23]. In this regard, the major difference between these viruses is the prominent role of treatment for halting HIV transmission that only marginally applies to HCV (Fig. 5). On the other hand, the possibility of truly eradicating HCV with therapy is a unique opportunity that does not apply to HIV. While enthusiasm is unabated, a more open consideration of treatment for chronic hepatitis C has unveiled important gaps that must be filled properly if advances in therapeutics are to be translated into significant public health benefits. Whereas HCV has surpassed HIV in total annual deaths in the USA (15,000 vs. 13,000), more than a half of chronic HCV cases remain undiagnosed. In response, the US health authorities have now initiated an unprecedented nationwide campaign to screen all baby boomers born between 1945 and 1965 for HCV[24].

The advent of DAA targeting different key lifecycle elements of HCV replication is eagerly awaited for treating the HIV/HCV-coinfected population. However, the complexity of the proper use of DAA is further increased in the HIV setting, where drug-drug interactions,

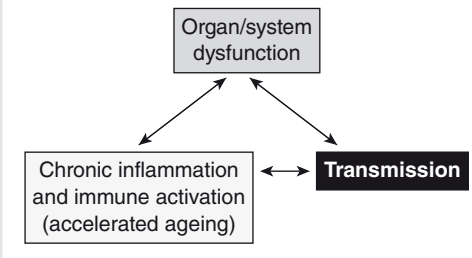

Figure 5. *Rationale for "Test and Treat" strategies for HIV and HCV. HCV: hepatitis C virus.*

overlapping toxicities, and adherence issues derived from poly-medication are challenging[11]. In this regard, several healthcare considerations merit discussion. In the HIV/AIDS field there has been a shift in the attention of patients. Hospitalizations due to severe opportunistic infections or cancers in the 1980s and 1990s have been largely replaced by periodic visits to specialized HIV outpatient clinics. However, as antiretroviral treatment progressively becomes simpler, with very high success rates, the management of this chronic condition is expected to rapidly move to general practitioners and telemedicine will play a major role, providing assistance when difficult management issues are present[25].

In the past, the face of hepatitis C was mainly represented by end-stage liver disease complications, such as ascites, encephalopathy, and variceal bleeding. Hepatitis C was largely managed in hepatology units that took care of hospitalized patients with decompensated cirrhosis events, hepatocellular carcinoma, or liver transplantation. On the other hand, asymptomatic HCV patients, being by far the vast majority, were largely followed by general practitioners. Only recently, and especially following the approval of the first DAA in May 2011, the interest for treating HCV patients has been awakened. Given the complexities surrounding the use of the new hepatitis C drugs, a growing number of HCV patients are being referred to specialized outpatient clinics. Moreover, given the way new antivirals are used, mainly based on virologic tests, more infectious diseases specialists have become interested in treating hepatitis C. However, the current shift of hepatitis C patients from family/general medicine to specialized outpatient clinics must be viewed as temporary. We can envision that over the next couple of years interferon-free regimens will be available and HCV therapeutics will become easier, using more potent, safer, and convenient drugs than the recently marketed first-generation HCV protease inhibitors. Ideally, hepatitis C treatment will be given as co-formulations of drugs in one or two pills, taken once a day, and provided for no longer than 3-6 months. Then, hepatitis C care will mostly return to primary care providers.

Furthermore, several public health implications of a rapid and wide use of DAA can be envisioned. First, constraints in cost and availability of well-trained personnel will limit the use of new hepatitis C drugs in the short-term. Second, the benefit of the new HCV therapies in terms of reduced liver decompensation episodes and the need for liver transplantation will be significant, but only in the long-term. Third, selection of drug resistance in HCV in patients treated with most of the new drugs will require the design of second-line or rescue regimens, as cross-resistance may jeopardize the success of recycling drugs within the same family. Fourth, as previously mentioned, a shift in care providers must be expected, with more involvement of infectious diseases specialists, due to the new way hepatitis C is managed, targeting asymptomatic infected individuals instead of end-stage liver disease patients, and making decisions largely based on virologic parameters, for which infectious disease providers may be more familiar than hepatologists and gastroenterologists. Finally, due to economic constraints and access to healthcare, a shift in HCV populations will occur, with indirect marginalization of patients. In rich countries, the homeless, illegal immigrants, alcohol abusers, the mentally disabled, prisoners, and active intravenous drug users, among others, will not benefit from the new HCV therapies in the short and midterm. On the other hand, the high cost of DAA will represent a huge barrier for their widespread use in resource-limited regions[26].

Hepatitis B

Despite the availability of an HBV vaccine for the past 30 years, chronic hepatitis B remains the most frequent chronic viral infection worldwide, and new infections continue to occur. Expanding universal HBV vaccination of children in resource-rich countries will not solve the problem in the short-to-midterm, given the ongoing immigration from regions where HBV is highly endemic to Western countries.

As HIV and HBV are both efficiently transmitted sexually and parenterally, coinfection is common. The prevalence tends to be higher in men who have sex with men (MSM) than in other risk groups, and in persons living in or from regions where HBV is highly endemic, such as South East Asia and South Africa. Several studies have highlighted that HIV and HBV produce harm bi-directionally. In the MACS cohort, HBV-related liver disease was accelerated in HIV patients[27], whereas in the SMART study, HIV-associated immunodeficiency was enhanced by active HBV replication[28].

The use of lamivudine as single anti-HBV agent has been discouraged in HIV/HBV-coinfected patients, given its limited potency and the risk for selecting drug resistance[29]. Almost uniformly, the most recent guidelines recommend tenofovir-based combinations for HIV/HBV-coinfected patients[7,22,23]. However, tenofovir

is relatively expensive and not available in many regions where HBV is highly endemic. Moreover, a subset of patients on tenofovir develops kidney function abnormalities, more often recognizable as silent tubular damage than overt renal insufficiency or Fanconi syndrome[30]. Furthermore, the long-term consequences of hypophosphatemia, causing bone demineralization and favoring fractures, are a growing concern for long-term tenofovir therapy[31]. Given that the success of lamivudine as single anti-HBV agent is relatively high, it is worth noting that prescription of lamivudine as a single anti-HBV agent is successful in suppressing HBV replication in a large proportion of HIV/HBV-coinfected individuals, especially in those with low HBV DNA and/or negative HBeAg. Thus, in the absence of tenofovir, "doing something is better than doing nothing", a situation that hopefully will change in poor regions within the near future[26]. Indeed, increasing access to tenofovir and other anti-HBV agents is already seen in some resource-poor regions. However, utilization will remain limited as long as HBV testing resources are not ensured. Moreover, the impact of wide lamivudine use on generation of transmissible, drug-resistant HBV remains unclear.

Hepatitis delta

Hepatitis D virus (HDV) causes the most severe form of viral hepatitis. The delta agent carries the smallest genome of animal viruses. It is a circular single-stranded RNA 1,700 nt long. Hepatitis D virus is unique as it requires the HBsAg to form the viral particle. Although close to viroids, the HDV genome codes for a single protein, the delta antigen. HDV infection only occurs in association with HBV either simultaneously (coinfection) or sequentially (superinfection). The proportion of patients with chronic hepatitis B that have delta hepatitis varies geographically, with an estimated 15 million people infected worldwide[6]. However, it is a neglected disease as screening for HDV is frequently forgotten in HBsAg carriers. The prevalence of HDV infection is higher among intravenous drug users than in other risk groups, such as homosexual men. In a survey recently conducted by EuroSIDA, the overall prevalence of HDV was 14.5% in HIV/HBV-coinfected patients living in Europe[32].

There is no effective treatment for chronic hepatitis D. The administration of peginterferon for at least 12 months is currently recommended in patients with elevated liver enzymes and evidence of significant liver fibrosis[6]. However, less than a third of treated individuals achieve normalization of transaminases and suppression of viral replication, a benefit that persists in only a fraction of patients following treatment discontinuation[33]. The advent of interferon lambda might be a good therapeutic option for hepatitis delta in the near future. In the meantime, HBV suppression using potent nucleos(t)ide analogues such as tenofovir may provide some benefit in a subset of hepatitis delta individuals[6,34,35].

Hepatitis E

Hepatitis E virus (HEV) infection is the most common cause of acute viral hepatitis worldwide[36]. Until recently, HEV infection was considered a travel-associated, acute, self-limiting liver disease that occasionally may cause fulminant hepatic failure, mainly in pregnant women[36]. However, HEV infection by genotypes 3 (Europe and North America) and 4 (Japan) can also be acquired in developed countries as a zoonosis, with pigs and rodents serving as animal reservoirs[37-39]. Cases of chronic HEV infection associated with progressive liver disease have been reported among immunocompromised individuals, mainly solid organ transplant recipients[40]. So far, only a few cases of chronic hepatitis E have been reported in HIV-infected individuals, uniformly in subjects with low CD4 counts[13,14,41]. HEV may be an important cause of acute-on-chronic hepatic decompensation. Indeed, it has been recognized as the true etiology of liver injury in patients previously classified as having a drug-related liver injury.

Antiretroviral-associated liver disease

Liver enzyme elevations following the initiation of antiretroviral therapy have always been a relatively frequent complication of HIV treatment[8-10]. However, the most recently approved antiretroviral agents tend to depict a safer hepatic profile, with the current risk of hepatotoxicity grades 3-4 below 3%[42,43]. However, HIV-infected individuals with underlying liver disease, such as those coinfected with HBV or HCV, tend to experience more frequent flare-ups in transaminases[42].

During the last five years, reports of HIV-infected individuals presenting unexpectedly with variceal bleeding have attracted much attention[44,45]. All tested negative for known etiologies of liver disease. Most cases occurred in subjects with prior exposure to didanosine[46,47], an antiretroviral nucleoside analogue with well-known potential for mitochondrial toxicity. It has recently been postulated that individuals with a

predisposing genetic background might be more susceptible to developing vascular hepatic damage when treated with didanosine[48].

Non-alcoholic fatty liver disease

As the life expectancy of HIV individuals improves, organ dysfunction associated with ageing may become more relevant. Besides viral hepatitis, one of the major causes of hepatic disease in Western countries is non-alcoholic fatty liver disease (NAFLD), as primary manifestation of the metabolic syndrome in the liver. Lifestyle, including low exercise and convenient diet, mainly accounts for it. Moreover, HIV itself or insulin resistance and dyslipidemia associated to some antiretroviral agents may contribute to the higher rate and severity of NAFLD characteristically seen in HIV patients. Fat deposition in the liver may result in local inflammation (steatohepatitis), liver enzyme elevations, and liver fibrosis, eventually leading to cirrhosis[15].

Nearly half of HIV patients that undergo evaluation for unexplained liver test abnormalities have NAFLD[15,49]. In a French study that examined 30 HIV patients with persistently elevated liver enzymes, the authors found steatosis in 18 of them as determined by liver biopsy, with severe hepatic fibrosis in six cases[50]. In current clinical practice, a combination of clinical features and laboratory parameters, along with progress in non-invasive tools for assessing liver damage, may permit to overcome the need for a liver biopsy to make the diagnosis of NAFLD[15] and consider specific therapeutic interventions, encouraging changes in lifestyle. In this regard, it should be noted that alcohol abuse remains common in HIV-infected patients and causes a hepatic injury pattern indistinguishable from that seen in non-alcoholic steatohepatitis (cellular ballooning, pericellular fibrosis, pericentral fibrosis, Mallory bodies). Therefore, clinicians must account for alcohol use and counsel patients at risk of other liver diseases that alcohol represents an important cofactor for other forms of liver injury.

Conclusion

Liver disease remains an important modifier of health in persons with HIV infection. The epidemiology of liver disease in this population reflects an evolution in our understanding of the causes of hepatic damage and the tools available for both diagnosis and treatment. While some diseases processes (e.g. hepatitis B) are now easily identifiable and treatable, others like hepatitis C are just entering the stage when safe, effective therapies will become available to large segments of the HIV/HCV-coinfected population[51]. Other disease processes including HDV, HEV, and non-alcoholic steatohepatitis will increase in both recognition and importance over the next decade of the worldwide HIV epidemic.

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