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# Are HIV-infected patients candidates for liver transplantation?☆

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## 1. Introduction (D. Samuel)

This forum aims to review the current situation of liver transplantation in HIV-infected patients. A few years ago, the possibility of transplantation in HIV-infected patients was considered an unrealizable dream. Several major improvements have made this therapeutic intervention possible. First, the advent of highly active antiretroviral therapy (HAART) has dramatically modified the prognosis of HIV-infected patients. Second, the very effective prophylaxis of HBV reinfection using a combination of hyperimmune globulin anti-HBs and nucleos/tide analogues after liver transplantation has dramatically improved the prognosis of liver transplantation in HBV-infected patients. Third, the greater understanding of mechanisms involved in HCV recurrence after liver transplantation and the improvement in antiviral therapy post-transplantation gives a reasonably optimistic view of the future of liver transplantation in HCV-infected patients. Here, it is our aim to explore new indications for this group of patients.

## 2. How big is the problem? (R. Weber)

Worldwide, an estimated 33.2 million persons are currently living with HIV infection including 15.4 million women and 2.5 million children under 15 years [1]. In 2007, 2.1 million adults and 0.4 million children were newly infected, and 2.1 million died from HIV infection. Globally, HIV infection is mostly transmitted via heterosexual contacts, but intravenous drug use or homosexual contacts contribute to HIV epidemiology in some geographic areas. Regional statistics show enormous differences in prevalence and incidence of HIV infection. Only a minority of infected persons – 0.76 million persons in Western and Central Europe and 1.3 million in North America – are living in resource-rich countries with unrestricted access to therapy. Based on projections of economic and social development and considering the historically observed relationships of those with burden of disease, global HIV/AIDS-related mortality is projected to possibly rise to 6.5 million in 2030. This model assumes coverage with antiretroviral drugs will have reached 80% by 2012. Under optimistic assumptions including increased prevention activities, HIV/AIDS deaths are projected to increase to 3.7 million in 2030 [2]. In higher income countries mortality is expected to stabilize or to decrease during the next decades, therefore, the burden of HIV-related diseases and death will mainly affect low-income countries.

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*Abbreviations:* DILI, drug-induced liver injury; AUC, area under the curve; HBV, hepatitis B Virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; MELD, model for end-stage liver disease; CPT, child-pugh-turcott.


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Modern combination of antiretroviral therapy completely suppresses HIV-1 replication which results in restoration of cellular immune function, clinical improvement, and a dramatic decrease of mortality from 20–30 per 100 person-years before introduction of potent drug regimens in 1995 to 1.5–2.5 per 100 person-years in recent years [3]. Nevertheless, the risk of death from AIDS is still substantial due to therapeutic failure, late initiation of treatment, interruption or refusal of treatment, incomplete adherence to therapy, or drug resistance. Unfortunately, the search for a vaccine has failed so far, and there is currently no reasonable evidence that there will ever be one [4].

Hepatic opportunistic infections and malignancies were found among 30–75% of patients with AIDS at autopsy prior to the availability of antiretroviral therapy, but liver disease rarely was the primary cause of morbidity and rarely contributed to mortality. Such a finding is still true in resource-poor countries without treatment programs. HIV itself appears not to affect liver function and no findings specific or pathognomonic for AIDS were identified in liver tissue. In contrast, in patients with access to potent antiretroviral therapy, deaths due to immunodeficiency-related complications have decreased and an increasing proportion of deaths are due to complications of liver diseases. Among 1246 deaths observed in the prospective D:A:D cohort study between 1999 and 2004, liver-related death was even the most frequent cause of non-AIDS-related deaths: 31.1% of the patients died from AIDS, 14.5% due to liver-related diseases, 11.0% from cardiovascular diseases, 9.4% from non-AIDS malignancies, and 33.8% from other causes [3]. In this study, liver-related deaths were a consequence of chronic hepatitis B (HBV) or hepatitis C virus (HCV) co-infection in 76% of the patients. Interestingly, there was a strong association between severity of cellular immunodeficiency and risk of liver-related death [3]. A total of 2.7% of deaths were reported to be directly associated with antiretroviral medication.

Liver-related diseases among HIV-infected persons are caused by HBV and HCV co-infections, hepatotoxic medication, alcohol, illegal drugs, malignancies, metabolic and immunologic mechanisms, and non-HIV-related diseases (Table 1). Globally, an estimated 370 million persons are affected by chronic HBV and 130 million by HCV infection [5]. Because HIV, HBV and HCV share common routes of transmission, an estimated 2–4 million HIV-infected persons are co-infected with HBV and 4–5 million with HCV. The prevalence of co-infections differ by geographic region and by patients' demographic and behavioral characteristics. The prevalence of chronic HBV infection is between 6–17% among HIV-infected persons living in HBV endemic areas, and 4–17% among persons living in Europe or the USA depending on sexual or injection drug use behavior. The prevalence of HCV co-infection ranges from 1–5% in persons who acquired HIV infection by heterosexual or homosexual contacts to 70–95% in current or former injection drug users and transfused hemophiliac patients. Thus, co-infections due to HBV and HCV are the most frequent causes of liver disease in HIV infection and substantially contribute to morbidity and mortality [5,6].

**Table 1**
**Causes of liver disease in HIV-infected persons**

| |
|---|
| Co-infections |
| • HIV-associated opportunistic infections (e.g., cytomegalovirus infection, tuberculosis, non-tuberculous mycobacterial infections, *Bartonella henselae* infection (peliosis hepatis) |
| • Tropical infections (e.g., visceral leishmaniasis, schistosomiasis) |
| Hepatotoxicity |
| • Antiretroviral drug-related toxicity |
| • Non-HIV medication-related toxicity |
| • Alcohol use |
| • Illegal drugs |
| Malignancies |
| • Hepatitis B and C virus-associated hepatocellular carcinoma |
| • HIV-associated malignancies (Non-Hodgkin's lymphoma, Kaposi's sarcoma) |
| • Metastases of other malignancies |
| Metabolic |
| • Non-alcoholic steatosis hepatitis (NASH) |
| Immune-mediated |
| • Immune reconstitution inflammatory syndrome (IRIS) in hepatitis virus co-infected persons |
| Non-HIV-related diseases |

HCV and HIV infections adversely affect each other: HIV infection accelerates the progression of HCV disease by increasing hepatitis C viremia, causing cellular immunodeficiency, increasing the risk of liver fibrosis and cirrhosis or leading to the rare fibrosing cholestatic hepatitis [7,8]. Vice versa, although debated [9], HCV may adversely affect the course of HIV infection [10], reduces the effectiveness of antiretroviral treatment, and increases the rate of antiretroviral medication-related hepatotoxicity [7,11]. Antiretroviral therapy has been reported to reduce liver-related mortality in HCV co-infected persons [12], but others did not find such an effect [3]. Despite clinical and psychosocial obstacles encountered in clinical practice, HCV treatment in HIV co-infected persons is feasible with results similar to those observed in randomized clinical trials. However, many co-infected persons are not eligible for HCV treatment due to somatic or psychosocial co-morbidities, and contraindications for HCV drugs and those with decompensated cirrhosis are not candidates for treatment [13].

HBV does not seem to enhance HIV progression or affect antiretroviral treatment response, but increases liver-related mortality in co-infected persons [8]. HBV-associated morbidity, however, is substantially reduced among persons with access to care because nucleoside and nucleotide reverse-transcriptase inhibitors used to