HIV coinfection and HCC

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Increasing burden of HCC in HIV-infected patients

Risk factors

Clinical approaches
Increasing burden of end-stage complications of liver disease in HIV-infected patients
Cirrhosis and HCC in HIV patients

• Leading causes of death among HIV patients
• In countries where widespread introduction of highly active antiretroviral treatment (HAART) since 1996 led to a dramatic reduction in deaths due to HIV
Evolving epidemic of HCV-related cirrhosis and HCC in HIV-infected patients

• France
  – 2% in 1995 to 17% in 2005

• Europe, the United States, and Australia
Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study
  – 14.5% in 1999-2004

• Swiss
  – 18% (including 3% from HCC) 2005-2009
    • Ruppik M et al. CROI 8, 2012.
Liver diseases in HIV patients

- Cirrhosis: 2%
- Decompensated liver disease: 1%
- HCC: 0.3%
- HCV: 28%
- HBV: 11%
Epidemiology of HIV and Liver Diseases

• High morbidity and mortality
  – In the U.S. general population, cirrhosis accounts for 40,000 deaths per year and for the loss of more than 228,000 years of potential life.

• As HIV patients with access to ART survive longer, comorbidities such as chronic liver disease have become leading causes of illness and death.
  – ESLD is now a leading cause of death in patients with HIV/HCV or HIV/HBV coinfection

• HIV infection accelerates progression of liver disease associated with HCV or HBV

• Other factors that cause more severe liver disease
  – Alcohol misuse, drug-associated hepatotoxicity, male gender, and fatty liver (steatosis), are also more common in the HIV-infected population
Prevalence of viral hepatitis among HIV-infected individuals in the United States

30-40% coinfectected with HCV
  – 9-27% of heterosexuals
  – 1-12% of men who have sex with men
  – 72-95% of injection drug users
  – 31% of veterans

6-14% coinfectected with HBV
  – 4-6% of heterosexuals
  – 9-17% of men who have sex with men
  – 7-10% of injection drug users
  – 14% of veterans
Why increase HCC in HIV patients?

- Potent ART prolonged survival of HIV-infected individuals to allow HCC, a late complication of cirrhosis, to emerge in patients with known risk factors for HCC

- In vitro and animal studies have suggested that HIV may play a role in viral hepatitis and alcohol-induced hepatocarcinogenesis mediated via the Tat protein

- Only modest SVR with HCV treatment with IFN/R (12%) and PR (40%)

- Improved management of liver cirrhosis by clinicians attending HIV-infected patients lead to a better management and prevention of other liver decompensations, resulting in longer survival of HIV-infected patients with cirrhosis, which enables HCC to develop
Risk factors
Risk factors

- HCV infection
- HBV infection
- Age
- Low CD4 cell count
Trends in the prevalence of (A) cirrhosis, (B) decompensated cirrhosis, (C) HCC, and (D) mortality in HIV-infected veterans during 1996-2009 presented according to HCV status

HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)

• Liver-related mortality rate
  – 1·1/1000 person years
  – HIV-1+ and HBsAg+ (14·2/1000) Vs HIV-1+ (1·7/1000, p<0·001) or only HBsAg+ (0·8/1000, p<0·001).

• In coinfection individuals, the liver-related mortality rate was highest with lower nadir CD4+ cell counts and was twice as high after 1996, when highly active antiretroviral therapy (HAART) was introduced.
Influence of HIV-related immunodeficiency on the risk of HCC

• A case-control study nested in the Swiss HIV Cohort Study
  – 26 HCC patients were identified and were individually matched to 251 controls according to Swiss HIV Cohort Study centre, sex, HIV-transmission category, age and year at enrollment

• All HCC patients were positive for HBsAg + or anti-HCV+

• HAART was not significantly associated with HCC risk

• Lower CD4+ cell counts
  – increased the risk for HCC
  – particularly evident for HBV-related HCC arising in non-injecting drug users

Clifford GM et al., AIDS. 2008;22(16):2135-41.
The release of cytolytic molecules by CD4+ CTLs was decreased in HCC patients

Clinical approaches
Clinical presentation and prognosis of hepatocellular carcinoma in HIV

• Clinical features
  – Younger
  – Symptomatic
  – Advanced tumor stages
  – Median survival -7 months

• Survival was similar to HIV-uninfected patients among those who underwent potentially curative treatment.
Screening for hepatocellular carcinoma in persons living with HIV

- No definitive data are available for the cost–effectiveness of screening for HCC in patients with HIV infection and cirrhosis

- HCC diagnosed at screening had a better survival and screening is feasible in PLHIV and cirrhosis  

- European guidelines recommend 6-monthly liver ultrasound and serum alpha-fetoprotein testing in HIV-infected patients with HCV-related cirrhosis  

- Recent availability of validated, accurate, and sensitive noninvasive methods, such as blood tests and transient elastometry, allows physician caring for PLHIV to easily identify those with HCV-induced cirrhosis  
Treatment of hepatocellular carcinoma in persons living with HIV

• The management and treatment of HCC in HIV patients is the same as that of patients without HIV

• Aggressive treatment strategy (usage of potentially curative treatment and treatment of recurrences) is associated with increased survival

Treatment of hepatocellular carcinoma in persons living with HIV

•SORAFENIB, BEVACIZUMAB
  –Limited data

•Liver transplantation
  –especially on HCV viral cirrhosis, was reported to be worse than in non-HIV-infected patients, in terms of both HCV recurrence and HCC recurrence
Prevention of hepatocellular carcinoma in persons living with HIV

• Both anti-HIV and anti-HCV therapy may have a role for the prevention of HCC

• Role of anti-HIV therapy
  – The Swiss HIV cohort was investigated in order to assess whether HIV-related immunodeficiency was a risk factor for HCC
  – Latest CD4 cell count were significantly associated with HCC
  – Highly active antiretroviral therapy use was not significantly associated with HCC risk
Role of anti-HCV therapy

• SVR
  – standard IFN/ ribavirin (12% ) and pegIFN/ribavirin(40%)
  – associated with a lower incidence of HCC even after adjusting for other variables such as disease stage

• Anti-HCV DAAs
  – ↑ SVR rates in coinfected patients
  – concern on drug – drug interactions, tolerability, and HCV drug resistance
  – use limited in HIV-infected patients with comorbid psychiatric disease and anemia
Boceprevir versus placebo with pegylated interferon alfa-2b and ribavirin for treatment of HCV genotype 1 in patients with HIV: a randomised, double-blind, controlled phase 2 trial

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<th>PR 48</th>
<th>PR4➔PR/BOC44</th>
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<tbody>
<tr>
<td>SVR</td>
<td>10/34(29%)</td>
<td>40/64(63%)</td>
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<td>Adverse events</td>
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<tr>
<td>Anaemia</td>
<td>9(26%)</td>
<td>26(41%)</td>
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<tr>
<td>Pyrexia</td>
<td>7(21%)</td>
<td>23(36%)</td>
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<td>Decreased appetite</td>
<td>6(18%)</td>
<td>22(34%)</td>
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<tr>
<td>Dysgeusis</td>
<td>5(15%)</td>
<td>18(28%)</td>
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<tr>
<td>Neutropenia</td>
<td>2(6%)</td>
<td>12(19%)</td>
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- Non-nucleoside reverse-transcriptase inhibitors, zidovudine, and didanosine were not permitted.

Virological response rates for telaprevir-based HCV triple therapy in patients with and without HIV coinfection

- 33 coinfected Vs 116 monoinfected patients

- SVR12 rates were 60.6% in coinfected patients vs. 42.2% in monoinfected patients ($P = 0.06$).

- Telaprevir-based triple therapy is a promising option for coinfected patients with well-controlled HIV infection

Conclusions

• Hepatocellular carcinoma (HCC)
  - Rising dramatically among HIV-infected patients, particularly those coinfected with HCV
  - Likely to constitute some of the most important clinical problems for HIV-infected patients and their physicians during the decade 2010-2020
  - Treatment or prevention of the modifiable risk factors especially HCV and HBV coinfection, may ameliorate the burden of cirrhosis and HCC and reverse their upward trends