

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
 - Rosenthal E et al HIV Med 2009;10:282-289.
- Europe, the United States, and Australia

Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study

- 14.5% in 1999-2004
 - Weber R et al. Arch Intern Med 2006;166: 1632-1641.
- 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% coinfecting 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% coinfecting 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?

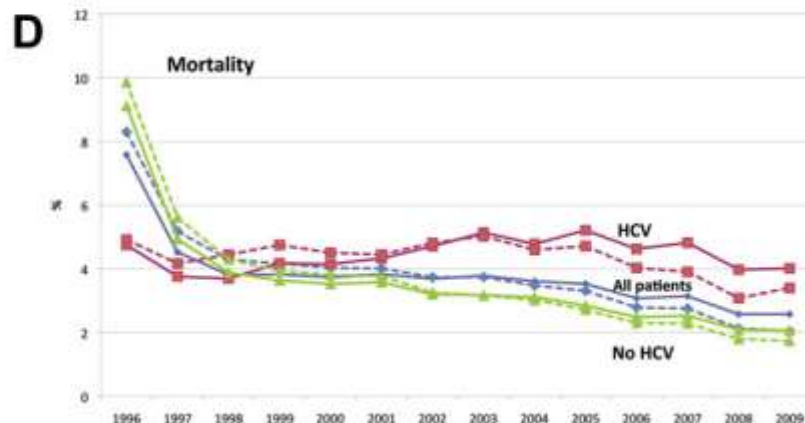
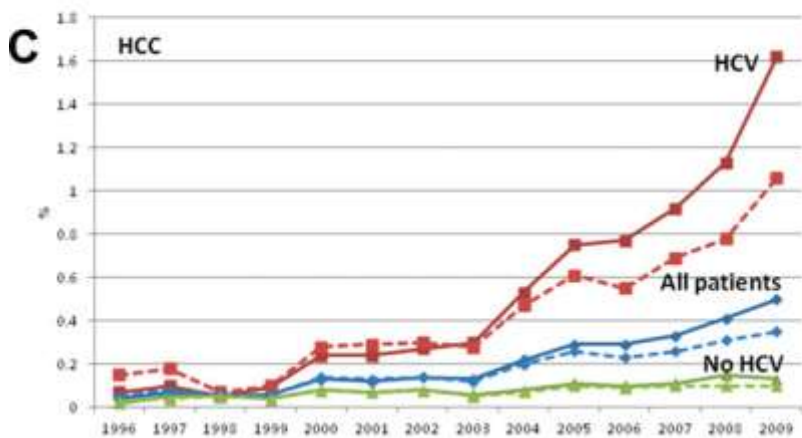
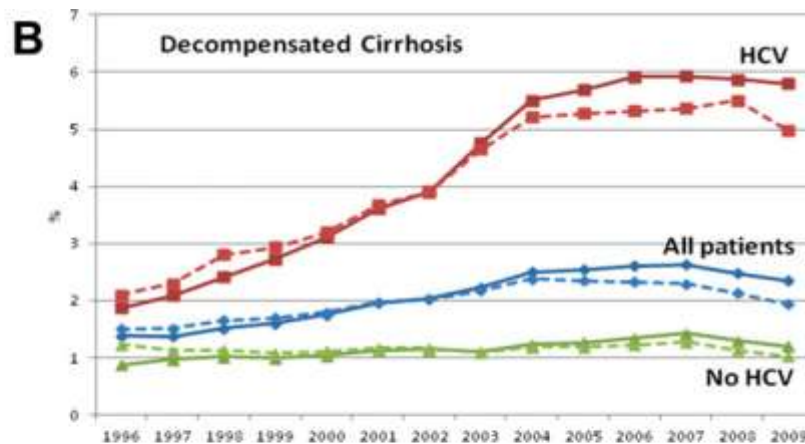
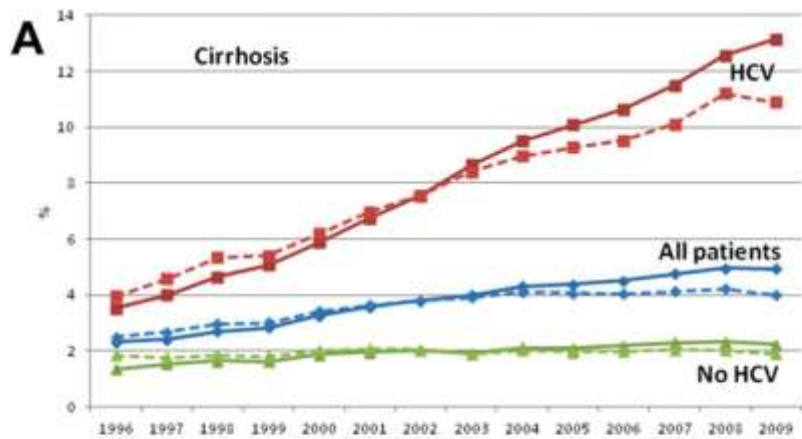
- Potent ART prolonged survival of HIV-infected individuals to allow HCC, a late complication of cirrhosis, to emerge in patients with known risk factors for HCC
 - El-Serag HB et al. N Engl J Med 2011;365:1118–27.
- In vitro and animal studies have suggested that HIV may play a role in viral hepatitis and alcohol-induced hepatocarcinogenesis mediated via the Tat protein
 - Altavilla G et al. Am J Pathol 2000; 157:1081–9.
- 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



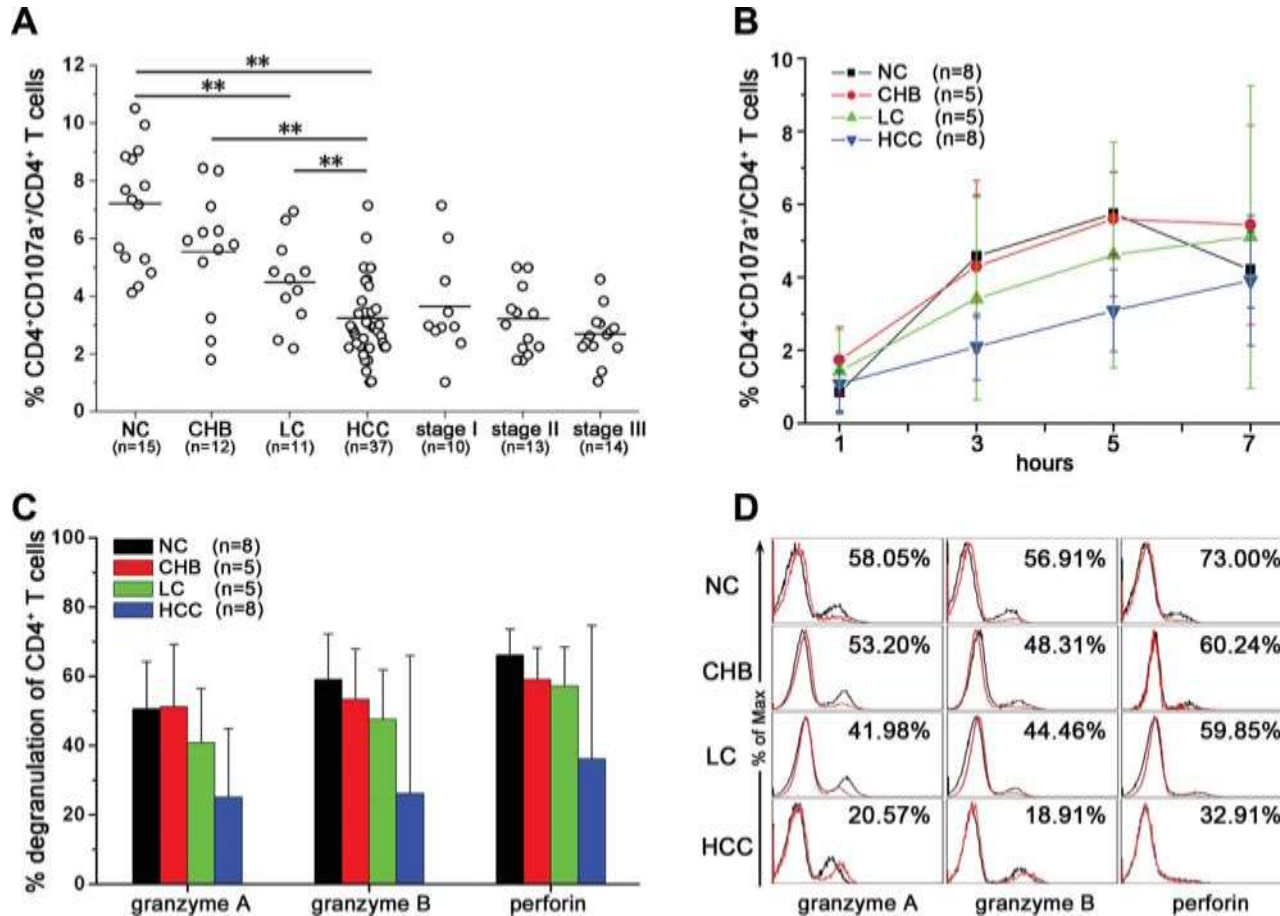
HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS)

- 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 coinfecting 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

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
 - » Sulkowski M. J Hepatol 2009; 50:655–658.
- Survival was similar to HIV-uninfected patients among those who underwent potentially curative treatment.
 - » Garlassi E et al. Infection 2010; 38 (Suppl I):82–182.

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
 - Joshi D et al. Lancet 2011; 377:1198–1209.
- European guidelines recommend 6-monthly liver ultrasound and serum alpha-fetoprotein testing in HIV-infected patients with HCV-related cirrhosis
 - Rockstroh JK et al. HIV Med 2008; 9:82–88.
- 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
 - Kelleher TB, Afdhal N. J Hepatol 2006; 44 (1 Suppl):S126–S131.

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
 - Perboni G et al. *Oncologist* 2010; 15:142 – 145.
 - Baraboutis IG et al. *Eur J Gastroenterol Hepatol* 2008; 20:472–473.
- 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
 - Vibert E et al. *Hepatology* 2011; 53:475–482.

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
 - Clifford GM et al. AIDS 2008; 22:2135– 2141

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
 - Berenguer J et al. Hepatology 2009; 50:407–413.
- Anti-HCV DAAs
 - ↑ SVR rates in coinfecting patients
 - concern on drug – drug interactions, tolerability, and HCV drug resistance
 - use limited in HIV-infected patients with comorbid psychiatric disease and anemia
 - [Sulkowski M et al.](#) Lancet Infect Dis. 2013;13(7):597-605.

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

	PR 48	PR4→PR/BOC44	
SVR	10/34(29%)	40/64(63%)	P=0.0008
Adverse events			
Anaemia	9 (26%)	26 (41%)	
Pyrexia	7 (21%)	23 (36%)	
Decreased appetite	6(18%)	22 (34%)	
Dysgeusis	5 (15%)	18 (28%)	
Neutropenia	2(6%)	12 (19%)	

- 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 coinfecting Vs 116 monoinfected patients
- SVR12 rates were 60.6% in coinfecting patients vs. 42.2% in monoinfected patients (P = 0.06).
- Telaprevir-based triple therapy is a promising option for coinfecting patients with well-controlled HIV infection

Conclusions

- Hepatocellular carcinoma (HCC)
 - Rising dramatically among HIV-infected patients, particularly those coinfecting 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