Changing Epidemiology of HCV Mortality and Morbidity in HIV patients

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Conflict of interest

I have received honoraria for speaking at educational events or consulting from:

Abbott, Abbvie, Bionor, BMS, Boehringer, Gilead, Janssen, Merck, Novartis, Pfizer, Roche, Tibotec, Tobira and ViiV
Changing Epidemiology of HCV Mortality and Morbidity in HIV Patients

• Why is the natural history of HCV different in HIV?

• Which impact has successful HIV therapy on the further course of HCV associated liver disease and how does it change the liver disease burden of HCV in HIV?

• Can HCV therapy induced SVR or cure of HCV change the outcome of clinical endpoints in HIV/HCV coinfection?
New HCV /HIV epidemiological data.
Center for Disease Analysis 2013

HIV and Hepatitis C:
Percent of HIV+ Individuals with HCV Co-infection, by Country
Background

- HIV accelerates the natural course of hepatitis particularly with declining CD4 counts\(^1\)
- Liver disease associated with HCV infection has become a leading cause of morbidity and mortality among HIV-infected patients\(^2\)

Morbidity and Mortality in Patients with HIV and HCV

Rockstroh JK et al., Am J Gastroenterology 1996;91:2563-2568
Mechanism of the effect of HIV on the progression of hepatitis C

• HIV may increase HCV replication and fibrogenesis via TGF β1.
• Enhanced intrahepatic inflammatory cytokine response could be the main cause of accelerated progression.
• Increases in profibrogenic cytokine expression and secretion, generation of enhanced oxidative stress, and increases in hepatocyte apoptosis which may be further augmented in the presence of increased microbial translocation in the setting of HIV.
• Impaired IL-2 secretion of CD4+ T cells resulting in an ineffective stimulation of anti-fibrotic NK cell function.
• Altered levels of matrix metalloproteinases; HIV-associated gut depletion of CD4.

3Lin W et al., J Infect Dis 2013;207:S13-18
4Glässner et al., J Hepatol 2013;59: 427-433
5Mastroianni Cm et al., Int J Mol Sci 2014;15:9184-9208
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Cumulative Proportion of Patients With Cirrhosis by PI Exposure: MultivirC Group

- Retrospective cohort study
  - 182 HIV/HCV-coinfected patients
- At liver biopsy
  - PI-based HAART (n=63)
  - Never treated with PI-based HAART (n=119)
- PI exposure versus no PI exposure
  - Lower liver fibrosis stage ($P=0.03$)
  - Cirrhosis rates ($P=0.0006$)
    - 5-year: 2% versus 5%
    - 15-year: 5% versus 18%
    - 25-year: 9% versus 27%

Impact of ART on Overall Liver Mortality in HIV/HCV-Coinfected Patients

- Bonn cohort (1990-2002)
  - 285 HIV/HCV coinfected patients
- Liver-related mortality rates per 100 person-years
  - HAART: 0.45
  - ART: 0.69
  - No therapy: 1.70
- Predictors for liver-related mortality
  - No HAART
  - Low CD4 cell count
  - Increasing age

Impact of HIV RNA, CD4, or Both on Liver Fibrosis Progression Rate

Time to cirrhosis estimated using liver fibrosis progression rate based on Ishak Fibrosis units/year.

Effect of HAART on liver fibrosis progression: Sequential studies.

Factors independently associated with fibrosis progression

- Adjusted Odds Ratio (95% CI)
  - Year 1st LBx (p=0.58)
  - ART between LBx (p=0.8)
  - Undetectable HIV-RNA (p=0.017)
  - High necroinflammatory activity (p=0.008)
  - Response to HCV Rx (p=0.018)

ART and SVR to HCV therapy are associated with slower liver fibrosis progression in HIV-HCV-coinfected patients: study from the ANRS CO 13 HEPAVIH cohort.

• **Methods:**
  – HIV-HCV-coinfected adults enrolled in the ANRS CO 13 HEPAVIH cohort, for whom two results of LS, evaluated over ≥24 months, were available.

• **Results:**
  – In multivariate linear and logistic analyses, excessive alcohol intake (β coefficient 6.8; P=0.0006) and high HCV viral load (OR 1.7, 95% CI 1.1, 2.5; P=0.01) were independently associated with an increase in LS, whereas time on ART>114.5 months (OR 0.5, 95% CI 0.3, 0.9; P=0.03) and achievement of sustained virological response (OR 0.1, 95% CI 0.01, 0.9; P=0.04) were independently associated with no increase in LS.

Antiretroviral Therapy Reduces the Rate of Hepatic Decompensation Among HIV- and Hepatitis C Virus–Coinfected Veterans

- **Objective:** To evaluate 10 090 HIV/HCV-coinfected males from the Veterans Aging Cohort Study Virtual Cohort, who had not initiated ART at entry, for incident hepatic decompensation between 1996 and 2010.
- **Results:** Initiation of ART significantly reduced the rate of hepatic decompensation by 28%–41% on average.

**Study aim:** To compare the incidence of hepatic decompensation between ART-treated HIV/HCV-coinfected and HCV-monoinfected pts

- **Hepatic decompensation** was defined as a hospital diagnosis indicated by ICD-9 code or two or more outpatient diagnoses of ascites, spontaneous bacterial peritonitis, or esophageal variceal hemorrhage.
Standardized Cumulative Incidence of Hepatic Decompensation*

HD risk was 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)

* Based on competing risk regression analysis.
HIV Suppression Is Associated with Less Hepatic Necroinflammatory Activity

Mehta SH et al. *Hepatology* 2005
Probability of remaining free of developing a hepatic decompensation
HAART induces recovery of specific T-cell response to HCV core proteins

Any additional benefits or impact of ART?

• The changing pattern of glomerular disease in HIV and hepatitis C co-infected patients in the era of HAART¹
• ART is associated with lower post-IFN HCV-RNA levels; that change is linked to reduced hepatic interferon stimulating gene (ISG) expression²; these data support recommendations to provide ART prior to IFN-based treatment of HCV

¹Mohan S et al., Clin Nephrol 2013;79:285-291
²Balagopal A et al., Hepatology 2014; April 5th Epub ahead of print
Has the outcome of liver disease in HIV/HCV-coinfected patients become similar to that in HCV monoinfection?

**Metanalysis of 26 studies**

**No HAART**

- Allory, 2000
- Bierhoff, 1997
- Di Martino, 2001
- Eyster, 1993
- Grabczewska, 2005
- Lesens, 1999
- Makris, 1996
- Pol, 1996a
- Pol, 1998b
- Romeo, 2000
- Serfaty, 2001
- Soto, 1997
- Teller, 1994
- Fixed effects
- Random effects

**HAART**

- Benhamou, 1999
- Breu, 2006
- Gaslightwala & Bini, 2006
- Gonzalez, 2006
- Macias, 2005
- Marine-Barjoan, 2004
- Martinez-Sierra, 2003
- Mohsen, 2003
- Monto, 2005
- Rodriguez-Torres, 2006
- Sarmento-Castro, 2007
- Valle Tovo, 2007
- Verma, 2006
- Fixed effects
- Random effects

EACS Guidelines: When to Start

- Initiation of ART
  - ART is always recommended if CD4 count < 350 cells/mm³

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4 + lymphocyte count</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>350–500</td>
<td>&gt;500</td>
</tr>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td>R</td>
<td>C</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment not feasible</td>
<td>R</td>
<td>C</td>
</tr>
</tbody>
</table>

C = CONSIDER; D = DEFER; R = RECOMMENDED

Changes in death causes over time

1999-2000  
N=255

- AIDS-related: 34%
- CVD-related: 8%
- Other/Unknown: 32%
- Liver-related: 10%

2009-2011  
N=548

- AIDS-related: 39%
- CVD-related: 10%
- Other/Unknown: 22%
- Liver-related: 9%

- 3,802 deaths in 49,734 HIV positive individuals followed for 304,695 person-years
- Death rate fell from 17.4 deaths per 1000 py in 1999-2000 to 8.3 deaths in 2009-2011

Causes of death in PLWHIV 2000–2010: Results from a French national survey

- 90 medical departments
- 728 death for HIV+ patients in 2010
- Age (median) = 50 y
- Current rate CD4 < 200/mm³ = 56%
- Current VL > 500 c/ml = 30%
- Smokers = 71%
- Alcohol = 25%
- 9% of deceased patients were diagnosed within last 6 months

PLWHIV: people living with HIV.

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HCV infection can be cured

Clinical events after HCV treatment for 493 patients with no SVR and 218 patients with SVR

Overall mortality

Liver decompensation

• Treatment of chronic infection: SVR is possible\textsuperscript{1}, durable\textsuperscript{2}, and prevents death\textsuperscript{3}

Patients included in the study

- Patients in the database: 1,599
- Patients with F0, F1, F2: 695
- Patients with SVR: 274 (35%)

Berenguer J, et al. ICAAC 2013, Denver, Session 204 - Abstract # H-1527
Kaplan Meier estimates of events

Median FU (IQR): No SVR: 59.3 mo (40.6–79.2); SVR: 59.5 mo (42.8–81.8)

Berenguer J, et al. ICAAC 2013, Denver, Session 204 - Abstract # H-1527
Effects of ART on the liver in HIV/HCV-coinfected patients: Conclusions

• The short- and mid-term effects of ART on the progression of HCV-related liver disease largely outweigh the potential risks for long-term toxicity.

• This supports an earlier starting of ART in patients with HIV/HCV-coinfection.

• However, surveillance of possible new side effects, as well as of changes in the natural history of hepatitis C infection in patients on HAART is required.

• SVR does not only decrease liver disease associated morbidity and mortality but also overall survival and this for all fibrosis stages