Effect of HAART on liver related survival

Ninth International Workshop on HIV and Hepatitis Co-infection, 30-31 May 2013, Rome, Italy

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Morbidity and Mortality in Patients with HIV and HCV

Retrospective study of 144 HIV/HCV patients in an outpatient hemophilia clinic from 1990–1995

- 49 HIV/HCV coinfected patients with AIDS or CD4 <100/µl; 10 of 20 deaths due to liver failure
- 95 HIV/HCV coinfected patients with stable CD4 counts; 2 deaths due to OIs/malignancies
- 72 patients with HCV mono infection; no deaths
- 24 HIV+/HCV- patients with CD4 <100/ml or AIDS; 16 deaths due to OIs/malignancies

Rockstroh JK et al., Am J Gastroenterology 1996;91:2563-2568
Morbidity and Mortality in Patients with HIV and HCV

Group A (n=49)

Group B-D (n=191)

p < 0.001

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 β1¹.
- Enhanced intrahepatic inflammatory cytokine response could be the main cause of accelerated progression².
- 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.³
- HCV/HIV co-infection was associated with an impaired IL-2 secretion of CD4+ T cells resulting in an ineffective stimulation of anti-fibrotic NK cell function.

³Lin W et al., J Infect Dis 2013;207:S13-18
Glässner et al., J Hepatol 2013; epub ahead of print
Mortality of HIV-infected patients in France (GERMIVIC Study Group)

Rosenthal et al. J Viral Hepatitis 2007;14:183–188
Which questions need to be addressed?

» Is HAART beneficial or harmful for further liver disease progression?

» Does successful HAART lead to the same outcome (CD4-count increase etc.) in HIV patients with concomitant liver disease?

» When should we administer ART and which antiretroviral drugs should we choose in coinfection?
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If fibrosis progression and subsequent liver disease associated morbidity and mortality is linked to progressive immunodeficiency will HAART induced immunoreconstitution delay further liver disease progression?
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 HAART on Liver Fibrosis in HIV/HCV-Coinfected Patients

• Retrospective chart review (2000-2002)
  – Puerto Rico, New York

• Patients
  – HCV (n=388)
  – HIV/HCV (n=278)

  • 95% on HAART
  • Median CD4 cell count: 376 cells/mm³, HIV RNA <400 copies/mL: 51.2%
  – HCV genotype 1: 79%
  – Mean age of HCV infection: 22.7 years

  • Duration of HCV infection: 24.3 years

• Fibrosis progression rate
  – Ishak necroinflammatory score/duration of HCV infection
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.

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

Has the outcome of liver disease in HIV/HCV-coinfected patients become similar to that in HCV monoinfection?

**Metanalysis of 26 studies**

### No HAART

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (95% CI)</th>
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<tbody>
<tr>
<td>Allory, 2000</td>
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<td>Bierhoff, 1997</td>
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<td>Di Martino, 2001</td>
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<td>Eyster, 1993</td>
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<td>Grabczewska, 2005</td>
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<td>Lesens, 1999</td>
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<td>Makris, 1996</td>
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<tr>
<td>Pol, 1996a</td>
<td></td>
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<tr>
<td>Pol, 1998b</td>
<td></td>
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<td>Romeo, 2000</td>
<td></td>
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<tr>
<td>Serfaty, 2001</td>
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<td>Soto, 1997</td>
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<td>Teller, 1994</td>
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<td>Fixed effects</td>
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<tr>
<td>Random effects</td>
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### HAART

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<th>Study</th>
<th>Risk Ratio (95% CI)</th>
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<td>Benhamou, 1999</td>
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<tr>
<td>Breu, 2006</td>
<td></td>
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<td>Gasightwala &amp; Bini, 2006</td>
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<td>Gonzalez, 2006</td>
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<td>Macias, 2005</td>
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<td>Marine-Barjoan, 2004</td>
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<td>Martinez-Sierra, 2003</td>
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<tr>
<td>Mohsen, 2003</td>
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<td>Monto, 2005</td>
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<td>Rodriguez-Torres, 2006</td>
<td></td>
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<tr>
<td>Sarmento-Castro, 2007</td>
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<tr>
<td>Valle Tovo, 2007</td>
<td></td>
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<tr>
<td>Verma, 2006</td>
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<tr>
<td>Fixed effects</td>
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<tr>
<td>Random effects</td>
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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
HD risk was 83% higher in the coinfected group (aHR 1.83, 95% confidence interval [CI] 1.54 to 2.18)
Which questions need to be addressed?

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» Does successful HAART lead to the same outcome (CD4-count increase etc.) in HIV patients with concomitant liver disease?

» When should we administer ART and which antiretroviral drugs should we choose in coinfection?
HCV seropositivity was associated with a smaller CD4-cell recovery (hazard ratio for a CD4-cell count increase of at least 50 cells/μL = 0.79 [0.72—0.87]).

Figure 4: Evolution of CD4-cell count after start of potent antiretroviral therapy according to HCV serostatus. Error bars = SE.
Kaplan-Meier curve showing time to achieving a plasma HIV-1 RNA load of <500 copies/mL after initiation of highly active antiretroviral therapy (HAART), by hepatitis C virus (HCV) serostatus when HAART was initiated.

P = .99 (log-rank test)

No. under follow-up

<table>
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<tr>
<th></th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
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<tr>
<td>Negative</td>
<td>1340</td>
<td>1064</td>
<td>728</td>
<td>596</td>
<td>494</td>
<td>430</td>
<td>385</td>
</tr>
<tr>
<td>Positive</td>
<td>675</td>
<td>559</td>
<td>390</td>
<td>326</td>
<td>262</td>
<td>231</td>
<td>205</td>
</tr>
</tbody>
</table>

Rockstroh J K et al. J Infect Dis. 2005;192:992-1002
A Kaplan-Meier curve showing time to achieving a $\geq 50\%$ increase in CD4 cell count after initiation of highly active antiretroviral therapy (HAART), by hepatitis C virus (HCV) serostatus when HAART was initiated.

Rockstroh J K et al. J Infect Dis. 2005;192:992-1002

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Liver damage associated with HAART

- Acute toxic hepatitis
- Long-term injury
  - NASH
  - Portal hypertension and nodular regenerative hyperplasia
  - Fibrosis?
Mitochondrial Toxicity

Fischer et al. 2003
Liver damage associated with HAART in the long-term: Noncirrhotic Portal Hypertension and Nodular Regenerative Hyperplasia

- Cases of noncirrhotic PHT increasingly reported in HIV-monoinfected patients\(^{(1-3)}\).

- Histological findings: NRH and hepatoporal sclerosis.

- Associated with long-term ddI exposure.

- Improvement with ddI removal.

## Do PIs contribute to liver steatosis?

Predictors of steatosis in HCV/HIV-coinfected patients in multivariate analyses in studies based on biopsy

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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Geno 3</td>
<td>↑ Plasma triglycerides</td>
<td>ddN (current)</td>
<td>d4T</td>
<td>Fibrosis</td>
<td>Necro-inflammatory activity</td>
<td>d4T (ever)</td>
</tr>
<tr>
<td>BMI</td>
<td>ART≥4 years</td>
<td></td>
<td>Alcohol</td>
<td></td>
<td></td>
<td>Caucasian race</td>
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<tr>
<td>HCV-RNA load</td>
<td></td>
<td></td>
<td>Weight</td>
<td></td>
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<tr>
<td>Ferritin</td>
<td></td>
<td></td>
<td>No LPV-r</td>
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<td>Hyperglicemia</td>
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<tr>
<td>Fibrosis</td>
<td></td>
<td></td>
<td>Fibrosis</td>
<td></td>
<td></td>
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</tbody>
</table>
### EACS Guidelines: When to Start

» **Initiation of ART**

**ART is always recommended if CD4 count <350 cells/mm3**

Serodiscordant couples: Early ART should be considered and actively discussed

<table>
<thead>
<tr>
<th>Condition</th>
<th>Current CD4 + lymphocyte count (II, III)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>350-500</td>
</tr>
<tr>
<td>Asymptomatic HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis</td>
<td>R</td>
</tr>
<tr>
<td>Primary HIV infection</td>
<td>C</td>
</tr>
<tr>
<td>Pregnancy (before third trimester)</td>
<td>R</td>
</tr>
<tr>
<td>Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:</td>
<td></td>
</tr>
<tr>
<td>HIV-associated kidney disease</td>
<td>R</td>
</tr>
<tr>
<td>HIV-associated neurocognitive impairment</td>
<td>R</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>R</td>
</tr>
<tr>
<td>HPV-associated cancers</td>
<td>R</td>
</tr>
<tr>
<td>Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy</td>
<td>C</td>
</tr>
<tr>
<td>Autoimmune disease — otherwise unexplained</td>
<td>C</td>
</tr>
<tr>
<td>High risk for CVD(&gt;20% estimated 10 yr risk) or history of CVD</td>
<td>C</td>
</tr>
<tr>
<td>Chronic viral hepatitis</td>
<td>R</td>
</tr>
<tr>
<td>HBV requiring anti-HBV treatment</td>
<td>R</td>
</tr>
<tr>
<td>HBV not requiring anti-HBV treatment</td>
<td>C/R (IV)</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment is being considered or given</td>
<td>R (VI)</td>
</tr>
<tr>
<td>HCV for which anti-HCV treatment not feasible</td>
<td>R</td>
</tr>
</tbody>
</table>

C = CONSIDER, D = DEFER, R = RECOMMENDED

www.eacs.eu (October 2012)
Median CD4-Nadir according to year of ART start and different HIV transmission groups (n=3094)

- Median CD4-Nadir 45 days prior to and up to 15 days after ART initiation (treatment was initiated ≥1996 and only inclusion of patients with treatment start after being in the cohort for at least 3 months)
Changes in death causes over time

1999-2000
N=255

- AIDS-related: 34%
- Liver-related: 16%
- CVD-related: 10%
- Other/Unknown: 8%

2009-2011
N=548

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

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.
• Favorable liver tolerability and lack of drug-drug interactions make new drug classes appear as attractive components of ART in coinfected patients (particularly after OLTX and during HCV therapy) which need to be further explored.