Hepatic Decompensation Among HIV/Hepatitis C Patients

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VACS Liver Core:
Research Interests

- Natural history of chronic viral hepatitis
  - Chronic hepatitis B (HBV), hepatitis C (HCV)
- Evaluate hepatic decompensation events
  - Screen, confirm events in VACS-8
  - Validity of ICD-9 diagnoses, lab tests
- Determinants, outcomes of liver diseases
  - Initial focus: HIV/HCV-coinfected
Natural History of HCV in HIV

- Emphasis on histologic outcomes
  - Limitations

- Hepatic decompensation
  - Main endpoint of HCV (biopsy not needed)
  - Few studies, esp. in HIV/HCV

- Implications:
  - Assess incidence rates in cohorts
  - Evaluate host, viral, genetic risk factors
  - Predict future decompensation
Specific Aim

- **Specific Aim**: To assess the incidence and determinants of decompensation among ART-treated HIV/HCV-coinfected veterans
  - **Determinants of interest**:
    - History of alcohol abuse / dependence
    - Diabetes mellitus
    - Pre-ART CD4 cell count
    - Hepatitis B coinfection
    - Race
    - FIB-4
Study Design / Setting

- Retrospective cohort study
  - Large sample of HIV/HCV pts
  - Decompensation dxs available, validated
  - Laboratory, pharmacy data available
  - Sufficiently long follow-up
Study Subjects:
Inclusion / Exclusion Criteria

• Inclusion criteria:
  – HCV infection (anti-HCV+, HCV RNA+)
  – HIV infection (anti-HIV+, HIV RNA+)
  – Prescribed ART between 1997 and 2008
  – Detectable HIV RNA (>500 copies/mL) recorded 180 days prior to starting ART

• Exclusion: decompensation at baseline
Main Study Outcome

• Hepatic decompensation:
  – Clinical diagnoses of liver failure
  – 1 inpatient or ≥2 outpatient ICD-9 codes for:
    • Ascites
    • Spontaneous bacterial peritonitis
    • Variceal hemorrhage
  – 91% of patients with this algorithm had decompensation by chart review in VACS-8*

## Data Collection: Covariates

*Variables highlighted in yellow denote primary determinants of decompensation.*

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Health Condition</th>
<th>Lab Data</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Alcohol abuse</td>
<td>ALT</td>
<td>Antiretrovirals</td>
</tr>
<tr>
<td>Sex</td>
<td>Drug abuse</td>
<td>AST</td>
<td>Azole antifungal</td>
</tr>
<tr>
<td>Race</td>
<td>Diabetes mellitus</td>
<td>CD4 count</td>
<td>Duloxetine</td>
</tr>
<tr>
<td>BMI</td>
<td>Decomposition</td>
<td>Creatinine</td>
<td>Interferon</td>
</tr>
<tr>
<td>VA region</td>
<td>Liver transplant</td>
<td>FIB-4</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>Year of ART</td>
<td></td>
<td>Platelets</td>
<td>Methadone</td>
</tr>
<tr>
<td>Death (NDI)</td>
<td></td>
<td>HBsAg</td>
<td>Naltrexone</td>
</tr>
</tbody>
</table>

### Data Collection: Covariates

- **Demographic**: Age, Sex, Race, BMI, VA region, Year of ART, Death (NDI)
- **Health Condition**: Alcohol abuse, Drug abuse, Diabetes mellitus, Decomposition, Liver transplant
- **Lab Data**: ALT, AST, CD4 count, Creatinine, FIB-4, Platelets, HBsAg, Hemoglobin, HIV RNA
- **Medications**: Antiretrovirals, Azole antifungal, Duloxetine, Interferon, Isoniazid, Methadone, Naltrexone, Metformin / TZD, Statins, Valproic acid
Data Collection: Baseline
Risk Factors for Decompensation

- Alcohol abuse: ICD-9 codes*
- Diabetes mellitus (DM):
  - Random glucose level \( \geq 200 \text{ mg/dL} \)
  - Oral hypoglycemic drug / insulin
- Hepatitis B coinfection: HBsAg+
- FIB-4 score: >3.25 \( \rightarrow \) advanced fibrosis
- Pre-ART CD4 count (per 100/mm\(^3\))
- Race: Black vs. other

Data Analysis: Follow-up

- **Baseline period:** initial 365 days on ART
  - Collect baseline covariate data
- **Start of follow-up:** day 366 of ART
- **End of follow-up:**
  - Hepatic decompensation
  - Death
  - Last visit before 12/31/2010
Data Analysis: Incidence, Risk of Decompensation

- Cumulative incidence of decompensation
- Median time to:
  - Hepatic decompensation
  - Death from decompensation
- Cox regression:
  - Adjusted HRs of decompensation for risk factors of interest
Results: Subject Selection

9,967 HIV/HCV Patients Prescribed ART in VACS Virtual Cohort (1996-2008)

3,577 Excluded:
- 122 Hepatic decompensation at baseline
- 875 Prescribed ART before 1997
- 1,487 HIV RNA <500 within 180 days prior to ART
- 1,093 missing HIV RNA within 180 days prior to ART

6,390 ART-Treated HIV/HCV Patients
## Results: Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=6,390)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs, IQR)</td>
<td>48 (44-52)</td>
</tr>
<tr>
<td>Male sex (no., %)</td>
<td>6,278 (98.2%)</td>
</tr>
<tr>
<td>Black race (no., %)</td>
<td>3,984 (62.3%)</td>
</tr>
<tr>
<td>Alcohol abuse (no., %)</td>
<td>1,546 (24.2%)</td>
</tr>
<tr>
<td>Drug abuse (no., %)</td>
<td>2,047 (32.0%)</td>
</tr>
<tr>
<td>Diabetes mellitus (no., %)</td>
<td>438 (6.9%)</td>
</tr>
</tbody>
</table>
## Results: Laboratory Data

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>(n=6,390)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Med log&lt;sub&gt;10&lt;/sub&gt; pre-ART HIV RNA (c/mL, IQR)</strong></td>
<td>4.7 (3.9-5.2)</td>
</tr>
<tr>
<td><strong>Med Pre-ART CD4 (/mm&lt;sup&gt;3&lt;/sup&gt;, IQR)</strong></td>
<td>209 (87-335)</td>
</tr>
<tr>
<td><strong>HBsAg+ (no., %)</strong></td>
<td>596 (9.3%)</td>
</tr>
<tr>
<td><strong>FIB-4 &gt;3.25 (no., %)</strong></td>
<td>916 (16.8%)</td>
</tr>
<tr>
<td><strong>Hemoglobin &lt;10 gm/dL (no., %)</strong></td>
<td>189 (3.5%)</td>
</tr>
</tbody>
</table>
# Results: Follow-up and Clinical Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>(n=6,390)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (mo, IQR)</td>
<td>75.7 (38.6-120.7)</td>
</tr>
<tr>
<td>Hepatic decompensation (no., %)</td>
<td>381 (6.0%)</td>
</tr>
<tr>
<td>Median time to decomp (mo, IQR)</td>
<td>48.3 (23.5-72.0)</td>
</tr>
<tr>
<td>Liver transplantation (no., %)</td>
<td>17 (0.3%)</td>
</tr>
<tr>
<td>Deaths (no., %)</td>
<td>2,390 (37.4%)</td>
</tr>
<tr>
<td>Deaths among decomp (no., %)</td>
<td>289 (75.9%)</td>
</tr>
<tr>
<td>Time to death from decomp (mo, IQR)</td>
<td>4.7 (0.9-16.0)</td>
</tr>
</tbody>
</table>
# Risk Factors for Decompensation

<table>
<thead>
<tr>
<th>Baseline Risk Factor</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of alcohol abuse</td>
<td>1.18 (0.88 – 1.60)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.15 (0.75 – 1.77)</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1.33 (0.96 – 1.83)</td>
</tr>
<tr>
<td>Pre-ART CD4 (per 100/mm$^3$)</td>
<td>0.99 (0.94 – 1.05)</td>
</tr>
<tr>
<td>Black race</td>
<td>0.57 (0.45 – 0.71)</td>
</tr>
<tr>
<td><strong>FIB-4 (ref, FIB-4&lt;1.45)</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;3.25</td>
<td>8.17 (6.00 – 11.11)</td>
</tr>
<tr>
<td>1.45 – 3.25</td>
<td>2.14 (1.57 – 2.92)</td>
</tr>
<tr>
<td>Hemoglobin &lt;10 gm/dL</td>
<td>2.15 (1.27 – 3.62)</td>
</tr>
</tbody>
</table>

* Additionally adjusted for age, sex, drug use, region, and serum creatinine.
Preliminary Conclusions

• High cumulative incidences of:
  – Hepatic decompensation
  – Death

• Short time to death from decompensation

• Risk factors for decompensation:
  – ↑ FIB-4
  – Hemoglobin <10 gm/dL
  – Non-Black race
Future VACS Liver Core Work

- Meds as risk factors for decompensation
- Compare outcomes in HIV/HCV vs. HCV
- Develop predictive index to stratify HIV/HCV pts by risk of decompensation
- Examine endpoints in chronic HBV
- Evaluate acute liver failure among pts with drug-induced hepatitis (AHRQ R01)
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