Occult liver cirrhosis diagnosed by transient elastography is frequent and under-monitored in HIV-infected patients: results of a large-scale screening program

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Disclosures

- Speaker for Merck, Gilead, ViiV, Abbvie
- Advisory board member for Merck
- I received unrestricted research funding from Merck, Echosens
Background

- Liver disease has become a leading cause of death in aging HIV+ patients on cART

- Multiple and unique risk factors
  - Metabolic conditions
    - Abdominal obesity
    - Insulin resistance
    - Diabetes
    - Lipids
  - Prolonged cART use
    - Lipodystrophy
    - Hepatotoxicity
    - Insulin resistance
  - HIV itself
    - HIV viral load
    - Pro-apoptotic effect of HIV on hepatocytes
  - Patient features
    - HCV / HBV co-infection
    - Gut dysbiosis
    - Alcohol

- Diagnosis of liver cirrhosis at preclinical stage is challenging due to lack of any clinical sign


Occult liver cirrhosis

Trasient elastograhy (TE) measurement ≥13kPa without any clinical sign suggesting cirrhosis (ultrasonographic, endoscopic or laboratory)

871 HCV/HBV/NAFLD

- Clinically evident cirrhosis: 19%
- Occult cirrhosis: 12%
- No cirrhosis: 69%

2,876 HBV

**LIVEHIV Cohort**  
(LIVER disease in HIV)

- Prospective routine screening program for liver disease started in September 2013 at McGill targeting epidemiology, natural history and potential interventions.
- Consecutive patients undergo a screening for liver disease (HCV and HBV serology, AUDIT-C, TE examination).
- As of September 2017, 725 HIV mono-infected patients have been enrolled.

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**The Canadian Coinfection Cohort**  
2003-2017 (n=1,756)

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*Canadian Coinfection Cohort, unpublished*
Aims of the Study

- To investigate prevalence and predictors of occult cirrhosis (OC) diagnosed by TE in HIV+ patients in the LIVEHIV Cohort and the Canadian Coinfection Cohort

- To determine evolution of OC and patterns of surveillance for HCC and esophageal varices

Study Design

Observational longitudinal cohort study

**Inclusion criteria:** Age >18 years, HIV+

**Exclusion criteria:**
- Failure or unreliable TE examination by M or XL probe
- Pregnant at cohort entry; Pacemaker
- Decompensated cirrhosis, HCC at entry

**Statistics:**
- Logistic regression analysis for predictors of OC
- Survival analysis for time to outcomes
Methods: Occult Cirrhosis and Outcomes

**OC**

TE >13 kPa and absence of:
- Thrombocytopenia (PLT < 140 000)
- US signs of advanced liver disease (nodularity/irregularity of liver surface, hypertrophy of caudate lobe, coarseness/increased attenuation of liver texture, splenomegaly ≥ 14cm)
- Ascites
- Endoscopic signs of portal hypertension (esophageal varices, portal hypertensive gastropathy)

**Outcomes**

- Ascites
- Varices with bleeding/banding
- SBP
- Hepatic encephalopathy
- Hepato-renal syndrome
- ESLD-related death

Figure 1: Sample Selection Flow Chart

<table>
<thead>
<tr>
<th>All patients enrolled in the Canadian Co-Infection Cohort (CCC) and the LIVEHIV Cohort</th>
<th>n=1,228</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCC</td>
<td>LIVEHIV</td>
</tr>
<tr>
<td>n = 1,756</td>
<td>n = 725</td>
</tr>
</tbody>
</table>

Excluding CCC patients enrolled in centers not participating in the FibroScan sub-study

<table>
<thead>
<tr>
<th>CCC</th>
<th>LIVEHIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 877 (49.9%)</td>
<td>n = 725 (100%)</td>
</tr>
</tbody>
</table>

Excluding patients with no available FibroScan measures

<table>
<thead>
<tr>
<th>CCC</th>
<th>LIVEHIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 586 (66.8%)</td>
<td>n = 725 (100%)</td>
</tr>
</tbody>
</table>

Excluding patients with no available FibroScan measures considered reliable

<table>
<thead>
<tr>
<th>CCC</th>
<th>LIVEHIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 545 (93%)</td>
<td>n = 683 (94.2%)</td>
</tr>
</tbody>
</table>

Excluding patients who were not aged 18 years or older at their first FibroScan measure

<table>
<thead>
<tr>
<th>CCC</th>
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<td>n = 545 (100%)</td>
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</tr>
</tbody>
</table>
# Results

## Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No cirrhosis (n=1,064)</th>
<th>OC (n=33)</th>
<th>Overt cirrhosis (n=131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>49 (41-55)</td>
<td><strong>51 (45-55)</strong></td>
<td>53 (48-58)</td>
</tr>
<tr>
<td>Female sex (%)</td>
<td>26</td>
<td>28</td>
<td>21</td>
</tr>
<tr>
<td>Black non-Hispanic (%)</td>
<td>21</td>
<td><strong>10</strong></td>
<td>8</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>18</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>13</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>25 (23-28)</td>
<td>27 (24-31)</td>
<td>25 (22-28)</td>
</tr>
<tr>
<td>Time since HIV diagnosis (yrs)</td>
<td>11 (6-19)</td>
<td><strong>19 (14-26)</strong></td>
<td>19 (12-24)</td>
</tr>
<tr>
<td>Nadir CD4 (cells/mL)</td>
<td>209 (99-350)</td>
<td><strong>121 (28-290)</strong></td>
<td>153 (89-277)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>29 (20-47)</td>
<td><strong>41 (29-84)</strong></td>
<td>45 (29-79)</td>
</tr>
</tbody>
</table>
Overall Prevalence

- **Whole cohort**: 86.6% (20% of all cirrhatics, 2.7% occult cirrhosis, 10.7% overt cirrhosis)
- **HIV mono-infected**: 95.6% (45% of all cirrhatics, 2% occult cirrhosis, 2.4% overt cirrhosis)
- **HIV/HCV co-infected**: 79% (15% of all cirrhatics, 3.2% occult cirrhosis, 17.8% overt cirrhosis)

Incidence of OC (per 100 PY)

- **HIV/HCV**: 0.8
- **HIV mono**: 1.2
### Independent predictors of OC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>0.97 (0.42 ; 2.03)</td>
<td>1.29 (0.54 ; 2.84)</td>
</tr>
<tr>
<td>Alcohol abuse in past year</td>
<td>1.04 (0.35 ; 2.51)</td>
<td>1.19 (0.39 ; 3.03)</td>
</tr>
<tr>
<td>BMI (per 5 units)</td>
<td>1.19 (0.9 ; 1.5)</td>
<td>1.27 (0.96 ; 1.62)</td>
</tr>
<tr>
<td>Diabetes in past year</td>
<td>1.67 (0.73 ; 3.52)</td>
<td>1.85 (0.74 ; 4.34)</td>
</tr>
<tr>
<td>Nadir CD4 count (per 100 cells)</td>
<td>0.94 (0.77 ; 1.12)</td>
<td>0.93 (0.76 ; 1.11)</td>
</tr>
<tr>
<td>Detectable HIV RNA in past year</td>
<td>0.69 (0.2 ; 1.79)</td>
<td>0.77 (0.22 ; 2.08)</td>
</tr>
<tr>
<td>Hepatitis C co-infection</td>
<td>1.21 (0.61 ; 2.36)</td>
<td>1.7 (0.75 ; 3.85)</td>
</tr>
<tr>
<td>HIV duration (per 5 years)</td>
<td>1.39 (1.15 ; 1.69)</td>
<td>1.47 (1.17 ; 1.84)</td>
</tr>
</tbody>
</table>

Results reported as median (IQR) or proportion

- Incidence rates of any liver event: 3.3 per 100 PY in OC
  - 3.7 per 100 PY in overt cirrhosis
  - 0.3 per 100 PY no cirrhosis

Kaplan-Meier curve: Any liver event during follow-up

- 50% ascites, 25% HCC, 25% ESLD death
## Surveillance

<table>
<thead>
<tr>
<th></th>
<th>OC</th>
<th>Overt cirrhosis</th>
<th>No cirrhosis</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasound</td>
<td>1.93 (1.82)</td>
<td>3.10 (1.53)</td>
<td>1.27 (1.23)</td>
<td>0.005</td>
</tr>
<tr>
<td>Gastroscopies</td>
<td>0.33 (0.73)</td>
<td>1.17 (1.43)</td>
<td>0.16 (0.47)</td>
<td>0.007</td>
</tr>
<tr>
<td>Surveillance for cirrhosis</td>
<td>11%</td>
<td>46%</td>
<td>NA</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Results reported as mean (standard deviation) or proportion*

## Summary

- OC diagnosed by TE is relatively **frequent** in two large cohorts of Canadians living with HIV
- The main risk factor is **duration of HIV infection**
- HIV+ patients with OC are **undermonitored** and they can develop serious liver complications
- Our findings suggest the need for implementing **screening strategies** for early detection and appropriate surveillance to prevent long-term liver complications
Investigators in the CCC participating into the Fibroscan substudy
Dr. Conway, Vancouver ID Research centre
Dr Cooper, Ottawa Hospital
Dr. Haider, Hamilton Health Sciences
Dr. Pick - Oak Tree
Dr. Vachon, CHUL
Dr. Walmsley, Toronto General Hospital
Dr. Wong, Regina General Hospital