HCV viremia increases the risk of chronic kidney disease in HIV-infected patients

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Background

- Although cART has resulted in a decrease in HIV-associated nephropathy, chronic kidney disease (CKD) is still an important cause of morbidity and mortality in HIV patients.

- High prevalence of risk factors (hypertension, diabetes, smoking) for CKD in HIV patients.

- In Europe around a third of all HIV patients are co-infected with hepatitis C virus (HCV).
HCV can cause glomerulonephritis (± cryoglobulinemia)

HCV has been associated with higher risk of diabetes mellitus, which may contribute to the development of CKD

HCV-related liver disease can cause CKD (hepatorenal syndrome)
The Impact of HCV coinfection of HIV-related CKD: a meta-analysis

Limitation: Hepatitis C diagnosis based on antibody status

EuroSIDA

Wyatt et al; AIDS 2008
Objectives

• To investigate the association of HCV viremia and genotype with incidence of CKD in the EuroSIDA observational cohort
Methods (1)

- Eligible patients:
  - ≥3 serum creatinine measurements after 01.01.04,
  - body weight measured within ≤12 months of each creatinine measurement
  - known HCVAb status

- Baseline was the first available estimated glomerular filtration rate (eGFR) (Cockcroft-Gault equation)
  - $eGFR = \frac{(140 \text{- age}) \times \text{weight (kg)} \times 0.85 \text{ (if female)}}{\text{Serum creatinine} \times 72}$

- eGFR standardised for body surface area
Methods (2)

- **CKD:**
  - i) a confirmed eGFR ≤ 60 mL/min/1.73m² for patients with eGFR >60 mL/min/1.73m² at baseline, or
  - ii) a confirmed 25% decline in eGFR for patients with eGFR <60 mL/min/1.73m² at baseline

- **HCV viremic defined as HCV-RNA >615 IU/mL**
  - Low viremia: 615 – 500,000 IU/ml
  - High viremia: >500,000 IU/ml

- **Follow-up was from baseline to either CKD or the last eGFR measurement**

- **Incidence rates of CKD were compared between groups using Poisson regression**
EuroSIDA
N=16597

Patients that meet entry criteria
N=8014

Anti-HCV negative
N=6047

HCV-RNA negative
N=184

HCV-RNA RNA 615 – 500,000 IU/ml
N=452

Anti-HCV positive
N=1967

HCV-RNA unknown
N=826

HCV-RNA RNA >500,000 IU/ml
N=505
Baseline Characteristics of 8014 HIV patients according to HCV serostatus

<table>
<thead>
<tr>
<th></th>
<th>Anti-HCV+ N=1967 (24.5%)</th>
<th>Anti-HCV– N=6047 (75.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) years</td>
<td>39 (33 – 44)</td>
<td>42 (36 – 50)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>68.0%</td>
<td>75.9%</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>91.8%</td>
<td>85.7%</td>
</tr>
<tr>
<td>Risk group (IDU)</td>
<td>71.2%</td>
<td>2.5%</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>6.7%</td>
<td>5.9%</td>
</tr>
<tr>
<td>CD4 nadir, median (IQR) cells/µl</td>
<td>131 (49 – 223)</td>
<td>146 (51 – 245)</td>
</tr>
<tr>
<td>cART at baseline</td>
<td>82.8%</td>
<td>86.6%</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>4.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>51.5%</td>
<td>28.2%</td>
</tr>
<tr>
<td>ACE inhibitor use</td>
<td>2.2%</td>
<td>4.6%</td>
</tr>
<tr>
<td>eGFR median (IQR) ml/min per 1.73m²</td>
<td>100 (86.6 – 116.1)</td>
<td>96.6 (82.8 – 112.0)</td>
</tr>
</tbody>
</table>

All P-values <0.0002
## Baseline Characteristics of anti-HCV+ patients according to HCV-RNA status

<table>
<thead>
<tr>
<th></th>
<th>HCV-RNA+ N=957</th>
<th>HCV-RNA– N=184</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) years</td>
<td>40 (36 – 45)</td>
<td>41 (38 – 45)</td>
<td>0.12</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>68.1%</td>
<td>64.1%</td>
<td>0.29</td>
</tr>
<tr>
<td>Risk group (IDU)</td>
<td>74.0%</td>
<td>64.1%</td>
<td>0.0001</td>
</tr>
<tr>
<td>HBsAg+</td>
<td>5.4%</td>
<td>14.7%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>cART at baseline</td>
<td>90.5%</td>
<td>90.2%</td>
<td>0.64</td>
</tr>
<tr>
<td>CD4+ nadir median (IQR) cells/µl</td>
<td>124 (41 – 211)</td>
<td>92 (23.5 – 176)</td>
<td>0.013</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.8%</td>
<td>5.4%</td>
<td>0.29</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>5.0%</td>
<td>4.4%</td>
<td>0.70</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>56.3%</td>
<td>54.4%</td>
<td>0.21</td>
</tr>
<tr>
<td>ACE inhibitor use</td>
<td>2.2%</td>
<td>4.4%</td>
<td>0.94</td>
</tr>
<tr>
<td>eGFR median (IQR) ml/min per 1.73m²</td>
<td>99.9 (86.8 – 115.2)</td>
<td>102.0 (86.7 – 114.6)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Results

- Median number of eGFR measurements/patient was 11 (IQR 7-16)
- A total of 419 patients (5.5%) progressed to CKD during 30164 PYFU
- Incidence of CKD 13.9/1000 PYFU (95% CI 12.6–15.2)
Progression to CKD
(All patients; 419 events)

Incidence Rate Ratio (95% CI)

Age (per 10 years older)
Gender (men vs women)
AIDS during follow up
CD+ nadir (per 100 cells higher)
Hypertension
Anti-HCV (pos vs neg)
Tenofovir*
Indinavir*
Atazanavir*
Lopinavir*
Baseline eGFR (per 5 ml higher)

Univariate
Multivariate

*per year cumulative exposure
Progression to CKD
(All patients; 419 events)

Incidence Rate Ratio (95% CI)

- Age (per 10 years older)
- Gender (men vs women)
- AIDS during follow up
- CD+ nadir (per 100 cells higher)
- Hypertension
- Anti-HCV (pos vs neg)
- Tenofovir*
- Indinavir*
- Atazanavir*
- Lopinavir*
- Baseline eGFR (per 5 ml higher)

*per year cumulative exposure
Role of HCV Viremia and Genotype in Progression to CKD

Adjusted incidence rate ratio (95% CI) p-value

**HCVAb negative**

- HCVAb positive

**HCVAb negative**

- HCVAb+ / <615 IU/ml
- 615 – 500.000 IU/ml
- >500.000 IU/ml
- Unknown

**HCV genotype 2-4**

- HCV genotype 1

**EuroSIDA**
Sensitivity analysis

• Adjustment for intravenous drug use did not change the results, and was not included in the final model due to collinearity between this variable and HCV status
Summary

• Patients with chronic HCV infection were at higher risk of CKD

• Higher HCV-RNA levels were associated with an increased risk of CKD

• The risk of CKD was similar in anti-HCV negative patients and anti-HCV+ patients with resolved infection

• HCV genotype was not significantly associated with risk of CKD
Perspectives

- The mechanisms by which HCV may affect renal function are unclear and warrant further study
  - Direct effect of the virus?
  - Marker of severe liver disease?

- Should HIV/HCV coinfected patients avoid ARVs associated with risk of CKD?
- Does anti-HCV treatment reverse the decline in renal function in HCV patients with CKD?
The multi-centre study group of EuroSIDA (national coordinators in parenthesis).

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