Plasma cystatin C as a marker for estimated glomerular filtration rate assessment in HIV-1-infected patients with dolutegravir-based antiretroviral therapy

• Dolutegravir (DTG) is the most recent integrase inhibitor, widely used in current antiretroviral therapies (ART).

• Inhibition of OCT-2 renal tubule transporter by DTG leads to plasma creatinine increase, without renal impairment, with decrease of creatinine-based estimated glomerular filtration rate (eGFR).

Osterholzer, CID, 2014
Maggi, AIDS Rev, 2014
Koteff, Br J Clin Pharmacol, 2013
• To monitor the renal function is a daily clinical concern, especially in aging patients with comorbidities, including cancers, requiring the use of nephrotoxic drugs.

• Plasma cystatin C is a non-OCT-2 dependent routinely available marker, which could estimate GFR on DTG with a validated equation.
To evaluate the changes in creatinine- and cystatin-based eGFR after DTG initiation, in HIV-infected patients from a French reference center
Methods


DTG initiation (in the 6 last months)

- No ART or DTG-free ART regimen
- DTG-based ART regimen

ART naïve patient or pretreated patient (without systemic inflammation or thyroïd dysfunction)

0-90 days

Plasma creatinine and cystatin C measurements

GFR estimation (CKD-EPI_\text{creat} and CKD-EPI_\text{cyst})

21-180 days

Plasma creatinine and cystatin C measurements

GFR estimation (CKD-EPI_\text{creat} and CKD-EPI_\text{cyst})

Paired t-test
176 eligible patients (DTG initiation), 44 patients included.

<table>
<thead>
<tr>
<th>Patients’ characteristics (N=44)</th>
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<tbody>
<tr>
<td>Men</td>
<td>28</td>
</tr>
<tr>
<td>Women</td>
<td>16</td>
</tr>
<tr>
<td>Caucasian subjects</td>
<td>29</td>
</tr>
<tr>
<td>Black subjects</td>
<td>15</td>
</tr>
<tr>
<td>Age (median [IQR])</td>
<td>48 years (36-58)</td>
</tr>
<tr>
<td>CD4 count at baseline (median [IQR])</td>
<td>592/mm$^3$ (388-728)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>12</td>
</tr>
<tr>
<td>Treated high blood pressure</td>
<td>13</td>
</tr>
<tr>
<td>Treated diabetes</td>
<td>3</td>
</tr>
<tr>
<td>HBV co-infection</td>
<td>0</td>
</tr>
<tr>
<td>Cured HCV co-infection</td>
<td>4</td>
</tr>
</tbody>
</table>
Antiretroviral regimens (n=44)

<table>
<thead>
<tr>
<th></th>
<th>Before DTG introduction</th>
<th>After DTG introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve patients</td>
<td>6 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>More than 3 drugs</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Triple therapy</td>
<td>32 (73%)</td>
<td>27 (61%)</td>
</tr>
<tr>
<td>Dual therapy</td>
<td>5 (12%)</td>
<td>16 (37%)</td>
</tr>
<tr>
<td>TDF-based regimen*</td>
<td>20 (46%)</td>
<td>9 (20%)</td>
</tr>
</tbody>
</table>

* 3 TDF toxicities involved ART switch.

- For ART naive patients: median pVL $4.8 \log_{10}$ cp/ml (IQR 4.3-5.2).
- For pretreated patients: median ART duration 13 years (IQR 5-20), 28 (64%) with pVL <50 cp/ml.

Plasma creatinine and cystatin C values at baseline

<table>
<thead>
<tr>
<th></th>
<th>Creatinine (micromol/l)</th>
<th>Cystatin C (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (micromol/l)</td>
<td>85.6 ($\pm$21.5)</td>
<td></td>
</tr>
<tr>
<td>Cystatin C (mg/l)</td>
<td>0.80 ($\pm$0.29)</td>
<td></td>
</tr>
</tbody>
</table>

Creatinine-associated eGFR

<table>
<thead>
<tr>
<th></th>
<th>&gt;90 ml/min</th>
<th>&lt;90 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 (57%)</td>
<td></td>
<td></td>
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</table>

Cystatin-associated eGFR

<table>
<thead>
<tr>
<th></th>
<th>&gt;90 ml/min</th>
<th>&lt;90 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>33 (75%)</td>
<td></td>
<td></td>
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<tr>
<td>11 (25%)</td>
<td></td>
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</tbody>
</table>
Median time for samples: 9 days (2-17) before DTG introduction and 41 days (29-72) after DTG introduction.

**All patients (n=44)**

- Creatinine-based eGFR <90 ml/min after DTG initiation (n=19)
  - Before DTG initiation: 91.5 ml/min
  - After DTG initiation: 106.2 ml/min
  - p=0.57

- Creatinine-based eGFR >90 ml/min after DTG initiation (n=19)
  - Before DTG initiation: 83.8 ml/min
  - After DTG initiation: 108.7 ml/min
  - p<0.001

**Creatinine-based eGFR**

- Before DTG initiation: 109.6 ml/min
- After DTG initiation: 117 ml/min
- p<0.001

**Cystatin-based eGFR**

- Before DTG initiation: 65.2 ml/min
- After DTG initiation: 98.4 ml/min
- p=0.46
Conclusion

• Creatinine-based eGFR decreased after DTG initiation. In the same time, cystatin-based eGFR remained stable after DTG initiation, regardless the creatinine value at baseline.

• **In patients with DTG-based ART regimen, renal function can be assessed by the monitoring of plasma cystatin C.**

• Creatinine-based eGFR were lower than cystatin-based eGFR at baseline. Cystatin-based equation (CKD-EPI\textsubscript{cyst}) could be better than creatinine-based equations (MDRD, CKD-EPI\textsubscript{creat}) in HIV-infected patients.

• Limits: sample size (especially for patients with advanced chronic kidney disease), only one value of creatinine / cystatin C after DTG initiation.
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