Exposure to antiretrovirals (ARVs) and development of chronic kidney disease (CKD) in HIV infection

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Introduction

• Some commonly used antiretrovirals in HIV associated with higher risks of renal impairment which increases with antiretroviral exposure\textsuperscript{1-4}
  
  … Exposure to tenofovir associated with initial decline in eGFR which does not persist with increasing exposure\textsuperscript{5-6}
  
  … Ritonavir-boosted protease inhibitors inhibit creatinine secretion associated with minor eGFR changes\textsuperscript{7}

• Clinical trials report short term toxicities, cohort studies give a more realistic picture of potential toxicities associated with long term use

\textsuperscript{1}\textsuperscript{Ryom JID 2013; 2Mocroft AIDS 2010; 3Scherzer AIDS 2012; 4Hamada CID 2012; 5Laprise CID 2013; 6Arribas JAIDS 2008; 7Yombi AIDS 2014.}
Study Objective

• Determine the cumulative effect of increasing exposure to antiretrovirals on development of CKD in HIV+ persons with an initially normal renal function (>90 mL/min/1.73m²)
The D:A:D study

The Data Collection on Adverse events of Anti-HIV Drugs Study

- Prospective multi-cohort collaborative study of HIV+ persons under active follow up
- Initiated in 2001 to assess the incidence of MI among HIV+ persons receiving ART
- 11 participating cohorts, > 49,000 HIV+ persons from 212 clinics in 33 countries in Europe, USA and Australia
- Data collection at least every 8 months
- Each cohort gathers/computerises data which is subsequently merged at CHIP
- Central validation of key clinical events – CV, malignancies, liver, end stage renal disease
- Data analyses primarily at UCL
Methods (1)

• Baseline: first eGFR after 1/1/2004

• D:A:D* participants followed from baseline until earliest of
  ... CKD
  ... last eGFR
  ... 1/1/2013
  ... last visit plus 6 months

• Exclusions
  ... <2 eGFRs after baseline
  ... baseline eGFR <90 ml/min/1.73m²

• eGFRs calculated using Cockcroft Gault, standardised for body surface area

*The Data Collection on Adverse events of Anti-HIV Drugs
Definitions
• CKD: confirmed (>3 mths apart) eGFR <60

Statistical methods
• Poisson regression to estimate the incidence of CKD associated with cumulative exposure to
  … Tenofovir (TDF)
  … Ritonavir-boosted atazanavir (ATV/r)
  … Lopinavir (LPV/r)
  … Other ritonavir-boosted protease inhibitors (PI/r)
  … Abacavir (ABC)
### Patient characteristics at baseline

**N=23560**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Did not develop CKD</th>
<th>Developed CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>All</td>
<td>23350</td>
<td>99.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16982</td>
<td>72.7</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>10647</td>
<td>45.6</td>
</tr>
<tr>
<td>HIV Risk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM / IDU</td>
<td>10495</td>
<td>44.9</td>
</tr>
<tr>
<td></td>
<td>/ 3002</td>
<td>12.9</td>
</tr>
<tr>
<td>Hypertension¹</td>
<td>Yes</td>
<td>1812</td>
</tr>
<tr>
<td>CVD¹</td>
<td>Yes</td>
<td>106</td>
</tr>
<tr>
<td>Diabetes¹</td>
<td>Yes</td>
<td>705</td>
</tr>
<tr>
<td>HCV+</td>
<td>Yes</td>
<td>3057</td>
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<tr>
<td>AIDS</td>
<td>Yes</td>
<td>5096</td>
</tr>
<tr>
<td>VL &lt; 400</td>
<td>Yes</td>
<td>13142</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>39</td>
</tr>
<tr>
<td>CD4</td>
<td>/mm³</td>
<td>441</td>
</tr>
<tr>
<td>Nadir CD4</td>
<td>/mm³</td>
<td>240</td>
</tr>
<tr>
<td>eGFR</td>
<td>mL/min/1.73m²</td>
<td>110</td>
</tr>
</tbody>
</table>

¹Ryom et al, JID 2013; IQR interquartile range. Baseline: first eGFR after 1 January 2004
Exposure to antiretrovirals at/before baseline

Ever started antiretroviral at/before baseline

<table>
<thead>
<tr>
<th>Drug</th>
<th>N</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>5353</td>
<td>24.4</td>
</tr>
<tr>
<td>Atazanavir/r</td>
<td>1298</td>
<td>5.5</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>5185</td>
<td>22.0</td>
</tr>
<tr>
<td>Other boosted PI/r</td>
<td>4376</td>
<td>18.6</td>
</tr>
<tr>
<td>Abacavir</td>
<td>5272</td>
<td>22.4</td>
</tr>
</tbody>
</table>

Percentage

Median (IQR) years exposure to antiretroviral among those ever started at/before baseline

- Tenofovir
- Atazanavir/r
- Lopinavir/r
- Other boosted PI/r
- Abacavir

- Off antiretroviral at baseline
- On antiretroviral at baseline
Crude incidence rates of CKD and cumulative exposure to tenofovir and abacavir

**Cumulative exposure to drug**
- □: 0 (never exposed)
- ○: 2 – 3 years
- ·: 3 – 4 years
- ◇: 5 – 6 years
- ◊: > 6 years
- X: 1 – 2 years
- □: 4 – 5 years

**Crude incidence rate / 1000 PYFU (95% CI)**

**Number of events**
- Tenoforvir: 45, 27, 27, 19, 23, 22, 18, 29, 91, 39, 19, 10, 12, 12, 6, 21
- Abacavir: 45, 27, 27, 19, 23, 22, 18, 29, 91, 39, 19, 10, 12, 12, 6, 21

CKD; chronic kidney disease; confirmed (>3 months part) eGFR < 60 mL/min/1.73m²
Crude incidence rates of CKD and cumulative exposure to atazanavir/r, lopinavir/r and other boosted PI/r

**Cumulative exposure to drug**
- ■ 0 (never exposed)
- ○ 2 – 3 years
- — 5 – 6 years
- ● 3 – 4 years
- ◇ > 6 years
- X 1 – 2 years
- □ 4 – 5 years

CKD; chronic kidney disease; confirmed (>3 months part) eGFR < 60 mL/min/1.73m²
Relationship between increasing exposure to antiretrovirals and CKD

Univariate

Incidence rate ratio per year additional exposure to ARV (95% CI)
Relationship between increasing exposure to antiretrovirals and CKD

- **Univariate**  
- **Multivariate**

Multivariate models are adjusted for race, risk, study, gender, nadir CD4, date of baseline, eGFR at baseline, and hbv, hcv, smoking status, BMI, family history, viral load, CD4, a new AIDS diagnosis within the past 12 months, all as time updated variables where appropriate.  
Models were additionally adjusted for cumulative exposure to indinavir.
Limitations

• D:A:D does not have data on proteinuria and limited information on race from some participating cohorts

• Not yet enough power / follow-up to look at unboosted atazanavir or newer antiretrovirals

• Considerably longer follow-up needed to determine if plateau in increased risk reached after longer exposure

• Analyses with CKD as endpoint confounded by switching antiretrovirals (esp. tenofovir) as eGFR declines
Conclusions

• Study shows cumulative increasing risk of CKD with increasing exposure to tenofovir, atazanavir/r, lopinavir/r in persons with an initially normal eGFR

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>ATV/r</th>
<th>LPVr</th>
</tr>
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<tbody>
<tr>
<td>1 year</td>
<td>1.12</td>
<td>1.27</td>
<td>1.16</td>
</tr>
<tr>
<td>2 years</td>
<td>1.25</td>
<td>1.61</td>
<td>1.35</td>
</tr>
<tr>
<td>5 years</td>
<td>1.76</td>
<td>3.30</td>
<td>2.10</td>
</tr>
<tr>
<td>10 years</td>
<td>3.11</td>
<td>10.92</td>
<td>4.41</td>
</tr>
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• Although a modest effect per year, risk is cumulative over time

• These data demonstrate the importance of cohort studies, including large numbers of patients over long periods of time, where routinely measured data can be used to provide important information not available from shorter studies
Perspective

• Analyses show value of data mining and bioinformatics analyses

• Linking immunodeficiency and interventions with organ dysfunction

• PERSIMUNE can expand on our understanding in relation to other patient groups, interventions and outcomes
Acknowledgements

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