Chronic kidney disease and exposure to antiretroviral drugs in a large cohort with long-term follow-up: The EuroSIDA Study

Ole Kirk, Amanda Mocroft, Peter Reiss, Stephane De Wit, Dalibor Sedlacek, Marek Beniowski, Jose Gatell, Andrew Phillips, Bruno Ledergerber, Jens Lundgren, for the EuroSIDA Study Group
Background

- Renal impairment in HIV-positive persons might be caused by traditional and HIV-related factors

- Impact of long-term exposure to specific antiretrovirals (ARVs) remains poorly elucidated

- Chronic kidney disease (CKD)*: a persistent reduction in glomerular filtration rate (GFR) to below 60 ml/min/1.73m² and/or albuminuria

*: National Institute of Diabetes and Digestive and Kidney Diseases
Methods (I)

- The EuroSIDA study, 103 clinics in 35 countries

- Eligible patients: ≥3 serum creatinine and corresponding body weight measurements from 2004 and onwards

- CKD defined as confirmed:
  - eGFR ≤60 if baseline eGFR >60 mL/min/1.73m²
  - 25% decline if baseline eGFR ≤60 mL/min/1.73m²

- Primary analysis: Cockcroft-Gault formula

- Poisson regression used to determine factors (incl. ARVs) associated with CKD

*: (2 measurements ≥3 months apart)
Methods (II)

- ARV exposure calculated as cumulative exposure on a monthly basis and modelled as time-updated variable

- Sensitivity analyses:
  - using MDRD and CKD-EPI formulas for assessment of eGFR
  - variety of censoring strategies
  - alternative means of categorizing ARV/cART status:
    - never used / <1 year / 1-2 years / 2-3 years / > 3 years
    - never exposed / exposed but not currently taking / exposed and currently taking
    - on any cART regimen/ non-PI cART / non-boosted PI, non-ritonavir cART / non-boosted PI, ritonavir cART / ritonavir boosted cART
Results

Baseline characteristics (n=6843):
• 24.9% females
• 85.5% Caucasians
• 42.8% MSM
• 31.2% prior AIDS
• 23.1% HCV+ ab
• 89.8% exposed to cART
• 21.7% arterial hypertension
• 4.9% diabetes mellitus
• Median age: 42.8 (IQR: 37.5-50.0) years
• Median CD4 cell count: 450 (IQR: 305-638) cells/mm³

Follow-up:
21,482 PYFU; median 3.7 (IQR: 2.8-5.7) years
• 225 (3.3%) progressed to CKD
CKD, confirmed (persisting for >3 months) decrease in eGFR ≤ 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR ≤ 60 mL/min/1.73m²

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Kaplan-Meier progression to CKD

Incidence: 1.1 (0.9–1.2)/100 PYFU
203/225 (90%) had a baseline eGFR >60 mL/min/1.73m²
150/203 (74%) had a decline in eGFR of >10 mL/min/1.73m²

CKD, confirmed (persisting for >3 months) decrease in eGFR ≤ 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR ≤ 60 mL/min/1.73m²
Crude incidence rate of CKD and increasing exposure to ARVs

N with CKD

86 21 34 29 55
67 31 35 25 67
127 20 19 11 48
143 23 20 18 21

Incidence per 100 PYFU (95% CI)

Tenofovir
Indinavir
Atazanavir
Lopinavir/r

Years of exposure to ARV

Not started
0-1 1-2 2-3 >3
Not started
0-1 1-2 2-3 >3
Not started
0-1 1-2 2-3 >3
Not started
0-1 1-2 2-3 >3

CKD, confirmed (persisting for >3 months) decrease in eGFR < 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR <60 mL/min/1.73m²

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# Poisson models

## Cumulative exposure to ARVs and risk of CKD

<table>
<thead>
<tr>
<th></th>
<th>Univariable</th>
<th>Multivariable¤</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRR*/year</td>
<td>95%-CI</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>1.32</td>
<td>1.21-1.41</td>
</tr>
<tr>
<td>Indinavir</td>
<td>1.18</td>
<td>1.13-1.24</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>1.48</td>
<td>1.35-1.62</td>
</tr>
<tr>
<td>Lopinavir/r</td>
<td>1.15</td>
<td>1.07-1.23</td>
</tr>
</tbody>
</table>

¤: also included baseline eGFR and AIDS, AIDS during follow-up*, use of nephrotoxic drugs*, current CD4 count*, age*, HIV-RNA*, any cardiovascular event*, arterial hypertension*, diabetes*, HCV antibody status*, non-AIDS malignancy*, and gender *

*: variable included as time-updated

No other ARVs or types of regimens associated with CKD

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*: Incidence rate ratio
Cumulative exposure to ARVs and risk of CKD
Adjusted IRRs (per year of exposure)

- **Tenofovir**
- **Indinavir**
- **Atazanavir**
- **Lopinavir/r**

Cockcroft-Gault (n=225)
MDRD (n=277)
CKD-EPI (n=258)
INSIGHT def (n=129)
Cumulative exposure to ARVs and risk of CKD
Adjusted IRRs (per year of exposure)

- Tenofovir
- Indinavir
- Atazanavir
- Lopinavir/r

Censoring ATV
Censoring TDF
Censoring boosted PI

Adjusted IRRs (per year of exposure)

- Cockcroft-Gault
- MDRD
- CKD-EPI
- INSIGHT def
Stopping ARVs and risk of CKD

• Among patients stopping tenofovir during prospective follow-up:
  • Within first 12 months: IRR: 4.05 (2.51-6.53) compared with patients never exposed to tenofovir
  • After 12 months: IRR: 1.12 (0.63-1.99)

• The risk of CKD among patients stopping atazanavir or lopinavir/r is similar to that of patients not exposed to the specific ARVs
Limitations and strengths

- Non-randomised study, but based on a well described large cohort
- Heterogeneous study population with high levels of co-morbidity (contrast to randomised trials)
- A median follow-up of nearly 4 years
- Robustness of results using a large variety of different methods and estimations of GFR
- Insufficient follow-up to exclude association with the more recently introduced ARVs (darunavir, tipranavir, etravirine, maraviroc, raltegravir)
Summary

- Prevalence and incidence rate of CKD consistent with other studies
- Traditional risk factors for CKD also present in our study
- AIDS, non-AIDS malignancies and coinfection with HCV were also independently associated with CKD
- Increasing exposure to tenofovir associated with a higher risk of CKD
- Association with CKD also identified for indinavir and atazanavir
- Results for lopinavir/r less clear
Perspectives

- We have identified several ARVs associated with progressive, long-term renal impairment/CKD

- This may be due to
  - glomerular and tubular dysfunction (tenofovir)
  - high renal excretion rates and crystalluria/ crystal nephropathy/ nephrolithiasis (PIs)

- Although biologically plausible, the exact pathogenesis behind these findings remains to be elucidated

- Further follow-up and data needed to establish whether the risk of CKD continues to increase with longer exposure to the specific ARVs

- Studies on the clinical implications of the findings and the long-term consequences are warranted

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Q&As on our findings available at

www.cphiv.dk
Definitions

GFR (CG) = \frac{(140-\text{age}) \times \text{weight (kg)} \times 0.85 \text{ (if female)}}{\text{Serum creatinine} \times 72}

GFR (MDRD) = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (female)} \times 1.21 \text{ (black)}

CKD-EPI: Algorithm depending on race, gender and serum-creatinine

Our definition of CKD: confirmed (persisting for >3 months) decrease in eGFR ≤ 60 mL/min/1.73m² if eGFR at baseline >60 mL/min/1.73m² or confirmed 25% decrease in eGFR if baseline eGFR <60 mL/min/1.73m²

INSIGHT definition: 25% decrease in eGFR to <60 for those with a baseline eGFR >60 mL/min/1.73m², or 25% decrease in eGFR if baseline eGFR <60 mL/min/1.73m²


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**Definitions**

CKD-EPI: Algorithm depending on race, gender and serum-creatinine

<table>
<thead>
<tr>
<th>Race and Sex</th>
<th>Serum Creatinine Level, ( \mu \text{mol/L} ) ((\text{mg/dL}))</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Female</td>
<td>( \leq 62 ) (( \leq 0.7 ))</td>
<td>( \text{GFR} = 166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td></td>
<td>( &gt; 62 ) (&gt;0.7)</td>
<td>( \text{GFR} = 166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td>Male</td>
<td>( \leq 80 ) (( \leq 0.9 ))</td>
<td>( \text{GFR} = 163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td></td>
<td>( &gt; 80 ) (&gt;0.9)</td>
<td>( \text{GFR} = 163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td>White or other Female</td>
<td>( \leq 62 ) (( \leq 0.7 ))</td>
<td>( \text{GFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td></td>
<td>( &gt; 62 ) (&gt;0.7)</td>
<td>( \text{GFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}} )</td>
</tr>
<tr>
<td>Male</td>
<td>( \leq 80 ) (( \leq 0.9 ))</td>
<td>( \text{GFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}} )</td>
</tr>
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<td>( &gt; 80 ) (&gt;0.9)</td>
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