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Plasma NRTI concentrations and renal function in people with HIV

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Presenter Disclosure Information

No conflict of interest
Background

- 30% of PLWH present some renal function alteration
  - HIV -> acute kidney injury (AKI) and chronic kidney disease (CKD)
  - ART-related nephrotoxicity

- Nucleoside reverse transcriptase inhibitor (NRTI)
  - Tenofovir (TFV) - exposure associated with renal complications
  - Emtricitabine (FTC), abacavir (ABC) and lamivudine (3TC) - no established links between exposure and nephrotoxicity

- Effects of long-term NRTI exposure?

Objective

- To evaluate associations between plasma TFV, FTC, ABC and 3TC pharmacokinetics (PK) and renal function among participants in the POPPY study
The POPPY study

- Multicentre, prospective, observational study to examine the effects of ageing on the clinical outcomes of PLWH in UK and Ireland

- Cohorts of PLWH aged ≥50 and <50 years, and lifestyle-matched ≥50 HIV-negative individuals

1073PLWH
- white/black African ethnicity
- acquired HIV via sexual routes

304 HIV-negative ≥50 years
frequency matched on gender, ethnicity, sexual orientation and location (in/out London)

Bagkeris et al, The international journal of Epidemiology, accepted
Workflow

- NRTI plasma concentration measurement
- Population PK modelling
- Regression analysis
Assay development to measure NRTIs

Blood taken in EDTA tube → centrifugation → Plasma → Solid phase extraction → Extracted sample

Analytes are separated on chromatogram

Ultra High Performance Liquid Chromatography
Population PK Modelling

**POPPY PK: visit 1**
- Single sample per patient
  - Tenofovir: n=555
  - Emtricitabine: n=519
  - Abacavir: n=109
  - Lamivudine: n=143

**Structural Model**
- e.g. 1 or 2 compartment
- (Statistical methods, diagnostic plots)

**Covariate Model**
- weight, age, sex, ethnicity
- (statistical & graphical methods, biologically plausible)

**Simulations & visual predictive check**
- 90% prediction interval (P5, P50, P95)

**NONMEM (v. 7.3)**

**Individual predicted PK parameters**
- AUC_{0-24}, C_{max}, C_{24}
Regression analysis

- $\text{AUC}_{0-24}$, $C_{\text{max}}$, $C_{24}$ parameters predicted for each patient
- eGFR was estimated using three equations:
  - CKD-EPI (used for primary analysis)
  - MDRD
  - Cockcroft-Gault
- Linear regression models built to assess associations between eGFR and $\text{AUC}_{0-24}$, $C_{\text{max}}$, $C_{24}$ parameters
- Adjusted for age, gender, race and receipt of concomitant medications and boosted protease inhibitors (bPI)
### Baseline characteristics (1)

<table>
<thead>
<tr>
<th></th>
<th>TFV (n=554)</th>
<th>FTC (n=516)</th>
<th>ABC (n=109)</th>
<th>3TC (n=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Gender/race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White male</td>
<td>476 (86)</td>
<td>446 (86)</td>
<td>80 (73)</td>
<td>112 (79)</td>
</tr>
<tr>
<td>White female</td>
<td>20 (4)</td>
<td>18 (4)</td>
<td>11 (10)</td>
<td>11 (8)</td>
</tr>
<tr>
<td>Black African male</td>
<td>58 (11)</td>
<td>52 (10)</td>
<td>18 (17)</td>
<td>19 (13)</td>
</tr>
<tr>
<td>Black African female</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older HIV cohort</td>
<td>353 (64)</td>
<td>326 (63)</td>
<td>71 (65)</td>
<td>99 (70)</td>
</tr>
<tr>
<td>Younger HIV cohort</td>
<td>201 (36)</td>
<td>190 (37)</td>
<td>38 (35)</td>
<td>43 (30)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>399 (72)</td>
<td>370 (72)</td>
<td>73 (67)</td>
<td>96 (68)</td>
</tr>
<tr>
<td>No</td>
<td>155 (28)</td>
<td>146 (28)</td>
<td>36 (33)</td>
<td>46 (32)</td>
</tr>
<tr>
<td>Boosted PIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>165 (30)</td>
<td>146 (28)</td>
<td>39 (36)</td>
<td>54 (38)</td>
</tr>
<tr>
<td>No</td>
<td>389 (70)</td>
<td>370 (72)</td>
<td>70 (64)</td>
<td>88 (62)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>317 (57)</td>
<td>299 (58)</td>
<td>53 (49)</td>
<td>66 (47)</td>
</tr>
<tr>
<td>No</td>
<td>237 (42)</td>
<td>217 (42)</td>
<td>56 (51)</td>
<td>76 (54)</td>
</tr>
<tr>
<td>IIs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67 (12)</td>
<td>63 (12)</td>
<td>15 (14)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>No</td>
<td>487 (88)</td>
<td>453 (88)</td>
<td>94 (86)</td>
<td>119 (84)</td>
</tr>
</tbody>
</table>
Baseline characteristics (2)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>TFV</th>
<th>FTC</th>
<th>ABC</th>
<th>3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>52 (23, 82)</td>
<td>52 (23, 82)</td>
<td>52 (25, 82)</td>
<td>54 (25, 82)</td>
<td></td>
</tr>
<tr>
<td>eGFR MDRD (mL/min/1.73m²)</td>
<td>89 (45, 169)</td>
<td>89 (45, 169)</td>
<td>89 (36, 178)</td>
<td>88 (36, 151)</td>
</tr>
<tr>
<td>eGFR CKD-EPI (mL/min/1.73m²)</td>
<td>91 (42, 145)</td>
<td>90 (43, 145)</td>
<td>91 (35, 144)</td>
<td>90 (35, 143)</td>
</tr>
<tr>
<td>Cockcroft-Gault (mL/min)</td>
<td>100 (43, 223)</td>
<td>100 (43, 223)</td>
<td>99 (44, 220)</td>
<td>99 (43, 161)</td>
</tr>
<tr>
<td>Drug duration (years)</td>
<td>5.9 (0.0, 15)</td>
<td>5.3 (0.0, 11)</td>
<td>6.9 (0.0, 16)</td>
<td>10.4 (0, 19)</td>
</tr>
<tr>
<td>NRTI duration (years)</td>
<td>8.3 (0.0, 25)</td>
<td>7.8 (0.0, 23)</td>
<td>11.8 (1, 26)</td>
<td>12.6 (1, 26)</td>
</tr>
</tbody>
</table>
**eGFR**

- **TFV**
  - Median 90.8, range (42, 145)

- **FTC**
  - Median 90.4, range (43, 145)

- **ABC**
  - Median 91, range (35, 144)

- **3TC**
  - Median 89.7, range (35, 143)
Regression analysis beta coefficient at 95% CI

Tenofovir

- TFV AUC_{0-24} (mg.h/L)
  - p-value < 0.001
- TFV C_{max} (mg/L)
  - p-value = 0.003
- TFV C_{min} (mg/L)
  - p-value < 0.001
Regression analysis  beta coefficient at 95% CI

Emtricitabine

p-value< 0.001  p-value< 0.001  p-value< 0.001
Regression analysis beta coefficient at 95% CI

Lamivudine

p-value=0.03  p-value=0.78  p-value=0.03
Regression analysis  

**Abacavir**

- **ABC AUC$_{0-24}$ (mg.h/L)**
  - $p$-value = 0.11

- **ABC $C_{\text{max}}$ (mg/L)**
  - $p$-value = 0.25

- **FTC $C_{\text{min}}$ (mg/L)**
  - $p$-value = 0.06
Regression analysis (PK parameters considered simultaneously for TFV+FTC)

<table>
<thead>
<tr>
<th></th>
<th>TFV</th>
<th>FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β-coef. (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>AUC0-24 quintiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1- lowest</td>
<td>Ref.</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>-3.02 (-6.73,0.68)</td>
<td>-2.00 (-5.80,1.79)</td>
</tr>
<tr>
<td>3</td>
<td>-2.86 (-6.71,0.98)</td>
<td>-1.51 (-5.48,2.46)</td>
</tr>
<tr>
<td>4</td>
<td>-3.38 (-7.52,0.76)</td>
<td>-4.92 (-9.09,-0.76)</td>
</tr>
<tr>
<td>5 - highest</td>
<td>-9.85 (-14.16,-5.53)</td>
<td>-7.93 (-12.46,-3.41)</td>
</tr>
<tr>
<td>Cmax quintiles</td>
<td></td>
<td>0.23</td>
</tr>
<tr>
<td>1- lowest</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.00 (-1.78,5.79)</td>
<td>-2.60 (-6.43,1.23)</td>
</tr>
<tr>
<td>3</td>
<td>1.14 (-2.59,4.87)</td>
<td>-2.44 (-6.44,1.56)</td>
</tr>
<tr>
<td>4</td>
<td>2.49 (-1.34,6.32)</td>
<td>-5.98 (-10.13,-1.84)</td>
</tr>
<tr>
<td>5 - highest</td>
<td>-1.55 (-5.62,2.52)</td>
<td>-11.15 (-15.55,-6.76)</td>
</tr>
<tr>
<td>C24 quintiles</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1- lowest</td>
<td>Ref.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-1.48 (-5.25,2.29)</td>
<td>-1.44 (-5.20,2.31)</td>
</tr>
<tr>
<td>3</td>
<td>-4.88 (-8.78,-0.98)</td>
<td>-1.24 (-5.24,2.77)</td>
</tr>
<tr>
<td>4</td>
<td>-5.61 (-9.80,-1.41)</td>
<td>-3.18 (-7.44,1.09)</td>
</tr>
<tr>
<td>5 - highest</td>
<td>-12.30 (-16.79,-7.81)</td>
<td>-6.22 (-10.79,-1.65)</td>
</tr>
</tbody>
</table>
Limitations of the study

- Only eGFR used to assess renal function
- Not adjusted for other ARV drugs that might affect renal function
- Cross sectional study – cannot comment on the direction of any associations seen
- As TFV and FTC are often used in combination, it may be difficult to separate their associations
Conclusions

- We confirm robust associations between TFV PK and renal function
- We also show associations between FTC and 3TC PK and renal function
- TFV and FTC PK parameters appear to be independently associated with renal function
- No clear associations with ABC were apparent
- Our findings may support the use of individual dose/drug adjustments in people living with HIV
Acknowledgments

**POPPY Management Team:** Daphne Babalis, Marta Boffito, Laura Burgess, Paddy Mallon, Frank Post, Caroline Sabin, Memory Sachikonye, Alan Winston

**POPPY Scientific Steering Committee:** Jane Anderson, David Asboe, Marta Boffito, Lucy Garvey, Paddy Mallon, Frank Post, Anton Pozniak, Caroline Sabin, Memory Sachikonye, Jaime Vera, Ian Williams, Alan Winston

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**POPPY Sites and Trials Unit:**
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- St Stephen’s Centre, Chelsea and Westminster Hospital (Marta Boffito, David Asboe, Anton Pozniak, Margherita Bracchi, Nicole Pagani, Maddalena Cerrone, Daniel Bradshaw, Francesca Ferretti, Chris Higgs, Elisha Seah, Stephen Fletcher, Michelle Anthonipillai, Ashley Moyes, Katie Deats, Irtiza Syed, Clive Matthews, Peter Fernando, Chido Chiwome, Shane Hardwick)
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**POPPY methodology/statistics/analysis:** Caroline Sabin, Davide De Francesco, Emmanouil Bagkeris

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Supplementary slides
PK parameters with and without bPI

- AUC (mg·h/L): p=0.04
- Cmax (mg/L): p=0.002
- Trough (mg/L): p=0.002
- CL/F (L/h): p=0.003