Methods

- ACTG 5175 (PEARLS): greater risk of treatment failure in ddI-EC/FTC/ATV vs. 3TC/ZDV/EFV. A population pharmacokinetic study identified geographic associations with ATV kinetics (AUC$_{0-24}$, CL/F, C$_{24}$).

- Objective: To evaluate the associations between CYP3A5 polymorphisms and the pharmacokinetics of unboosted ATV in patients from US, South Africa and Peru enrolled in PEARLS.

- Stored DNA samples were genotyped for CYP3A5 *3, *6 and *7 using PCR-pyrosequencing.
  - Expressor (at least one copy of the *1 allele).
  - Non-expressor (*3/*3, *6/*6 or *7/*7 homozygous).

- ATV metabolites M1 and M2 were measured with LC-MS/MS. M1/ATV and M2/ATV ratios were calculated.

- PK parameters and metabolite ratios were log$_e$ transformed; statistical analysis used unpaired $t$ tests between CYP3A5 expressors vs. non-expressors. A p value $\leq 0.05$ was used as the level of significance.
ATV PK/Metabolism according to 3A5 expression

<table>
<thead>
<tr>
<th>Parameter (mean ± SD)</th>
<th>CYP3A5 Status (n=69)</th>
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<tbody>
<tr>
<td></td>
<td>Expressor (n=45)</td>
<td>Non-expressor (n=24)</td>
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<tr>
<td>AUC\textsubscript{0-24} (ng*hr/mL)</td>
<td>31823 ± 11340</td>
<td>32068 ± 6659</td>
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<tr>
<td>CL/F (L/hr)</td>
<td>13.70 ± 3.52</td>
<td>13.03 ± 2.87</td>
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<tr>
<td>C\textsubscript{24} (ng/mL)</td>
<td>198 ± 353.8</td>
<td>193 ± 158.4</td>
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ATV PK parameters did not differ by pre-defined CYP3A5 expressor status.

M1/ATV and M2/ATV were higher in pre-defined CYP3A5 expressors.
CONCLUSIONS:

Genetically-determined \textit{CYP3A5} expressors in the PEARLS study showed a unique ATV metabolism phenotype compared to non-expressors.

\textit{CYP3A5*3} genotype is associated with differences in ATV clearance and metabolism.
Acknowledgements

- Univ of Colorado
  - Peter Anderson, PharmD
  - Christina Aquilante, PharmD
  - Michael Wempe, PhD

- A5175 Leadership
  - Thomas Campbell, MD
  - Laura Smeaton, MS

- A5175 PK Study
  - Courtney Fletcher, PharmD
  - Adriana Andrade, MD

- A5128/A5243
  - David Haas, MD

- Funding
  - ACTG: NIH/NIAID ACTG Minority Investigator Award AI0 68636.
  - CCSTI: NIH/NCRR Colorado CTSI Grant Number UL1 RR025780

- International sites.
  - Cindy Firnhaber, MD
  - Alberto La Rosa, MD

- Study Participants.