Pharmacogenetics of Efavirenz Discontinuation for Central Nervous System Symptoms

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Background

- Efavirenz is frequently prescribed in first-line regimens for HIV-1 infection.
- Central nervous system (CNS) symptoms affect 10-30% of patients, and cause treatment discontinuation in about 5%.
- Single nucleotide polymorphism (SNPs) in CYP2B6 and CYP2A6 predict increased plasma EFV exposure.
  - **CYP2B6**
    - 516G→T (rs3745274)
    - 983T→C (rs28399499)
    - 15582C→T (rs4803419)
  - **CYP2A6**
    - -48T→G (rs28399433), secondary pathway.
Estimated $C_{\text{min}}$ by CYP2B6 Haplotype

(CYP2B6 haplotype

(516G→T, 983T→C, 15582C→T))

Genetics of Efavirenz Discontinuation in Swiss HIV Cohort Study (N = 272)

Lubomirov et al, J Infect Dis 2011;203:246
Genetics and CNS Events with Efavirenz (ACTG384 and A5095, N = 643)

Ribaudo et al. *J Infect Dis* 2010, 202: 717
Specific Aims

1. To determine whether we can predict EFV discontinuation for CNS symptoms within the first 12 months with the SNPs associated with EFV metabolism.

2. To determine whether genetic associations with EFV discontinuation differ by race.

3. To replicate previous genetic associations with EFV side effects and discontinuation.

4. To explore associations between smoking, genetics, and EFV discontinuation (cotinine may induce CYP2B6 in brain).
Methods

• **Study participants**
  – HIV+ patients who initiated EFV-containing ART at Vanderbilt Comprehensive Care Clinic (Nashville, TN) from 1998 to 2012 and with >1 year follow-up data.
  – Consented DNA available for genetic research.

• **Genetic variants**
  – Extensive, intermediate and slow metabolizers defined by 4 SNPs in \textit{CYP2B6} and \textit{CYP2A6}.
  – >500,000 SNPs (Illumina HumanCore Exome) used to adjust for population stratification by multidimensional scaling (MDS).

• **Statistical analysis**
  – Cox proportional hazard regression model, adjusted for population stratification was used to examine associations between genotype and EFV discontinuation.
### Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Cases</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 464</td>
<td>n = 99</td>
<td>N = 563</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>408 (88)</td>
<td>78 (79)</td>
<td>486 (86)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>56 (12)</td>
<td>21 (21)</td>
<td>77 (14)</td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>38.1 (31.8 – 44.7)</td>
<td>37.2 (29.7 – 46.2)</td>
<td>37.9 (31.5 – 45.4)</td>
</tr>
<tr>
<td>Self-identified race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>283 (61)</td>
<td>49 (49.5)</td>
<td>332 (59)</td>
</tr>
<tr>
<td>Black</td>
<td>144 (31)</td>
<td>39 (39.5)</td>
<td>183 (32.5)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18 (4)</td>
<td>6 (6)</td>
<td>24 (4)</td>
</tr>
<tr>
<td>Asian</td>
<td>5 (1)</td>
<td>-</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Not reported</td>
<td>14 (3)</td>
<td>5 (5)</td>
<td>19 (3.5)</td>
</tr>
</tbody>
</table>
# Reasons for EFV Discontinuation

<table>
<thead>
<tr>
<th>Cause</th>
<th>Number of cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central nervous system symptoms</td>
<td>29</td>
<td>29.3</td>
</tr>
<tr>
<td>Rash</td>
<td>23</td>
<td>23.2</td>
</tr>
<tr>
<td>Viral drug resistance mutations</td>
<td>16</td>
<td>16.2</td>
</tr>
<tr>
<td>Non-adherence</td>
<td>9</td>
<td>9.1</td>
</tr>
<tr>
<td>Gastrointestinal side effects</td>
<td>6</td>
<td>6.1</td>
</tr>
<tr>
<td>Drug-drug interaction</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>Unspecified</td>
<td>10</td>
<td>10.1</td>
</tr>
</tbody>
</table>

*Based on review of provider notes in the electronic medical record.*
MDS Coordinates to Adjust for Genetic Ancestry
(N = 563 patients)

White
Hispanic
Black
Asian
Not reported
EFV Discontinuation for CNS Symptoms

A. All patients
   HR: 4.86  P: 0.001

B. Whites
   HR: 6.50  P: 0.001

C. Blacks
   HR: 2.59  P: 0.27

D. Slow metabolizer (White vs. Black)
   HR: 0.33  P: 0.08
EFV Discontinuation for CNS symptoms by Smoking Status

• In all subjects, hazard ratio (HR) for EFV discontinuation in smokers vs. non-smokers = 1.4 (95% C.I: 0.6 to 3.0; P = 0.45).

• In White heavy smokers (> 3.5 packs/week) HR in slow metabolizers = 18.3 (95% C.I: 4.0 to 82.8; P < 0.001).
Predictive Values of Slow Metabolizer Genotype for EFV Discontinuation for CNS symptoms

• **Positive predictive value**
  – All: 16.1% (95% C.I. 8.0% to 27.7%)
  – Whites: 27.2% (95% C.I. 10.7% to 50.2%)
  – Blacks: 10.8% (95% C.I: 3.0% to 25.4%)

• **Negative predictive value**
  – All: 95.6% (95% C.I. 93.2% to 97.3%)
  – Whites: 95.0% (95% C.I. 91.8% to 97.3%)
  – Blacks: 96.1% (95% C.I. 91.1% to 98.7%)
Conclusions

- Slow metabolizer genotypes were associated with EFV discontinuation for CNS symptoms.
- This association was stronger in Whites than in Blacks, consistent with a prior ACTG analysis.
- The reason for a difference by race is not known, but could reflect ascertainment, biology, or behavior.
- Predictive values suggest limited utility of genotyping alone to predict EFV discontinuation for CNS symptoms.
- Further study of interactions between smoking, genetics, and EFV CNS effects are warranted.
Acknowledgements

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  • Cara Sutcliffe
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