Obese HIV-infected patients treated with efavirenz-containing regimens are at risk of virological failure

Catia Marzolini for the Efavirenz and Obesity Project Team of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord
Background

- While effective ART has reduced the prevalence of HIV-associated wasting, the prevalence of obesity has increased\(^1\)
- Obesity is characterized by physiological changes which can impact on drug pharmacokinetics\(^2\) as well as immune responses\(^3\)
- Treatment failure has been reported in an obese patient receiving a standard efavirenz (EFV) dose\(^4\)
- Physiologically-based pharmacokinetic modelling shows that EFV dose increase is needed to maintain sufficient levels in obese individuals\(^4\)
- Obesity may therefore be a risk factor for EFV underdosing and, thus, for virological failure

\(^1\)Crum-Cianflone N et al. AIDS 2010; \(^2\)Brill M et al. Clin Pharmacokinet 2012; \(^3\)Koethe JR et al. JID 2013; \(^4\)de Roche M et al. AVT 2012
Aims

- To use data from COHERE\(^1\), a collaboration of 33 cohorts across Europe, to compare:
  - the time to initial viral suppression after treatment initiation, and
  - the time to virological rebound after initial suppression

in obese and non-obese ART-naive patients starting an EFV-based regimen

- Patients were grouped according to weight:
  - Group I: <80 kg
  - Group II: ≥80, <85 kg
  - Group III: ≥85, <90 kg
  - Group IV: ≥90, <95 kg
  - Group V: ≥95 kg

\(^1\)COHERE: Collaboration of Observational HIV Epidemiological Research Europe
Patients and definitions

- Adults (>16 years of age) who were ART-naive when starting an EFV-based regimen
- Data available on weight prior to EFV start, as well as follow-up viral loads (VL) after EFV start
- Initial viral suppression: first VL ≤50 copies/ml, or coded as «undetectable» by cohorts
- Virological rebound: first of 2 consecutive VL >50 copies/ml
Statistical methods

- Time to each event was described using Kaplan-Meier plots, with groups compared using Cox proportional hazard regression analyses.

- Analyses were adjusted for:
  - Gender
  - Age
  - Mode of HIV acquisition
  - Ethnicity
  - Cohort and calendar year
  - Hepatitis/abnormal LFT
  - Pre-EFV CD4 count
  - Pre-EFV VL
  - Prior AIDS
  - NRTI backbone
  - PI co-administration
Selection of the study population

ART-naive patients starting EFV-based regimens
N = 66,320

Exclusions:
- Unknown EFV start date: 39
- Children: 731
- Prior ART experience: 37764
- Cohorts without data on weight or few patients: 4074
- EFV monotherapy: 161
- Suppressed VL at EFV start: 1037

Eligible cohort
N = 22,514

Exclusions:
- Patients without weight data prior to EFV start: 7455
- Patients without follow-up: 2384

Study population
N = 13,431

Study groups

I: <80 kg
N= 10,455 (77.8%)

II: ≥80, <85 kg
N= 1178 (8.8%)

III: ≥85, <90 kg
N= 731 (5.4%)

IV: ≥90, <95 kg
N= 463 (3.5%)

V: ≥95 kg
N= 604 (4.5%)

Median time between weight measurement and EFV initiation: 1 day, IQR: 0-41 days
### Selected characteristics of patients at EFV start

<table>
<thead>
<tr>
<th>Total number of patients</th>
<th>13431</th>
<th>(100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR) age (years)</td>
<td>38</td>
<td>(32, 45)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>3121</td>
<td>(23.2%)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td>2920</td>
<td>(21.7%)</td>
</tr>
<tr>
<td>black</td>
<td>256</td>
<td>(1.9%)</td>
</tr>
<tr>
<td>other</td>
<td>108</td>
<td>(0.8%)</td>
</tr>
<tr>
<td>prohibited</td>
<td>9411</td>
<td>(70.1%)</td>
</tr>
<tr>
<td>not known</td>
<td>736</td>
<td>(5.5%)</td>
</tr>
<tr>
<td>AIDS prior to EFV, n (%)</td>
<td>2493</td>
<td>(19.2%)</td>
</tr>
<tr>
<td>Year of EFV start, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2000</td>
<td>1494</td>
<td>(11.1%)</td>
</tr>
<tr>
<td>2001/2002</td>
<td>1690</td>
<td>(12.6%)</td>
</tr>
<tr>
<td>2003/2004</td>
<td>2215</td>
<td>(16.5%)</td>
</tr>
<tr>
<td>2005/2006</td>
<td>2479</td>
<td>(18.5%)</td>
</tr>
<tr>
<td>2007/2008</td>
<td>3208</td>
<td>(23.9%)</td>
</tr>
<tr>
<td>2009/2010/2011</td>
<td>2345</td>
<td>(17.5%)</td>
</tr>
<tr>
<td>Median (IQR) CD4 count (cells/mm³)</td>
<td>242</td>
<td>(106, 350)</td>
</tr>
<tr>
<td>Median (IQR) VL (log₁₀ copies/ml)</td>
<td>4.8</td>
<td>(4.3, 5.3)</td>
</tr>
</tbody>
</table>

IQR = interquartile range
Selected characteristics stratified by weight group

- The proportions of women and persons with AIDS were comparable in the obese groups, but were lower than the proportions in those with normal/low weight.

- Overall, mode of infection, the co-administration of a PI and the median VL prior to EFV initiation were comparable among groups.

- TDF/FTC was used more in obese whereas ZDV/3TC was used more in those with normal/low weight.

- There was a trend towards a higher median CD4 cell count in those who were heavier.
Weight distribution among those starting EFV in different calendar periods

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</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>1494</td>
<td>1690</td>
<td>2215</td>
<td>2479</td>
<td>3208</td>
<td>2345</td>
</tr>
</tbody>
</table>

- >95 kg
- 90-95 kg
- 85-90 kg
- 80-85 kg
- < 80 kg
Time to initial undetectable viral load

- Overall, 11310 (84.2%) experienced an undetectable VL after EFV start

- Median time to initial undetectable VL (Kaplan-Meier analysis)
  
<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Median Time (years)</th>
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</thead>
<tbody>
<tr>
<td>Weight &lt;80kg</td>
<td>0.39</td>
</tr>
<tr>
<td>Weight ≥80, &lt;85kg</td>
<td>0.36</td>
</tr>
<tr>
<td>Weight ≥85, &lt;90kg</td>
<td>0.38</td>
</tr>
<tr>
<td>Weight ≥90, &lt;95kg</td>
<td>0.38</td>
</tr>
<tr>
<td>Weight ≥95kg</td>
<td>0.35</td>
</tr>
</tbody>
</table>

  \[ P = 0.0001, \text{log-rank test} \]
Relative hazards for time to initial undetectable VL

Adjusted for demographic, viral and treatment–related factors, cohort and calendar year

1 Adjusted for gender, age, mode of HIV acquisition, ethnicity, cohort and calendar year, hepatitis/abnormal LFT, pre-EFV CD4 count and VL, prior AIDS, NRTI backbone, PI co-administration
- Of the 11310 patients with an undetectable VL, 3867 (34.2%) subsequently experienced viral load rebound

P = 0.0003, log-rank test
Relative hazards for time to subsequent VL rebound

- patients experiencing an undetectable VL, N = 11310
- patients subsequently experiencing VL rebound, N = 3867

1Adjusted for gender, age, mode of HIV acquisition, ethnicity, cohort and calendar year, hepatitis/abnormal LFT, pre-EFV CD4 count and VL, prior AIDS, NRTI backbone, PI co-administration
Analyses stratified by gender and ethnicity

- Adjusted relative hazards for time to subsequent VL rebound

Adjusted for gender, age, mode of HIV acquisition, ethnicity, cohort and calendar year, hepatitis/abnormal LFT, pre-EFV CD4 count and VL, prior AIDS, NRTI backbone, PI co-administration
Limitations

- No data available on EFV dose or EFV drug levels
- Due to the lower inclusion number of women compared to men, further studies are warranted to evaluate the impact of gender on EFV response in obese individuals
- For a large proportion of participating cohorts, the collection of information on ethnicity was prohibited; as a result, this information was unavailable for around 70% of the study participants
- Height was not always available and problems of data transcription for body mass index were recorded
Conclusions

- No significant differences seen between groups in time to initial undetectable VL, however time tended to be shorter for those with weight ≥95 kg vs. <80 kg
- Probability of VL rebound was significantly higher for those with weight ≥95 kg vs. <80 kg
- Association with time to VL rebound was predominantly seen in white individuals and in men, suggesting the presence of gender and ethnicity-related differences in drug exposure and/or obesity-induced immunomodulatory activity
- Response to EFV should be monitored carefully in patients with severe obesity; TDM might be a useful tool
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Nicola Gianotti
Jade Ghosn
Amanda Mocroft
Geneviève Chêne
Jesper Grarup
Manuel Battegay

Steering committee:

• Executive committee: Ian Weller (Chair, University College London), Manuel Battegay (SHCS, MoCHIV), Jordi Casabona (PISCIS), Dominique Costagliola (FHDH), Antonella d’Arminio Monforte (ICONA), Stéphane de Wit (St. Pierre Cohort), Julia Del Amo (Co-RIS), Jesper Grarup (Head, Copenhagen Regional Co-ordinating Center), Geneviève Chene (Head, Bordeaux Regional Co-ordinating Centre).

• Contributing cohorts: Robert Zangerle (AHIVCOS), Giota Touloumi (AMACS), Josiane Warszawski (ANRS CO1 EPF), Laurence Meyer (ANRS CO2 SEROCO), François Dabis (ANRS CO3 AQUITAINE), Murielle Mary Krause (ANRS CO4 FHDH), Jade Ghosn (ANRS CO6 PRIMO), Catherine Leport (ANRS CO8 COPILOTE), Ferdinand Wit (ATHENA), Peter Reiss (ATHENA), Maria Prins (CASCADE), Heiner Bucher (CASCADE), Caroline Sabin (CHIC), Diana Gibb (CHIPS), Gerd Fätkenheuer (Cologne Bonn), Julia Del Amo (Co-RIS), Niels Obel (Danish HIV Cohort), Claire Thorne (ECS), Amanda Mocroft (EuroSIDA), Ole Kirk (EuroSIDA), Christoph Stephan (Frankfurt), Santiago Pérez-Hoyos (GEMES-Haemo), Antoni Noguera-Julian (NENEXP and CORISPE-cat), Andrea Antonini (ICC), Antonella d’Arminio Monforte (ICONA), Norbert Brockmeyer (KOMPNET), José Ramos (Madrid Cohort), Manuel Battegay (SHCS, MoCHIV), Andri Rauch (SHCS), Cristina Mussini (Modena Cohort), Pat Tookey (NSHPC), Jordi Casabona (PISCIS), Jose M. Miró (PISCIS), Antonella Castagna (San Raffaele), Stephan de Wit (St. Pierre Cohort), Tessa Goetghebuer (Belgian Pediatric cohort, St Pierre), Carlo Torti (Italian Master Cohort), Ramon Teira (VACH), Myriam Garrido (VACH).

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