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

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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

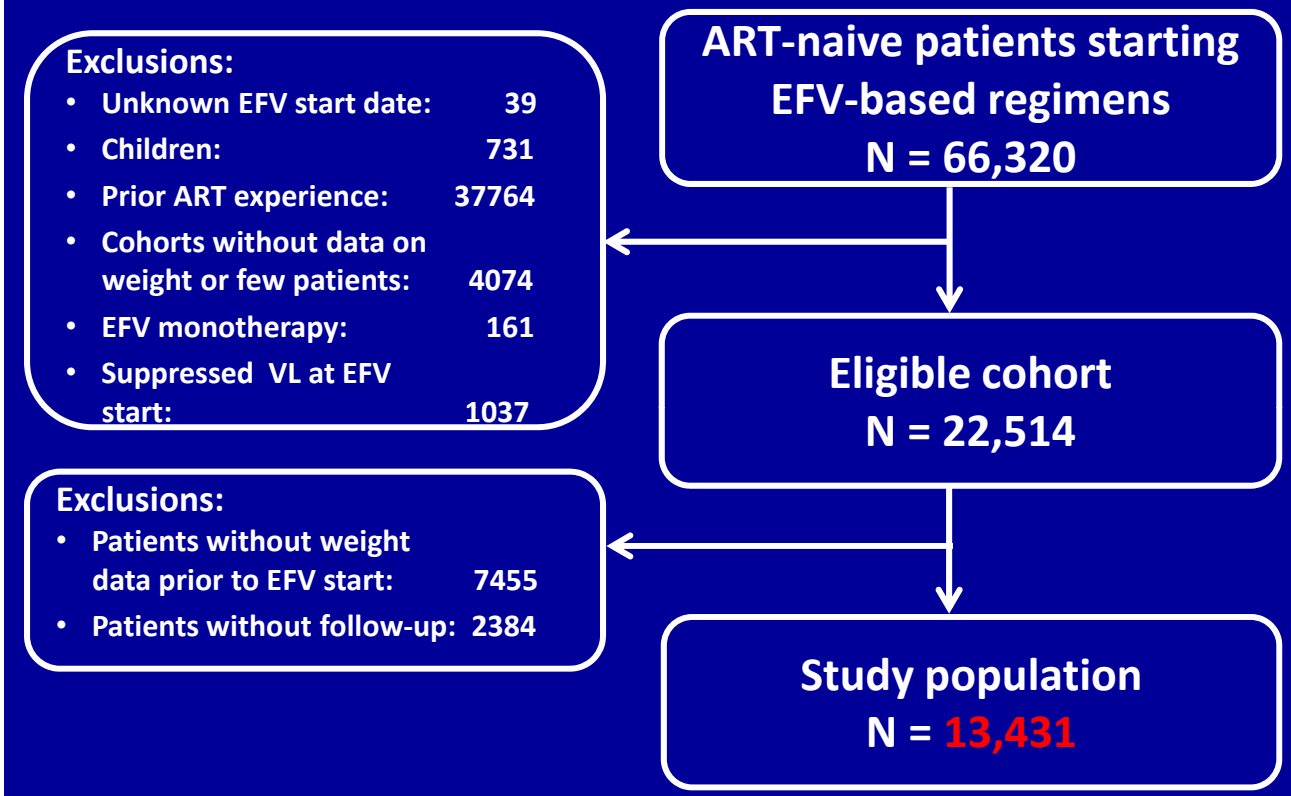
Patients and definitions

- 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



Study groups

I: <80 kg	II: ≥80, <85 kg	III: ≥85, <90 kg	IV: ≥90, <95 kg	V: ≥95 kg
N= 10,455 (77.8%)	N= 1178 (8.8%)	N= 731 (5.4%)	N= 463 (3.5%)	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

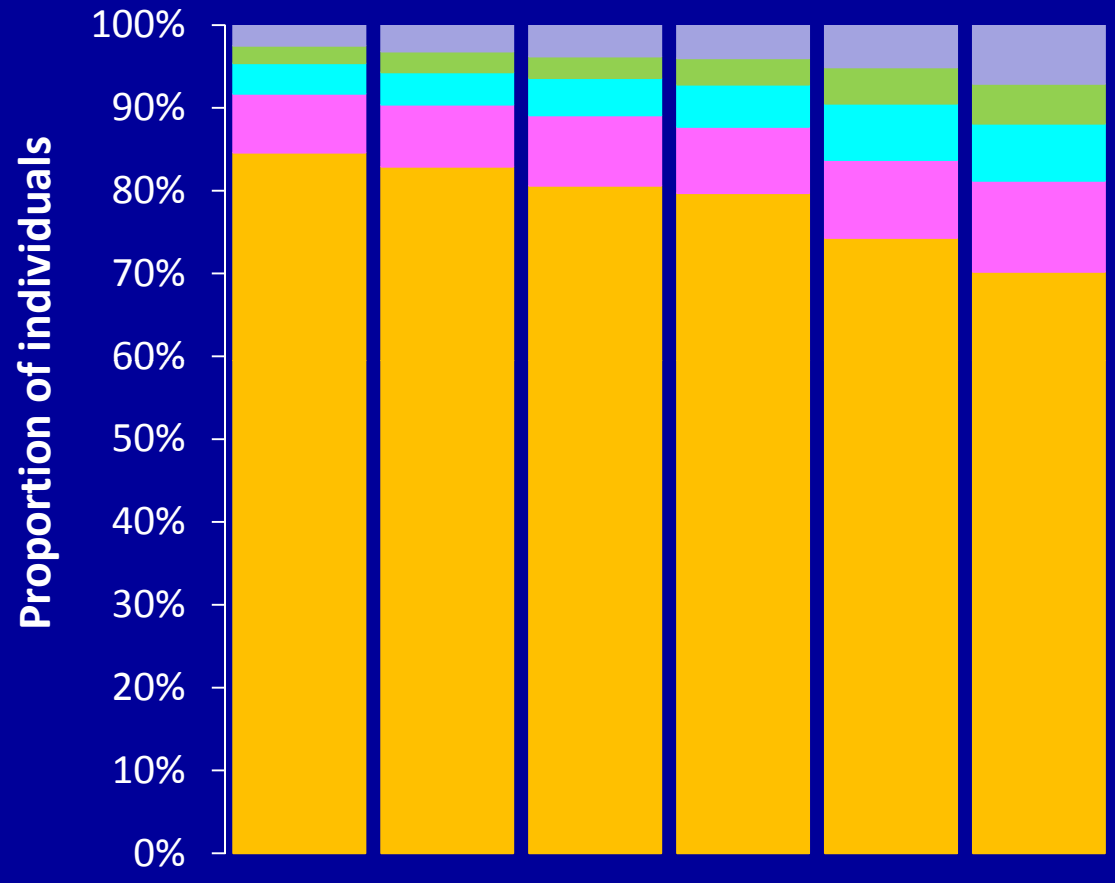
Total number of patients		**13431**	**(100%)**
Median (IQR) age (years)		38	(32, 45)
Female gender, n (%)		3121	(23.2%)
Ethnicity, n (%)	white	2920	(21.7%)
	black	256	(1.9%)
	other	108	(0.8%)
	prohibited	9411	(70.1%)
	not known	736	(5.5%)
AIDS prior to EFV, n (%)		2493	(19.2%)
Year of EFV start, n (%)	≤2000	1494	(11.1%)
	2001/2002	1690	(12.6%)
	2003/2004	2215	(16.5%)
	2005/2006	2479	(18.5%)
	2007/2008	3208	(23.9%)
	2009/2010/2011	2345	(17.5%)
Median (IQR) CD4 count (cells/mm^3)		242	(106, 350)
Median (IQR) VL ($\log_{10}$ copies/ml)		4.8	(4.3, 5.3)

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



Year of EFV start	≤2000	2001/ 2002	2003/ 2004	2005/ 2006	2007/ 2008	2009/ 2010/ 2011
Total patients	1494	1690	2215	2479	3208	2345

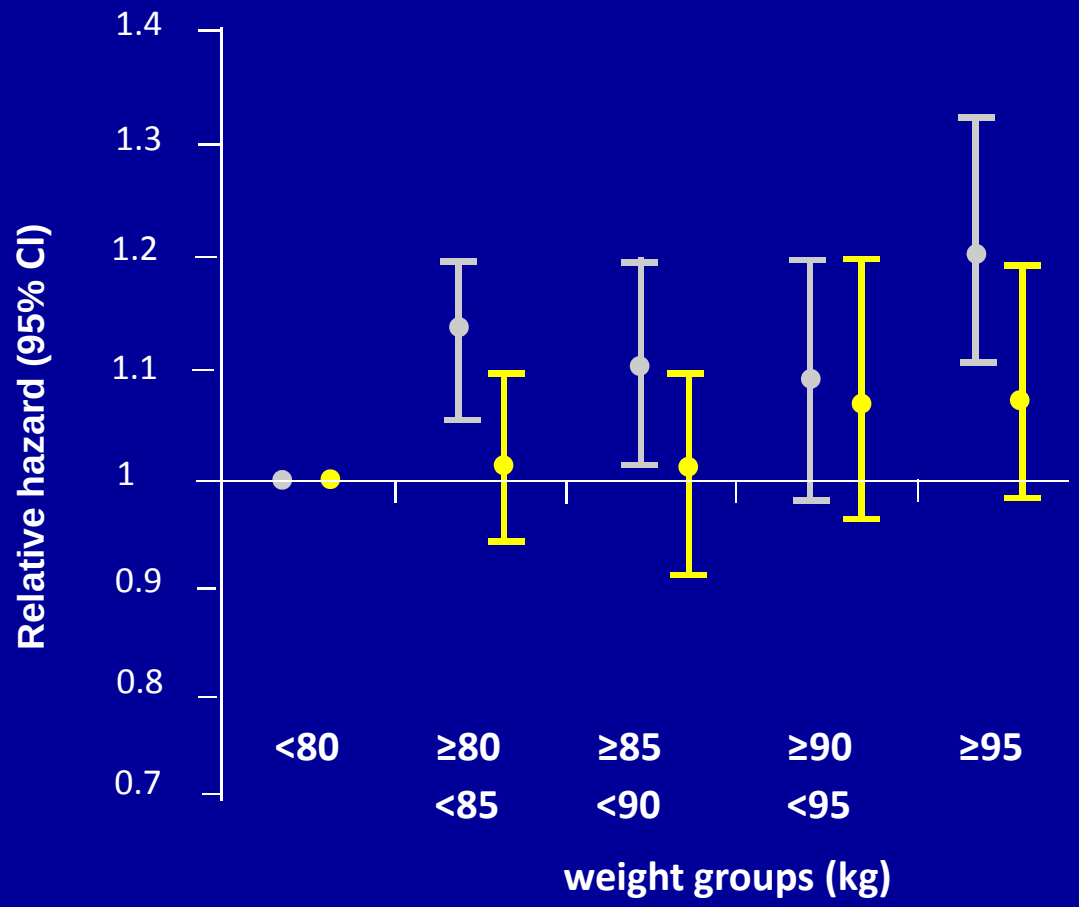
Time to initial undetectable viral load

- Overall, 11310 (84.2%) experienced an undetectable VL after EFV start
- Median time to initial undetectable VL (Kaplan-Meier analysis)

Weight <80kg:	0.39 years
Weight ≥80, <85kg:	0.36 years
Weight ≥85, <90kg:	0.38 years
Weight ≥90, <95kg:	0.38 years
Weight ≥95kg:	0.35 years

P = 0.0001, log-rank test

Relative hazards for time to initial undetectable VL



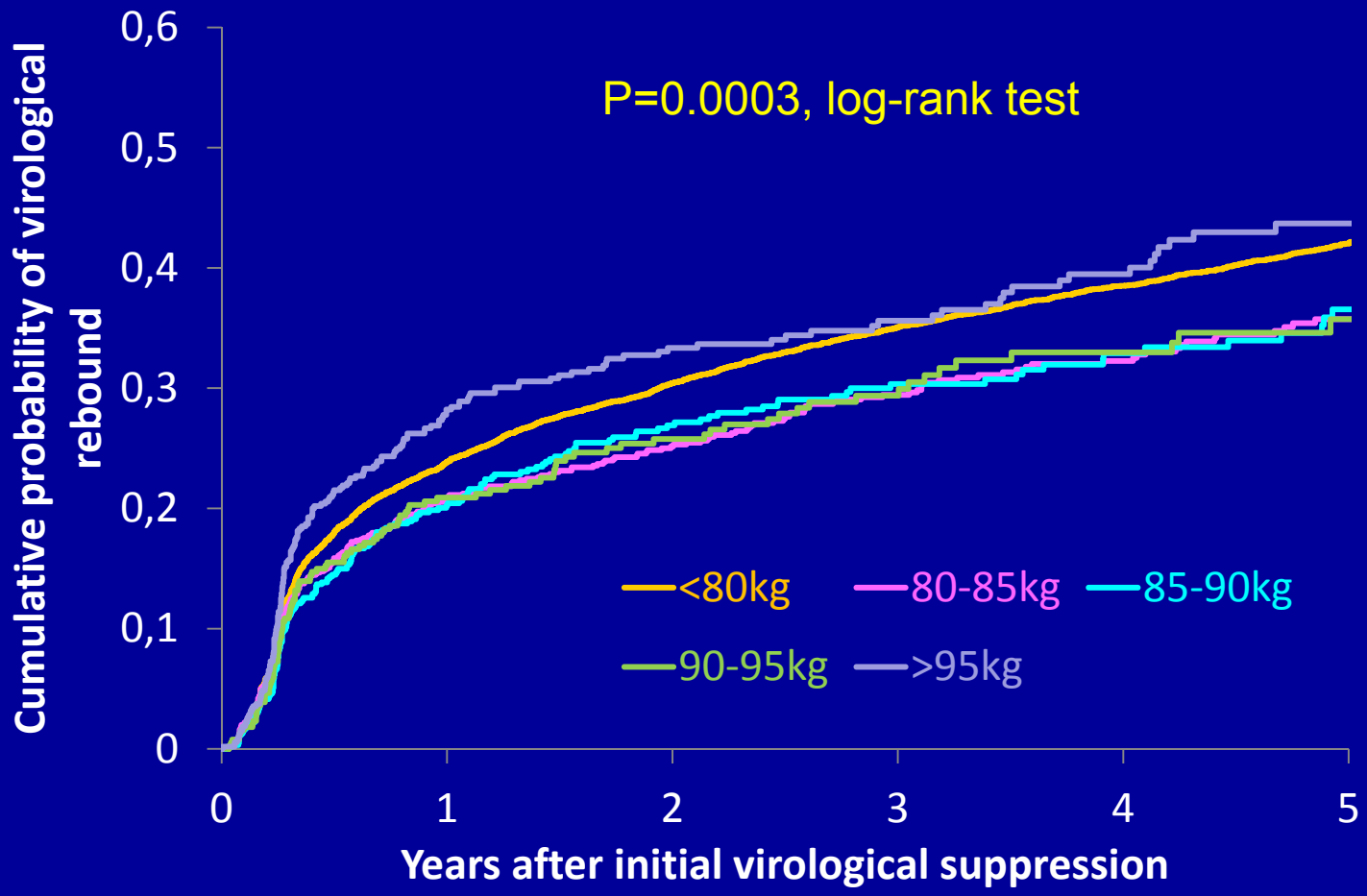
unadjusted

adjusted for demographic, viral and treatment–related factors, cohort and calendar year[1]

[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

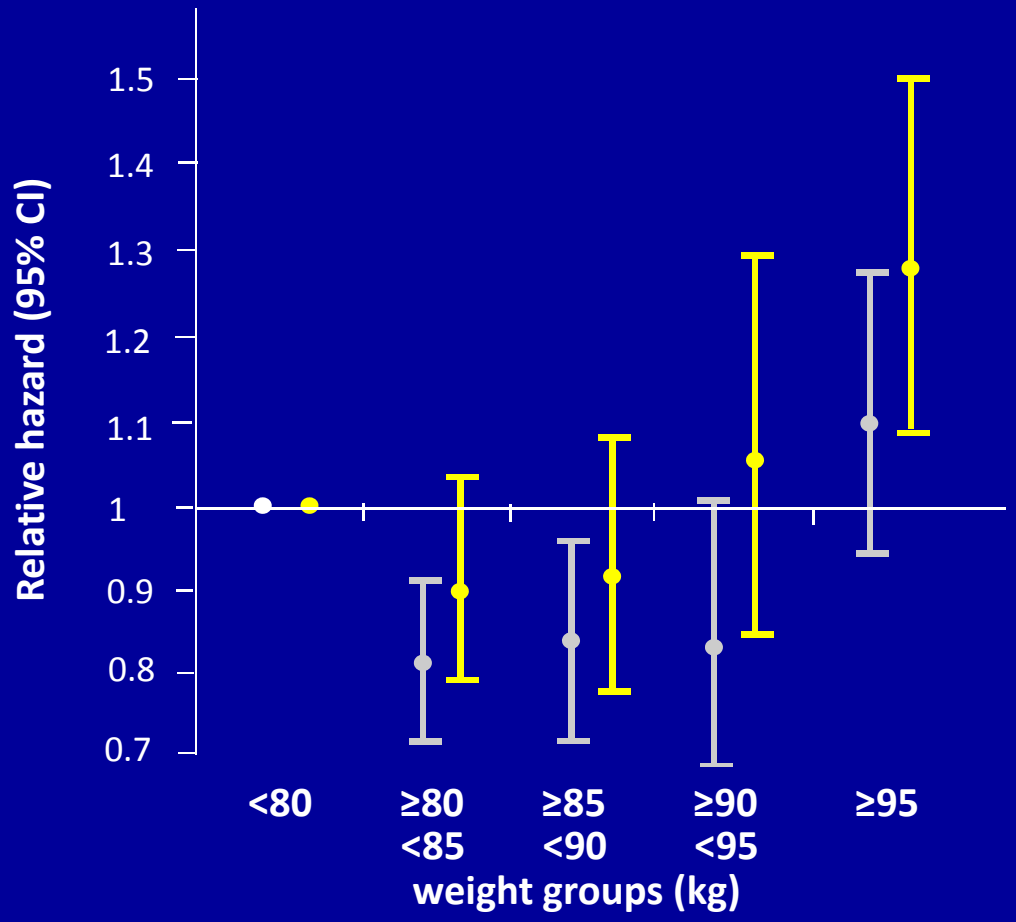
Kaplan-Meier plot for time to virological rebound

- **Of the 11310 patients with an undetectable VL, 3867 (34.2%) subsequently experienced viral load rebound**



Relative hazards for time to subsequent VL rebound

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



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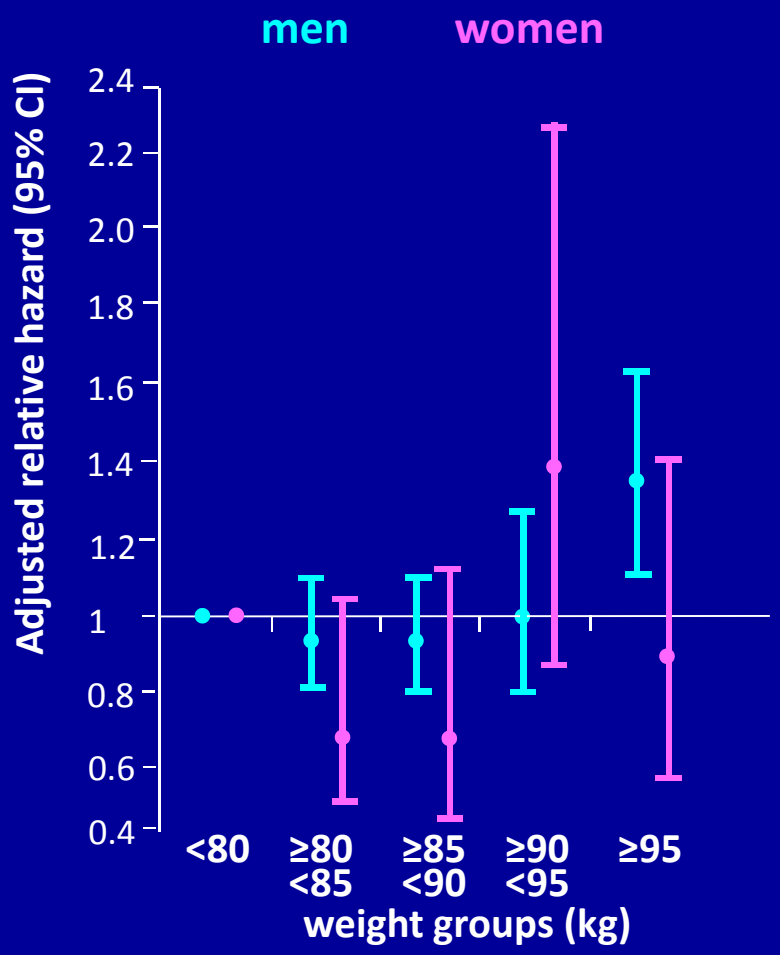
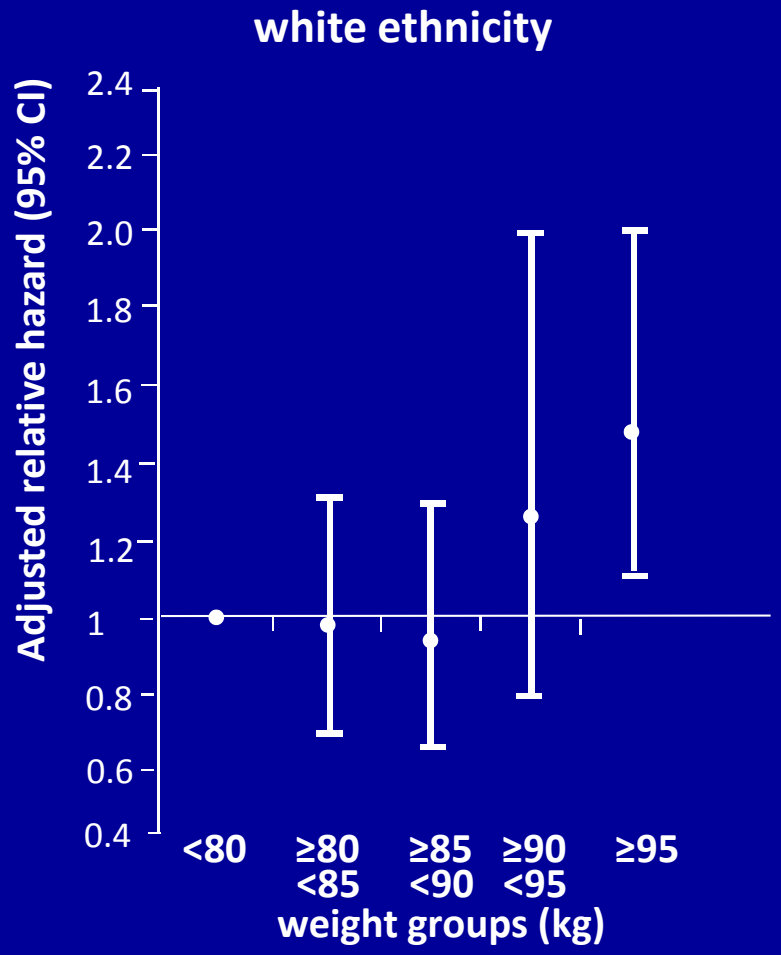
[1]Adjusted for gender, age, mode of HIV acquisition, ethnicity, cohort and calendar year, hepatitis/abnormal LFT, pre-EFV CD4 count and VL, prior AIDS, NRTI backbone, PI co-administration

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

IMIT AMACS ECS-Mothers & ECS-Infants NSHPC-Mothers & NHPS-Infants PISCIS KOMPNET CASCADE ANRS CO2 SEROCO Frankfurt HIV Cohort Study San Raffaele ANRS CO1/CO10 EPF UK CHIC Athena ITLR-Mothers & ITLR-Infants Swiss HIV Cohort Study ICC ANRS CO6 PRIMO Co-RIS MOCHIV-Mothers & MoCHIV-Infants The Italian MASTER Cohort CHIPS ANRS CO4 French Hospital's Database on HIV HIV-MIP-Mothers & HIV-MIP-Infants GEMES-Haemo ANRS CO3 AQUITAINE EuroSIDA Madrid Cohort HIV Children VACH Modena Cohort Study Danish HIV Study ANRS CO8 COPILOTE ICONA St. Pierre

Collaboration of Observational HIV Epidemiological Research Europe

Coordination: Copenhagen HIV Programme (CHIP) & Institut de Santé Publique,d'Epidémiologie et de Développement (ISPED)

Acknowledgements

Project leaders and statistical analysis:

Julia Bohlius, Vincent Bouteloup, Heiner Bucher,Alessandro Cozzi-Lepri, François Dabis, Antonella d'Arminio Monforte, Maria Dorucci, Matthias Egger, Frederik Engsig, Hansjakob Furrer, Ole Kirk, Olivier Lambotte, Charlotte Lewden, Rebbeca Lodwick, Sophie Matheron, Laurence Meyer, Jose Miro, Amanda Mocroft, Niels Obel, Roger Paredes,Andrew Phillips, Massimo Puoti, Joanne Reekie, Caroline Sabin, Alexandra Scherrer, Colette Smit, Jonathan Sterne, Rodolphe Thiebaut, Claire Thorne, Carlo Torti, Viktor von Wyl, Linda Wittkop

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Jesper Grarup
Manuel Battegay

Regional co-ordinating centers:
Bordeaux RCC cohorts: Diana Barger, Geneviève Chêne (Head), Christine Schwimmer, Monique Termote
Copenhagen RCC cohorts: Maria Campbell, Nina Friis-Møller, Jesper Grarup (Head), Jesper Kjaer, Dorthe Raben

Sources of funding: The COHERE study group has received generic funding from: Agence Nationale de Recherches sur le SIDA et les Hépatites Virales (ANRS), France; HIV Monitoring Foundation, the Netherlands; and the Augustinus Foundation, Denmark. COHERE receives funding from the European Union Seventh Framework Programme (FP7/2007-2013) under EuroCoord grant agreement n° 260694. A list of the funders of the participating cohorts can be found on the Regional Coordinating Centre websites at http://www.cphiv.dk/COHERE/tabid/295/Default.aspx and http://etudes.isped.u-bordeaux2.fr/cohere."

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