Poster 816

CROI 2007

Underutilization of recommended interventions for prevention of cardiovascular (CV) disease in HIV-infected patients with established CV disease or diabetes

CA Sabin*[1], R Weber[2], E Fontas[3], F Dabis[4], P Reiss[5], S De Wit[6], W El-Sadr[7], A D'Arminio Monforte[8], M Law[9], O Kirk[10], S Worm[11], N Friis-Møller[11], JD Lundgren[11], and the D:A:D Study Group

[1]Royal Free and UC Medical School, UK; [2]SHCS, Centre Hospitalier Universitaire Vaudois, Switzerland; [3]Nice Cohort, CHU Nice Hôpital de l'Archet, France; [4]Aquitaine Cohort, Bordeaux University Hospital, INSERM U593, France; [5]ATHENA, Academic Medical Center, University of Amsterdam, The Netherlands; [6]Saint-Pierre Cohort, C.H.U.Saint-Pierre Hospital, Belgium; [7]CPCRA, Columbia University/Harlem Hospital, NY, USA; [8]ICONA, L Sacco Hospital, University of Milan, Italy; [9]AHOD, National Centre in HIV Epidemiology and Clinical Research, Australia; [10]EuroSIDA, Hvidovre University Hospital, Denmark; [11]Copenhagen HIV Programme (CHIP), Hvidovre University Hospital, Denmark;

Caroline A Sabin, PhD
Department of Primary Care and Population Sciences, Royal Free and UCL Medical School, Rowland Hill Street, London, UK
Tel: +44 207 8302239 ext 34752
Fax: +44 207 7941224
E-mail: c.sabin@pcps.ucl.ac.uk

INTRODUCTION

- In HIV-uninfected populations with established CV disease and/or diabetes mellitus, a number of interventions are recommended for the prevention of further CV events and CV-related mortality (1,2)
- Whilst some studies have reported lower than anticipated uptake of these interventions in HIV-uninfected individuals (3,4), their utilization by HIV-infected individuals has not been described
- In particular, little information is available on the use of lipid-lowering drugs (LLD) or the frequency of smoking cessation in these individuals
- We used information from the large, multicentre D:A:D Study to describe the use of LLD and frequency of smoking cessation in HIV-infected individuals with established CV disease or diabetes

METHODS

- We identified all individuals who had a first CV event (myocardial infarction [MI], stroke or invasive CV procedure) or who were newly diagnosed with diabetes mellitus during follow-up in the D:A:D study between December 1999 and February 2006
- Use of LLD, smoking cessation and other CV risk factors (see Table 1), prior to the CV event/diagnosis and over the subsequent six months, were assessed
- Patients with established CV disease and diabetes mellitus were analysed separately; individuals were excluded from each analysis if they had <6 months of follow-up
- Statistical analysis was performed using Chi-squared tests and multiple logistic regression

RESULTS

Interventions in individuals with established CV disease

- 348 individuals in D:A:D with a first CV event during prospective follow-up and no newly diagnosed diabetes mellitus were included in analyses (Table 1). A further 585 patients with a CV event were excluded, either because of an earlier diagnosis of DM (n=116), because the event occurred prior to enrolment in D:A:D (n=306) or the individual had <6 months of follow-up after the event (n=163). Those excluded because of insufficient follow-up tended to be more likely to have had an MI or stroke as their first event, and were more likely to have their first event in 2005/2006
- 80 (23.0%) patients were already receiving LLD at the time of their CV event; of the 268 patients who were not receiving LLD at the time of CV event, 121 (45.2%) started these drugs in the subsequent six months (Figure 1). The proportion starting LLD varied significantly according to the type of CV event experienced, being much higher in those with an MI or those who underwent an invasive procedure than in those who experienced a stroke (p=0.007). Furthermore, there was an increasing tendency for patients to initiate LLD in later calendar years (p=0.007)
- Further analyses suggested that those who initiated LLD were more likely to be male (p=0.04), to have lipodystrophy (p=0.05) and had more severe metabolic abnormalities, as suggested by higher total cholesterol (p=0.01) and triglyceride levels (p=0.01) (Table 2). However, of these factors, total cholesterol was the only factor independently associated with the receipt of LLD in this group (odds ratio [OR] for receipt of LLD in those with total cholesterol levels ≥6.2 mmol/l: 2.28 [95% confidence interval [CI] 1.23-4.24]; p=0.009)
- Of the 149 individuals who were known to be current smokers at the time of the CV event, 24 (16.1%) were recorded as ex-smokers by six months after their event; discontinuation of smoking was more common in those experiencing an MI than in those with other events (p=0.03) but did not vary by calendar year
- Other interventions utilised by this group in the subsequent 6 months included platelet aggregation inhibitors (158/287; 55.1%), ACE inhibitors (72/318; 22.6%), and anti-hypertensive drugs (109/276; 39.5%). Thirty-eight of the 184 patients (20.7%) receiving a protease inhibitor at the time of their event had discontinued this class of drugs by six months after the event

Interventions in individuals with diabetes mellitus

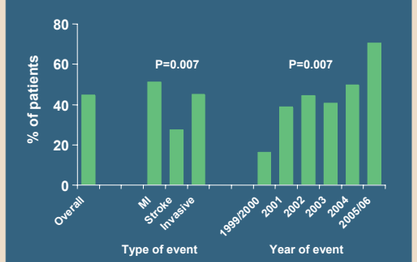
- 626 individuals in D:A:D newly diagnosed with diabetes mellitus during prospective follow-up and with no prior CV event were included in analyses. A further 891 patients with diabetes mellitus were excluded, either because of a prior CV event (n=835), a diagnosis prior to enrolment in D:A:D (n=781) or less than 6 months of follow-up (n=56). Those excluded because of insufficient follow-up were more likely to have been diagnosed in 2005/2006
- 114 (18.2%) patients were already receiving LLD at the time of their diagnosis; of the 512 patients who were not receiving LLD, 99 (19.3%) started these drugs in the subsequent six months (Figure 2). There were no significant variations in the proportion that started LLD over calendar time (p=0.27)

Table 1
Characteristics of 348 individuals with a first CV event and 626 patients with diabetes mellitus included in the analysis at the time of their event/diagnosis

	CV event n (%)	Diabetes mellitus n (%)
Number of patients	348 (100.0)	626 (100.0)
Male sex	317 (91.1)	516 (82.4)
Median (range) age (years)	49 (29-92)	46 (21-76)
Type of event		
MI	204 (58.6)	0 (-)
Stroke	73 (21.0)	0 (-)
Invasive Procedure	71 (20.5)	0 (-)
Diabetes mellitus	0 (-)	626 (100.0)
Other CV risk factors		
Current smokers	149 (42.8)	193 (30.8)
Family history of CV disease	47 (13.5)	60 (9.6)
Lipodystrophy	139 (39.9)	289 (43.0)
Median (range) BMI	23.1 (14.1-33.8)	24.9 (15.6-39.4)
Other concomitant medications		
Lipid-lowering drugs	80 (23.0)	114 (18.2)
ACE inhibitors	30 (8.6)	48 (7.7)
Platelet aggregation inhibitors	61 (17.5)	30 (4.8)
Anti-hypertensive agents	72 (20.7)	85 (13.6)
Lipid parameters		
Total cholesterol ≥6.2 mmol/l	140 (40.2)	68 (10.9)
HDL cholesterol ≤0.9 mmol/l	71 (20.4)	187 (29.9)
Triglyceride ≥2.3 mmol/l	175 (50.3)	364 (58.1)
Use of ART		
Ever received ART	340 (97.7)	599 (95.7)
Ever received NNRTIs	227 (65.2)	352 (56.2)
Ever received PIs	308 (88.5)	526 (84.0)
Receiving PIs at time of event	184 (52.9)	316 (50.5)

* Table entries are n (%) or median (range) as appropriate

Figure 1
Initiation of lipid-lowering drugs in six months following a first CV event among 268 patients who were not receiving these drugs at the time of the event



RESULTS (continued)

- Those who initiated LLD were more likely to have lipodystrophy (p=0.01) and had higher total cholesterol (p=0.003) and triglyceride (p=0.04) levels than those who did not initiate LLD (Table 3). Of these factors, both the presence of lipodystrophy (adjusted OR: 2.62 [1.24-5.52]; p=0.01) and a total cholesterol level ≥6.2 mmol/l (2.96 [1.42-6.16]; p=0.004) were independently associated with the initiation of LLD
- Of the 193 individuals known to be current smokers at the time of diagnosis, 10 (5.2%) were recorded as ex-smokers by six months after their event; whilst there was significant variation in the proportion of individuals who ceased smoking over time (p=0.006), there was no consistent trend to these proportions
- Other interventions utilised by this group included platelet aggregation inhibitors (10/619; 1.6%), ACE inhibitors (6/620; 1.0%), and anti-hypertensive drugs (8/622; 1.3%). 86 of the 316 patients (27.2%) who were receiving a protease inhibitor at the time of diabetes diagnosis discontinued this class of drugs within the subsequent six months

SUMMARY

- Initiation of LLD following a CV event has increased over time, but even in the most recent time period a substantial minority remained off these drugs. This proportion was larger in those experiencing a stroke than in those experiencing MIs or undergoing invasive procedures. Initiation of LLD was more likely in those with elevated total cholesterol levels. Other drug interventions, including initiation of platelet aggregation inhibitors, ACE inhibitors and anti-hypertensive agents, were relatively common
- Only a fifth of patients with diabetes mellitus who were not on LLD at the time of diagnosis of diabetes, a group considered at high risk for CV morbidity and mortality in the general population, initiated such primary prevention; use of other drug interventions was also rare in this group
- Smoking cessation was rare in both groups of patients, despite being strongly recommended

CONCLUSIONS AND DISCUSSION

- Whilst the use of LLD has increased over time, reflecting an increased awareness of CV disease in HIV-infected individuals, many patients at high risk of CVD are not receiving such preventative therapy as recommended. The reasons for this are unclear, but may include patient choice as well as concerns about high pill burden and potential interactions with antiretroviral drugs
- Whilst concerning, our findings of lack of uniform utilization of LLD in individuals at risk of CVD are not dissimilar from findings in HIV-negative populations at high-risk of CVD, in which targets for management of dyslipidaemia (3, 4) are not always achieved. Unfortunately, information is not collected on the type of LLD used (fibrate or statin) so we cannot comment on the appropriateness of the specific interventions used
- Whilst evidence of the efficacy of LLD in HIV-infected individuals receiving cART remains limited (5), the finding of an increased risk of CV disease associated with prolonged exposure to PI therapy (6), as well as the presence of other established risk factors for CV events, emphasises the importance of the appropriate interventions in these patients. Given this, it is somewhat surprising that a high proportion of individuals receiving protease inhibitors at the time of a CV event remained on this class of drug over the next 6 months
- Smoking, as a modifiable and important risk factor for CV disease, should be emphasized and concerted smoking cessation interventions should be supported
- Further ongoing analyses in the D:A:D study will consider the impact of these interventions on CV mortality, the use of such interventions in other, lower-risk, individuals, and the role of other prevention interventions

ACKNOWLEDGEMENTS:
Cohort PI's: W E-Sadr * (CPCRA), G Calvo * (BASS), F Dabis * (Aquitaine), O Kirk (EuroSida), M Law * (AHOD), A d'Arminio Monforte * (ICONA), L Morfeldt * (HivBIVUS), C Pradier * (Nice), P Reiss * (ATHENA), R Weber * (SHCS), S De Wit * (Brussels). **Cohort coordinators and datamanagers**: S Zaheri, L Gras (ATHENA), R Thiébaut, E Balestre (Aquitaine), K Petoumenos (AHOD), S Mateu,F Torres (BASS), B Sommereijns, B Poll (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær (EuroSIDA), P Pezzotti (ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach, O Keiser (SHCS). **Statisticians**: CA Sabin, AN Phillips *. **Community representative**: S Collins *. **DAD coordinating office**: N Friis-Møller, S Worm, A Sawitz, JD Lundgren *¢. **Steering Committee**: Members indicated w/*; ¢ chair; **Additional members**: E Loeliger *, R Tressler *, I Weller *. **Funding**: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMEA and a consortium of "Abbott, Agouron, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Hoffman-La Roche"

REFERENCES

1. National Cholesterol Education Program (NECP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *Circulation* 2002; **106**: 3143-342; 2. De Backer G et al. *Eur Heart J* 2003; **24**: 1601-1610; 3. Yan AT et al. *Am J Med* 2006; **119**: 676-683; 4. Rodondi N et al. *Ann Int Med* 2006; **144**: 475-484; 5. Dubé MP et al. *Clin Infect Dis* 2003; **37**:613-627; 6. Friis-Moller N et al. Abstract 144, 13th CROI, Denver, February 5-8, 2006.

Table 2
Comparison of individuals with a CV event, not receiving LLD at the time of the event, who did and did not initiate these drugs in the subsequent six months

	Initiated LLD in next six months: No	Yes	P-value
Number of patients	147	121	
Male sex	128 (87.1)	115 (95.0)	0.04
Current smoker	69 (46.9)	61 (50.4)	0.66
Family history of CVD	16 (10.9)	21 (17.4)	0.13
Lipodystrophy	46 (31.3)	53 (43.8)	0.05
Hypertension	34 (24.6)	39 (35.1)	0.10
Age at time of event (years)	48 (41-56)	47 (41-56)	0.89
BMI at time of event	22.8 (20.7-25.5)	23.4 (20.9-25.2)	0.87
Total cholesterol ≥6.2 mmol/l	45 (30.8)	56 (46.7)	0.01
HDL cholesterol ≤0.9 mmol/l	31 (24.6)	21 (21.4)	0.69
Triglyceride ≥2.3 mmol/l	61 (41.5)	59 (49.2)	0.26
Ever used protease inhibitors	129 (87.8)	104 (86.0)	0.80
Current use of protease inhibitors	78 (53.1)	58 (47.9)	0.48

* Table entries are n (%) or median (inter-quartile range) as appropriate

Figure 2
Initiation of lipid-lowering drugs in six months following a diagnosis of diabetes mellitus among 512 patients who were not receiving these drugs at the time of their diagnosis

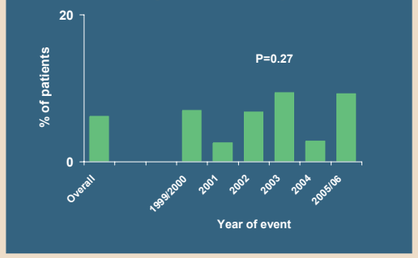


Table 3
Comparison of individuals with a diagnosis of diabetes, not receiving LLD at the time of diagnosis, who did and did not initiate these drugs in the subsequent six months

	Initiated LLD in next six months: No	Yes	P-value
Number of patients	480	32	
Male sex	393 (81.9)	25 (78.1)	0.77
Current smoker	156 (32.5)	6 (18.8)	0.15
Family history of CVD	42 (8.8)	3 (9.4)	1.00
Lipodystrophy	181 (37.7)	20 (62.5)	0.01
Hypertension	56 (11.7)	4 (12.5)	1.00
Age at time of event (years)	46 (40-53)	45 (41-53)	0.81
BMI at time of event	24.6 (22.3-27.5)	25.9 (22.4-28.3)	0.74
Total cholesterol ≥6.2 mmol/l	106 (22.1)	15 (46.9)	0.003
HDL cholesterol ≤0.9 mmol/l	136 (28.3)	10 (31.3)	0.88
Triglyceride ≥2.3 mmol/l	247 (51.5)	23 (71.9)	0.04
Ever used protease inhibitors	400 (83.3)	25 (78.1)	0.61
Current use of protease inhibitors	236 (49.2)	18 (56.3)	0.55

* Table entries are n (%) or median (inter-quartile range) as appropriate

CHIP COPENHAGEN HIV PROGRAMME

Download poster at: www.cphiv.dk