Poster 707

CROI 2009

Amanda Mocroft
University College London, Royal Free Campus
Tel : 44 (0) 2078302239
Fax : 44 (0) 2077941224
E-mail: a.mocroft@pcps.ucl.ac.uk

Serious Fatal and Non-Fatal Non-AIDS Defining Illnesses (non-ADI) in Europe

A Mocroft[1], P Reiss[2], J Gasiorowski[3], B Ledergerber[4], A Chiesi[5], J Gatell[6], A Rakhmanova[7], MA Johnson[8], O Kirk[9], JD Lundgren[9,10] for the EuroSIDA study group

[1]University College Medical School, UK, [2]Academisch Medisch Centrum bij de Universiteit van Amsterdam, The Netherlands, [3]Medical University, Poland, [4]Zurich University Hospital, Switzerland, [5]Istituto Superiore di Sanità, Italy, [6]Hospital Clinic i Provincial, Spain, [7]Medical Academy Botkin Hospital, Russia, [8]Royal Free Hospital, UK, [9]Copenhagen HIV Programme, Panum Institute, Denmark, [10]Centre for Viral Disease KMA, Rigshospitalet, Denmark

BACKGROUND

There is a perception that diseases thought to be non-HIV related, such as non-AIDS malignancies, cardiovascular disease, renal disease and liver failure, are becoming increasingly common, but little is known about the incidence and risk factors for serious non-AIDS defining illnesses (non-ADI) in HIV infected patients.

PATIENTS

All patients in the EuroSIDA study with prospective follow-up after 1 January 2002 were included in analyses.

METHODS

The incidence of non-ADI (malignancies, end-stage renal disease [ESRD], liver failure [grade III/IV hepatic encephalopathy, death from liver-related disease], pancreatitis, cardiovascular disease [acute myocardial infarction or stroke; CVD]) after 1/1/02 was investigated and compared to the incidence of ADIs; poisson regression was used to investigate factors associated with non-ADI and ADI. Person-years of follow-up (PYFU) accrued from later of 1/1/02 or recruitment to the study (baseline) until development of either an ADI or a non-ADI. Recurrences of ADI or non-ADI were excluded from analyses.

RESULTS

10,341 patients were included in the study, as described in **Table 1**.

There were 684 non-ADIs (incidence 16.5 per 1,000 PYFU; 95% CI 15.3-17.7), and 641 ADIs (incidence 15.5 per 1,000 PYFU; 95% CI 14.3-16.7); 316 (46.5%) and 219 (34.5%) patients died respectively. The frequency of non-ADI and ADI are shown in **Figure 1**; the most common non-ADI were malignancies, CVD and liver failure, of ADIs were oesophageal candidiasis, PCP and pulmonary tuberculosis.

Table 1
Baseline characteristics of 10,341 patients

		N	%
Gender	Male	7675	74.3
Exposure Group	Homosexual	4182	40.4
	IDU	2372	22.9
	Heterosexual	3079	29.8
Exposure to ARVs	ARV naive	1261	12.2
	cART	8536	82.6
		Median	**IQR**
CD4	(/mm³)	405	250 – 591
CD4 nadir	(/mm³)	166	67 – 286
HIV RNA	(log_{10}copies/ml)	1.90	1.69 – 3.41
Age	(years)	40.0	34.5 – 46.9
Baseline	(month/year)	1/02	1/02 – 12/03

Figure 1
Non-ADIs and ADIs diagnosed during follow-up

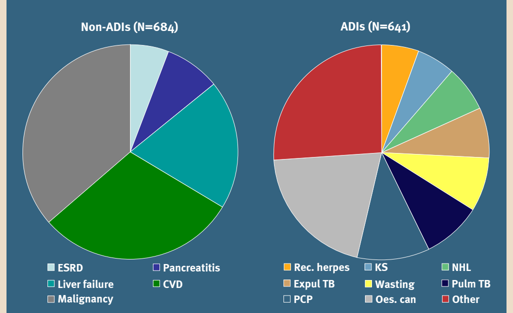

Table 2
Characteristics at date of diagnosis

		Non-ADI (N=684) N	%	ADI (N=641) N	%
Started cART		627	92.2	521	82.2
Prior AIDS diagnosis		309	45.4	258	40.7
Hepatitis B co-infection		70	10.3	47	7.4
Hepatitis C co-infection		218	32.1	200	31.6
Diabetes		80	11.8	27	4.3
Hypertension		251	36.9	111	17.5
Current smoker		339	49.9	282	44.5
Anaemia*		229	33.7	219	34.5
		Median	**IQR**	**Median**	**IQR**
CD4	(/mm³)	328	177 – 533	198	63 – 370
Viral load	(log_{10}copies/ml)	1.77	1.69 – 3.52	4.08	1.92 – 5.11
Age	(years)	47.7	41.8 – 56.6	41.1	34.9 – 47.4

*Defined as ≤12 g/dl or ≤ 14 g/dl for females and males respectively

The characteristics of the patients at diagnosis of the ADI and non-ADI are shown in **Table 2**.

The incidence of non-ADI was markedly lower at lower current (or latest) CD4 counts and was similar to, or exceeded, the incidence of ADI at all current CD4 counts ≥ 100/mm³ (**Figure 2**).

Table 3 shows the adjusted incidence rate ratios for developing a non-ADI or an ADI. Co-infection with hepatitis B, C, having diabetes, hypertension, being a current smoker or having anaemia all significantly increased the incidence of non-ADIs. A patient with a current (i.e. latest) CD4 count twice the level of a comparable patient had a 23% lower incidence of a non-ADI. Increased duration of immunosupression with a CD4 count ≤200/mm³ was also associated with an increased incidence of non-ADIs.

In contrast, diabetes, hypertension and hepatitis B or C co-infection were not associated with developing an ADI. Current viral load and current CD4 count were much stronger markers for developing an ADI and duration of immunosupression was not related to the incidence of ADI after adjustment.

CONCLUSIONS

Non-ADIs were more common than ADIs in the cART era, they have considerably mortality and should be routinely reported in clinical trials and observational studies. The risk factor profile for non-ADIs was diverse with multiple potentially modifiable immunodeficiency and lifestyle-related risk factors. Evidence on the impact of modifying these factors on the risk of non-ADI is an important but unmet research need.

Figure 2
Incidence of ADIs, Non-ADIs and current CD4 count

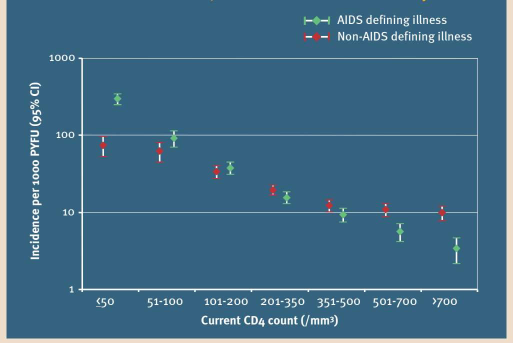

Table 3
Factors associated with development of ADI or non-ADI

	Non-ADI IRR	Non-ADI 95% CI	Non-ADI P	ADI IRR	ADI 95% CI	ADI P
Hepatitis B co-infected	1.52	1.17–1.97	0.0017	1.10	0.80–1.51	0.57
Hepatitis C co-infected	1.41	1.09–1.82	0.0081	1.09	0.83–1.43	0.52
Age (per 10 yr older)	1.68	1.55–1.83	<0.0001	1.15	1.04–1.27	0.0079
AIDS*	1.35	1.13–1.60	0.0007	1.29	1.06–1.58	0.010
Diabetes	1.56	1.22–2.00	0.0001	0.90	0.63–1.35	0.61
Hypertension	1.40	1.18–1.66	<0.0001	0.91	0.73–1.13	0.39
Current smoker	1.74	1.44–2.09	<0.0001	1.25	1.02–1.54	0.028
CD4 (per doubling)	0.77	0.72–0.83	<0.0001	0.59	0.56–0.63	<0.0001
HIV RNA (per log_{10} higher)	1.11	1.03–1.19	0.0050	1.54	1.43–1.64	<0.0001
Anaemia⁺	2.11	1.73–2.58	<0.0001	1.55	1.25–1.93	<0.0001
Duration with CD4≤ 200/mm³ (>2 vs ≤ 2 yrs)	1.40	1.06–1.86	0.017	0.98	0.74–1.30	0.90

IRR; incidence rate ratio. All variables are time-updated except *included as a time-updated covariate for non-ADIs and a fixed covariate at baseline for ADIs. Model also adjusted for calendar year of follow-up, CD4 nadir, starting cART, region of Europe, gender, HIV exposure category and ethnic origin. ⁺Defined as ≤12 g/dl or ≤ 14 g/dl for females and males respectively

The EuroSIDA Study Group (National Coordinators)

Argentina: (M Losso), C Elias, Hospital JM Ramos Mejia, Buenos Aires. **Austria:** (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna; (R Zangerle) Medical University Innsbruck, Innsbruck. **Belarus:** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk. **Belgium:** (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp; (L Vandekerckhove) University Ziekenhuis Gent, Gent. **Bosnia:** (V Hadziosmanovic) Klinicki Centar Univerziteta Sarajevo, Sarajevo. **Bulgaria:** K Kostov, Infectious Diseases Hospital, Sofia. **Croatia;** J Begovac, University Hospital of Infectious Diseases, Zagreb. **Czech Republic:** (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark:** (J Nielsen) G Kronborg,T Benfield, M Larsen, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus. **Estonia:** (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve. **Finland:** (M Ristola), Helsinki University Central Hospital, Helsinki. **France:** (C Katlama) Hôpital de la Pitié-Salpétière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux. **Germany: (**J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne. **Greece:** (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambatakou, Ippokration Genereal Hospital, Athens. **Hungary:** (D Banhegyi) Szent Lásló Hospital, Budapest. **Ireland:** (F Mulcahy) St. James's Hospital, Dublin. **Israel:** (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa;S Maayan, Hadassah University Hospital, Jerusalem. **Italy:** (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d'Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan. **Latvia:** (B Rozentale) P Aldins, Infectology Centre of Latvia, Riga. **Lithuania:** (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. **Luxembourg:** (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. **Netherlands:** (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. **Poland:** (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk; (E Jablonowska) E Malolepsza, K Wojcik, Wojewodzki Szpital Specjalistyczny, Lodz. **Portugal:** (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon. **Romania:** (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest. **Russia:** (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod. **Serbia:** (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia:** (M Mokráš) D Staneková, Dérer Hospital, Bratislava. **Slovenia:** (J Tomazic) University Clinical Centre Ljubljana, Ljubljana. **Spain:** (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; (S Moreno) Hospital Ramon y Cajal, Madrid; B Clotet, A Jou, R Paredes, C Tural, J Puig, I Bravo, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona. **Sweden:** (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö. **Switzerland:** (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel. **Ukraine:** (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev; (G Kutsyna) Luhansk AIDS Center, Luhansk; (S Servitskiy), Odessa Region AIDS Center, Odessa; (S Antoniak) Kiev; (M Krasnov) Kharkov State Medical University, Kharkov. **United Kingdom:** (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; C Leen, Western General Hospital, Edinburgh.

Virology group: B Clotet, R Paredes(Central Coordinators) plus ad hoc virologists from participating sites in the EuroSIDA Study.
Steering Committee: F Antunes, B Clotet, D Duiculescu, J Gatell, B Gazzard, A Horban, A Karlsson, C Katlama, B Ledergerber (Chair), A D'Arminio Montforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh
Coordinating Centre Staff: J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie, J Kowalska

Download poster at: www.cphiv.dk

COPENHAGEN HIV PROGRAMME