Poster 828

CROI 2007

Detection of chronic renal failure (CRF) among HIV-patients within the EuroSIDA Study

A Mocroft[1], O Kirk[2], J Gatell[3], P Reiss[4], P Gargalianos[5], K Zilmer[6], M Beniowski[7], JP Viard[8], S Staszewski[9], JD Lundgren[2] for the EuroSIDA study group*

[1]Royal Free and University College Medical School, London, UK; [2]Copenhagen HIV Programme, Hvidovre, Denmark; [3]Hospital Clinic i Provincial, Barcelona, Spain; [4]Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam, The Netherlands; [5]Athens General Hospital, Athens, Greece, [6]West-Tallinn Central Hospital, Tallinn, Estonia; [7]Medical University of Silesia in Katowice, Chorzow, Poland; [8]Hôpital Necker-Enfants Malades, Paris, France; [9]JW Goethe University Hospital, Frankfurt, Germany.

Amanda Mocroft, PhD
Royal Free Centre for HIV Medicine and Dept Primary Care and Population Sciences, Royal Free and University College London Medical Schools
Royal Free Campus, Rowland Hill St, London, NW3 2PF, United Kingdom
Tel: 44-(0)2078302239
Fax: 44-(0)2077941224
E-mail: a.mocroft@pcps.ucl.ac.uk

INTRODUCTION

- HIV infection is associated with several types of renal dysfunction, including HIV-associated nephropathy (HIVAN), immune complex kidney disease and acute renal failure.
- A number of antivirals (indinavir, ritonavir, and tenofovir DF) and other drugs commonly used to treat opportunistic infections (acyclovir, amphotericin B, foscarnet, cidofovir, adefovir and pentamidine) may be associated with nephrotoxicity.
- The glomerular filtration rate (GFR) is a measure of kidney function and can be measured via
  - Cockcroft-Gault (CG) equation
  - Modification of Diet in Renal Disease (MDRD) equation

AIMS

- To characterise patients with CRF, as measured by 2 consecutive abnormally reduced GFR measurements (< 60 mL/min per 1.73m²).
- To describe antiretroviral treatment and experience in relation to CRF.

METHODS

Patients from EuroSIDA with ≥ 2 serum creatinine measurements measured after 1 January 2004 were included providing they had weight measured within 6 months of the serum creatinine measurement and had height recorded. Baseline was defined as the date of the first GFR measurement. GFR was calculated using the CG formula and MDRD formula, both were standardized for body surface area using the Mostellar formula;

$$\text{GFR (CG)} = \frac{(140\text{-age}) \times \text{weight (kg)}}{\text{Serum creatinine} \times 72} \times 0.85 \text{ (if female)}$$

$$\text{GFR (MDRD)} = 186 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ (if black)}$$

CRF was defined by a confirmed GFR of ≤60 mL/min per 1.73m². For each ARV and specific combinations, the number of days exposure to each drug was calculated. Logistic regression was used to determine the factors related to CRF at baseline, using forward selection (p<0.1 inclusion criteria). Use of each antiretroviral was added to a model with the selected demographic factors. Use of ritonavir was considered in a single-PI or a boosted PI-regimen. Use of tenofovir DF and ritonavir occurred almost exclusively (96.8% of exposure) in patients taking ritonavir as part of a boosted PI regimen, and was not subdivided further. ARV use was modeled as ever exposed (yes/no), and cumulative exposure prior to baseline (continuous and categorical).

RESULTS

- 4474 patients satisfied the inclusion criterion and are described in **Table 1**, stratified by CRF at baseline.
- There was a high degree of correlation between the CG and MDRD methods (correlation coefficient 0.773, p<0.0001).
- 158 patients (CG, 3.5%) and 209 patients (MDRD, 4.7%) had CRF at baseline. 101 patients (2.3%) had CRF with both formulae.

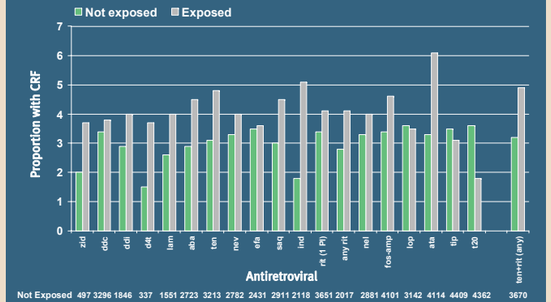
Table 1

Patient characteristics and GFR at baseline; standardised for BSA

		All patients N	All patients %	CG CRF N	CG CRF %	MDRD CRF N	MDRD CRF %
All patients		4474	100	158	3.5	209	4.7
Gender	Male	3404	76.1	131	82.9	183	87.6
	Female	1070	23.9	27	17.1	26	12.4
Race	White	3807	85.1	140	88.6	187	90.4
	Other	667	14.9	18	11.4	20	9.6
Risk	Homosexual	2032	45.4	79	50.0	113	54.1
	IDU	833	18.6	12	7.6	29	13.9
	Heterosexual	1300	29.1	49	31.0	48	23.0
	Other	309	6.9	18	11.4	19	9.1
Atherosclerosis	No	3853	86.1	123	77.9	169	80.9
	Yes	123	2.9	16	10.1	17	8.1
	Unknown	494	11.0	19	12.0	23	11.0
Diabetes	No	3877	86.7	121	76.6	162	77.5
	Yes	210	4.7	26	16.5	32	15.3
	Unknown	387	8.7	11	7.0	15	7.2
Hypertension	No	2551	57.0	52	32.9	73	34.9
	Yes	1223	27.3	85	53.5	114	54.6
	Unknown	700	15.7	21	13.3	22	10.5
Smoking Status	No	2048	45.8	92	58.2	117	56.0
	Past	227	5.1	13	8.2	14	6.7
	Current	1533	34.3	31	19.6	51	24.4
	Unknown	666	14.9	22	13.9	27	12.9
		Median	IQR	Median	IQR	Median	IQR
Age		43.4	38.950.8	61.9	55.0-69.1	54.6	45.4-62.4
CD4		455	310-645	403	265-538	430	314-575
Viral load		1.70	1.70-2.61	1.70	1.70-2.48	1.70	1.70-2.30
CD4 nadir		135	148 - 239	80	27-180	88	25 - 211

Figure 1

CRF at baseline
(confirmed GFR < 60 ml/min per 1.73m² using CG formula)



	zid	ddc	ddi	d4t	3tc	aba	ten	nev	efa	saq	ind	rit (1 PI)	any rit	nel	fos-amp	lop	ata	tip	t20	tenavirit (any)
Not Exposed	497	3296	1846	337	1551	2723	3213	2782	2431	2911	2118	3651	2017	2881	4101	3142	4114	4409	4362	3670
Exposed	3977	1178	2628	4137	2923	1751	1261	1692	2043	1563	2356	823	2457	1593	373	1332	360	65	112	804

zid: zidovudine, ddc; zalcitabine, ddi: didanosine, d4t; stavudine, 3tc; lamivudine, aba; abacavir, ten; tenofovir DF, nev; nevirapine, efa; efavirenz, saq; saquinavir, ind; indinavir, rit; ritonavir, PI; protease inhibitor, nel; nelfinavir, fos-amp; amprenavir, lop; lopinavir, ata; atazanavir, tip; tipranavir; t20; enfurvitide

RESULTS (continued)

- In general, patients with CRF were more likely to have atherosclerosis, diabetes, and hypertension, were older and had lower CD4 count nadirs than patients without CRF (both CG and MDRD formulae).
- Due to the similarity of the results, only results using the CG formula are presented from here.
- **Figure 1** illustrates the proportion of patients exposed to each antiretroviral, or combinations of antiretrovirals, stratified according to CRF at baseline, using the CG formula.
- For example, for indinavir, 1.8% (38/2118) of patients never exposed had CRF compared to 5.1% (120/2356) of patients exposed to indinavir. The corresponding figures for tenofovir DF were 3.1% (93/3213) and 4.8% (60/1261) respectively.
- The results of logistic regression models are shown in **Table 2**. After adjustment, patients from Eastern Europe, older patients, patients with a higher CD4 nadir at baseline, or those with a higher viral load at baseline, had significantly increased odds of CRF at baseline
- Use of indinavir or tenofovir DF was associated with increased odds and use of enfurvitide was associated with decreased odds of CRF at baseline.
- Use of ritonavir as a single or as part of a boosted PI-regimen was not associated with increased odds of CRF at baseline, and use of tenofovir DF and ritonavir as part of the same regimen was not associated with increased odds of CRF at baseline.

Table 2

Factors associated with CRF at baseline
(confirmed GFR ≤ 60 ≤ mL/min per 1.73m² at baseline; Cockcroft-Gault formula)

	Univariate OR	Univariate 95% CI	Univariate P	Multivariate OR	Multivariate 95% CI	Multivariate P
Eastern Europe	0.92	0.57–1.50	0.74	2.45	1.35–4.45	0.0033
Prior AIDS	1.82	1.32–2.51	0.0002	1.34	0.88–2.02	0.17
Age	4.90	4.08–5.88	<0.0001	5.47	4.45–6.72	<0.0001
CD4 nadir	0.90	0.84–0.96	0.0023	0.90	0.82–0.99	0.028
Baseline	1.57	1.07–2.29	0.022	1.65	1.04–2.62	0.033
Viral load	0.92	0.63–1.35	0.68	1.54	0.98–2.41	0.062
Hypertension	3.25	2.36–4.48	<0.0001	1.34	0.92–1.95	0.12
Any tenofovir DF use	1.59	1.14 –2.21	0.0057	2.18	1.25–3.81	0.0061
Any indinavir use	2.94	2.03–4.25	<0.0001	2.49	1.62–3.83	<0.0001
Any enfurvitide use	0.49	0.12–2.00	0.32	0.13	0.03–0.65	0.013
Any ritonavir use (single PI regimen)	1.23	0.83–1.81	0.30	0.77	0.39–1.50	0.44
Any ritonavir use (≥2 PI regimen)	1.47	1.06–2.05	0.021	0.89	0.56–1.43	0.64
Any tenofovir DF/ritonavir use	1.52	1.05–2.20	0.026	1.27	0.82–1.98	0.29
Any renal-toxic prophylactic drug	1.99	1.39–2.85	0.0002	1.47	0.94–2.30	0.089

CONCLUSIONS

We have described the prevalence and risk factors for CRF (2 consecutive GFR < 60 mL/min per 1.73m²) in HIV-infected patients, including the most important risk factors known from the general population; highly consistent results were found using the CG and MDRD formula to calculate GFR.

- Patients with lower CD4 nadir, those with a prior diagnosis of AIDS, and older patients also had higher odds of CRF. Among antiretrovirals, only exposure to indinavir or tenofovir DF was associated with increased odds of CRF.
- We used a confirmed low GFR to define CRF to increase the robustness of our analysis, although there are several potential biases associated with this cross-sectional analysis.
- A causal relationship cannot be identified using a cross sectional analysis. Future analyses should focus on confirmed changes in GFR, requiring large numbers of patients and serial estimates of creatinine clearance.
- Ideally, serum creatinine should be measured prior to starting drugs so that the effect on serum creatinine can be described in detail, both whilst on treatment and if treatment is interrupted or modified.

Acknowledgements: The European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713) and the 5th framework (QLK2-2000-00773) programs were the primary sponsors of the study. Unrestricted grants were also provided by Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche and Boehringer-Ingelheim. The participation of centres from Switzerland in EuroSIDA was supported by a grant from the Swiss Federal Office for Education and Science.

STUDY GROUP

The multicentre study group o-n EuroSIDA (national coordinators in parenthesis)

Argentina (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires. **Austria** (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna. **Belarus** (I Karpov), A Vassilenko, Belarus State Medical University, Minsk. **Belgium** (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; B Colebunders, Institute of Tropical Medicine, Antwerp. **Czech Republic** (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen. **Denmark** () Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense; **Estonia** (K Zilmer) West-Tallinn Central Hospital, Tallinn. **France** (C Katlama) Hôpital de la Pitié-Salpêtière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; T Saint-Marc, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, UnitÉ INSERM, Bordeaux. **Germany** M Dietrich, C Manegold, Bernhard-Nocht-Institut for Tropical Medicine, Hamburg; J van Lunzen, H-J Stellbrink, Eppendorf Medizinische Kernklinik, Hamburg; S Staszewski, M Bickel, JW Goethe University Hospital, Frankfurt; F.D Goebel, Medizinische Poliklinik, Munich; G. Fätkenheuer, Universität Köln, Cologne; J Rockstroh, Universitäts Klinik Bonn; P Schmidt, Medizinische Hochschule Hannover. **Greece** () Kosmidis) P Gargalianos, H Sambatakou, J Perdios, Athens General Hospital, Athens; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital, Athens. **Hungary** (D Banhegyi) Szent Lásló Hospital, Budapest. **Ireland** (F Mulcahy) St. James's Hospital, Dublin. **Israel** () Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; Z Shhoeger, Kaplan Hospital, Rehovot; S Maayan, Hadassah University Hospital, Jerusalem. **Italy** (S Vella, A Chiesi) Istituto Superiore di Sanita, Rome; C Arici, Ospedale Riuniti, Bergamo; R Pristerà, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S. Maria Annunziata, Florence; R Esposito, A Bedini, Universita di Modena, Modena; A Chirianni, E Montesarchio, Presidio Ospedaliero A.D. Cotugno, Naples; V Vullo, P Santopadre, Università di Roma La Sapienza, Rome; P Narciso, A Antinori, P Franci, M Zaccarelli, Ospedale Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; A D'Arminio Monforte, Osp.S Paolo, Milan; AL Ridolfo, Osp. L. Sacco, Milan. **Latvia** (L Viksna) Infectology Centre of Latvia, Riga. **Lithuania** (S Chaplinskas) Lithuanian AIDS Centre, Vilnius. **Luxembourg** (R Hemmer), T Staub, Centre Hospitalier, Luxembourg. **Netherlands** (P Ross) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway** () Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo. **Poland** (B Knysz) J Gasiorowski, Medical University, Wrocław, A Horban, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wierzinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical University, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk. **Portugal** (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Matez, Hospital Curry Cabral, Lisbon. **Romania** (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucarest; A Streinu-Cercel, Institute of Infectious Diseases, Bucarest. **Russia** E Vinogradova, St Petersburg AIDS Centre; A Rakhmanova, Medical Academy Botkin Hospital, St Petersburg. **Serbia & Montenegro** (D Jevtovic) The Institute for Infectious and Tropical Diseases, Belgrade. **Slovakia** (M Mokráš) D Staneková, Dérer Hospital, Bratislava. **Spain** () González-Lahoz) P Barreiro, T Garcia-Benayas, L Martin-Carbonero, V Soriano, Hospital Carlos III, Madrid; B Clotet, A Jou, I Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona. **Sweden** (A Blaxhult) Karolinska University Hospital, Solna; A Karlsson, Karolinska University Hospital, Stockholm; P Pehrson, Karolinska University Hospital, Huddinge. **Switzerland** (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, A Telenti, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschel, V Soravia-Dunand, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern. **Ukraine** (N Chentsova) Kyiv Centre for AIDS, Kyiv. **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; R Brettle, Western General Hospital, Edinburgh.

Virology group: B Clotet (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, Karlsson, C Kallama, B Ledergerber (Chair), A D'Arminio Monforte, A Phillips, A Rakhmanova, P Reiss (Vice-Chair), J Rockstroh
Coordinating Centre Staff: J Lundgren (project leader), I Gjørup, O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, C Holtkmann Olsen, J Kjær

CHIP COPENHAGEN HIV PROGRAMME

Download poster at: www.cphiv.dk

EuroSIDA