EuroCoord

SEVENTH FRAMEWORK PROGRAMME

a multicentre study

EuroSIDA

The spectrum of clinical disease and relationship with measures of deteriorating renal function

Amanda Mocroft, Lene Ryom, Josip Begovac, Antonella D'Arminio Monforte, Anne Vassilenko, Jose Gatell, Eric Florence, Vidar Ormaasen, Ole Kirk, Jens D Lundgren on behalf of EuroSIDA in EuroCoord

UCL

Background

- In HIV-negative
  - impaired renal function associated with mortality, ESRD, and CVD[1]
  - Short term changes in renal function associated with clinical outcomes[2]
- In HIV-positive
  - Low eGFR associated with CVD and mortality[3]
  - Range of clinical disease and relationship with eGFR not well described

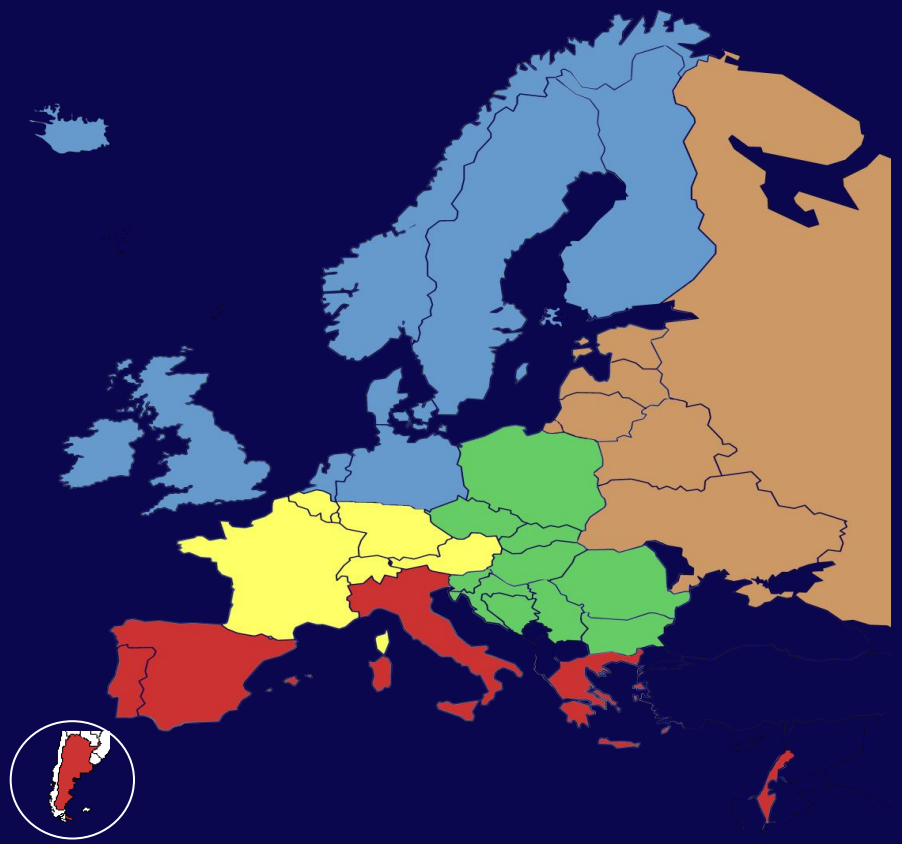
[1]Hemmelgarn JAMA 2010; [2]Turin Am J Nephrol 2012; [3]Choi Am J Kidney Dis 2010

Aims

- Describe the incidence of fatal and non-fatal AIDS and non-AIDS events according to current eGFR
- Determine whether current eGFR, or other measures of renal insufficiency were independent predictors of clinical events

Methods - EuroSIDA

EuroSIDA is a large prospective cohort with 18,791 patients from 108 clinics in 34 European countries, Israel and Argentina.
Regularly collecting:



- HIV transmission risk group
- CD4 counts, HIV viral loads
- SCr since 1/1/2004
- All treatment start/stop dates
- Clinical AIDS events
- Non-AIDS events (since 2001)
- Deaths and causes of death

UCL

Patients and Definitions

- Patients with ≥1 eGFR ≥ 1/1/2004 were included
- eGFRs calculated using CKD-EPI
- Baseline : first eGFR measured during prospective FU > 1/1/2004
- FU to latest of last clinic visit, last eGFR or death
- Poisson regression to investigate relationships between renal function and outcomes
  - All cause mortality
  - Fatal and non-fatal AIDS
  - Fatal and non-fatal non-AIDS[1]

[1]Mocroft, JAIDS 2010 : *Non-AIDS malignancies, pancreatitis, end stage liver disease, end stage renal disease and cardiovascular events*

Markers of renal function

- Current eGFR
- Nadir eGFR
- %FU eGFR≤60 mL/min/1.73m^2

Markers of renal function

Month	eGFR (mL/min)	Nadir eGFR	Current eGFR	%FU eGFR ≤ 60
0*	72	72	72	0
3	60	60	60	0
7	65	60	65	4/7 (57%)
9	62	60	62	4/9 (44%)
15	75	60	75	4/15 (27%)
20	80	60	80	4/20 (20%)
24	78	60	78	4/24 (17%)

eGFRs calculated using CKD-EPI and all markers modelled as time-updated (current)

*Baseline; 1st eGFR ≥1/1/2004

EuroSIDA

UCL

Characteristics of 11409 patients (1)

		N (%)
Gender	Male	8521 (74.7)
Exposure group	MSM	4799 (42.1)
	IDU	2232 (19.6)
	Heterosexual	3493 (30.6)
Race	White	9904 (86.8)
Viral load	<400	7805 (68.4)
ARV naïve	Yes	1422 (12.5)
		Median (IQR)
Age	Years	42 (36 – 49)
Baseline	mm/yy	01/05 (06/04 – 07/07)
CD4	/mm^3	434 (290 – 621)
eGFR	ml/min/1.73m^2	99 (85 – 111)

Characteristics of 11409 patients (2)

	N (%)
HBV coinfected	691 (6.1)
HCV coinfected	2383 (20.9)
Diabetic	545 (4.8)
Hypertensive	3221 (28.2)
Anaemic*	2590 (22.7)
Prior AIDS	3324 (29.1)
Prior non-AIDS	718 (6.3)

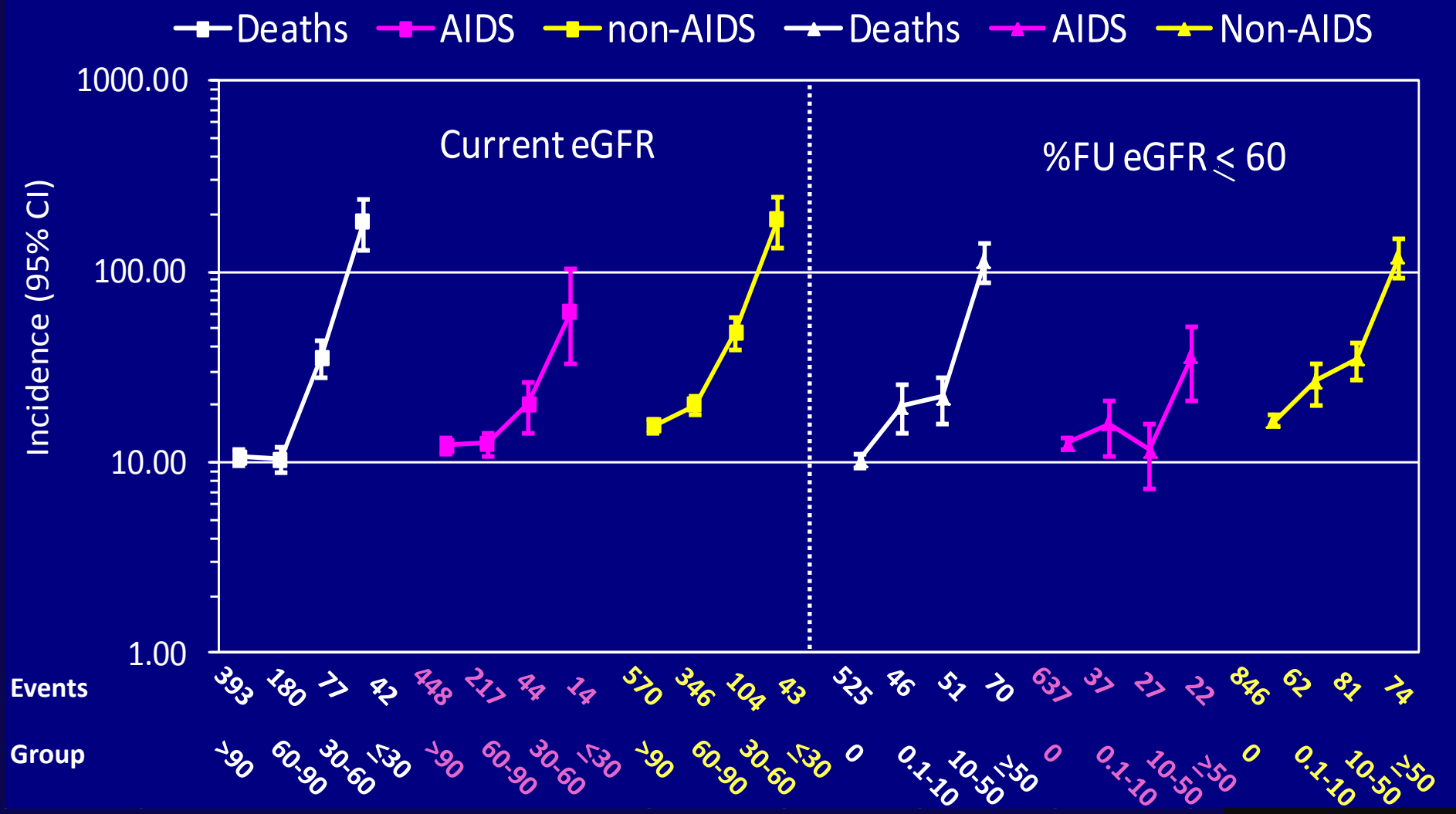
- 146857 eGFRs included
- 56452 PYFU
- Median 5.7 (IQR 3.3 – 7.2) yrs follow-up
- Median (IQR) 13 (6-18) eGFRs pp
- Median 3.7 (2.8-5.5) mths apart

EuroSIDA

*Haemoglobin ≤14/12 g/dl males/females

UCL

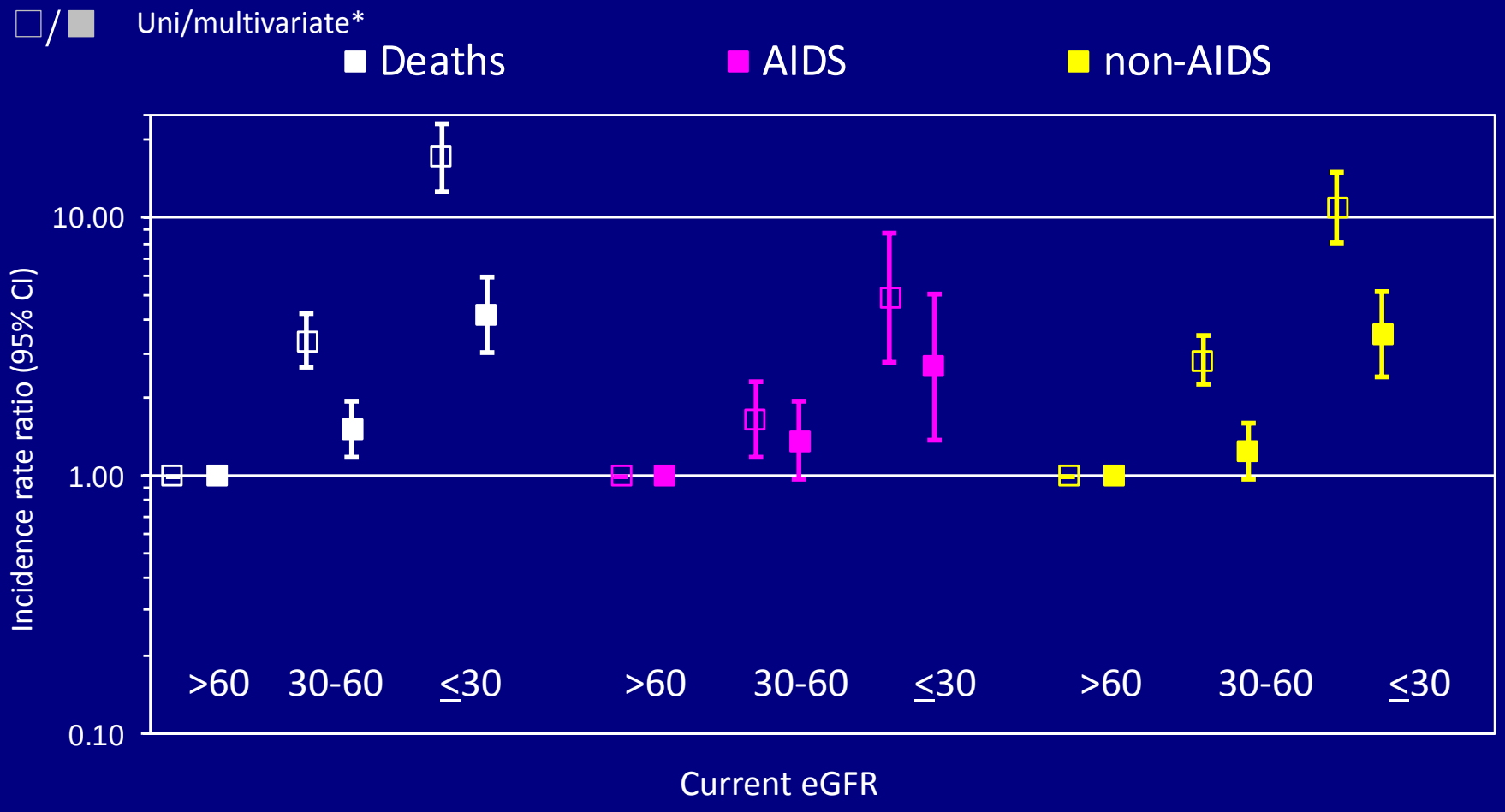
Crude incidence rates (/1000 PYFU)
Deaths, AIDS and non-AIDS



EuroSIDA

UCL

Incidence rate ratios of clinical events
Current eGFR



*Adjusted for gender, race, region of Europe, age, CD4 nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, CD4, viral load (all time-updated) and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events). as time-updated

EuroSIDA

UCL

Incidence rate ratios of clinical events per 10% longer FU with eGFR ≤ 60

	Univariate			Multivariate*		
	IRR	95% CI	P	IRR	95% CI	P
Deaths	1.41	1.37 – 1.45	<0.0001	1.24	1.19 – 1.28	<0.0001
AIDS	1.16	1.08 – 1.24	<0.0001	1.15	1.06 – 1.24	0.0006
Non-AIDS	1.31	1.27 – 1.36	<0.0001	1.14	1.09 – 1.19	<0.0001

*Adjusted for gender, race, region of Europe, age, CD4 nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, CD4, viral load (all time-updated) and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events). as time-updated

Nadir eGFR and clinical events

- Nadir eGFR was not a strong predictor of clinical events after accounting for current eGFR

IRR (95% CI) for deaths (per 10 mL/min lower nadir eGFR)

Univariate	Multivariate*
1.20 (1.16 – 1.24)	0.98 (0.94 – 1.03)
p<0.0001	p=0.30

*Adjusted for gender, race, region of Europe, age, CD4 nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, CD4, viral load and current eGFR

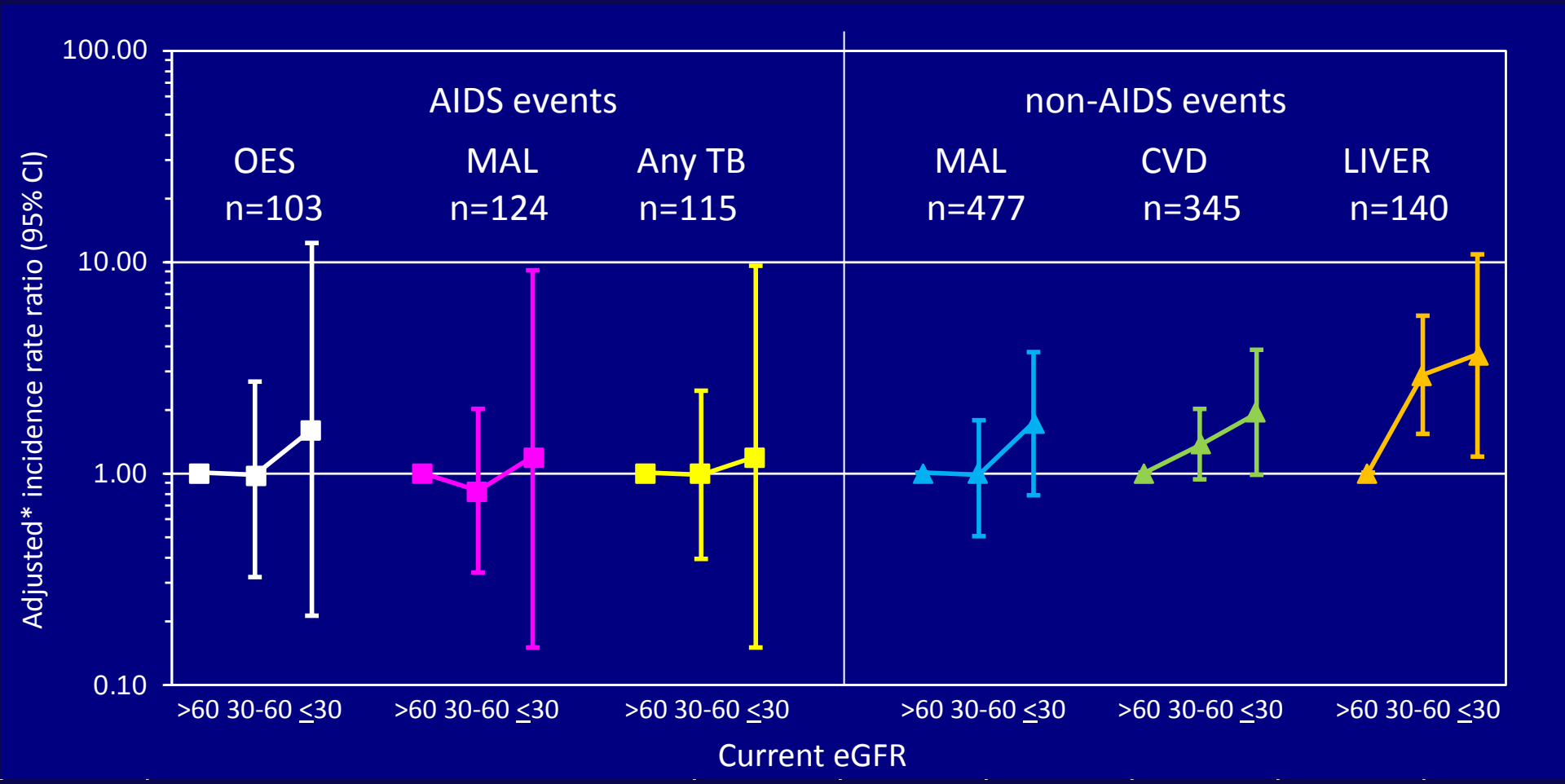
Fatal versus non-fatal events

Adjusted* incidence rate ratios (95% CI); p

		Fatal events	Non-fatal events
AIDS		N=134	N=601
Current eGFR	>60	1.00	1.00
	30-60	2.56 (1.44 – 4.54); 0.0013	1.09 (0.73 – 1.62); 0.69
	≤30	4.26 (1.33 – 13.61); 0.015	1.96 (1.00 – 3.86); 0.051
%FU eGFR ≤60 (10% longer)		*1.57 (0.88 – 2.82); 0.13*	*0.78 (0.28 – 1.06); 0.11*
Non-AIDS		N=262	N=823
Current eGFR	>60	1.00	1.00
	30-60	1.41 (0.82 – 2.42); 0.21	1.09 (0.84 – 1.41); 0.52
	≤30	4.28 (2.26 – 8.09); <0.0001	1.72 (1.20 – 2.46); 0.0030
%FU eGFR ≤60 (10% longer)		*1.90 (1.31 – 2.77); 0.0008*	*0.99 (0.82 – 1.21); 0.95*

*Adjusted for gender, race, region of Europe, age, CD4 nadir, risk group, started cART, baseline date, and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, CD4, viral load and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events).

Adjusted* incidence rate ratios of individual clinical events (fatal and non-fatal; n>75) and current eGFR



*Adjusted for gender, race, region of Europe, age, CD4 nadir, risk group, started cART, baseline date, AIDS and non-AIDS (all measured at baseline) and hepatitis B, hepatitis C coinfections, smoking status, diabetes, hypertension, anaemia, CD4, viral load (all time-updated) and development of a non-AIDS event as time-updated variables (AIDS events) or AIDS (non-AIDS events). as time-updated.

EuroSIDA

UCL

Conclusions

- Lower current eGFR and higher %FU eGFR ≤60 were associated with death and non-AIDS events
- Consistent relationship between renal function and different non-AIDS events
- Relationship between renal function and AIDS was mainly explained by fatal AIDS events
- Stronger relationship with fatal events; a marker for clinical disease or a consequence of underlying deteriorating health?

Implications

- Findings highlight the association between underlying renal dysfunction and morbidity/mortality in HIV infection
- Regular screening for non-renal morbidities is crucial in HIV-positive patients with chronic renal impairment
- Future studies could assess whether renal interventions lead to reduction in risk of non-AIDS events

The EuroSIDA Study Group

The multi-centre study group of EuroSIDA (national coordinators in parenthesis).

Argentina: (M Losso), M Kundro, 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, M Delforge, Saint-Pierre Hospital, Brussels; E Florence, Institute of Tropical Medicine, Antwerp; L Vandekerckhove, University Ziekenhuis Gent, Gent. **Bosnia-Herzegovina:** (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), D Jilich, 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 Ostergaard, Skejby Hospital, Aarhus, U B Dragsted, Roskilde Hospital, Roskilde; L N Nielsen, Hillerod Hospital, Hillerod. **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, Hôtel-Dieu, Paris; P-M Girard, Hospital Saint-Antoine, Paris; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l'Archet, Nice; F Dabis, D Neau, Unité INSERM, Bordeaux, C Duvivier, Hôpital Necker-Enfants Malades, Paris. **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; M Bickel, 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; H Sambatakou, Ippokration Genereal Hospital, Athens. **Hungary:** (D Banhegyi), Szent Lásló Hospital, Budapest. **Iceland: (**M Gottfredsson), Landspitali University Hospital, Reykjavik. **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; H Elinav, M Haouzi, Hadassah University Hospital, Jerusalem. **Italy:** (A D'Arminio Monforte), Istituto Di Clinica Malattie Infettive e Tropicale, Milan; 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 D`Offizi, C Taibi , A Antinori, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, A Castagna, N Gianotti, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan. **Latvia:** (B Rozentale), I Zeltina, Infectology Centre of Latvia, Riga. **Lithuania:** (S Chaplinskas), Lithuanian AIDS Centre, Vilnius. **Luxembourg:** (T Staub), R Hemmer, Centre Hospitalier, Luxembourg. **Netherlands:** (P Reiss), Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam. **Norway:** (V Ormaasen), A Maeland, J Bruun, Ullevål Hospital, Oslo. **Poland:** (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, E Bakowska, Centrum Diagnostyki i Terapii AIDS, Warsaw; A Grzeszczuk, R Flisiak, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, M Parczewski, 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:** (M Doroana), M Doroana, L Caldeira, 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; A Rakhmanova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod, I Khromova, Centre for HIV/AIDS & and Infectious Diseases, Kaliningrad; E Kuzovatova, Nizhny Novgorod Scientific and Research Institute, Nizhny Novogrod. **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, P Labarga, Hospital Carlos III, Madrid; S Moreno, J. M. Rodriguez, 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; J Medrano, Hospital Universitario de Alava, Vitoria-Gasteiz. **Sweden:** (A Blaxhult), Venhaelsan-Sodersjukhuset, Stockholm; L Flamholc, Malmö University Hospital, Malmö, A Thalme, A Sonnerborg, Karolinska University Hospital, Stockholm. **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; P Vernazza, Kantonsspital, St. Gallen. **Ukraine:** (E Kravchenko), N Chentsova, Kiev Centre for AIDS, Kiev; V Frolov, G Kutsyna, Luhansk State Medical University; Luhansk; S Servitskiy, Odessa Region AIDS Center, Odessa; A Kuznetsova, Kharkov State Medical University, Kharkov; G Kyselyova, Crimean Republican AIDS centre, Simferopol. **United Kingdom:** (B Gazzard), St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, E Simons, Mortimer Market Centre, London; A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); C Orkin, Royal London 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.

Steering Committee: J Gatell, B Gazzard, A Horban, I Karpov, B Ledergerber, M Losso, A D'Arminio Monforte, C Pedersen, A Rakhmanova, M Ristola, J Rockstroh (Chair), S De Wit t(Vice-Chair)

Additional voting members: J Lundgren, A Phillips, P Reiss

Coordinating Centre Staff: O Kirk, A Mocroft, A Cozzi-Lepri, D Grint, A Schultze, L Shepherd, D Raben, D Podlekareva, J Kjær, L Peters, J E Nielsen, C Matthews, A H Fischer, A Bojesen

EuroSIDA representatives to EuroCoord: O. Kirk, A. Mocroft, J. Grarup, P. Reiss, A. Cozzi-Lepri, R. Thiebaut, J. Rockstroh, D. Burger, R. Paredes, J. Kjær. L. Peters

Statement of Funding:
Primary support for EuroSIDA is provided by the European Commission BIOMED 1 (CT94-1637), BIOMED 2 (CT97-2713), the 5th Framework (QLK2-2000-00773), the 6th Framework (LSHP-CT-2006-018632), and the 7th Framework (FP7/2007-2013, EuroCoord n° 260694) programmes. Current support also includes unrestricted grants by Bristol Myers Squibb, Janssen R&D, Merck and Co. Inc., Pfizer Inc., GlaxoSmithKline LLC. The participation of centres from Switzerland was supported by The Swiss National Science Foundation (Grant 108787)

EuroSIDA

UCL