D:A:D

Development of a definition for Rapid Progression (RP) of renal disease in HIV-positive persons

L Ryom, DA Kamara, SW Worm, MJ Ross, P Reiss,
CA Fux, P Morlat, O Moranne, O Kirk, C Smith and JD Lundgren
for the D:A:D study group

D:A:D

Background I

- Several trials have demonstrated that most HIV-positive individuals maintain a relative stable renal function in the cART era

- Studying those who do progress from a normal renal function is, however, still warranted and should be carried out in large cohort settings due to the low frequency

D:A:D

Background II

- A normal age-related decline in eGFR is ~1 ml/min/1.73m^2 /year

- A number of definitions for an abnormally rapid deterioration in renal function, *Rapid Progression (RP),* have been suggested;
  - doubling of creatinine levels in ‹4 weeks[1]
  - ›50% decrease in baseline eGFR[2]
  - annual eGFR decline ›3 ml/min/1.73m^2 [3-7]

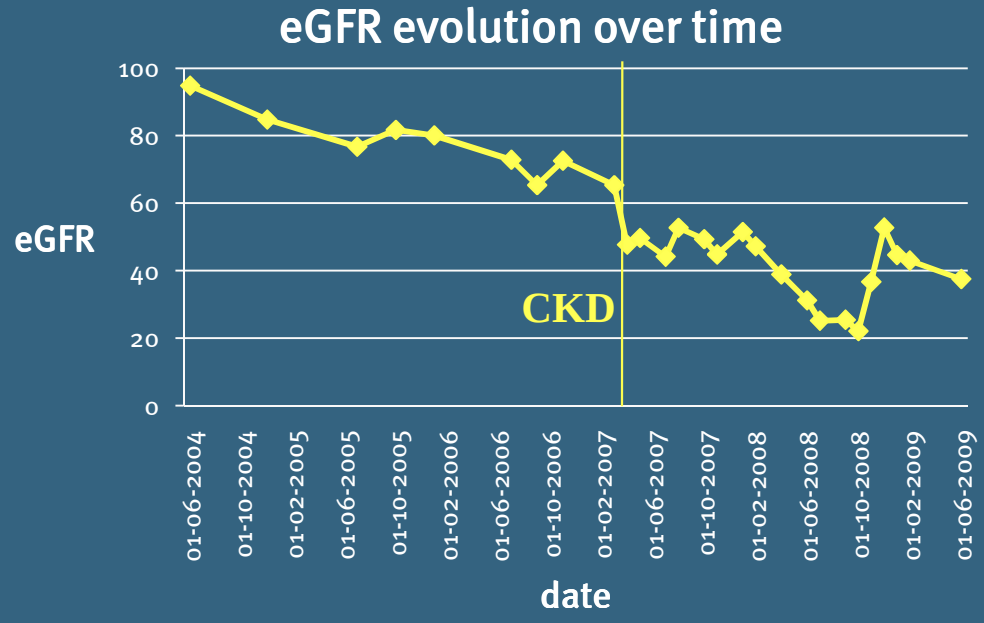
  - However, still unclear whether:
    - the annual changes should be average (all eGFRs) or absolute (difference between first and last eGFR)
    - how long the decline should be sustained to be a RP

1 Moger V 2005 Ren fail, 2 Alves TP 2010 Clin J Am Soc Nephrol, 3 Longenecker CT 2009 AIDS, 4 Kop WJ 2011 Clin J AM Soc Nephrol, 5 Lin J 2011 Am J Kidney Dis, 6 Rifkin DE, 2008 Arch intern Med, 7 Keller C 2010 Nephrol dial transplant

D:A:D

Background III

- In D:A:D the interest for RP arose during another project where eGFR slopes were investigated
- A sizable number of patients had a sustained fast declining renal function over time
- CKD is defined as confirmed eGFR‹60 ml/min/1.73m² (› 3 months) whereas RP is more dynamic and describes a steep and above normal annual eGFR slope - supplement to the CKD definition



Purpose

The purpose of this exploratory study was to develop a definition of RP that could capture individuals at the highest risk of a sustained deterioration of renal function from initial normal levels (eGFR >90 ml/min/1,73m^2)

D:A:D

Hypothesis

- Only using annual absolute decline (difference between first and last eGFR per year) may be too restrictive for a RP definition
- An annual average decline (based on all eGFRs during FU) to define RP may not reflect a sustained decline properly in that negative changes might be compensated by positive changes in renal function
- Therefore, our proposed primary definition of RP will combine absolute and average annual decline during FU

D:A:D

Methods

- eGFR was calculated via the Cockcroft-Gault (CG) equation
- As the optimal RP cut off is unknown, we used a restrictive cutoff of › 5 ml/min/1,73m² to avoid noise and to catch only the clinically most relevant cases
- For our primary analyses we identified patients with
  - eGFR›90 ml/min/1,73m² after 2004 (where creatinine was first collected routinely in D:A:D)
  - ≥4 consecutive years of FU between 2004-2010
  - ≥3 eGFR measurements annually

  These patients were then assessed for two RP definitions

D:A:D

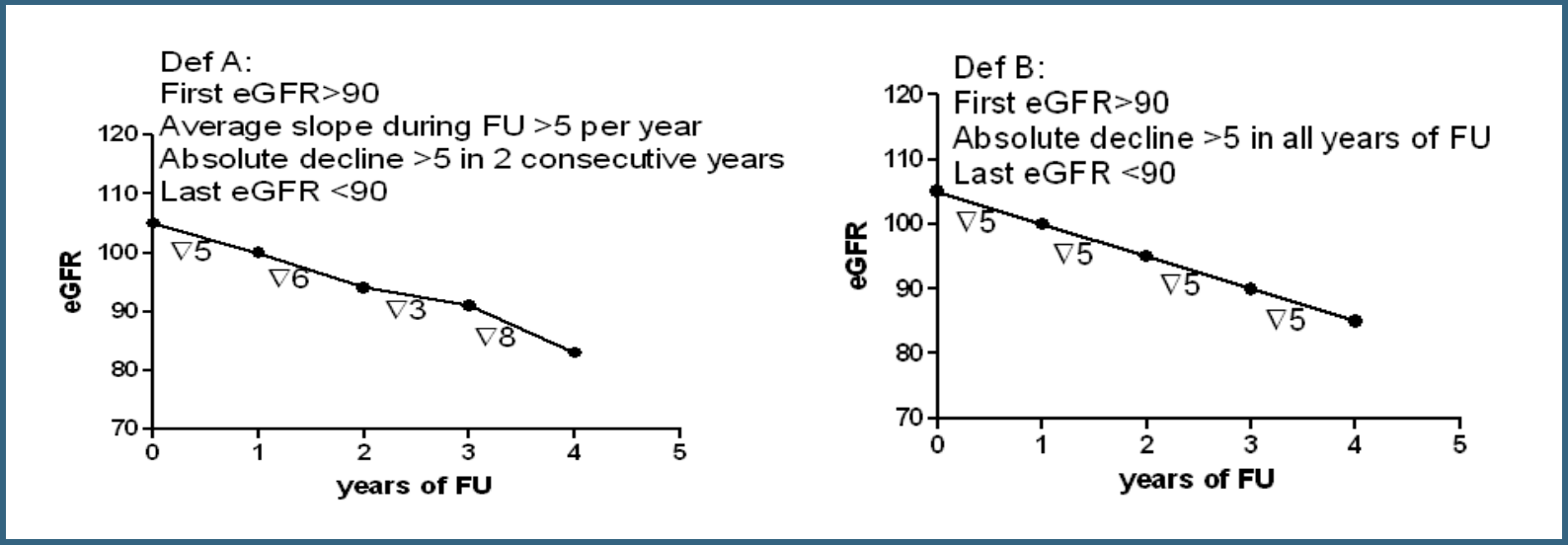
RP definitions

RP definition A (primary definition)

- An average annual eGFR decline ›5 ml/min/1,73m² over the 4 year FU period (≥20 ml/min/1,73m² in total)
- An absolute eGFR decline ›5 ml/min/1,73 m² in 2 consecutive years
- ≥3 eGFR measurements/year
- An eGFR level at the end of the 4 year FU ‹90 ml/min/1,73m²

RP definition B (secondary definition)

- As for RP def A , except the annual decline must be an absolute decline of ›5 ml/min/1,73 m² in each of the 4 consecutive years´ FU



D:A:D

Methods continued

- Analyses were repeated using
  - A shortened FU of 2 and 3 years instead of 4
  - Replacement of ≥3 with ≥2 eGFR measurements/year
  - A composite endpoint with RP or all cause mortality
- Additional investigation included
  - Number of RP that progressed to confirmed CKD
  - Level of last eGFR ever measured to test possible leveling of in renal function after RP
- The association between RP and very well documented traditional renal risk factors (diabetes, age, hypertension) was assessed using Logistic Regression

D:A:D

Patient characteristics

		all pt.s eGFR › 90	pt.s 3 yrs FU ≥2 eGFR	RP def A 3 yrs FU ≥2 eGFR
	Total	21700 (100%)	10530 (100%)	324 (100%)
Race	White	47%	47%	59%
Gender	Male	73%	73%	72%
HIV risk group	Homo-sexual	44%	45%	46%
Diabetes	Yes	3%	4%	4%
Age	›50yrs	10%	11%	20%
AIDS diagnosis	Yes	22%	25%	28%
Hepatitis C	Yes	17%	17%	24%
Hypertension	Yes	12%	13%	20%

Table 1: logistic regression (adjusted)*- Rapid progression

		≥ 3 eGFR measurements/year				≥ 2 eGFR measurements/year			
		RP definition A		RP definition B		RP definition A		RP definition B	
≥ 4 yrs FU	RP/total included	95/ 2952 (3.2%)		9/2952 (0.3%)		223/ 6739 (3.3%)		34/6739 (0.5%)	
	Age (>50)	2.65 (1.64 - 4.30)	<0.0001	**	**	2.13 (1.52 - 2.98)	<0.0001	2.50 (1.10 - 5.67)	0.02
	Hyperten-sion	1.60 (0.97 - 2.64)	0.07	**	**	1.48 (1.05 - 2.10)	0.03	0.94 (0.35 - 2.51)	0.91
≥ 3 yrs FU	RP/total included	165/5378 (3.1%)		78/5378 (1.5%)		324/10530 (3.1%)		160/10530 (1.5%)	
	Age (>50)	2.21 (1.52 - 3.23)	<0.0001	3.20 (1.93 -5.32)	<0.0001	2.12 (1.60 - 2.81)	<0.0001	2.93 (2.02 -4.25)	<0.0001
	Hyperten-sion	1.85 (1.27 - 2.71)	0.002	1.30 (0.73 -2.30)	0.37	1.46 (1.09 - 1.95)	0.01	0.78 (0.48 - 1.27)	0.33
≥ 2 yrs FU	Rp/total included	297/9338 (3.2%)		399/9338 (4.3%)		531/ 15051 (3.5%)		683/ 15051 (4.5%)	
	Age (>50)	2.33 (1.76 - 3.09)	<0.0001	2.61 (2.05 -3.32)	<0.0001	2.38 (1.91 - 2.97)	<0.0001	2.69 (2.22 - 3.26)	<0.0001
	Hyperten-sion	1.36 (1.00 - 1.85)	0.05	1.26 (0.96 -1.65)	0.1	1.16 (0.91 -1.48)	0.25	1.13 (0.91 - 1.41)	0.26

*** Adjusted for diabetes but due to very few events, results not shown. ** Too few events**

D:A:D

RP and progression to incident CKD

Neither specificity /sensitivity can be assessed
Instead we tested if RPs progress to incident CKD

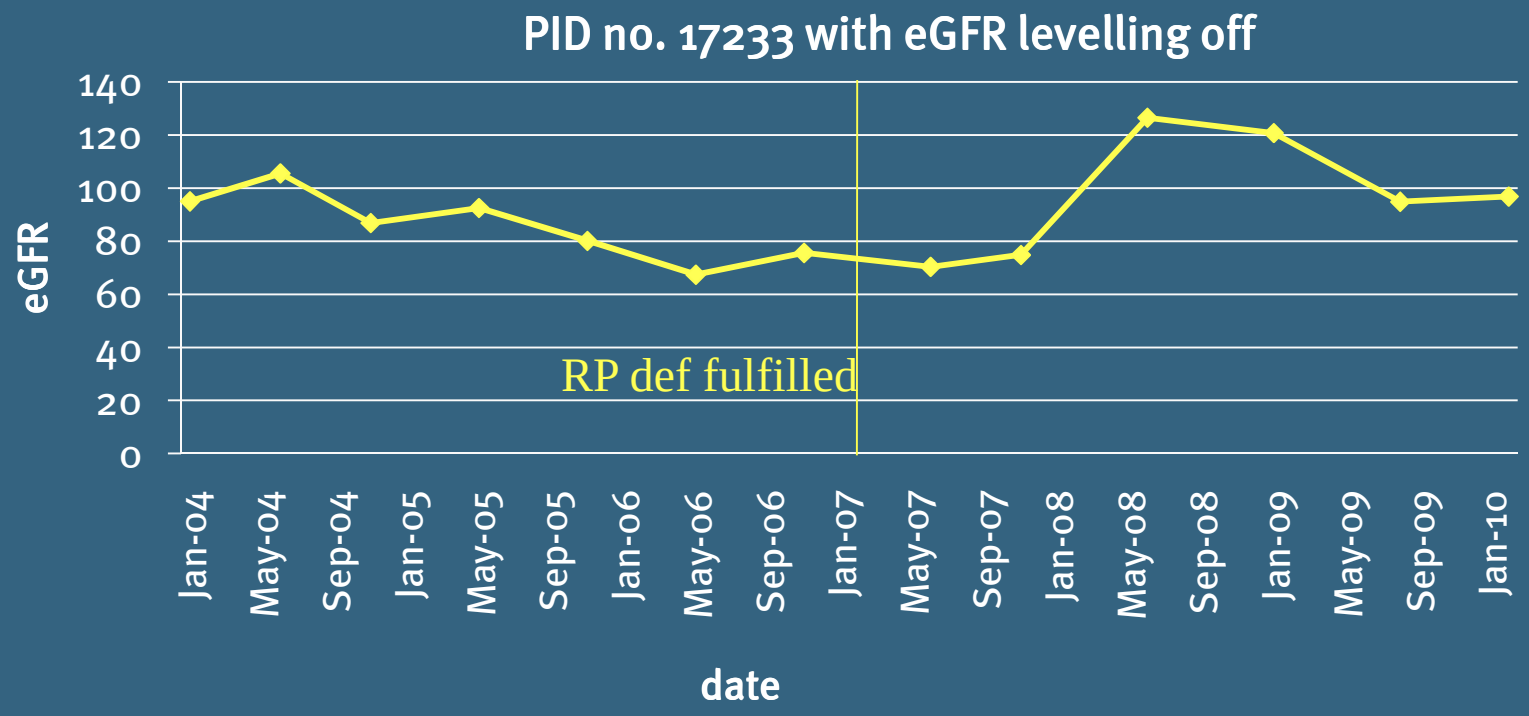
Requirements	Excluded from analysis	CKD among RP def A	CKD among non-RP def A
3 years FU and 2 eGFR	25/11170 (0.2%)	22/324 (6.8%)	47/10206 (0.5%)
3 years FU and 3 eGFR	47/16322 (0.3%)	15/165 (9.1%)	32/5213 (0.6%)
4 years FU and 2 eGFR	47/14961 (0.3%)	19/223 (8.5)%	28/6516 (0.4%)
4 years FU and 3 eGFR	65/18748 (0.4%)	11/95 (11.6%)	18/2857 (0.6%)

- >90% experiencing RP did not reach CKD with a 5 year median FU
- As this decline is substantial inadequate FU could be an explanation
- Alternatively this could be caused by levelling off in renal function due to interventions, longer FU may provide this answer

D:A:D

Level of last eGFR recorded for RPs

	›90	80-90	70-80	60-70	50-60	40-50	30-40	‹30
Def A, 3 FU 2 eGFR (324 pt.s)	119 (37%)	85 (26%)	67 (21%)	32 (10%)	15 (5%)	2 (0,6%)	3 (0,9%)	1 (0,3%)



D:A:D

Discussion

Def A or B

- RP def A combines absolute and average decline; is based on all eGFRs, has more significant risk factor associations and is less restrictive for longer FU
- Frequencies of RP were more stable for def A
- More RP progressed to incident CKD with def A

Number of measurements

- ≥3 rather than ≥2 eGFR measurements/year provides a more precise slope, slightly stronger risk factor associations and more incident CKD
- However, more pts are eligible for analyses using ≥2 eGFRs
- ≥2 measurements are more applicable in routine clinical care

Length of FU

- The optimal length of FU could not be definitively determined, but 3 years appears preferable with regards to number of events

D:A:D

Limitations

- No information on proteinuria
- By intention only very well documented risk factors were used to develop the RP definition. This, however, poses a risk for unmeasured confounding (especially HIV related factors)
- Possible selection bias;
  - › 21,000 had eGFR›90 ml/min/1.73m^2, but fewer were eligible for the individuals analyses
  - Those with a progressive renal disease have more measurements and are more likely to be included in analyses; however, with our recommendation only 324 of ~11,000 eligible patients were RPs
- Missing information on ethnicity for 43%

D:A:D

Conclusions and perspectives

- In this exploratory study, we aimed to develop a definition for RP that was neither too restrictive nor too loosely defined

- In future analyses D:A:D will use
  - RP definition A
  - 3 years of FU
  - 2 eGFR measurements/year

  to investigate the association between RP and HIV related risk factors

- The frequency of RP from normal renal function was ~3%
  - Of these ~7% progressed to CKD during a 5 years median FU

- We suggest using this RP definition as a supplement to the CKD definition to also include a dynamic tool in the investigation of renal function decline

D:A:D

Acknowledgement

- 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 *(st.Pierre)
- Cohort coordinators and data managers: S Zaheri, L Gras (ATHENA), R Thiébaut, E Balestre(Aquitaine), K Petoumenos (AHOD), S Mateu, F Torres (BASS), M Delforge(Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær (EuroSIDA), I Fanti T Formenti(ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach (SHCS)
- Statisticians: CA Sabin*, D Kamara, C Smith, AN Phillips *
- Community representative: S Collins *
- DAD coordinating office: S Worm, L Ryom, R Salbøl Brandt, JD Lundgren*¢
- Steering Committee: Members indicated w/*; ¢chair;
- Additional members: R Rode*, D Butcher *, N Shortman *
- Funding: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMA and a consortium of "Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, ViiV Heathcare, Merck, Pfizer, and Hoffman-La Roche"