

# Baseline renal function is an independent predictor of death and progression to severe chronic kidney disease

Fowzia Ibrahim, Lisa Hamzah, Rachael Jones, Loveleen Bansi, Dorothea Nitsch, Caroline Sabin and Frank Post for the UK CHIC / CKD Study Group



## Background

Stage	Description	GFR (mL/min/1.73m <sup>2</sup> )
1	Kidney damage with normal or ↓ GFR	≥90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

- In the absence of information on proteinuria or renal morphology, chronic kidney disease (CKD) can be defined as glomerular filtration rate (GFR) <60mL/min/1.73m<sup>2</sup> for >3 months<sup>1</sup>
- The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was developed to more accurately estimate GFR<sup>2</sup>

<sup>1</sup>NKF KDOQI Clinical Practice Guidelines for Chronic Kidney Disease  
<sup>2</sup>Ann Intern Med. 1999;130:461-470



## Kidney Disease in HIV

- Based on the presence of ↓ GFR and/or proteinuria, CKD affects 15-20% HIV infected individuals<sup>1</sup>
- End stage renal failure (ESRF) prevalence has increased in the HAART era, 0.31% in the UK<sup>2</sup>
- A number of factors are associated with developing CKD<sup>3,4</sup>
  - HIV-related:
    - CD4 <200, AIDS
    - Exposure to indinavir, tenofovir, and atazanavir
  - Non-HIV related:
    - Age, diabetes, hypertension

<sup>1</sup>Curr Opin Infect Dis 2009, 22:43-48

<sup>2</sup>AIDS 2009, 23: 2517

<sup>3</sup>AIDS 2004, 18: 2171

<sup>4</sup>AIDS 2007, 21: 1119



## Aims

- To assess the impact of baseline renal function on mortality and progression to severe CKD (stage 4/5)
- To compare estimates of the prevalence of CKD, and the prognostic value of this when estimated using the MDRD and CKD-EPI formulae in an HIV infected population



## Methods -1

- UK Collaborative HIV Cohort (CHIC) Study
  - Ongoing observational cohort initiated in 2001
  - Dataset includes clinical data collected as part of routine HIV care; current dataset includes data on 32,607 patients seen from 1996-2008 from 11 UK centres
- Inclusion criteria
  - Adults (>16 yrs) with at least one creatinine level  $\geq$  3 months after HIV diagnosis (n=19,111)
- Baseline renal function determined on the basis of the first available eGFR > 3months after HIV diagnosis<sup>1</sup>

<sup>1</sup>CID 2008:47

## Methods -2

- GFR was estimated using MDRD and CKD-EPI and stratified by stage of CKD
  - 1 ( $\geq$ 90), 2 (60-89), 3 (30-59), 4 (15-29), and 5 (<15 mL/min/1.73m<sup>2</sup>)
  - Stage 2 was further divided into 75-89 and 60-74 mL/min/1.73m<sup>2</sup>
- Stage 4/5 or severe CKD was defined as an eGFR <30 mL/min/1.73m<sup>2</sup> for >3 months
- Statistical methods used include
  - Kappa statistics
  - Kaplan-Meier graphs
  - Cox regression for mortality
  - Competing-risk regression for progression to severe CKD, allowing for competing risk of mortality



## Patient characteristics at baseline

Total N (%)		19,111 (100)
Male N (%)		15,094 (79)
Ethnicity N (%)	Black	4,640 (24)
	White/Other	14,471 (76)
Hepatitis B surface antigen positive	N (%)	1,097 (6)
Hepatitis C antibody positive	N (%)	1,333 (7)
CD4 cell count (cells/mm <sup>3</sup> )	Median (IQR)	352 (212, 520)
Viral load (copies/ml)	Median (IQR)	1995 (50, 32154)
eGFR-MDRD ml/min/1.73m <sup>2</sup>	Median (IQR)	95 (83, 108)
eGFR-CKD-EPI ml/min/1.73m <sup>2</sup>	Median (IQR)	100 (87, 112)
On cART	N (%)	12,034 (62)

–Median time from HIV diagnosis to baseline eGFR was 4 [3, 9] months

–Median follow up was 5.7 [2.7-9.1] years

–1,837 (9.6%) died

–79 (0.41%) progressed to stage 4/5 CKD



## Baseline eGFR using MDRD and CKD-EPI

GFR mL/min/1.73m <sup>2</sup>	MDRD n (%)	CKD-EPI n (%)
≥90	11,628 (60.8)	13,584 (71.1)
89-75	5,227 (27.4)	3,948 (20.7)
74-60	1,808 (9.5)	1,199 (6.3)
59-30	341 (1.8)	290 (1.5)
29-15	48 (0.3)	45 (0.2)
<15	44 (0.2)	45 (0.2)



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	<b>2.3%</b>	



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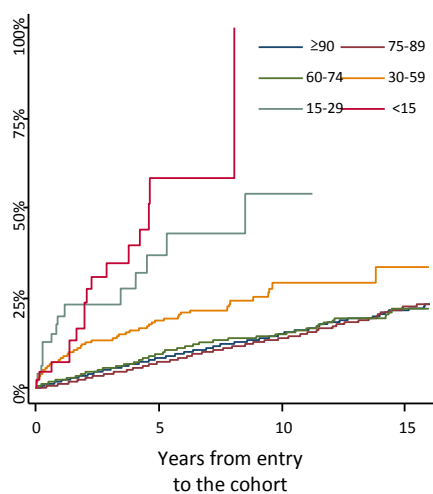
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Good agreement was observed between eGFR MDRD and CKD-EPI (kappa 72%; 95% CI: 70%, 73%)

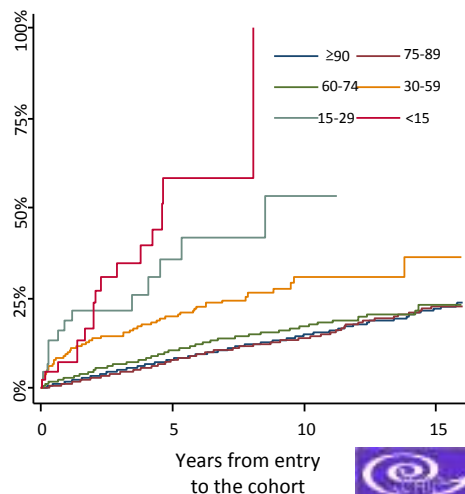


## Time to death stratified by baseline eGRF

(a) eGFR-MDRD (mL/min/1.73m<sup>2</sup>)



(b) eGFR-CKD-EPI (mL/min/1.73m<sup>2</sup>)



## Adjusted mortality hazard ratios (95% CI) stratified by baseline eGRF

Baseline eGFR mL/min/1.73m <sup>2</sup>	MDRD			CKD-EPI		
	Adjusted <sup>1</sup> HR (95%CI)	P		Adjusted <sup>1</sup> HR (95%CI)	P	
≥90	1			1		
60-89	0.93 (0.84, 1.02)	0.13		1.02 (0.92, 1.13)	0.75	
30-59	1.98 (1.53, 2.56)	<0.001		2.24 (1.72, 2.94)	<0.001	
15-29	5.31 (3.13, 9.01)	<0.001		5.25 (3.04, 9.08)	<0.001	
<15	6.69 (4.07, 11.00)	<0.001		6.90 (4.20, 11.33)	<0.001	

<sup>1</sup> Estimates were adjusted for gender, ethnicity, age at entry to cohort, and AIDS, CD4 cell count and cART at baseline



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## Factors associated with progression to stage 4/5 CKD

Baseline eGFR mL/min/1.73m <sup>2</sup>	MDRD			CKD-EPI		
	Adjusted SHR (95%CI)	P		Adjusted SHR (95%CI)	P	
≥90	1			1		
89-75	3.50 (0.98, 12.6)	0.054		2.17 (0.61, 7.7)	0.23	
74-60	11.86 (3.2, 44.5)	<0.001		14.00 (4.6, 43.1)	<0.001	
59-30	140.9 (42.4, 463.1)	<0.001		115.9 (42.1, 319.6)	<0.001	
<b>Ethnicity</b>						
Black	3.38 (1.58, 7.25)	0.002		2.52 (1.20, 5.28)	0.01	
CD4 cell count <sup>1</sup> (cells/mm <sup>3</sup> )	0.95 (0.87, 1.04)	0.27		0.95 (0.86, 1.03)	0.26	

Estimates were adjusted for all the variables in table

SHR= Sub-hazard ratios, CI=Confidence intervals

<sup>1</sup>per 50 cell increase



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## Summary

- Severe CKD is strongly associated with subsequent mortality risk
- Those with baseline eGFR values <90 mL/min/1.73m<sup>2</sup> are at increased risk of progression to severe CKD
- CKD-EPI is more restrictive when describing the severity of CKD, however, mortality and progression to severe CKD was similar for patients stratified by eGFR using both methods



## Discussion

- Limitations of study
  - Baseline eGFR at 3 months excludes patients with ARF, who may have had CKD and died within 3 months
  - Analysis of clinical outcomes with renal disease is limited by the observational nature of the data, selection bias and loss to follow-up
  - MDRD and CKD-EPI are not validated for this population
  - No available proteinuria data limits interpretation Stage 1/2 CKD
- Data suggest monitoring of patients with reduced eGFR (<90 mL/min/1.73m<sup>2</sup>) may be warranted to reduce the risk of progression to severe CKD



## Acknowledgements

### *UK CHIC/CKD study group*

Brighton:	Steve Holt, Martin Fisher
C&W:	Amelia Hughes, Jeremy Levy, Rachael Jones, Mark Nelson
Edinburgh:	Clifford Leen, Sheila Morris
LSHTM:	Dorothea Nitsch
King's:	Frank Post, Fowzia Ibrahim, Lisa Hamzah, Lucy Campbell, Bruce Hendry
St Mary's:	Nicky Mackie
Royal Free/Mortimer Market:	Loveleen Banshi, Teresa Hill, Caroline Sabin, Sanjay Bhagani, John Connolly, Margaret Johnson, Simon Edwards, Ian Williams

### *UK CHIC Steering Committee*

*Jonathan Ainsworth, Jane Anderson, Abdel Babiker, David Dunn, Philippa Easterbrook, Martin Fisher, Brian Gazzard (Chair), Richard Gilson, Mark Gompels, Teresa Hill, Margaret Johnson, Clifford Leen, Chloe Orkin, Andrew Phillips, Deenan Pillay, Kholoud Porter, Caroline Sabin, Tariq Sadiq, Achim Schwenk, Nicky Mackie, Alan Winston, Valerie Delpech.*

### *Central Co-ordination*

*Medical Research Council Clinical Trials Unit (MRC CTU), London (David Dunn, Kholoud Porter, Stephen Sheehan); Royal Free NHS Trust and RFUCMS, London (Loveleen Banshi, Teresa Hill, Andrew Phillips, Caroline Sabin).*

### *Participating Centres*

*Barts and The London NHS Trust, London (Chloe Orkin, Kevin Jones, Rachel Thomas); Brighton and Sussex University Hospitals NHS Trust (Martin Fisher, Nicky Perry, Anthony Pullin, Duncan Churchill, Wendy Harris); Chelsea and Westminster NHS Trust, London (Brian Gazzard, Steve Bulbeck, Sunthiya Mandala, Jemima Clarke); Health Protection Agency – Centre for Infections London (HPA) (Valerie Delpech); Homerton University Hospital NHS Trust, London (Jane Anderson, Selina Gann); King's College Hospital, London (Frank Post, Hardik Korat, Chris Taylor, Mary Poulton, Lucy Campbell, Fowzia Ibrahim); Medical Research Council Clinical Trials Unit (MRC CTU), London (Abdel Babiker, David Dunn, Kholoud Porter, Stephen Sheehan); Mortimer Market Centre, Royal Free and University College Medical School (RFUCMS), London (Richard Gilson, Julie Dodds, Shuk-Li Man, Ian Williams); North Middlesex University Hospital NHS Trust, London (Achim Schwenk); Royal Free NHS Trust and RFUCMS, London (Margaret Johnson, Mike Youle, Fiona Lampe, Colette Smith, Helen Grabowska, Clinton Chaloner, Dewi Ismajani Puradiredja, Loveleen Banshi, Teresa Hill, Andrew Phillips, Caroline Sabin); St. Mary's Hospital, London (John Walsh, Jonathan Weber, Christian Kemble, Mark Carder); The Lothian University Hospitals NHS Trust, Edinburgh (Clifford Leen, Alan Wilson).*

*All the patients in the participating centres*

*UK CHIC is funded by the UK Medical Research Council*



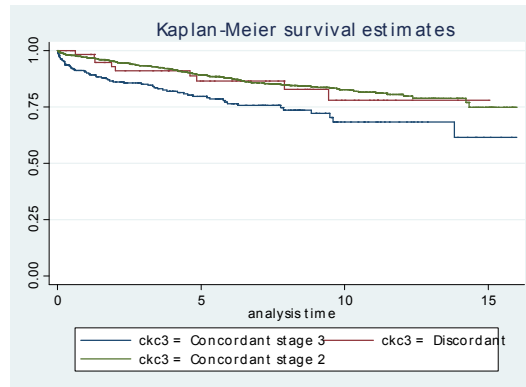
## Agreement between MDRD and CKD-EPI formulae

eGFR-CKD-EPI	eGFR-MDRD						Total
	≥90	89-75	74-60	59-30	29-15	<15	
≥90	11,628	1,956	0	0	0	0	13,584
89-75	15	3,255	678	0	0	0	3,948
74-60	0	16	1,118	65	0	0	1,199
59-30	0	0	12	276	2	0	290
29-15	0	0	0	0	45	0	45
<15	0	0	0	0	1	44	45
Total	11,643	5,227	1,808	341	48	44	19,111

- Good agreement was observed between eGFR MDRD and eGFR CKD-EPI (kappa 72%; 95% CI: 70%, 73%)



## Disconcordant stage 3 MDRD vs. Stage 2 CKD-EPI



- The survival rate for patients with discordant is similar to stage 2 CKD-EPI than stage 3 -MDRD



## Time to stage 4/5 CKD stratified by ethnicity

