650 Factors associated with rapid eGFR decline while receiving TDF and/or ATV

Hamzah L[1,6], Jose S[2], Jones R[3], Williams D[4], Chadwick D[5], Phillips A[2], Sabin C[2], Post F[6]

[1]King's College London, [2]University College London, [3]Chelsea and Westminster NHS Foundation Trust, [4]Brighton and Sussex University Hospitals NHS Trust, [5]South Tees Hospitals NHS Foundation Trust
[6]King's College Hospital NHS Foundation Trust, United Kingdom

Background

Rapid estimated glomerular filtration rate (eGFR) decline is a risk factor for cardiovascular events in diabetics [1] and for mortality in the general population [2]. Tenofovir (TDF) and atazanavir (ATV) have been associated with rapid eGFR decline [3]. Although the clinical significance of rapid eGFR decline in association with TDF and/or ATV remains uncertain, recent studies have linked rapid eGFR decline to chronic kidney disease [4] and, in those receiving TDF, the development of proximal tubulopathy [5].

Aims

This study aimed to determine:

1. The proportion of subjects receiving TDF and ATV with rapid eGFR decline
2. The factors associated with rapid eGFR decline on TDF and ATV
3. The association between rapid eGFR decline and mortality

Methods

Study population

- Data were drawn from the United Kingdom Collaborative HIV cohort (UK CHIC) study [6] and were available up to Dec 2014 for the 13 centres routinely providing creatinine data
- Eligible subjects included those with >1 year exposure to TDF or boosted/un-boosted ATV after 1st January 2000 with ≥1 year of follow up with ≥1 creatinine measurements (excluding the first three months of follow up)

Definitions

- The first TDF or ATV exposure was considered and follow up was from TDF or ATV start respectively
- Creatinine measurements were converted into eGFR in ml/min/1.73m^2 using the CKD Epidemiology Collaboration equation (CKD-Epi)
- Rapid eGFR decline was defined by an overall eGFR decline > 3 and > 5 ml/min/year
- A single non-fasted serum glucose ≥11.1mmol/L was used as a surrogate marker for diabetes

Statistical analysis

- Baseline characteristics were described overall and for those with TDF/ATV exposure
- Overall eGFR slopes for TDF and ATV were generated using mixed effects models using time, age, ethnicity and sex as fixed effects and time as a random effect
- Factors associated with eGFR decline >3 and >5 ml/min/year compared to those with no rapid decline (while receiving TDF or ATV) were identified using multivariate logistic regression models.
- The association between rapid decline in the first year of follow up and mortality thereafter was explored in multivariate Poisson regression for those on TDF and ATV respectively
- The following covariates: age; gender; ethnicity; risk group; baseline eGFR; AIDS defining illness; hepatitis B/C co-infection; nadir/current CD4; VL, and co-exposure to non-nucleoside reverse transcriptase inhibitors (NNRTIs), ATV, lopinavir (LPV), darunavir (DRV), other protease inhibitors (PI; for TDF) or TDF (for ATV), time updated where possible for Poisson regression, were considered for inclusion in the model

Baseline characteristics

- 16172 individuals commenced TDF and 4162 commenced ATV after 2000 **(Figure 1)** and baseline characteristics were similar between groups **(Table 1)**
- **Overall adjusted eGFR slope (95% CI) for TDF was -0.26 (-0.33, -0.19) ml/min/year**
  - 15.8% and 7.0% experienced rapid eGFR decline >3 and >5 ml/min/year
- **Overall adjusted eGFR slope (95% CI) for ATV was -0.61 (-0.79, -0.43) ml/min/year**
  - 21.7% and 12.0% experienced rapid eGFR decline >3 and >5 ml/min/year

Baseline characteristics continued

Figure 1: Subjects for inclusion

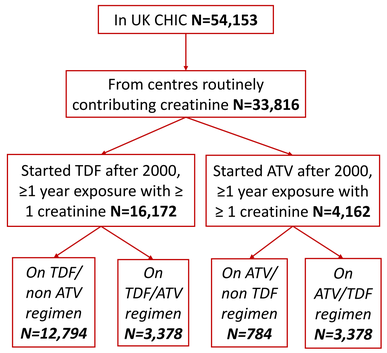


Table 1: Baseline characteristics at TDF/ATV start

	All (N=16,956)	TDF (N=16,172)	ATV (N=4,162)
Age mean [SD]	36.6 [9.7]	38.5 [9.6]	36.9 [9.6]
Male sex N [%]	13,258 [78.2]	12,745 [78.8]	3,012 [72.4]
Risk group N [%]			
MSM	10,065 [59.4]	9,691 [59.9]	2,268 [54.5]
Heterosexual	363 [2.14]	348 [2.15]	114 [2.74]
Other	5,523 [32.6]	5,168 [32.0]	1,570 [37.7]
White/other ethnicity N [%]	12,288 [72.5]	11,820 [73.1]	2,849 [68.5]
Prior ADI N [%]	4,172 [24.6]	3,958 [24.5]	1,165 [28.0]
Hepatitis B status N [%]			
Negative	16,213 [95.6]	15,453 [95.6]	3,986 [95.8]
Positive	731 [4.31]	707 [4.37]	173 [4.16]
Hepatitis C status N [%]			
Negative	16,752 [98.8]	15,977 [98.8]	4,107 [98.7]
Positive	164 [0.97]	156 [0.96]	48 [1.15]
Baseline eGFR mean [SD]	82.2 [22.3]	82.2 [21.9]	79.7 [23.6]
Nadir CD4 median [IQR]	212 [99, 346]	198 [100, 290]	170 [72, 266]
Died N [%]	577 [3.40]	544 [3.36]	179 [4.30]

Factors associated with rapid decline

- **Rapid decline >3ml/min/year**, in adjusted analyses, was associated with black ethnicity, lower baseline eGFR, shorter TDF/ATV exposure, plus younger age, and exposure to ATV/DRV or LPV In the TDF group and being female and TDF exposure in the ATV group **(Table 2)**
- **Rapid decline >5ml/min/year in the TDF group** remained associated with black ethnicity (OR 1.61 [1.37, 1.90]), lower baseline eGFR (0.98 [0.98, 0.98]), younger age (OR 0.94 [0.91, 0.97]) and ATV (OR 1.57 [1.30, 1.89]), DRV (OR 1.86 [1.50, 2.29]) or LPV/r exposure (OR 1.27 [1.04, 1.53])
- **Rapid decline >5ml/min/year in the ATV/r group** was only associated with black ethnicity (OR 1.39 [1.08, 1.79]), lower eGFR (OR 0.99 [0.99, 0.99]) and female sex (OR 1.84 [1.42, 2.37]) but not TDF use
- The effect sizes did not vary appreciably if analyses were limited to those with a nadir eGFR≤90 or with ≥2 years follow up

Table 2: Factors associated with rapid decline (>3 ml/min/1.73m^2/year) on TDF or ATV

		On TDF N=16,126				On ATV N=4,162			
		Crude OR [95% CI]	p-value	**Adj. OR*** [95% CI]	p-value	**Crude OR** [95% CI]	**p-value**	**Adj. OR* [95% CI]**	p-value
Age/5 year ↑		1.04 [1.01, 1.06]	0.001	0.97 [0.95, 1.00]	0.02	1.00 [0.97, 1.05]	0.8		
Sex	**Male**	1		1		1			
	Female	1.11 [1.00, 1.23]	0.04	1.11 [0.98, 1.26]	0.1	1.42 [1.21, 1.67]	<0.0001	**1.47 [1.19, 1.80]**	**<0.0001**
Ethnicity	**White/other**	1		1		1			
	Black	1.06 [0.96, 1.16]	0.2	**1.22 [1.08, 1.37]**	**0.001**	1.55 [1.27, 1.88]	<0.0001	**1.23 [1.01, 1.51]**	**0.04**
Prior ADI		1.22 [1.11, 1.34]	<0.0001	1.06 [0.96, 1.28]	0.2	1.06 [0.86, 1.30]	0.6		
Baseline eGFR ^		0.85 [0.83, 0.86]	<0.0001	**0.99 [0.98, 0.99]**	**<0.0001**	0.92 [0.89, 0.95]	<0.0001	**0.99 [0.98, 1.00]**	**<0.0001**
ART at TDF start	**NNRTI**	1							
	ATV/r	1.46 [1.29, 1.66]	<0.0001	**1.40 [1.23, 1.59]**	**<0.0001**	N/A			
	DRV/r	1.40 [1.19, 1.63]	<0.0001	**1.45 [1.24, 1.69]**	**<0.0001**	N/A			
	LPV/r	1.53 [1.34, 1.74]	<0.0001	**1.35 [1.18, 1.54]**	**<0.0001**	N/A			
	Other PI	1.24 [0.93, 1.64]	0.1	1.04 [0.78, 1.38]	0.8	N/A			
	Other	1.27 [1.08, 1.47]	0.004	1.10 [0.94, 1.30]	0.09	N/A			
ART at ATV start	**TDF**	N/A				1.29 [1.07, 1.54]	0.006	**1.37 [1.14, 1.64]**	**0.001**

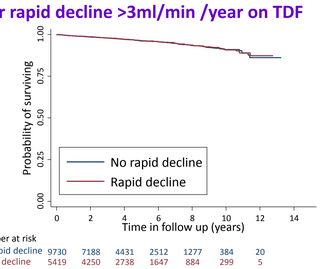
*adjusted for age, sex, ethnicity, prior AIDS defining illness, time on TDF or ATV and ART regime at TDF or ATV start. ^quadratic term best fits model, per 10ml/min increase. ADI: AIDS defining illness, eGFR: estimated glomerular filtration rate, TDF: tenofovir disosproxil fumarate, ATV: atazanavir, NNRTI: non nucleoside reverse transcriptase inhibitor, DRV: darunavir, LPV: lopinavir, PI: protease inhibitor, r: ritonavir boosted

Rapid decline and mortality

- Overall, during 65,694 person-years of follow up, 527 individuals died

Figure 2: Kaplan Meier survival curve for rapid decline >3ml/min /year on TDF

- Mortality rate was 7.9 (95%CI: 7.1, 8.9) per 1000 person-years for no rapid decline and 8.1 (95% CI: 7.0, 9.3) for rapid decline >3ml/min/ year and 8.3 (95% CI: 7.1, 9.6) for rapid decline >5ml/min/ year on TDF



- **On TDF, eGFR declines >3 and >5 ml/min in the first year of exposure were not associated with all-cause mortality**, after adjustment for age, sex, ethnicity, prior AIDS, diabetes, time updated current and nadir CD4, hepatitis status, baseline eGFR and ART regimen, adjusted HR [95% CI] was 0.90 [0.75, 1.08] and 0.93 [0.77, 1.13] respectively

Figure 3: Kaplan Meier survival curve for rapid decline >3ml/min /year on ATV

- Mortality rate was 10.3 (95%CI: 8.5, 12.6) per 1000 person-years for no rapid decline and 11.6 (95% CI: 9.1, 14.7) for rapid decline >3ml/min/ year and 11.5 (95% CI: 8.9, 15.0) for rapid decline >5ml/min/ year on ATV

- **On ATV, eGFR declines >3 and >5 ml/min/year in the first year of exposure were not associated with all-cause mortality**, after adjustment for age, sex, ethnicity and time updated current CD4 cell count and baseline eGFR; adjusted HR [95% CI] was 1.05 [0.77, 1.43] and 1.05 [0.76, 1.45] respectively
- If eGFR decline was defined after two or three years exposure to TDF or ATV, again there was no association with mortality

Conclusions

- Rapid eGFR decline was observed in 16% and 22% of those who received TDF/ATV respectively
- Black ethnicity, female sex, younger age, lower eGFR at TDF/ATV initiation and TDF/PI including TDF/ATV co-exposure were all associated with rapid eGFR decline
- Neither an eGFR decline of >3 and >5 ml/min/year identified individuals at increased risk of death, even after taking into account potential confounders
- **Limitations**: UK CHIC does not routinely collect data on other renal risk factors such as diabetes, hypertension, markers of renal disease such as proteinuria and concomitant medications which may contribute to renal function decline

Acknowledgments

UK CHIC Steering Committee Jonathan Ainsworth, Sris Allan, Jane Anderson, Abdel Babiker, David Chadwick, Duncan Churchill, Valerie Delpech, David Dunn, Brian Gazzard, Richard Gilson, Mark Gompels, Phillip Hay, Teresa Hill, Margaret Johnson, Sophie Jose, Stephen Kegg, Clifford Leen, Fabiola Martin, Dushyant Mital, Mark Nelson, Chloe Orkin, Adrian Palfreeman, Andrew Phillips, Deenan Pillay, Ashley Price, Jillian Pritchard, Frank Post, Caroline Sabin, Achim Schwenk, Anjum Tariq, Roy Trevelion, Andrew Ustianowski, John Walsh

Central co-ordination **Department of Infection & Population Health, UCL, London** (T Hill, S Huntington, S Jose, A Phillips, C Sabin); **Medical Research Council Clinical Trials Unit (MRC CTU), London** (D Dunn).

Participating centres **Barts and The London NHS Trust, London** (C Orkin, J Lynch, J Hand, C de Souza); **Brighton and Sussex University Hospitals NHS Trust** (N Perry, S Tilbury, D Churchill); **Chelsea and Westminster NHS Trust, London** (B Gazzard, M Nelson, M Waxman, D Asboe, S Mandalia); **Health Protection Agency Centre for Infections London** (V Delpech); **Homerton University Hospital NHS Trust, London** (J Anderson, S Munshi, D Awosika); **King's College Hospital, London** (F Post, C Taylor, L Campbell); **UCL Medical School and The Mortimer Market Centre, London** (R Gilson, N Brima, I Williams); **North Bristol NHS Trust** (M Gompels, S Allen); **North Middlesex University Hospital NHS Trust, London** (A Schwenk, J Ainsworth, C Wood, S Miller); **Royal Free NHS Trust and Department of Infection & Population Health, UCL, London** (M Johnson, M Youle, F Lampe, C Smith, H Grabowska, C Chaloner, D Puradiredja); **Imperial College Healthcare NHS Trust, London** (J Walsh, N Mackie, A Winston, J Weber, F Ramzan); **The Lothian University Hospitals NHS Trust, Edinburgh** (C Leen, A Wilson); **University of Leicester NHS Trust** (A Palfreeman, A Moore, L Fox); **South Tees Hospitals NHS Foundation Trust** (D Chadwick, K Baillie); **South London NHS Trust** (S Kegg, P Main); **Coventry NHS Trust** (S Allan); **St. George's NHS Trust** (P Hay, M Dhillon); **York Teaching Hospital** (F Martin, S Douglas) **Coventry & Warwick NHS Trust** ; **The Royal Wolverhampton NHS Trust** (A Tariq) **Ashford & St.Peter's Hospitals NHS Foundation Trust** (J Pritchard), **Pennine Acute Hospitals NHS Trust**, North Manchester (A Ustianowski) **Lewisham and Greenwich NHS Trust** (C Mazhude) **Milton Keynes University Hospital NHS Foundation Trust** (D Mital)

UK CHIC is funded by the UK Medical Research Council, project reference MR/M004236/1 . The views expressed in this poster are those of the researchers and not necessarily those of the Medical Research Council.

References: [1] Ragot S. et al, Diabetes Care 2016 [2] Rifkin D.E et al, Arch Intern Med 2008 [3] Scherzer R. et al, AIDS 2012 [4] Kamara D.A. et al, BMC Nephrol 2014 [5] Hamzah L. et al, J Infec 2017 (in press) [6] www.ctu.mrc.ac.uk/UKCHIC

Correspondence to: lisahamzah@nhs.net