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Predictors of Progression, Stabilisation or Improvement of eGFR After Chronic Renal Impairment

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BACKGROUND

- Knowledge of the outcomes in renal function after a diagnosis of chronic renal impairment (CRI) in HIV-positive persons and the relationship to antiretroviral (ARV) drug use is limited
- Most studies that have investigated whether eGFR abnormalities are potentially reversible have focused on mild and acute renal impairment and very few have used confirmed eGFR outcomes [1-5]
- Prior studies have shown increased tenofovir (TDF) discontinuation at eGFR<70 mL/min/1.73m^2 limiting the value of eGFR≤60 as a CRI cut-off in HIV-positive persons [6]
- The aim of this analysis was to investigate predictors of progression, stabilisation or improvement in eGFR after development of CRI

METHODS

- The D:A:D Study is a prospective cohort-collaboration study of >49,000 HIV-positive persons from 11 cohorts in Europe, Australia, and the United States
- eGFR was calculated using the Cockcroft-Gault equation and standardised by body surface area (BSA)
- Study participants were followed from the time of an initial eGFR value >80 after 1/1/2004 (baseline for systematic creatinine collection) to CRI defined as 2 consecutive eGFR≤70, measured at least 3 months apart, thus ensuring that the individual had experienced an eGFR decline of ≥10 before CRI was diagnosed, **Figure 1**
- The median of all (and minimum 2) eGFRs at 12-24 months after CRI was compared to the median eGFR that defined CRI, and changes in eGFR were grouped into: progression (decrease >-10), stabilisation (-10 to +10) and improvement (increase >+10)
- An ordered logistic regression model was used to assess odds of better eGFR outcomes after CRI, assuming eGFR improvement is better than stabilisation, which in turn is better than progression in eGFR. This implies that any change in odds comparing stable eGFR to progression in eGFR is considered similar to the change in odds comparing improvement in eGFR to stable eGFR
- The model was adjusted for use and discontinuation of ARVs that have previously been associated with renal impairment: TDF, atazanavir with (ATV/r) or without (ATV) ritonavir, lopinavir (LPV/r), other boosted protease inhibitors (PI/r) and abacavir (ABC), as well as demographics, HIV-related factors, HCV status and traditional renal risk factors such as diabetes and hypertension

Figure 1

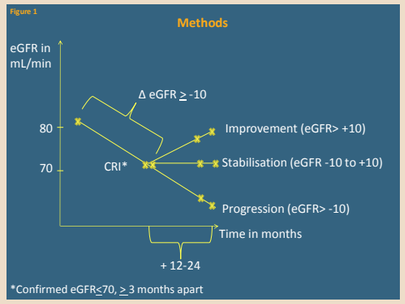


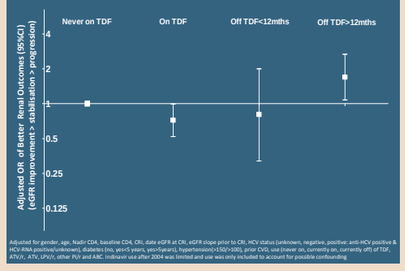
Table 1

Baseline Characteristics

		Improvement	Stabilisation	Progression	P
All n (%)		287 (23.2)	854 (69.0)	96 (7.8)	
Gender	Male	205 (71.4)	647 (75.8)	70 (72.9)	0.32
Risk	MSM	113 (39.4)	438 (51.3)	43 (44.8)	0.0065
	IDU	58 (20.2)	117 (13.7)	18 (18.8)	
HBV	Positive	34 (11.9)	90 (10.5)	16 (16.7)	0.50
HCV	Positive	41 (14.3)	78 (9.1)	10 (10.4)	0.15
ART	cART	267 (93.0)	791 (92.6)	91 (94.8)	0.85
Diabetes	Yes ≤5 yrs	13 (4.5)	37 (4.3)	5 (5.2)	0.013
	Yes > 5 yrs	14 (4.9)	50 (5.9)	14 (14.6)	
Smoking	Current	130 (45.3)	301 (35.3)	38 (39.6)	0.054
Hypertension	Yes	42 (14.6)	149 (17.5)	26 (27.1)	0.021
Prior CVD	Yes	21 (7.3)	75 (8.8)	14 (14.6)	0.094
Prior AIDS	Yes	116 (40.4)	292 (34.2)	40 (41.7)	0.085
VL < 400		243 (84.7)	763 (89.3)	86 (89.6)	0.095
		Median IQR	Median IQR	Median IQR	P
Age		49 44 – 56	54 48 – 62	56 51 – 65	<0.0001
CD4 Nadir		130 46 – 228	130 52 – 228	119 47 – 236	0.55
CD4 Baseline		430 264 – 655	484 337 – 690	502 313 – 679	0.0090
eGFR at CRI		64 60 – 66	66 63 – 67	65 61 – 67	<0.0001

Figure 2

TDF use at time of CRI & Odds Ratios of Better Renal Outcomes



Adjusted for gender, age, Nadir CD4, baseline CD4, CRI date, eGFR at CRI, eGFR slope prior to CRI, HCV status (unknown, negative, positive: anti-HCV positive & HCV-RNA positive/unknown), diabetes (no, yes<5 years, yes>5years), hypertension(<150/<100, prior CVD, use (never on, currently on, currently off) of TDF, ATV/r, ATV, LPV/r, other PI/r and ABC. Indinavir use after 2004 was limited and use was only included to account for possible confounding

RESULTS

- Baseline characteristics of included persons are shown in **Table 1**
- Of 1237 persons developing CRI, 23.2% experienced improvement in eGFR, 69.0% experienced stabilisation and 7.8% experienced progression at 12-24 months after CRI diagnosis
- Those using TDF at time of CRI had lower odds of better eGFR outcomes compared to those never exposed to TDF, while those off TDF for >12 months at time of CRI had higher odds of better outcomes compared to those not exposed to TDF, **Figure 2**
- Similar trends were seen for ATV/r, LPV/r and other PI/r, but not ATV or ABC, **Figure 3** There was not enough statistical power to subdivide the other ARV drugs into off for < or > 12 months
- Censoring follow-up for nephrotoxic ARVs used concomitantly (i.e. those on TDF for concomitant ATV/r use) showed similar results
- Older persons (adjusted odds ratio 0.61/10 years [95%CI 0.50-0.70]) and those with slower declining eGFR prior to CRI (0.72 [0.55-0.96], ≤-10 vs.- >10/year) had significantly lower odds of better eGFR outcomes, while those with diabetes for >5 years had marginally significant lower odds compared to non-diabetics (0.61 [0.36-1.05]), **Figure 4**
- No HIV-related factors were associated with better eGFR outcomes

CONCLUSION

- Improvement of eGFR after a CRI diagnosis is not infrequent among HIV-positive persons, although the majority experienced stabilisation and few continued to progress in eGFR
- Use of TDF, ATV/r, LPV/r and other PI/r, older age, diabetes and slowly declining eGFR were associated with decreased odds of better eGFR outcomes in HIV-positive persons after development of CRI
- TDF discontinuation prior to CRI was associated with better eGFR outcomes suggesting TDF-associated eGFR decline may be halted or reversed with early cessation
- There was some suggestion that this may also be true for use and cessation of ATV/r, LPV/r and other PI/r

REFRENCES

1 Nelson AIDS 2007 Jun 19;21(10):1273-81; 2 Wever JAIDS 2010 Sep;55(1):78-81; 3 Bonjoch CROI 2012 P870; 4 Campbell JAIDS Mar;56(3):e95-6; author reply e6; 5 Jose CROI 2013 P813; 6 Ryom JID 2013 May;207(9):1359-1369

Figure 3

ARV use at time of CRI & Odds Ratios of Better Renal Outcomes

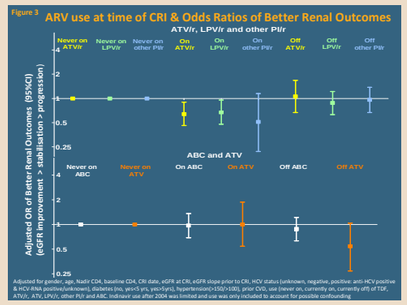


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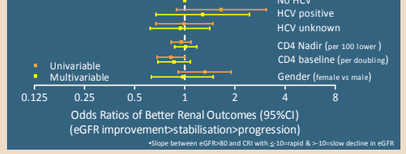
Figure 4

Other Factors Associated with Better Renal Outcomes



*Slope between eGFR=80 and CRI with ≤-10=rapid & >-10=slow decline in eGFR

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