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Amanda Mocroft
Dept Infection and Population Health
UCL
a.mocroft@ucl.ac.uk

Deferred antiretroviral therapy is associated with lower eGFR in HIV-positive individuals with high CD4 counts

A Mocroft[1], AC Achhra[2], M Ross[3], L Ryom[4], A Avihingsanon[5], E Bakowska[6], WH Belloso[7], A Clarke[8], H Furrer[9], G Lucas[10], M Ristola[11], M Rassool[12], J Ross[13], C Somboonwit[14], C Wyatt[3] for the INSIGHT study group

[1]University College London, London, UK. [2]Kirby Institute, UNSW Australia, Australia. [3]Icahn School of Medicine at Mount Sinai, New York, USA. [4]Dept. of Infectious diseases, CHIP, University of Copenhagen, Denmark. [5]HIV Netherlands Australia Thailand (HIV-NAT) Research Collaboration, Chulalongkorn University, Bangkok, Thailand. [6]Wojewodzki Szpital Zakazny, Warsaw, Poland. [7]CICAL and Hospital Italiano de Buenos Aires, Argentina. [8]Royal Sussex County Hospital, Brighton, United Kingdom. [9]Department of Infectious Disease, Bern University Hospital, University of Bern, Bern, Switzerland . [10]Department of Medicine, Johns Hopkins Medicine, Baltimore. [11]Helsinki University Central Hospital, Helsinki, Finland . [12]Department of Medicine, University of Witwatersrand and Helen Joseph Hospital, Johannesburg South Africa. [13]Queen Elizabeth Hospital Birmingham, Birmingham, UK. [14]Department of Medicine, University of South Florida, USA.

BACKGROUND

The impact of antiretroviral therapy (ART) on renal function in HIV-positive persons with high CD4 is largely unknown. The START trial is an ideal study design to compare kidney function between ART-treated and untreated HIV infection in a controlled fashion among persons with high CD4 counts.

AIM

To evaluate changes in estimated glomerular filtration rate (eGFR) among participants randomised to immediate or deferred ART within the INSIGHT START trial.

METHODS

eGFRs were calculated using the CKD-EPI equation. The primary outcome was the change in follow-up eGFR. Secondary outcomes included first recorded drop in eGFR by ≥30% from baseline, CKD defined as the first occurrence of eGFR <60 ml/min/1.73m^2 or ≥1+ proteinuria on urine dipstick, first occurrence of ≥1+ proteinuria alone and trial-reported CKD adverse event. The overall mean change from baseline in eGFR between the immediate and deferred arms was compared using random effects linear regression models. Sensitivity analyses used MDRD and censored follow-up at start of TDF or bPI to address the impact of ART on eGFR independently of the use of potentially nephrotoxic ARVs.

RESULTS

- Baseline characteristics of the 4629 included persons were well balanced between study arms [Table 1]. Total median (IQR) follow-up time was 2.1 (1.9-3.2) years.
- The eGFR tended to decline over time in both arms [Figure 1], with an initial dip at month 1 and then a slower decline over time. On average, the eGFR was 0.56 (95% CI: 0.003 to 1.11) mL/min/1.73m^2 higher in the immediate arm versus the deferred arm [Table 2].
- TDF was pre-specified for 89% of persons; 88.6% and 89.3% of persons then started TDF in the immediate and deferred arms, and 18.5 and 22.1% started a bPI.
- Figure 2 shows the change in eGFR over time when follow-up was censored at the initiation of TDF or bPI in either arm. Here, there was an initial increase in eGFR in the immediate arm and a higher overall eGFR, compared to the small decline in eGFR in the deferred arm. Adjustment for baseline variables did not impact the results [Table 2]. A sensitivity analysis restricted to those who were pre-specified to start TDF showed similar results.
- While the immediate arm tended to have lower rates of all secondary outcomes [Table 3], the difference was marginally statistically significant only in the case of ≥1+ proteinuria.
- Only 10 CKD adverse events were reported, 4 and 6 in the immediate and deferred arms, and 1 ESRD in each arm.
- The difference in eGFR between the treatment arms differed by race (black vs. non-black; p<0.001, test for interaction) [Table 4]. In blacks, on average the eGFR was 2.43 (95% CI: 1.43-3.42) ml/min/1.73m^2 higher in the immediate arm than the deferred arm. In non-blacks, the difference between treatment arms was less, on average -0.23 (95% CI: -0.87 to 0.42) ml/min/1.73m^2.

CONCLUSIONS

The immediate initiation of ART in persons with CD4 count >500 cells/mm^3, as compared to deferring ART till the CD4 count drops to below 350 cells/mm^3 or clinical symptoms appear, was associated with a higher overall eGFR over a median follow-up of 2.1 years.

Censoring for the use of TDF and bPI illustrates the effect of ART on eGFR among persons with high CD4 counts in the absence of potentially nephrotoxic ARVs. The difference in eGFRs was especially prominent when use of known nephrotoxic agents (TDF or a bPI) was accounted for and more prominent in blacks compared to non-blacks. Immediate ART was also associated with a lower risk of incident ≥1+ proteinuria with a trend towards lower risk of several other secondary CKD outcomes.

Our data illustrate the complex relationship between decreasing renal function, genetic disposition for renal decline, the use of renal toxic antiretrovirals and uncontrolled HIV. The mechanism of the short-term benefit from immediate ART should be examined carefully in future studies, as well as long term outcomes.

Acknowlegements

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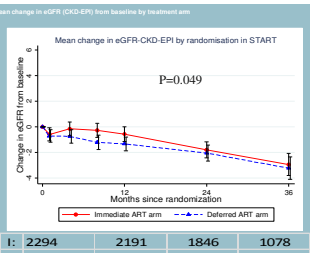
Table 1. Baseline characteristics of START study participants by treatment arm

	Immediate ART (N=2294)	Deferred ART (N=2335)
	N (%) or Median [IQR]	N (%) or Median [IQR]
Age, years	36 [29, 44]	36 [29, 44]
Female gender	610 (26.6)	631 (27.0)
Black Race	691 (30.1)	704 (30.2)
Region of enrolment		
US/Europe/Australia	1054 (45.9)	1070 (45.8)
S America/Africa/Asia	1240 (54.1)	1265 (54.2)
Likely mode of infection		
Injecting drug use	36 (1.6)	26 (1.1)
Sexual contact	2143 (93.4)	2181 (93.4)
Other	115 (5.0)	128 (5.5)
Baseline CD4, cells/μL	651 [585, 764]	651 [581-764]
Baseline HIV RNA, log_{10}copies/mL	4.1 [3.5, 4.6]	4.1 [3.5, 4.6]
Diabetes mellitus	74 (3.2)	79 (3.4)
Hypertension	428 (18.7)	461 (19.7)
Dyslipidemia	179 (7.8)	200 (8.6)
Coronary hear disease	8 (0.4)	10 (0.4)
Current smoker	721 (31.4)	755 (32.3)
eGFR-CKD-EPI, mL/min/1.73m²	112 [98 – 123]	111 [99 – 122]

Figure 1: Mean change in eGFR (CKD-EPI) from baseline by treatment arm



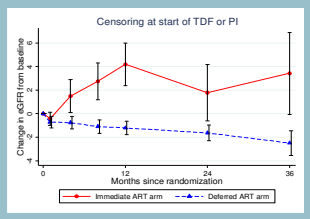
I:	2294	2191	1846	1078
D:	2335	2167	1822	1071

Table 2. Follow-up eGFR in the immediate vs. deferred ART arm in the START trial

Outcome	Mean difference Immediate arm vs. deferred arm (95% CI), P value		
	Adjusted Model 1*	Adjusted Model 2**	Adjusted Model 3***
eGFR-CKD-EPI mL/min/1.73m²	0.56 (0.003 to 1.11) 0.049	0.55 (0.03 to 1.07), 0.037	1.72 (1.11 to 2.34) <0.001
eGFR-MDRD mL/min	1.26 (0.38 to 2.14) 0.005	1.24 (0.41 to 2.08) 0.005	3.21 (2.17 to 4.25) <0.001

*Model 1: adjusted for baseline eGFR and years since randomization
**Model 2: Model 1 + additionally adjusted for age, gender, race, region of enrolment, time since HIV diagnosis, use of injecting drugs, CD4, viral load, proteinuria, body mass index, hepatitis B/C, diabetes, hypertension, dyslipidemia, cardiovascular disease, smoking status, ACE inhibitors or NSAIDS, all measured at randomisation. Not adjusted for TDF or boosted PI use
***Model 3: Model 2 + additionally adjusted for current receipt of TDF and boosted PI .

Figure 2: Mean change in eGFR (CKD-EPI) after censoring at start of TDF or PI in each arm



I	2067	160	116	74
D	2335	1874	1248	543

Table 3. Incidence of decline in eGFR by ≥30%, CKD and ESRD by treatment arms

Treatment Arm	Decline in eGFR by ≥30%		CKD defined as eGFR <60 or ≥1+ proteinuria		≥1+ Proteinuria	
	Events	*Rate (95%CI)*	*Events*	*Rate (95%CI)*	*Events*	*Rate (95%CI)*
Immediate ART	107	1.83 (1.52-2.22)	422	8.70 (7.90- 9.57)	390	7.96 (7.2-8.79)
Deferred ART	123	2.11 (1.77-2.51)	481	10.05 (9.19-11.0)	460	9.54 (8.70-10.45)
IRR I vs. D (95%CI)		0.85 (0.64-1.13)		0.79 (0.59-1.05)		0.74 (0.55-1.00)
P		0.27		0.10		0.049

Note: all rates in cases per 100 person-years of follow-up

Table 4. Follow-up eGFR in the immediate vs. deferred ART arm in the START trial stratified by race

Outcome	Mean difference Immediate arm vs. deferred arm (95% CI), P value	
	Black race	Non-Black race
eGFR-CKD-EPI mL/min/1.73m²	2.43 (1.43 – 3.42); p<0.001	-0.23 (-0.87 – 0.42); p=0.49
Adjusting for current use of TDF and/or PI	3.90 (2.48 – 4.97); p<0.001	1.05 (0.33 – 1.77); p=0.004

P<0.0001, test for interaction between race and randomisation arm

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