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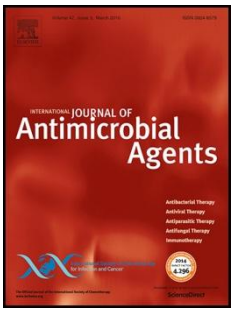

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Impact of early versus deferred antiretroviral therapy on estimated glomerular filtration rate in HIV-positive individuals in the START trial.

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Running title: Impact of immediate ART on kidney function

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Highlights

- This is a randomised study comparing immediate vs. deferred ART in asymptomatic HIV-positive individuals with CD4 count >500 cells/mm^3 for their impact on renal function
- Immediate ART was associated with high eGFR and lower rates of proteinuria over 2 years of follow-up.
- Whether this benefit translates in to lower risk of chronic kidney disease needs to be evaluated in future long-term studies.

ABSTRACT

Background

Both untreated HIV infection and antiretroviral therapy (ART) have been associated with worsening kidney function. The impact of earlier ART initiation on kidney function has not been studied.

Methods

The START trial was a randomized comparison of immediate versus deferred ART initiation among HIV+ persons with CD4+ counts >500 cells/mm^3. Serum creatinine and urine dipstick protein were measured at baseline, months 1, 4, 8, 12, and annually thereafter. We compared the two arms for changes in estimated glomerular filtration rate (eGFR, using the CKD-EPI equation) over time using longitudinal mixed models.

Findings

Of 4685 START participants, 4629 (n=2294 in immediate and 2335 in deferred arm) individuals were included. Median baseline CD4 and eGFR were 651 cells/mm^3 and 111·5 mL/min/1·73m^2. ART was initiated in 2271 participants (99%) in the immediate and 1127 participants (48%) in

the deferred arm, accounting for over 94% and 19% of follow-up time, respectively. Overall, 89% started ART using a tenofovir-based regimen. Over a median follow-up of 2·1 years, the mean eGFR was 0·56 (95% CI: 0·003-1·11) mL/min/1·73m^2 higher in the immediate arm than the deferred arm. This difference was more prominent after adjustment for current use of tenofovir or boosted-protease inhibitors (1·85, 95% CI: 1·21-2·50), and was more prominent in participants of black race (30% overall) (3·90, 95% CI: 2·84-4·97) compared to non-black (1·05, 95% CI: 0·33-1·77) (p<0·001 for interaction). Relative risk for proteinuria in the immediate vs. deferred arm was 0·74 (95% CI: 0·55-1·00), P=0·049. The incidence of chronic kidney disease as defined by eGFR < 60 or dipstick proteinuria was low, and there was no significant difference between treatment arms (incidence rate ratio 0.79, 95% CI 0.59-1.05).

Conclusion

In the short-term, immediate ART initiation was associated with a modestly higher eGFR and lower risk of proteinuria as opposed to deferring ART- a difference more pronounced in those with black race. Whether this early benefit translates into a lower risk of chronic kidney disease requires further follow-up.

Key words: HIV; kidney; CKD; HAART; eGFR; renal function; START;

INTRODUCTION

Despite dramatic reductions in the incidence of HIV-associated nephropathy (HIVAN- a unique form of kidney disease that occurs in the setting of advanced HIV disease) with the use of effective antiretroviral therapy (ART), HIV positive individuals continue to be at higher risk of chronic kidney disease (CKD) than the general population.(1) In addition to traditional risk factors such as diabetes and hypertension, HIV-associated immunodeficiency and inflammation have been shown to adversely affect renal function and increase the risk of CKD.(2, 3)

ART improves overall health and life-expectancy of HIV-positive individuals, and is first-line therapy for HIVAN.(4) However, prospective observational studies have demonstrated an association between cumulative exposure to tenofovir disoproxil fumarate (TDF) and boosted protease inhibitor (bPIs) and decline in estimated glomerular filtration rate (eGFR) and increased risk of CKD.(5, 6) Among participants in the D:A:D cohort with normal baseline eGFR followed for a median of over 7 years, TDF use was associated with 14% higher risk of CKD per year of use after adjusting for key confounders, with the relative risk nearly doubling in 5 years.(6) Prior studies were nonrandomized and were not powered to consider the risk:benefit of ART or specific ART agents in HIV-positive individuals with high CD4 counts, in whom ART initiation is now the standard of care.

The START (Strategic Timing of AntiRetroviral Treatment) trial is a randomized controlled clinical trial of immediate initiation of ART ('immediate' arm) versus deferral of ART initiation until CD4+ counts decline to <350 cells/mm^3 or clinical symptoms develop ('deferred' arm), among participants naïve to ART with CD4+ counts >500 cells/mm^3.(7) End-stage renal disease

(ESRD) was a component of the composite endpoint in START. There were, however, only two ESRD events, with 1 event occurring in each arm.(7)

In this study we compare the eGFR trajectory over time between the randomized arms of the START trial. START is an ideal study design to assess the effect of early ART upon kidney function among persons with relative immune preservation and low risk for AIDS complications.

METHODS

Study Design and Data Collection

The design and primary findings of the START trial have been described previously,(7) as has the baseline prevalence of CKD in START participants.(8) Change in eGFR from baseline and the development of proteinuria were pre-specified secondary endpoints in START. Serum creatinine and proteinuria by dipstick were measured at baseline, months 1, 4, 8, 12 and annually thereafter. All laboratory measures were performed on fresh specimens using standardized assays by clinical laboratories at the local clinical sites. Data in this report include visits up to the study unblinding on 26 May 2015.

We calculated eGFR using the CKD-EPI(9) equation for the primary analysis, with sensitivity analyses using the MDRD equation(10) to calculate eGFR. The main outcome was the change in follow-up eGFR. Data were analysed up to 60 months of follow-up, as few participants had annual visits beyond that time period. The following secondary outcomes were also analysed: (i) incidence of reduction in eGFR by ≥30% from baseline, which has been proposed as a

surrogate marker of CKD progression in clinical trials(11); (ii) incidence of CKD defined as eGFR ≤60 mL/min/1·73m^2 or ≥1+ proteinuria; (iii) incidence of a single reading of ≥1+ proteinuria alone; (iv) incidence of CKD as a reportable medical condition during the trial, defined by eGFR ≤ 60 mL/min/1·73m^2 and/or abnormal urine sediment over a period of at least three months. Outcomes (ii) to (iv) were analysed in those without CKD at baseline.

Statistical methods

The overall mean change from baseline in eGFR over follow-up between the immediate and deferred arms was compared using random effects linear regression (which account for repeat measurements in an individual) adjusting for follow-up time and baseline eGFR. Follow-up time was included as a quadratic term to allow for non-linear change in eGFR. We also assessed for any interaction effect between time and treatment arm. Next, models were further adjusted for time-updated use of TDF and bPIs. Finally, models were additionally adjusted for baseline variables including age, sex, race (black vs. other), region of enrolment (categorised as high-income, including Europe/Israel/United States/Australia vs. low-middle income, including Latin America/Africa/Asia), time since HIV diagnosis, use of injecting drugs, CD4 count, $\log_{10}$ HIV viral load, proteinuria, body mass index (measured as weight/(height)^2 and categorised at 18·5, 25 and 30 kg/m^2), hepatitis B or C virus co-infection (defined serologically), diabetes (defined as a composite based on known diagnosis or receipt of anti-diabetic medications or 8 hour fasting glucose ≥ 126 mg/dL), hypertension (systolic blood pressure (BP) > 140 mmHg or diastolic BP > 90 mmHg or receipt of anti-hypertensive medication), dyslipidemia (defined as receipt of lipid-lowering drugs or low density lipoprotein ≥ 160 mg/dL), coronary heart disease at baseline,

current smoking status, and current receipt of angiotensin converting enzyme inhibitors, angiotensin receptor blocker or non-steroidal anti-inflammatory drugs.

We performed several subgroup analyses for the primary outcome. Before randomization, clinicians pre-specified the likely ART regimen a participant would initiate as their first regimen. We assessed if eGFR changes by treatment arm differed by pre-specified regimen, focusing on the use of TDF or a bPI. Since choices of pre-specified regimens were made before randomization, these analyses allow a randomized comparison between the treatment arms among participants designated to initiate the same regimen. Other subgroup analyses included assessing eGFR treatment group differences by race; and stratifying the eGFR curves by the baseline 5 year CKD risk (calculated by the D:A:D CKD risk score and categorised as low: <0, moderate: 0-4 and high: >=5)(12). A sensitivity analysis was performed by censoring the follow-up on starting TDF/bPI; and censoring follow-up at first switch of ART.

Incidence rates of secondary outcomes were calculated, and the overall difference between the two arms was compared using random effects Poisson regression models.

RESULTS

Of 4685 START study participants, 10 individuals in the immediate arm and 11 individuals in the deferred arm did not have baseline creatinine values. A further 22 individuals in the immediate arm and 13 individuals in the deferred arm had no follow-up creatinine data. After exclusions, the analysis sample included 4629 individuals (2294 in the immediate arm and 2335 in the deferred arm). Baseline characteristics of the analysis sample were similar to the overall START study population (data not shown).

The median (interquartile range, IQR) follow-up time was 2·1 (1·9-3·2) years. Table-1 provides baseline characteristics by the treatment arm. The median age was 36 (29-44) years, 1241 (26·8%) were women, and 2124 (45·9%) were enrolled from high-income settings. The median CD4 count was 651 (584-764) cells/mm^3, and the median viral load was 4·1 (3·5-4·6) log_{10} copies/mL. The median eGFR was 111·5 (IQR 98·5-122·5) mL/min/1·73m^2 and only 22 (0·4%) individuals had an eGFR<60 mL/min/1·73m^2. A majority of individuals had a low 5-year predicted risk of CKD based on the D:A:D CKD risk score, and only 267 (5·8%) had a high 5-year predicted risk of CKD. Overall, baseline characteristics were well balanced between the two arms (Table-1).

ART was initiated in 2271 participants (99·0%) in the immediate arm and 1127 (48·2%) in the deferred arm, accounting for over 94% and 19% of follow-up time, respectively. Of those who started ART, 3017 (89%) included TDF in their initial regimen, and 668 (19·7%) had a bPI in their first regimen.

Follow-up eGFR by randomised arm

For sake of clarity, all figures show data only up to month 36 (3 years) where majority of the data were concentrated. Figure-1 provides mean change in eGFR from baseline over time and Table-2 provides the results from random effects models analysing change in eGFR by treatment arm. 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 over follow-up, the eGFR was 0·56 (95% CI: 0·003 to 1·11) mL/min/1·73m^2 higher in the immediate than the deferred arm (Table-2). The interaction term between time and treatment arm was not significant, meaning that the

rate of change over time was similar in both arms (p=0·73). Results were similar when eGFR was calculated using the MDRD equation with differences of larger magnitude (Figure-1 and Table-2). After adjustment for the time-updated use of TDF and bPI, the immediate arm had on average 1·85 (95% CI: 1·21 to 2·50) mL/min/1·73m^2 higher eGFR than the deferred arm.

Subgroup and sensitivity analyses of primary outcome

Over follow-up, the difference in eGFR between treatment arms differed by race (black vs. non-black) (P<0·001 for the interaction between treatment arm and race). In participants of black race, on average the eGFR was 2·43 (95% CI: 1·43-3·42) mL/min/1·73m^2 higher in the immediate than the deferred arm, increasing to 3·90 (95% CI: 2·84-4·97) mL/min/1·73m^2 after adjustment for current use of TDF and bPI. In participants of non-black race, the difference between treatment arms was less pronounced: the immediate compared to the deferred arm, had on an average -0·23 (95% CI: -0·87 to 0·42) mL/min/1·73m^2 difference in eGFR, or 1·05 (95% CI: 0·33 to 1·77) mL/min/1·73m^2 after adjustment for current use of TDF or bPI.

The choice of pre-specified ART regimen (with TDF or PI or both) did not differ significantly by treatment arm or by the presence of CKD (defined as eGFR$\leq$60 or ≥1+ proteinuria) or the mean eGFR at baseline (data not shown). However, there was a significant interaction between the pre-specified choice of a TDF-containing regimen and treatment arm for change in eGFR (Figure 2, p = 0·02). The difference in eGFR between treatment arms (immediate – deferred) in those who were not pre-specified TDF was 2·50 (0·86 to 4·15) mL/min/1·73m^2, compared to 0·38 (-0·20 to 0·96) mL/min/1·73m^2 in those with pre-specified TDF.

Supplementary figure-S1 illustrates the change in eGFR over time when follow-up was censored at the initiation of TDF or bPI in both arms. In the absence of use of TDF or a bPI, there was an initial increase in eGFR in the immediate arm and a higher overall eGFR, compared to the general small decline in eGFR in the deferred arm. Results were similar when follow-up was censored at the first switch/change in ART regimen (data not shown). Finally, after censoring the deferred arm at the initiation of ART (i.e. comparing treated vs untreated) and adjusting for the use of TDF or bPI in the treatment arm, the immediate (i.e. treated) arm had on average 2.24 (95% CI: 1.21 to 2.50) mL/min/1.73m2 higher eGFR than the deferred (i.e. untreated) arm.

Trajectories of change in eGFR and differences by treatment arm appeared to vary by baseline CKD risk as estimated by the D:A:D CKD risk score (see Supplementary Figure-S2), although with <6% of individuals at high baseline CKD risk, we did not have enough power to further analyse this subgroup. In those with low predicted CKD risk (78% of study participants), trends appeared similar to those in figure 1. In those with moderate or high CKD risk at baseline, eGFR tended to increase initially (Figure-S2) as opposed to the slight initial decline seen in those with low CKD risk. While the eGFR appeared to be higher in the immediate arm in those with moderate to high baseline CKD risk, over time the curves tended to overlap (Figure-S2).

Secondary outcomes

Table-3 provides a comparison of several secondary outcomes. Decline in eGFR by ≥30%, which has been proposed as a surrogate CKD endpoint, occurred in < 6% of participants with no significant difference between treatment arms. A composite CKD endpoint of eGFR < 60 or ≥1+ proteinuria occurred in 422 participants in the immediate arm and 481 participants in the

deferred arm, but this difference was not statistically significant (IRR 0.79; 95% CI 0.59-1.05, p=0.10). The development of ≥1+ proteinuria was significantly less common in the immediate arm compared to the deferred arm (IRR 0.74; 95% CI: 0.55-1.00, P=0.049), although this difference was only marginally significant. Of the 850 participants who developed ≥1+ proteinuria, only 161 (19%) had proteinuria of 2+ or higher. Finally, only 10 study-defined CKD events were reported in trial, 4 and 6 in the immediate and deferred arms, respectively.

DISCUSSION

In this large international randomised trial, we found that the immediate initiation of ART in those with CD4 count >500 cells/mm^3, as compared to deferring ART until the CD4 count drops to below 350 cells/mm^3 or clinical symptoms appear, was associated with a modestly higher overall eGFR over a median follow-up of 2·1 years. This difference was especially prominent when use of known nephrotoxic agents (TDF or a bPI) was accounted for and was more prominent in participants of black race compared to non-black. Immediate ART was also associated with a lower risk of incident ≥1+ dipstick proteinuria, with a trend towards lower risk of several other secondary CKD outcomes.

The START trial found clear benefit of immediate ART at high CD4 cell counts in terms of AIDS, mortality, and serious non-AIDS clinical events(7). Our study provides further support for immediate ART and suggests that at least in the short term, immediate ART is also beneficial in terms of its impact on kidney function (as assessed by eGFR and dipstick proteinria). The difference in eGFR between the treatment arms increased after adjusting for TDF or bPI use,

suggesting that their use may counteract some of the benefits of early ART. Of note, the actual difference in eGFR between the two arms was quite small, and the clinical impact of such eGFR differences on the long-term risk of CKD events is unclear. CKD is a slowly progressive disease, which can take years to manifest. In our study, the median follow-up was only 2.1 years, as the START trial was stopped by the Data and Safety Monitoring Board (DSMB) because of the overwhelming benefit to the immediate arm(7). It is therefore possible that early benefit from immediate ART on eGFR could be attenuated over time with cumulative toxicity from ART. Convergence of the curves with prolonged follow-up could reflect increasing use of ART in the deferred arm, attenuation of the benefit in the immediate arm as a result of cumulative nephrotoxicity, or a combination of both factors. In addition to the risk of progressive CKD, both lower eGFR and the presence of proteinuria have been associated with higher risk of overall and cardiovascular mortality.(13) Longer follow-up of this cohort will therefore be critical for better understanding of the long term impact of additional years spent on ART in the immediate arm.

The mechanism behind the initial beneficial effect of immediate ART is unclear and is likely to be multi-factorial. In our study, after censoring the data at the initiation of TDF/bPI, there appeared to be an initial gain in eGFR in the immediate arm vs. a general slow decline in eGFR in the deferred arm. ART reduces viral load as well as inflammation and immune activation, all of which have been associated with loss of eGFR and kidney disease.(14) In one prospective cohort study, use of ART (compared to no ART) was associated with a slower decline in eGFR over 3 years of follow-up.(15) Similarly, in another study, ART initiation was associated with an improvement in proteinuria and albuminuria, although that study did not have an untreated

control arm.(16) However, in both previous studies, the median baseline CD4 counts were around 200 to 250 cells/mm^3 suggesting significant immunodeficiency before ART initiation. Our data suggest that even in those with relatively preserved immune function, ART may provide benefit in terms of kidney function. In our study, results were robust to the adjustment for time-updated CD4 count and viral load. Whether this short-term benefit from immediate ART could be explained by changes in inflammatory mediators will need to be examined carefully in future biomarker studies. Interestingly, the benefit of immediate ART was more pronounced in individuals of black race. Because genetic susceptibility to HIVAN is strongly linked to West African ancestry,(17, 18) our findings could suggest a benefit of immediate ART on subclinical HIVAN or other forms of non-diabetic kidney disease in individuals of black race. The accuracy of GFR measurement may play a role: we found that the difference between the two arms was larger in magnitude in MDRD (vs CKD-EPI) eGFR. However, CKD-EPI equation is thought to be more accurate at GFRs> 60 mL/min/1·73m^2 which were the majority in our study.

Finally, we could not fully explain the initial dip in eGFR at month 1 in both arms of our cohort. The initial decline in eGFR may have been the result of regression to the mean in participants with higher baseline eGFR, as it was not observed in those with moderate/ high baseline CKD risk as estimated by the D:A:D risk score. Also, it was not observed in those who were prescribed a non-TDF regimen (Figure 2b) suggesting that TDF may have had a role at least in the treatment arm. Future biomarker studies could provide further insight into the mechanism behind eGFR trajectory over time.

Our study had several strengths, including a randomized study design with a large number of participants with a high baseline CD4 count and serial monitoring of creatinine during follow-up. Our sample was also diverse, with participants enrolled from 215 clinical sites in 35 countries, with 30% of self-reported black race and 27% females. The main limitation of our study was that our participants had a relatively low baseline risk of CKD, based on young age and low prevalence of traditional CKD risk factors; for example, both diabetes and hepatitis C virus co-infection were present in < 4% of participants. The follow-up period was also relatively short due to the early termination of the START trial. Of note, observed benefit in trials that are terminated early tends to overestimate the true benefit (e.g. benefit could be attenuated over longer follow-up).(19) Using changes in creatinine-based eGFR, we cannot differentiate between true changes in glomerular filtration rate and changes based on interference with the tubular secretion of creatinine. Although the use of cobicistat (n=150 ever used) and dolutegravir (n=85 ever used) was very rare in START, a similar effect on tubular secretion could influence the eGFR in the setting of low dose ritonavir, and has even been suggested with TDF.(20, 21) Changes in eGFR are also insensitive to tubular injury as may occur in individuals on TDF containing ART and additional markers of tubular injury were not collected in START.(22-25) START did not collect data on urine protein or albumin to creatinine ratio, which could help to quantify the degree of proteinuria and distinguish glomerular versus tubular proteinuria. Finally, newer ART agents such as tenofovir alafenamide, which may mitigate long-term renal toxicity from ART,(26, 27) were not able to be studied as these drugs were not licensed at the time.

In summary, our study suggests modest short-term benefit on kidney function from the immediate initiation of ART in HIV+ individuals with high CD4. This benefit was especially prominent in individuals of black race and in the absence of TDF or PI/r. Whether the small observed differences in eGFR will translate into a reduced risk of CKD, and whether the cumulative effects of nephrotoxic ART agents may counteract these benefits, should be studied in future long-term studies.

Declarations

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Competing Interests: None

Ethical Approval: The study was approved by the institutional review board or ethics committee at each participating site, and written informed consent was obtained from all patients.

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Figure-1: Mean change in eGFR from baseline by treatment arm in START trial

Figure-1a: eGFR (mL/min/1.73m^2) calculated by CKD-EPI

Figure-1b: eGFR (mL/min/1.73m^2) calculated by MDRD

Figure- 2: Mean change in eGFR (CKD-EPI) from baseline by pre-specified TDF or non-TDF regimen in START trial

Figure-2a: Pre-specified TDF regimen

Figure-2b: Pre-specified non-TDF regimen

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

	Immediate **N (%) or Median [IQR]**	**Deferred** **N (%) or Median [IQR]**
Number included	**2294**	**2335**
Demographics		
Age, years **Age >50 years**	36 [29, 44] 225 (9.8)	36 [29, 44] 238 (10.2)
Female	610 (26.6)	631 (27.0)
Race Black	 691 (30.1)	 704 (30.2)
Region of enrolment United States/Europe/Australia (High) Latin America/Africa/Asia (Low-Middle)	 1054 (45.9) 1240 (54.1)	 1070 (45.8) 1265 (54.2)
HIV History		
Likely mode of infection Injecting drug use Sexual contact Other	 36 (1.6) 2143 (93.4) 115 (5.0)	 26 (1.1) 2181 (93.4) 128 (5.5)
Time known to be HIV positive (years)	0.99 [0.35-2.99]	1.08[0.36-3.11]
Laboratory results		
Baseline CD4, cells/µL	651 [585, 764]	651 [581-764]
Log_{10} HIV RNA, copies/mL	4.1 [3.5, 4.6]	4.1 [3.5, 4.6]
Medical history		
Hepatitis C co-infection Missing	88 (3.9) 49 (2.1)	81 (3.6) 58 (2.5)

Hepatitis B co-infection	63 (2.8)	65 (2.9)
Missing	50 (2.2)	75 (3.2)
Clinical measures		
Body mass index, kg/m^2		
Median [IQR]	22.1 [24.6-28.0]	22.1 [24.5-27.7]
<18.5	68 (3.0)	66 (2.8)
18.5-25	1180 (51.4)	1216 (52.1)
25.1-29.9	665 (29)	676 (28.9)
≥30	381 (16.6)	377 (16.2)
Systolic blood pressure, mmHg		
Median [IQR]	120 [110, 130]	120.5 [111, 130.5]
> 140	220 (9.6)	237 (10.1)
Diastolic blood pressure, mmHg		
Median (IQR)	75.5 [69.5, 82.5]	76.5 [70, 83]
> 90	185 (8.1)	198 (8.5)
Diabetes mellitus	74 (3.2)	79 (3.4)
Hypertension	428 (18.7)	461 (19.7)
Dyslipidemia	179 (7.8)	200 (8.6)
Coronary heart disease (CHD)	8 (0.4)	10 (0.4)
Current smoker	721 (31.4)	755 (32.3)
Started ART at any time in the follow-up	2271 (99)	1127 (48.2)
Of those started ART, Initial regimen including		
Tenofovir disoproxil fumarate	2012 (88.6)	1005 (89.3)
Protease inhibitor/ ritonavir	419 (18.5)	249 (22.1)
Dolutegravir or cobicistat	2 (0.1)	67 (5.9)

Rilpivirine	97 (4.3)	140 (12.4)
Pre-specified ART regimens		
Containing TDF	2047 (89)	2067 (88.5)
Containing PI/r	381 (16.7)	424 (18.2)
Containing both TDF and PI/r	339 (14.8)	366 (15.7)
Concomitant medications at baseline		
ACE inhibitor/ angiotensin receptor blocker	127 (5.5)	117 (5.0)
NSAIDS (incl. Aspirin)	118 (5.1)	113 (4.8)
eGFR-CKD-EPI, mL/min		
Median (IQR)	111.7 [98.2, 123]	111.04 [98.9, 122.4]
≥ 90	1943 (84.7)	2001 (85.7)
60-89	334 (14.6)	319 (13.7)
≤60	7 (0.3)	15 (0.6
eGFR-MDRD, mL/min	107.6 [92.6, 125.2]	106.8 [93.9, 124.2]
Dipstick proteinuria ≥1+	136 (6.0)	131 (5.7)
Unavailable at baseline	9 (0.4)	18 (0.8)
Chronic kidney disease	142 (6.2)	143 (6.2)
D:A:D CKD risk score		
Low	1779 (77.6)	1834 (78.5))
Medium	330 (14.4)	291 (12.5)
High	130 (5.7)	137 (5.9)
Unavailable*	55 (2.4)	73 (3.1)

443 NOTE: *D:A:D CKD score could not be calculated largely due to either missing hepatitis C variable or
444 baseline eGFR below 60 mL/min/1.73m^2. Chronic kidney disease (CKD) at baseline defined as eGFR
445 < 60 mL/min and/or dipstick urine protein ≥ 1+ (defined only in those with available information on both
446 eGFR and dipstick proteinuria). NSAIDS= non-steroidal anti-inflammatory drugs.

Table-2 Mean difference (immediate minus deferred) in eGFR over follow-up

Outcome	Mean difference Immediate arm minus deferred arm (95% CI), P value		
	Adjusted Model 1*	**Adjusted Model 2****	**Adjusted Model 3*****
eGFR-CKD-EPI mL/min/1.73m^2	0.56 (0.003 to 1.11), 0.049	1.85 (1.21 to 2.50) , <0.001	1.72 (1.11 to 2.34) , <0.001
eGFR-MDRD mL/min	1.26 (0.38 to 2.14), 0.005	3.43 (2.35 to 4.51), <0.001	3.21 (2.17 to 4.25), <0.001

*Model 1: adjusted for baseline eGFR and follow-up time

**Model 2: Model 1 additionally adjusted for current receipt of TDF and boosted PI

***Model 3: Model 2 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, use of ACE inhibitors or NSAIDS, all measured at randomisation.

Table-3: Incidence of decline in eGFR by ≥30%, CKD , and Protenuria 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)
Immediate vs. deferred arm IRR (95%CI), P	0.85 (0.64-1.13), 0.27		0.79 (0.59-1.05), 0.10		0.74 (0.55-1.00), 0.049	

Note: Rate are per 100 person-years.