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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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ABSTRACT

The impact of early ART initiation (versus deferring) on kidney function has not been studied. START was a randomised comparison of immediate versus deferred ART initiation among HIV-positive persons with CD4⁺ (cells/mm³) counts >500. Serum creatinine and urine dipstick protein were measured at Months 0, 1, 4, 8 and 12, and annually thereafter. The two arms were compared for changes in eGFR (mL/min/1.73 m², calculated by CKD-EPI equation), over time using longitudinal mixed models. Of 4685 START participants, 4629 (2294 in immediate and 2335 deferred arm) were included. Median baseline CD4⁺ and eGFR were 651 and 111.5, respectively. ART was initiated in 2271 participants (99.0%) in the immediate and 1127 (48.3%) in the deferred arm, accounting for >94% and >19% of follow-up time, respectively. Overall, 89% started ART using a tenofovir-based regimen. Over 2.1 years median follow-up, mean eGFR was 0.56 (95% CI 0.003–1.11) higher in the immediate versus deferred arm, which was more prominent after adjustment for current tenofovir or bPI use (1.85, 95% CI 1.21–2.50) and in Black participants (30.1% overall) (3.90, 95% CI 2.84–4.97) versus non-Blacks (1.05, 95% CI 0.33–1.77) ($P < 0.001$ for interaction). Relative risk for proteinuria in the immediate versus deferred arm was 0.74 (95% CI 0.55–1.00) ($P = 0.049$). In the short-term, immediate ART initiation was associated with a modestly higher eGFR and lower proteinuria risk versus deferring ART (more pronounced in Black participants). Whether this early benefit translates into a lower risk of CKD requires further follow-up.

1. Introduction

Despite dramatic reductions in the incidence of human immunodeficiency virus (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

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traditional risk factors such as diabetes and hypertension, HIV-associated immunodeficiency and inflammation have been shown to adversely affect renal function and to increase the risk of CKD [2,3].

ART improves the 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 to boosted protease inhibitors (bPIs) and a decline in estimated glomerular filtration rate (eGFR) and an increased risk of CKD [5,6]. Among participants in the D:A:D cohort with normal baseline eGFR followed for a median of >7 years, TDF use was associated with a 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 non-randomised and were not powered to consider the risk:benefit of ART or specific ART agents in HIV-positive individuals with high CD4$^+$ cell counts, in whom ART initiation is now the standard of care.

The START (Strategic Timing of AntiRetroviral Treatment) trial is a randomised 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 one event occurring in each arm [7].

In this study, the eGFR trajectory over time was compared between the randomised 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 acquired immune deficiency syndrome (AIDS) complications.

2. Methods

2.1. 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 (SCr) and proteinuria by dipstick were measured at baseline, at Months 1, 4, 8 and 12, and annually thereafter. All laboratory measurements were performed on fresh specimens using standardised assays by clinical laboratories at the local clinical sites. Data in this report include visits up to the study unblinding on 26 May 2015.

The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) [9] equation for the primary analysis, with sensitivity analyses using the MDRD (Modification of Diet in Renal Disease) 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/1.73 m^2 or ≥1+ proteinuria; (iii) incidence of a single reading of ≥1+ proteinuria alone; and (iv) incidence of CKD as a reportable medical condition during the trial, defined by eGFR ≤ 60 mL/min/1.73 m^2 and/or abnormal urine sediment over a period of ≥3 months. Outcomes (ii) to (iv) were analysed in those without CKD at baseline.

2.2. 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 accounts 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. Any interaction effect between time and treatment arm was also assessed. 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 versus other), region of enrolment (categorised as high-income, including Europe/Israel/USA/Australia versus low-middle income, including Latin America/Africa/Asia), time since HIV diagnosis, use of injecting drugs, CD4$^+$ cell count, $\log_{10}$ HIV viral load, proteinuria, body mass index [measured as weight/(height)^2 and categorised as <18.5, 18.5–25.0, 25.1–29.9 and ≥30 kg/m^2], hepatitis B or C virus co-infection (defined serologically), diabetes mellitus (defined as a composite based on known diagnosis or receipt of antidiabetic medications or 8 h fasting glucose ≥126 mg/dL), hypertension (systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg or receipt of antihypertensive medication), dyslipidaemia (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 inhibitor, angiotensin receptor blocker or non-steroidal anti-inflammatory drugs.

Several subgroup analyses were performed for the primary outcome. Before randomisation, clinicians pre-specified the likely ART regimen a participant would initiate as their first regimen. We assessed whether 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 randomisation, these analyses allow a randomised 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.

3. Results

Of 4685 START study participants, 10 individuals in the immediate arm and 11 individuals in the deferred arm did not have baseline SCr values. A further 22 individuals in the immediate arm and 13 individuals in the deferred arm had no follow-up SCr 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) follow-up time was 2.1 (1.9–3.2) years. Table 1 provides baseline characteristics by treatment arm. The median age was 36 (29–44) years, 1241 (26.8%) were female 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 (98.5–122.5) mL/min/1.73 m^2 and only 22 individuals (0.5%) had an eGFR < 60 mL/min/1.73 m^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).

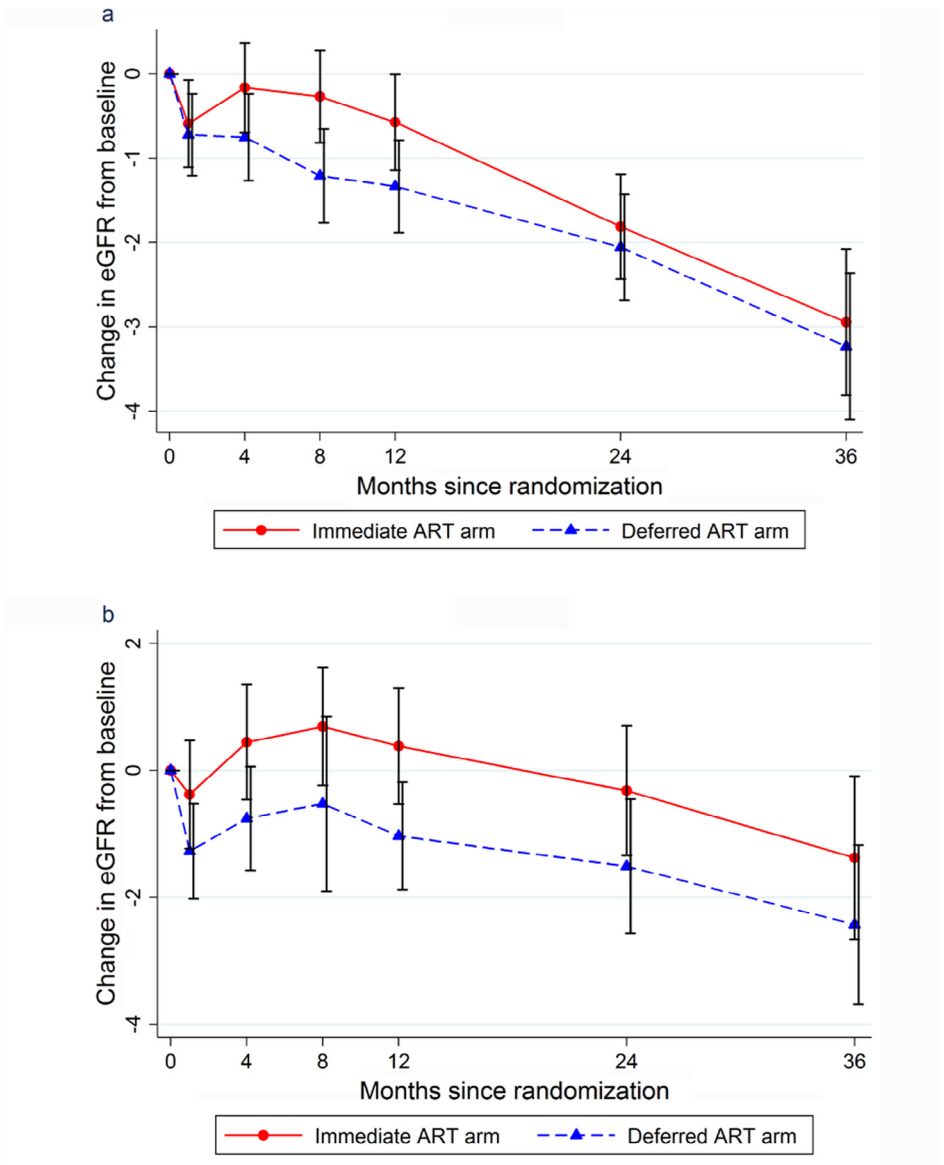
ART was initiated in 2271 participants (99.0%) in the immediate arm and 1127 participants (48.3%) in the deferred arm, accounting for over 94% and 19% of follow-up time, respectively.

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

	n (%) or median [IQR]	
	Immediate	Deferred
No. of patients	2294	2335
Demographics		
Age (years)	36 [29–44]	36 [29–44]
Age > 50 years	225 (9.8)	238 (10.2)
Female sex	610 (26.6)	631 (27.0)
Race Black	691 (30.1)	704 (30.1)
Region of enrolment		
USA/Europe/Israel/Australia (high-income)	1054 (45.9)	1070 (45.8)
Latin America/Africa/Asia (low-middle income)	1240 (54.1)	1265 (54.2)
HIV history		
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)
Time known to be HIV-positive (years)	0.99 [0.35–2.99]	1.08 [0.36–3.11]
Laboratory results		
Baseline $CD4^+$ count (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		
Yes	88 (3.9)	81 (3.6)
Missing	49 (2.1)	58 (2.5)
Hepatitis B co-infection		
Yes	63 (2.8)	65 (2.9)
Missing	50 (2.2)	75 (3.2)
Clinical measures		
BMI (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)
18.5–25.0	1180 (51.4)	1216 (52.1)
25.1–29.9	665 (29.0)	676 (29.0)
≥30	381 (16.6)	377 (16.1)
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)
Dyslipidaemia	179 (7.8)	200 (8.6)
Coronary heart disease	8 (0.3)	10 (0.4)
Current smoker	721 (31.4)	755 (32.3)
Started ART at any time in the follow-up	2271 (99.0)	1127 (48.3)
Of those started ART, initial regimen including:		
Tenofovir disoproxil fumarate (TDF)	2012 (88.6)	1005 (89.2)
Protease inhibitor/ritonavir (PI/r)	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 (89.2)	2067 (88.5)
Containing PI/r	381 (16.6)	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 (including aspirin)	118 (5.1)	113 (4.8)
eGFR-CKD-EPI ($mL/min/1.73\ m^2$)		
Median [IQR]	111.7 [98.2–123]	111.04 [98.9–122.4]
≥90	1943 (84.7)	2001 (85.7)
60–89	344 (15.0)	319 (13.7)
<60	7 (0.3)	15 (0.6)
eGFR-MDRD ($mL/min/1.73\ m^2$)	107.6 [92.6–125.2]	106.8 [93.9–124.2]
Dipstick proteinuria		
≥1+	136 (5.9)	131 (5.6)
Unavailable at baseline	9 (0.4)	18 (0.8)
Chronic kidney disease (CKD)	142 (6.2)	143 (6.1)
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[a]	55 (2.4)	73 (3.1)

IQR, interquartile range; HIV, human immunodeficiency virus; BMI, body mass index; ART, antiretroviral therapy; ACE, angiotensin-converting enzyme; NSAID, non-steroidal anti-inflammatory drug; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

[a] D:A:D CKD score could not be calculated largely due to either missing hepatitis C variable or baseline eGFR < 60 mL/min/1.73 m^2. CKD at baseline defined as eGFR < 60 mL/min and/or dipstick urine protein ≥1+ (defined only in those with available information on both eGFR and dipstick proteinuria).



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Immediate	2294	2191	1846	1078
Deferred	2335	2167	1822	1071

Fig. 1. Mean change in estimated glomerular filtration rate (eGFR) from baseline by treatment arm in the START trial: (a) eGFR (mL/min/1.73 m^2) calculated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration); and (b) eGFR (mL/min/1.73 m^2) calculated by MDRD (Modification of Diet in Renal Disease). ART, antiretroviral therapy.

Of the 3398 who started ART, 3017 (88.8%) included TDF in their initial regimen and 668 (19.7%) had a bPI in their initial regimen.

3.1. Follow-up estimated glomerular filtration rate (eGFR) by randomised arm

For the sake of clarity, all figures show data only up to Month 36 (3 years) where the majority of the data were concentrated. Fig. 1 shows the mean change in eGFR from baseline over time, and Table 2 provides the results from the random-effects models analysing change in eGFR by treatment arm. The eGFR tended to decline over time in both arms (Fig. 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% confidence interval (CI) 0.003–1.11] mL/min/1.73 m^2 higher in the immediate arm 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 (Fig. 1; Table 2). After adjustment for the time-updated use of TDF and bPI, the immediate arm had on average 1.85 (95% CI 1.21–2.50) mL/min/1.73 m^2 higher eGFR than the deferred arm.

3.2. Subgroup and sensitivity analyses of the primary outcome

Over follow-up, the difference in eGFR between treatment arms differed by race (Black versus 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/1.73 m^2 higher in the immediate than the deferred arm, increasing to 3.90 (95% CI 2.84–4.97) mL/min/1.73 m^2 after adjustment for current use of TDF and bPI. In participants of non-Black race, the difference

Table 2
Mean difference (immediate minus deferred) in estimated glomerular filtration rate (eGFR) over follow-up.

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

CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.
[a] Model 1: adjusted for baseline eGFR and follow-up time.
[b] Model 2: Model 1 additionally adjusted for current receipt of tenofovir disoproxil fumarate (TDF) and boosted protease inhibitor (bPI).
[c] Model 3: Model 2 additionally adjusted for age, sex, race, region of enrolment, time since HIV diagnosis, use of injecting drugs, CD4$^+$ cell count, viral load, proteinuria, body mass index, hepatitis B/C, diabetes mellitus, hypertension, dyslipidaemia, cardiovascular disease, smoking status, and use of angiotensin-converting enzyme inhibitors or non-steroidal anti-inflammatory drugs, all measured at randomisation.

between treatment arms was less pronounced: the immediate compared with the deferred arm had, on average, –0.23 (95% CI –0.87 to 0.42) mL/min/1.73 m^2 difference in eGFR, or 1.05 (95% CI 0.33 to 1.77) mL/min/1.73 m^2 after adjustment for current use of TDF or bPI.

The choice of pre-specified ART regimen (with TDF or bPI or both) did not differ significantly by treatment arm or by the presence of CKD (defined as eGFR ≤ 60 mL/min/1.73 m^2 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 ($P = 0.02$) (Fig. 2). The difference in eGFR between treatment arms (immediate minus deferred) in those who were not pre-specified TDF was 2.50 (95% CI 0.86 to 4.15) mL/min/1.73 m^2 compared with 0.38 (95% CI –0.20 to 0.96) mL/min/1.73 m^2 in those with pre-specified TDF.

Supplementary Fig. 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 with 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 versus 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 1.21–2.50) mL/min/1.73 m^2 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 Fig. S2), although with <6% of individuals at high baseline CKD risk, there was not sufficient power to further analyse this subgroup. In those with low predicted CKD risk (78.1% of study participants), trends appeared similar to those in Fig. 1. In those with moderate or high CKD risk at baseline, eGFR tended to increase initially (Supplementary Fig. S2) as opposed to the slight initial decline seen in those with low CKD risk. Whilst 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 (Supplementary Fig. S2).

3.3. Secondary outcomes

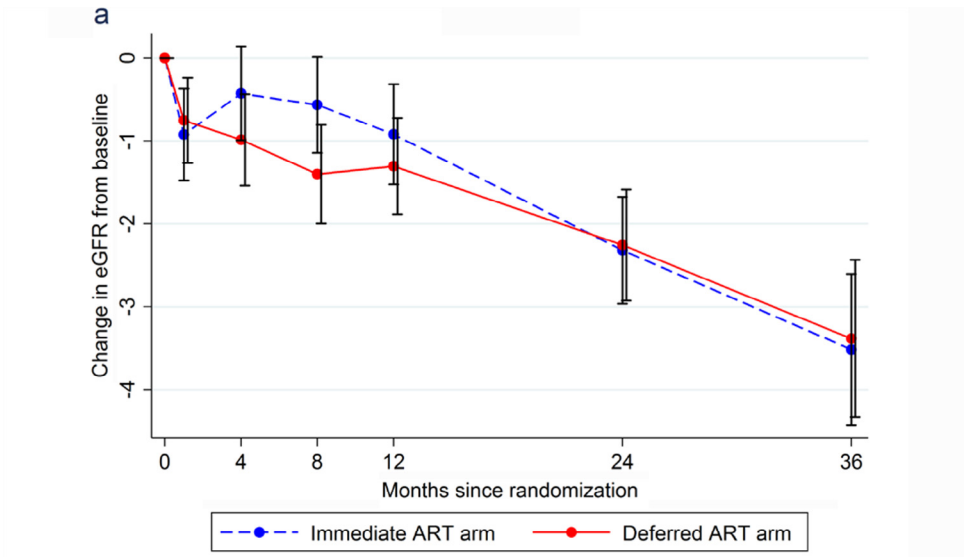
Table 3 provides a comparison of several secondary outcomes. Decline in eGFR by ≥30%, which has been proposed as a surrogate CKD endpoint, occurred in <6% of participants, with no significant difference between treatment arms. A composite CKD endpoint of eGFR < 60 mL/min/1.73 m^2 or ≥1+ proteinuria occurred in 422 participants in the immediate arm and 481 participants in the deferred arm, but this difference was not statistically significant [incidence rate ratio (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 with 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 (18.9%) had proteinuria of 2+ or higher. Finally, only ten study-defined CKD events were reported in the trial (four and six in the immediate and deferred arms, respectively).

4. Discussion

In this large, international, randomised trial, we found that immediate initiation of ART in those with CD4$^+$ count >500 cells/mm^3 compared with deferring ART until the CD4 count drops to <350 cells/mm^3 or clinical symptoms 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 with non-Blacks. 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]. This 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 proteinuria). 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 that can take years to manifest. In this 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 multifactorial. In this study, after censoring the data at the initiation of TDF/bPI, there appeared to be an initial gain in eGFR in the immediate arm versus a general slow decline in eGFR in the deferred arm. ART reduces the 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 with



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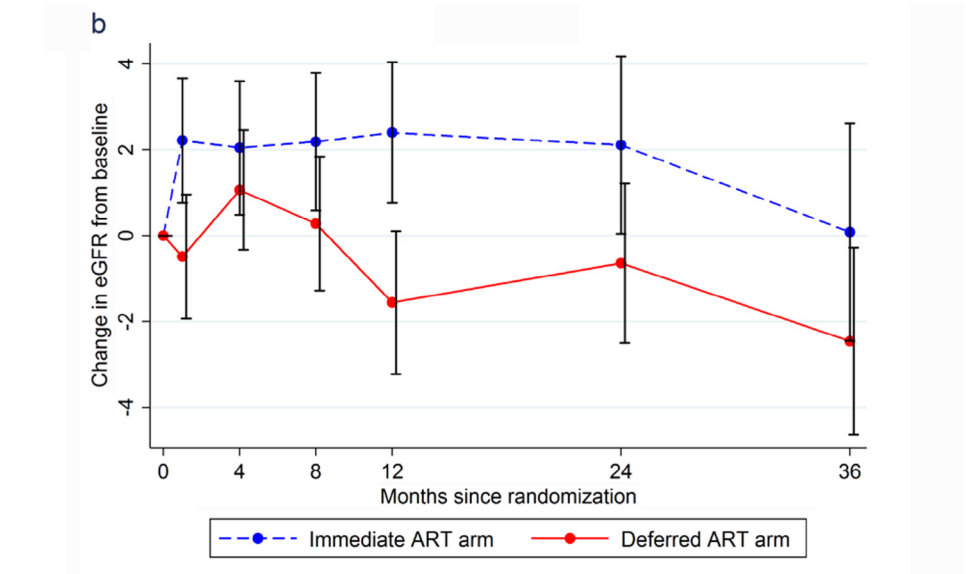
Immediate	2047	1961	1634	907
Deferred	2067	1918	1594	894



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Immediate	247	230	212	171
Deferred	268	249	228	177

Fig. 2. Mean change in estimated glomerular filtration rate (eGFR), calculated by (Chronic Kidney Disease Epidemiology Collaboration), from baseline by pre-specified regimen in the START trial: (a) pre-specified tenofovir disoproxil fumarate (TDF) regimen; and (b) pre-specified non-TDF regimen. ART, antiretroviral therapy.

Table 3
Incidence of decline in estimated glomerular filtration rate (eGFR) by ≥30%, chronic kidney disease (CKD) and proteinuria by treatment arm.

Treatment arm	Decline in eGFR by ≥30%		CKD defined as eGFR < 60 mL/min/1.73 m^2 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*-value	0.85 (0.64–1.13); 0.27		0.79 (0.59–1.05); 0.10		0.74 (0.55–1.00); 0.049	

CI, confidence interval; ART, antiretroviral therapy; IRR, incidence rate ratio.
Note: Rates are per 100 person-years.

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 ca. 200–250 cells/mm^3, suggesting significant immunodeficiency before ART initiation. The current data suggest that even in those with relatively preserved immune function, ART may provide benefit in terms of kidney function. In the present study, results were robust to the adjustment for time-updated CD4+ cell 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], the current 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 (versus CKD-EPI) eGFR. However, the CKD-EPI equation is thought to be more accurate at GFRs > 60 mL/min/1.73 m^2, which were the majority in this study.

Finally, we could not fully explain the initial dip in eGFR at Month 1 in both arms of this 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 (Fig. 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.

This study had several strengths, including a randomised study design with a large number of participants with a high baseline CD4+ cell count and serial monitoring of SCr during follow-up. The sample was also diverse, with participants enrolled from 215 clinical sites in 35 countries, with 30.1% of self-reported Black race and 26.8% females. The main limitation of this study was that 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 mellitus and hepatitis C virus co-infection were present in <4% of participants. The follow-up period was also relatively short owing 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 GFR 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: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, this study suggests modest short-term benefit on kidney function from the immediate initiation of ART in HIV-positive individuals with high CD4+ cell count. This benefit was especially prominent in individuals of Black race and in the absence of TDF or bPI. 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.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2017.04.021.

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