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

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BACKGROUND
The impact of antiretroviral therapy (ART) on renal function in HIV-positive persons with high CD4 counts 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/1.73 m² 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 PI 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: 0.03 to 1.11) ml/min/1.73 m² 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/1.73 m² 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/1.73 m².

CONCLUSIONS
The immediate initiation of ART in persons with CD4 count >500 cells/mm³, as compared to deferred ART till the CD4 count drops to below 350 cells/mm³ 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.

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