# Severe Renal Dysfunction and Risk Factors Associated with Renal Impairment in HIV-Infected Adults in Africa Initiating Antiretroviral Therapy

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***Background.*** We sought to investigate renal function in previously untreated symptomatic human immunodeficiency virus (HIV)–infected adults with $CD4^+$ cell counts of <200 cells/$mm^3$ who were undergoing antiretroviral therapy (ART) in Africa.

***Methods.*** The study was an observational analysis within a randomized trial of ART management strategies that included 3316 participants with baseline serum creatinine levels of ≤360 μmol/L. Creatinine levels were measured before ART initiation, at weeks 4 and 12 of therapy, and every 12 weeks thereafter. We calculated estimated glomerular filtration rate (eGFR) using the Cockcroft-Gault formula. We analyzed the incidence of severely decreased eGFR (<30 mL/min/1.73 $m^2$) and changes in eGFR to 96 weeks, considering demographic data, type of ART, and baseline biochemical and hematological characteristics as predictors, using random-effects models.

***Results.*** Sixty-five percent of the participants were women. Median values at baseline were as follows: age, 37 years; weight, 57 kg; $CD4^+$ cell count, 86 cells/$mm^3$; and eGFR, 89 mL/min/1.73 $m^2$. Of the participants, 1492 (45%) had mild (≥60 but <90 mL/min/1.73 $m^2$) and 237 (7%) had moderate (≥30 but <60 mL/min/1.73 $m^2$) impairments in eGFR. First-line ART regimens included zidovudine-lamivudine plus tenofovir disoproxil fumarate (for 74% of patients), nevirapine (16%), and abacavir (9%) (mostly nonrandomized allocation). After ART initiation, the median eGFR was 89–91 mL/min/1.73 $m^2$ for the period from week 4 through week 96. Fifty-two participants (1.6%) developed severe reductions in eGFR by week 96; there was no statistically significant difference between these patients and others with respect to first-line ART regimen received ($P = .94$). Lower baseline eGFR or hemoglobin level, lower body mass index, younger age, higher baseline $CD4^+$ cell count, and female sex were associated with greater increases in eGFR over baseline, with small but statistically significant differences between regimens ($P < .001$ for all).

***Conclusions.*** Despite screening, mild-to-moderate baseline renal impairment was relatively common, but these participants had greatest increases in eGFR after starting ART. Severe eGFR impairment was infrequent regardless of ART regimen and was generally related to intercurrent disease. Differences between ART regimens with respect to changes in eGFR through 96 weeks were of marginal clinical relevance, but investigating longer-term nephrotoxicity remains important.

Causes of renal disease in HIV-infected patients are multifactorial and include HIV infection itself, coinfections, comorbidities, and their treatments [1]. HIV-infected patients of African origin have a greater risk of renal diseases; however, there are few data from Africa itself [2, 3]. The antiretroviral tenofovir disoproxil fumarate (DF) has been associated with nephrotoxicity, such as acute renal failure or proximal tubular dysfunction [4–8]. To date, severe renal impairment has been rare in clinical trials of tenofovir-containing first-line antiretroviral therapy (ART) regimens (occurring in <1% of patients), and there have been no statistically

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significant differences between tenofovir-containing regimens and other regimens with respect to the frequency of severe renal impairment [9–12]; severe renal impairment has been reported in only 0.5% of patients taking tenofovir in a large postmarketing program [13]. Small but statistically significant reductions in estimated glomerular filtration rate (eGFR) after the initiation of tenofovir DF, compared with after the initiation of other drugs, have been reported in some studies [14–19], but other studies have not found such differences [20–22].

There are few data on the impact of ART on renal disease in Africa, and the long-term nephrotoxicity of tenofovir DF has not been studied in resource-limited settings, in which unfavorable combinations of risk factors are common. Here, we describe the effect of ART on eGFR in the Development of Antiretroviral Therapy (DART) trial in Uganda and Zimbabwe, in which 74% of participants received tenofovir DF as first-line treatment.

## METHODS

***Trial design and participants.*** DART is a randomized, controlled trial comparing 3-drug ART monitored by clinical monitoring only or by laboratory ($CD4^+$ cell measurements and toxicity) plus clinical monitoring in sub-Saharan Africa (ISCRTN13968779) [23]. Participants were 3316 symptomatic (World Health Organization disease stage $\geq$2 [24]), HIV-infected, ART-naive adults aged $\geq$18 years with $CD4^+$ cell counts of <200 cells/$mm^3$, randomized in Uganda (2 sites with 1 satellite) or Zimbabwe (1 site). A second randomization compared structured treatment interruptions with continuous ART among 813 participants until March 2006; at that time, the comparison was terminated, and participants who were randomized to structured treatment interruptions were changed to continuous ART [25]. Informed consent was obtained from each participant, and the trial was approved by ethics committees in Uganda, Zimbabwe, and the United Kingdom.

All participants initiated treatment with coformulated zidovudine-lamivudine plus a third drug, in line with World Health Organization guidelines [26]. Six hundred participants were randomized to receive either nevirapine or abacavir in a substudy (the nevirapine or abacavir [NORA] substudy). Others received open-label tenofovir DF or nevirapine, based on availability (in 2003, only tenofovir DF was available for logistical reasons) and concomitant medications (e.g., antituberculosis drugs).

***Laboratory and clinical investigations.*** In DART, serum creatinine levels are measured locally (by 3 laboratories, participating in the UK National External Quality Assessment Service) using a modified Jaffe method. No specific calibration was undertaken across centers. Exclusion criteria for DART enrollment include creatinine level of >360 $\mu$mol/L (4.1 mg/dL) and/or urea level >5 times the upper limit of normal. Creatinine levels, full blood cell counts, and other biochemistry analyses (urea, bilirubin, alanine aminotransferase, and aspartate aminotransferase levels) are assessed at baseline, at weeks 4 and 12, and every 12 weeks thereafter. Urinalysis is not routinely performed. In DART, results are returned to the treating clinicians for participants receiving laboratory plus clinical monitoring but not for participants receiving clinical monitoring only, unless tests are requested for a clinical reason or there is grade 4 toxicity. Laboratory tests may also be requested outside of scheduled assessments for clinical reasons for any participant. Clinical examinations, which are performed every 4 weeks, include weight measurement. Causes of death are reviewed by an independent End Point Review Committee.

Body mass index was calculated as weight in kilograms divided by the square of height in meters. Serum creatinine concentration was graded according to toxicity criteria of the National Institute of Allergy and Infectious Diseases [27], as follows: grade 1, >1.0 to 1.5 times the upper limit of normal; grade 2, >1.5 to 3 times the upper limit of normal; grade 3, >3.0 to 6.0 times the upper limit of normal; and grade 4, >6.0 times the upper limit of normal. eGFR was estimated from serum creatinine measurements using the Cockcroft-Gault formula [28], normalized per 1.73 $m^2$ body surface area, and graded according to the National Kidney Foundation [29], as follows: grade 1, 60 to <90 mL/min/1.73 $m^2$; grade 2, 30 to <60 mL/min/1.73 $m^2$; grade 3, 15 to <30 mL/min/1.73 $m^2$; and grade 4, <15 mL/min/1.73 $m^2$.

***Statistical analysis.*** Data for the period from January 2003 through October 2006 are included. Prevalence of impaired renal function was estimated at scheduled visits using the closest value to each visit week within equally spaced windows. The first occurrence of grade 3 or 4 impairment in eGFR after baseline was used to estimate incidence. Because we aimed to investigate effects of ART on eGFR, and because randomization (at week 52 or 72) should ensure that patients with structured treatment interruptions and patients with continuous ART were matched, we excluded measurements after randomization to structured treatment interruptions ($n = 408$) from all analyses and frequency-weighted measurements after randomization to continuous ART ($n = 405$).

Proportions were compared using Fisher's exact test. To explore changes in eGFR after initiation of ART while avoiding regression to the mean caused by measurement errors in baseline values [30], we used random-effects models, splitting time into 3 periods (baseline through 3 weeks, 4–47 weeks, and 48–96 weeks) and assuming a linear trend in each period. We evaluated the effect of demographic characteristics, World Health Organization stage of HIV disease, baseline biochemistry and hematology data and blood pressure, and first ART regimen on eGFR at baseline and on changes in eGFR in each period. The effect of baseline eGFR on subsequent changes in

eGFR was estimated through individual random effects. We analyzed the individual contribution to predicted baseline eGFR for all factors included in the final model by backwards selection, successively deleting the factor with the smallest contribution to adjusted $R^2$ in a linear regression model on baseline eGFR only.

## RESULTS

From January 2003 through October 2004, 3316 participants were randomized in DART (table 1). Analysis included 31,199 creatinine measurements, with eGFR calculable in 31,173. At baseline, 237 participants (7%) had grade 2 decreases and 7 (0.2%) had grade 3 decreases in eGFR. All participants with a grade 3 decrease in eGFR also had a grade 2 elevation in serum creatinine level (269–330 $\mu$mol/L). Overall, 16 participants had baseline serum creatinine measurements of grade 2 (none had measurements that were grade 3 or 4).

***Predictors of baseline eGFR.*** We found several independent predictors of baseline eGFR, including demographic characteristics, severity of HIV disease, comorbidities, and ecological effects (table 1). As expected, baseline eGFR was higher in men ($P < .008$), younger participants ($P < .001$), and those with lower systolic blood pressure ($P = .004$). Further, eGFR was lower in rural centers (Entebbe) than it was in urban or semiurban centers (Kampala, Mulago, and Harare), which likely reflects differences in diet, although it could potentially also reflect a calibration effect between centers. Although baseline eGFR was higher for participants with higher baseline body mass index ($P < .001$) and higher hemoglobin level ($P < .001$), it was lower for those with higher $CD4^+$ cell count ($P = .005$) and those with stage 2 HIV disease (compared with those with stage 3 HIV disease), most likely reflecting survivor and enrollment bias; that is, participants with lower $CD4^+$ cell counts and poorer renal function were less likely to survive to meet enrollment criteria to initiate ART in DART. Even after adjusting for other baseline factors, participants who initiated ART within NORA had slightly lower baseline eGFRs than did those starting tenofovir DF or open-label nevirapine ($P < .001$). Of all predictors, age, baseline body mass index, and center (in order of importance) had the greatest effect on baseline eGFR, each explaining 5.5%–7.5% of the adjusted $R^2$ (22% for the final model).

***Creatinine and eGFR: changes over time.*** The median duration of follow-up was 132 weeks (interquartile range, 96–156 weeks). Because this differed considerably between ART regimens, analysis was restricted to 96 weeks after ART initiation. Mean ($\pm$SD) serum creatinine concentrations increased from 80 $\pm$ 24 $\mu$mol/L at baseline to 85 $\pm$ 21 $\mu$mol/L at week 60 and decreased thereafter (figure 1*A*). During the first 60 weeks, there was a concomitant substantial increase in weight (mean $\pm$ SD, 6.4 $\pm$ 6.6 kg), remaining relatively stable thereafter. The mean ($\pm$SD) eGFR was 94 $\pm$ 32 mL/min/1.73 $m^2$ at baseline and varied between 91 and 95 mL/min/1.73 $m^2$ (median, 89–91 mL/min/1.73 $m^2$) between 4 and 96 weeks.

***Prevalence and incidence of grade 3 or 4 decreased eGFR.*** The prevalence of grade 3 or 4 decreased eGFR was 0.4% at week 4 and 0.15%–0.35% at subsequent visits. The prevalence of grade 3 or 4 increased serum creatinine concentration was less than one-half that of grade 3 or 4 decreased eGFR at each time point (figure 1*B*). Overall, by 96 weeks, 52 participants (1.6%) with normal or mild-to-moderate impaired renal function at baseline had experienced grade 3 (38 participants) or 4 (14 participants) decreased eGFR. Among these participants, the baseline eGFR was normal for 23 participants, grade 1 for 18, and grade 2 for 11. The first grade 3 or 4 episode occurred a median of 14 weeks after initiation of ART (interquartile range, 4–52 weeks; range, 2–96 weeks), with a median duration of 26 days (interquartile range, 5–121 days). The incidence of grade 3 or 4 decreased eGFR by first-line regimen was 1.7% (41 of 2469 participants) for tenofovir DF, 1.6% (4 of 247 participants) for open-label nevirapine, 1.0% (3 of 300 participants) for abacavir in the NORA substudy, and 1.3% (4 of 300 participants) for nevirapine in the NORA substudy ($P = .94$), and it was 1.3% (11 of 847 participants) for all nontenofovir regimens. Of note, some participants had already changed ART before the onset of renal impairment (including 1 participant who was receiving abacavir and 1 participant who was receiving nevirapine substituted by tenofovir DF; 4 participants who were receiving tenofovir DF substituted by abacavir-, nevirapine-, or lopinavir-ritonavir–containing second-line ART). Overall, the rate of exposure to the allocated drug plus 2 nucleoside reverse-transcriptase inhibitors was 95%, 81%, 90%, and 85% for tenofovir DF, open-label nevirapine, abacavir in the NORA substudy, and nevirapine in the NORA substudy, respectively. A total of 13 ART interruptions and/or substitutions because of renal toxicity (any grade) were reported before 96 weeks (8 participants interrupted all ART; 3 stopped, reduced, or substituted tenofovir DF only; 2 stopped, reduced, or substituted other ART only). Although participants developing grade 3 or 4 decreased eGFR were taking various other drugs, including antibiotics, only 1 patient was taking a definitively nephrotoxic drug (gentamicin) that could have contributed to abnormal renal function.

Thirty-one (60%) of 52 participants who developed severe decreases in eGFR did not have severe increases in creatinine concentration (2 had a maximum concentration of grade 1 and 29 had a maximum of grade 2). In 16 of the 21 patients with grade 3 or 4 increases in creatinine concentration, the episode started at the same time as the episode of grade 3 or 4 decreased eGFR; in the remaining 5, the episode started later (within 1 week for 3 patients, 16 weeks later for 1 patient, and 56 weeks later for 1 patient).

**Table 1. Characteristics of 3316 Development of Antiretroviral Therapy (DART) trial participants at initiation of antiretroviral therapy (ART).**

| Variable | DART participants ($n$ = 3316) | Effect on baseline eGFR[a], difference (95% CI) | $P$ |
|---|---|---|---|
| Serum creatinine level | | | |
| Median mg/dL (IQR) | 0.9 (0.8–1.0) | … | |
| ≤1.0 times ULN | 3162 (95) | … | |
| >1.0–1.5 times ULN (grade 1) | 138 (4) | … | |
| >1.5–3.0 times ULN (grade 2) | 16 (0.5) | … | |
| >3.0 times ULN (grade 3 or 4) | 0 | … | |
| eGFR | | | |
| Median mL/min/1.73 m$^2$ (IQR) | 89 (75–106) | … | |
| >90 mL/min/1.73 m$^2$ | 1580 (48) | … | |
| 60 to <90 mL/min/1.73 m$^2$ (grade 1) | 1492 (45) | … | |
| 30 to <60 mL/min/1.73 m$^2$ (grade 2) | 237 (7) | … | |
| <30 mL/min/1.73 m$^2$ (grade 3 or 4) | 7 (0.2) | … | |
| Center | | | |
| Harare, Zimbabwe | 999 (30) | −4.8 (−6.6 to −2.9) | |
| Entebbe, Uganda | 1020 (31) | −12.4 (−14.0 to −10.7) | |
| Kampala, Uganda | 997 (30) | 0 | <.001 |
| Mulago, Uganda[b] | 300 (9) | +2.6 (+0.1 to +5.1) | |
| Sex | | | |
| Male | 1160 (35) | 0 | |
| Female | 2156 (65) | −2.0 (−3.5 to −0.5) | .008 |
| Age, median years (IQR) | 36.8 (32.0–42.2) | −12.4 (−13.3 to −11.6)[c] | <.001 |
| WHO stage of HIV disease | | | |
| 2 | 673 (20) | −1.7 (−2.9 to −0.5) | |
| 3 | 1864 (56) | 0 | .020 |
| 4 | 779 (23) | −0.6 (−1.7 to +0.6) | |
| CD4$^+$ cell count, cells/mm$^3$ | 86 (31–139) | −0.8 (−1.3 to −0.2)[d] | .005 |
| Weight, kg | 56.7 (50.3–63.5) | +3.1 (+2.8 to +3.4)[e] | <.001 |
| BMI | 21.1 (19.1–23.6) | +1.9 (+1.7 to +2.0)[f] | <.001 |
| Blood pressure, mm Hg | | | |
| Systolic | 110 (100–120) | −1.2 (−2.1 to −0.4)[g] | .004 |
| Diastolic | 70 (60–80) | | |
| Hemoglobin level, g/dL | 11.4 (10.3–12.7) | +1.1 (+0.7 to +1.5)[h] | <.001 |
| Neutrophil count, cells × 10$^9$/L | 1.5 (1.1–2.1) | … | NS |
| Initial ART[i] | | | |
| Tenofovir disoproxil fumarate | 2469 (74) | 0 | <.001 |
| Open-label nevirapine | 247 (7) | +1.6 (−1.0 to +4.3) | |
| Abacavir[j] | 300 (9) | −6.0 (−8.3 to −3.7) | |
| Nevirapine[j] | 300 (9) | −5.8 (−8.1 to −3.5) | |

**NOTE.** Data are no. (%) of DART patients, unless otherwise indicated. or median (interquartile range). BMI, body mass index, calculated as weight in kilograms divided by the square of height in meters; eGFR, estimated glomerular filtration rate, determined using the Cockcroft-Gault formula; NS, not significant; ULN, upper limit of normal; WHO, World Health Organization.

[a] From multivariable random-effects model (see table 3 for reference category); difference gives change in eGFR in mL/min/1.73 m$^2$ compared with reference category or per unit increase for the continuous variables.

[b] Mulago is a satellite site of Kampala.

[c] Per 10 years.

[d] Per 50 cells/mm$^3$.

[e] Per 5 kg. Effect and $P$ value if weight is included in the model instead of BMI.

[f] Per 10 kg divided by the square of the height in meters.

[g] Per 20 mm Hg.

[h] Per 1 g/dL.

[i] Administered with zidovudine and lamivudine.

[j] In the NORA substudy, 600 patients were randomized between nevirapine and abacavir; other drug comparisons are nonrandomized.

***Outcomes for participants with severe renal impairment.*** Figure 2 shows the outcome for participants with grade 3 baseline eGFR (7 participants) and participants who developed grade 3 or 4 impairment subsequently (52 participants), including changes in ART. Of the participants with grade 3 baseline impairment, 6 started ART with tenofovir DF, and 1 started ART with nevirapine. Five participants (all taking tenofovir DF) died during follow-up without resolution of impairment (2 of

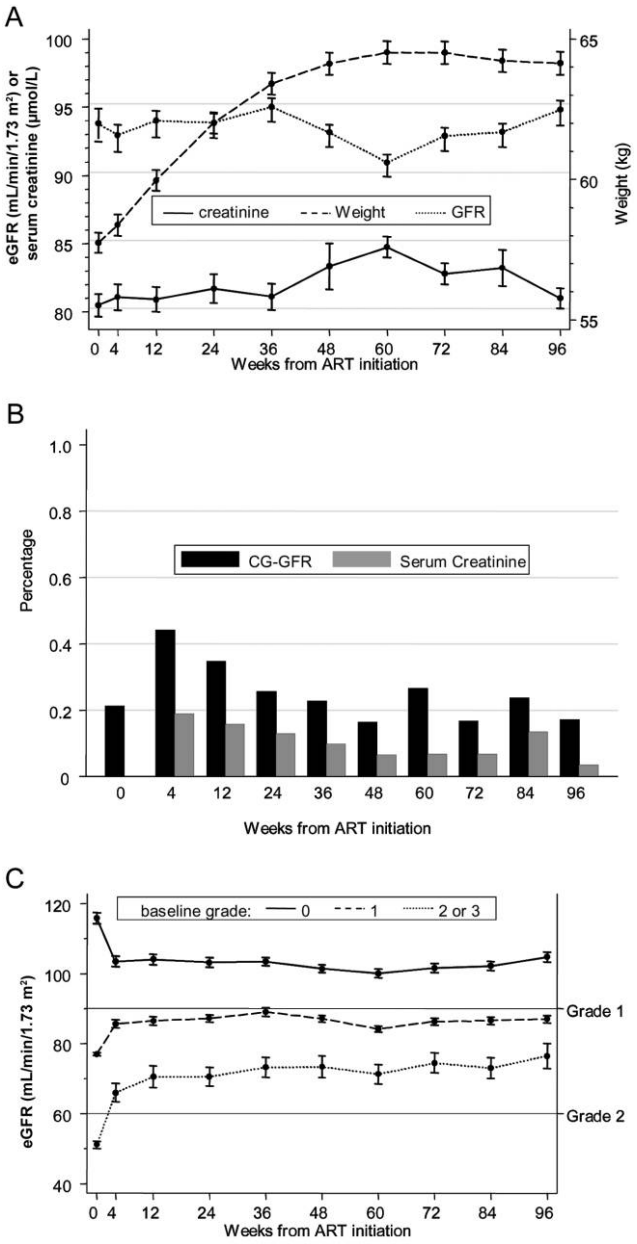


**Figure 1.** *A,* Serum creatinine level, estimated glomerular filtration rate (eGFR), and weight from initiation of antiretroviral therapy (ART) expressed as mean absolute levels (±95% CI). *B,* Prevalence of grade 3 or 4 decreased eGFR as determined by the Cockcroft-Gault formula (CG-GFR), compared with serum creatinine level. *C,* Mean eGFR (±95% CI) over time, by baseline eGFR grade.

chronic renal failure, 1 of glomerulonephritis, and 2 of nonrenal causes). The remaining 2 were alive at 96 weeks, both with grade 2 impairment in eGFR.

Among the 52 participants who developed grade 3 or 4 decreased eGFR, 26 died without resolution of eGFR impairment. However, in only 7 participants was death attributed to renal disease (acute renal failure in 5 and chronic renal failure in 2). One additional participant died from renal failure but did not have eGFR data available; this participant withdrew from the study at week 12 with a normal eGFR and was reported to have died from renal failure and tuberculosis in a non-DART center 83 weeks after randomization.

In summary, 11 (0.3%) of 3316 participants died because of renal disease (table 2); of these deaths, 1 was considered to be definitely or probably drug related (the participant was receiving zidovudine plus tenofovir DF), and 6 were possibly drug related (figure 2). All 11 participants who died had initiated ART with tenofovir DF ($P = .63$, vs. other first-line regimens), and most had contributing comorbidities.

***Baseline predictors of changes in eGFR after initiation of ART.*** Unadjusted analysis of changes in eGFR by baseline eGFR grade suggested improvement in those participants with reduced eGFR and deterioration in those with normal eGFR at baseline, albeit within the normal range (figure 1*C*). Although baseline eGFR was only one measurement, and although high variability could influence these results ("regression to the mean"), results of multivariable random-effects models supported the unadjusted results, suggesting that short-term increases in eGFR were indeed greatest in those with lowest baseline eGFR ($P < .001$ for correlation between baseline random effect and subsequent individual slopes). The changes at weeks 4 and 48 were estimated to be 2.3 and 4.9 mL/min/1.73 $m^2$ greater, respectively, for each 10 mL/min/1.73 $m^2$ lower baseline eGFR.

***First-line regimen.*** After adjustment for different characteristics of those receiving different first-line regimens, the eGFR slightly decreased initially (0–3 weeks) in those participants who were treated with tenofovir DF and abacavir, and it increased in the 2 nevirapine groups ($P < .001$). In the medium term (4–47 weeks), the eGFR increased with abacavir and nevirapine in NORA participants, but there was no change with tenofovir DF or open-label nevirapine. Differences between first-line regimens persisted over the longer term (48–96 weeks). Overall, adjusted means at baseline and changes to weeks 4, 48, and 96 were 97, −2, −2, and −1 mL/min/1.73 $m^2$, respectively, with tenofovir DF; 98, +2, +1, and −3, respectively, with open-label nevirapine; 91, +2, +8, and +16, respectively, with nevirapine in NORA participants; and 91, −2, +6, and +13 mL/min/1.73 $m^2$, respectively, with abacavir in NORA participants ($P < .001$ between regimens in each period).

***Other baseline predictors.*** Sex, age, and baseline hemoglobin level, body mass index, $CD4^+$ cell count, and systolic blood pressure all independently influenced subsequent changes in eGFR (i.e., had significant interactions with time; table 3). Higher baseline body mass index ($P = .02$) and systolic blood pressure ($P = .01$) were both associated with larger decreases in eGFR to 96 weeks, but effects were modest. Other baseline factors had varying impact across the 3 time periods. Over the

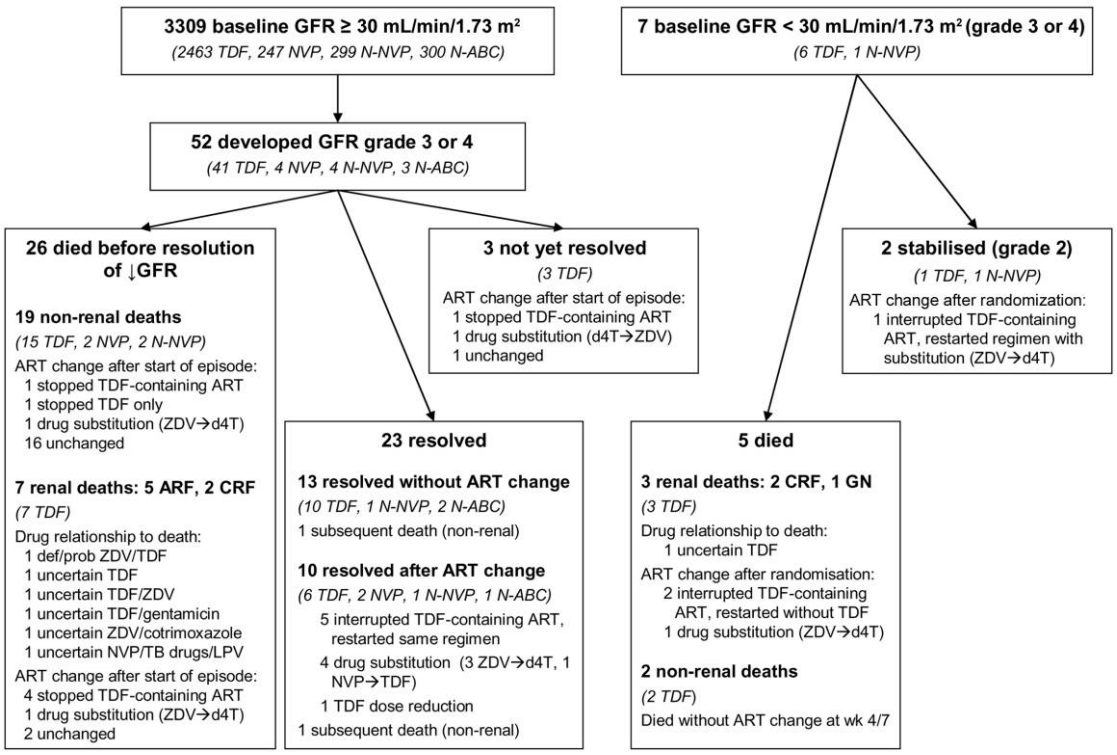


**Figure 2.** Outcomes for participants with grade 3 impairments in estimated glomerular filtration rate (eGFR) at baseline ($n = 7$) and those developing grade 3 or 4 impairment during the trial ($n = 52$). One additional participant died from a renal cause without developing grade 3 or 4 decreased GFR while in the Development of Antiretroviral Therapy trial; this patient withdrew from the study and died in a non-DART hospital. ABC, abacavir; ARF, acute renal failure; ART, antiretroviral therapy; CRF, chronic renal failure; d4T, stavudine; GN, glomerulonephritis; LPV, lopinavir; N, NORA substudy; NVP, open-label nevirapine; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; wk, week; ZDV, zidovudine.

short term, participants with lower baseline hemoglobin level and higher baseline $CD4^+$ cell count had smaller decreases in eGFR; because these participants also had lower baseline values, this may reflect threshold effects. In the medium term, changes in eGFR were better in women, in older participants, and in those with lower baseline hemoglobin levels; again, these factors were associated with lower eGFR at baseline, suggesting normalization over the medium term. No such influences were seen between 48 and 96 weeks.

## DISCUSSION

In this large cohort of previously untreated, HIV-infected, symptomatic African adults with low $CD4^+$ cell counts screened for existing renal impairment by using serum creatinine level, severe impairment in eGFR after initiation of triple-drug ART was infrequent, regardless of regimen. This is noteworthy, because in contrast with studies in resource-rich countries but similar to reports from Uganda and Kenya [31, 32], the majority of participants had slightly reduced baseline eGFRs. Because of the low sensitivity of serum creatinine level for detecting impaired glomerular function, 237 participants (7%) with grade 2 reduced eGFRs were enrolled into DART. On average, eGFRs improved for these participants, whereas rates deteriorated slightly in those with normal eGFRs at baseline, suggesting that ART had beneficial effects on impaired renal function. Furthermore, factors associated with lower baseline eGFRs were generally also associated with greater improvements in eGFR over the medium term, suggesting that renal function can normalize once effective ART is initiated.

Up to 96 weeks, the incidence of severe renal impairment was no different between tenofovir DF–containing and other ART regimens, which is reassuring for the use of tenofovir DF in first-line regimens in Africa. That finding is also consistent with results of other clinical trials of tenofovir DF in which participants had fewer risk factors for renal disease than in DART. Nevertheless, because allocation to tenofovir DF versus other regimens was not randomized, and because the incidence of severe renal impairment was low, we cannot exclude the possibility of a small excess risk in participants receiving tenofovir DF. Overall, 11 (0.3%) participants died with renal disease contributing to their death; however, these 11 deaths represented only 5% of all deaths to 96 weeks. Furthermore, the majority of participants with a renal cause of death had other comorbidities, making it likely—even though difficult to

**Table 2. Deaths in which renal impairment was considered to have contributed.**

| Patient | Death, study week | Renal illness | Nonrenal contributing conditions | Death related to HIV infection or drug?[a] | Which drug?[a] | ART history | Prior renal SAE | Time from SAE to death, no. of weeks | Other SAE(s) (grade) | Baseline eGFR grade | Ever new grade 3 or 4 eGFR? | Grade 3 or 4 episode[b] resolved? | Ever new grade 3 or 4 serum creatinine level? |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A | 91 | CRF | … | Uncertain | TDF | ZDV/3TC/TDF, ZDV/3TC/EFV | Yes | 79 | Elevated creatinine level (4), CHF (5) | 3 | No | No | Yes |
| B | 23 | GN | … | Unlikely | … | ZDV/3TC/TDF, d4T/3TC/NVP | Yes | 18 | Neutropenia (4) | 3 | No | No | Yes |
| C | 46 | CRF | Type I diabetes, hypertension | Unlikely | … | ZDV/3TC/TDF, d4T/3TC/TDF | No | | Vomiting (3) | 3 | No | No | Yes |
| D | 18 | ARF | *Escherichia coli* sepsis, neutropenia | Uncertain | ZDV, cotrimoxazole | ZDV/3TC/TDF, d4T/3TC/TDF | No | | Anemia (4) | 2 | Yes | No | Yes |
| E | 67 | ARF | Epilepsy, fits, convulsions | Uncertain | TDF, gentamicin | ZDV/3TC/TDF, d4T/3TC/TDF | No | | Neutropenia (3) | 1 | Yes | No | No |
| F | 9 | CRF | Clinical anemia | Uncertain | TDF, ZDV | ZDV/3TC/TDF, d4T/3TC/TDF | No | | Anemia (3) | 1 | Yes | No | Yes |
| G | 99 | ARF | Hepatic failure, cryptococcal meningitis | Uncertain | NVP, TB drugs, LPV | ZDV/3TC/TDF, NVP/LPV | No | | Overdose (1) | 1 | Yes | No | Yes |
| H | 29 | ARF | Presumed septicemia or bacteremia | Not known | … | ZDV/3TC/TDF | No | | … | 1 | Yes | No | Yes |
| I | 7 | ARF | Neutropenia, presumed septicemia or bacteremia | Drug | ZDV, TDF | ZDV/3TC/TDF | Yes | 1 | Anemia (5), neutropenia (5) | 0 | Yes | No | Yes |
| J | 94 | CRF | Cryptococcal meningitis | Uncertain | TDF | ZDV/3TC/TDF | Yes | 4 | Overdose (1), neutropenia (4) | 0 | Yes | No | Yes |
| K[c] | 83 | ARF | Pulmonary tuberculosis | HIV infection | … | ZDV/3TC/TDF | Yes | 9 | … | 0 | Not known | Not known | Not known |

**NOTE.** Patients are sorted by baseline estimated glomerular filtration rate (eGFR) grade and classification of cause of death. ARF, acute renal failure; CHF, congestive heart failure; CRF, chronic renal failure; d4T, stavudine; EFV, efavirenz; eGFR, estimated glomerular filtration rate; GN, glomerulonephritis; LPV, lopinavir-ritonavir; NVP, nevirapine; SAE, serious adverse event; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; ZDV, zidovudine; 3TC, lamivudine.

[a] As determined by End Point Review Committee.

[b] Baseline or new grade 3 or 4 episode.

[c] Withdrew from Development of Antiretroviral Therapy trial at week 12; eGFR at time of renal SAE or death was not available.

**Table 3. Predictors of change in estimated glomerular filtration rate (eGFR).**

| Variable | Change in eGFR, mL/min/1.73 m$^2$ | | | | | | *P* for heterogeneity across periods[a] | Global *P* for time[b] |
|---|---|---|---|---|---|---|---|---|
| | Baseline through week 3 | *P* | Week 4–47 | *P* | Week 48–96 | *P* | | |
| Initial ART[c] | | | | | | | | |
| Tenofovir disoproxil fumarate | −1.9 (−3.0 to −0.7) | .002 | 0.0 (−1.6 to +1.5) | .96 | +0.8 (−0.7 to +2.3) | .33 | | |
| Open-label nevirapine | +2.2 (−0.3 to +4.7) | .08 | −1.4 (−4.7 to +1.9) | .41 | −3.8 (−7.0 to −0.5) | .023 | <.001 | |
| Abacavir[d] | −1.6 (−3.6 to +0.3) | .10 | +7.6 (+5.0 to +10.1) | <.001 | +6.6 (+4.1 to +9.1) | <.001 | | <.001 |
| Nevirapine[d] | +2.0 (+0.0 to +3.9) | .046 | +5.5 (+2.9 to +8.1) | <.001 | +8.3 (+5.7 to +11.0) | <.001 | | |
| Overall difference | | <.001 | | <.001 | | <.001 | | |
| Sex, male vs. female | +0.6 (−0.6 to +1.8) | .35 | −3.9 (−5.6 to −2.3) | <.001 | +0.9 (−0.7 to +2.5) | .26 | .002 | <.001 |
| Age, per 10 years | −0.6 (−1.3 to +0.1) | .11 | +1.2 (+0.3 to +2.2) | .01 | −0.7 (−1.6 to +0.3) | .14 | .04 | .07 |
| WHO stage of HIV infection | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | **.28** | **.07** |
| 4 | | | | | | | | |
| CD4$^+$ cell count, per 50 cells/mm$^3$ | +0.6 (+0.1 to +1.1) | .01 | −0.4 (−1.0 to +0.2) | .24 | 0.0 (−0.6 to +0.6) | .96 | .03 | .07 |
| Body mass index, per 10 kg divided by the square of the height in meters | −0.1 (−0.2 to −0.0) | .02 | −1.1 (−2.1 to −0.2) | .02 | −1.2 (−2.2 to −0.2) | .02 | **.34** | .02 |
| Hemoglobin level, per 1 g/dL | −0.4 (−0.7 to −0.0) | .03 | −1.0 (−1.4 to −0.5) | <.001 | 0.0 (−0.4 to +0.4) | .95 | <.001 | <.001 |
| Neutrophil count, per 10$^3$ cells/mm$^3$ | | | | | | | **.15** | **.15** |
| Blood pressure, per 20 mm Hg | | | | | | | | |
| Systolic | −0.1 (−0.1 to −0.0) | .01 | −0.6 (−1.1 to −0.1) | .01 | −0.7 (−1.2 to −0.1) | .01 | **.53** | .01 |
| Diastolic | | | | | | | **.56** | **.99** |

**NOTE.** All models are multivariable and also adjust for center and the effects of baseline factors on eGFR, as in table 1; results are similar to those obtained with univariable models (data not shown). Reference categories and levels were female sex, WHO stage 3, and approximate mean of continuous factors (age, 40 years; CD4$^+$ cell count, 90 cells/mm$^3$; body mass index calculated as weight in kilograms divided by the square of height in meters, 22.5; hemoglobin level, 11.5 g/dL; and systolic blood pressure, 110 mm Hg). *P* values in boldface type show additional effect of nonsignificant predictors when added into multivariable model. WHO, World Health Organization.

[a] Indicates whether prediction of change in eGFR varied significantly between the 3 periods.

[b] Indicates whether there was an significant influence on change in eGFR over the entire follow-up period (baseline to week 96).

[c] Administered with zidovudine and lamivudine.

[d] Patients were participants in the NORA substudy.

define for each individual—that renal impairment was part of a systemic illness. In a recent study from the United States that assessed causes of acute renal failure in HIV-infected patients, 58 (52%) of 111 events were associated with infections, and acute renal failure was more common among those with advanced HIV disease, hepatitis C virus coinfection, and liver disease [33]; 36 (32%) had acute renal failure associated with drugs, mostly antibiotics. Antiretrovirals were associated with only 9 events; 2 of these were associated with tenofovir DF, although the number treated with this drug is unknown. Sick patients in our study were taking various other drugs during or before the onset of abnormal renal function, including cephalosporins, ciprofloxacin, cotrimoxazole, erythromycin, metronidazole, and antituberculosis drugs. One patient took gentamicin, which was the only drug considered to be related to development of abnormal renal dysfunction.

Although we did not find an excess risk of severe renal impairment in participants treated with tenofovir DF, greater decreases in eGFR from baseline were observed in these participants, compared with participants taking other first-line regimens. This is similar to observational studies from resource-rich countries, although these participants had more extensive ART experience, higher baseline eGFRs and CD4$^+$ cell counts, and shorter follow-up than did participants in DART [14–18]. However, in all studies, including DART, the differences between regimens were small (albeit statistically significant) and were likely to be of marginal clinical relevance, at least over the medium term.

Our study is limited, because comparisons are based on uncalibrated local creatinine measurements used for clinical management, and no renal parameters other than serum creatinine level were measured, making it impossible to distinguish between kidney disease of different origin or to look systematically for tubular impairment [4–6]. Creatinine assessment without analysis of proteinuria underestimates incidence of chronic renal failure, and renal tubular dysfunction can occur without eGFR impairment and may lead to bone abnormalities; as yet, there are no studies in Africa. Furthermore, eGFR was not directly measured but was estimated using the Cockcroft-Gault formula, and neither this nor any other formula has been validated in HIV-infected patients. However, creatinine-based GFR estimation is recommended by US guidelines generally and for HIV-infected patients [29, 34], being preferred to serum creatinine level alone, which is accepted to have a much lower sensitivity for detecting renal impairment [35]. Recent guidelines recommend the formula from the Modification of Diet

in Renal Disease study [29, 34, 36, 37] in addition to or instead of the Cockcroft-Gault formula. However, in contrast to the Cockcroft-Gault formula, the Modification of Diet in Renal Disease formula does not contain an explicit factor for weight. Instead, weight is implicitly adjusted for in the Modification of Diet in Renal Disease formula constants. In resource-limited settings where patients have severe HIV disease, this has the considerable disadvantage of ignoring substantial weight gain after ART initiation, with increases in muscle mass likely to be responsible for at least some of the increase in serum creatinine level. It is worth noting that, in the DART study, tenofovir DF was not coadministered with boosted protease inhibitors. Certain protease inhibitors increase plasma levels of tenofovir DF by 30% [38], which might have more impact on renal safety in adults in Africa than on adults in resource-rich countries, although this awaits more data.

In conclusion, despite a relatively high baseline prevalence of mild-to-moderate renal dysfunction in African adults with low $CD4^+$ cell counts, severe eGFR impairment after ART initiation was infrequent with all regimens, similar to findings in resource-rich countries. Furthermore, participants with moderate impairment at baseline showed improvements after starting ART, probably reflecting the fact that these patients had HIV-related renal disease, indicating the need for ART. Differences between regimens in changes in eGFR were statistically significant but small and likely to be of marginal clinical relevance. Follow-up of DART patients will continue through 2009, with routine laboratory test results being returned only to clinicians treating patients randomized to clinical monitoring only and with blinded data reviewed by the Data Monitoring Committee every 9–12 months. We will, thus, be able to assess the safety of tenofovir DF without laboratory monitoring, which will be important if tenofovir DF becomes more widely used as part of first-line ART, as some African countries are contemplating. In view of the high prevalence of baseline impairment in such settings, eGFR determination using the Cockcroft-Gault formula, rather than creatinine level, alone should be used to assess suitability for initiating tenofovir DF when biochemistry results are available; patients with grade 3 or 4 impairment should begin treatment with other antiretrovirals, whereas our data suggest that those with mild or moderate impairment may do well with a regimen of tenofovir DF, at least over the short to medium term. If monitoring is being performed, then eGFR should be used to adjust the dose of tenofovir DF or to indicate drug substitution [39]. In general, our study demonstrates that, when creatinine measurements are being performed, they are insufficient to monitor ART, and eGFR should always be considered. Because most patients with deaths due to renal impairment had other intercurrent diseases, general risk factors for renal impairment (e.g. sepsis or septicemia, diarrhea, malaria, hypertension, diabetes, liver failure or hepatitis, and nephrotoxic comedication) should be carefully monitored in patients receiving tenofovir DF. It will also be important to continue to investigate possible longer-term drug-related nephrotoxicity and to examine other aspects of renal function.

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