

Glomerular dysfunction and associated risk factors throughout four years following initiation of ART in adults with HIV infection in Africa in the DART trial

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Background

HIV-infection is associated with several types of renal disease. Causes are multifactorial and include HIV itself, coinfections, comorbidities and their treatments.

Recent data from sub-Saharan Africa suggest that HIV-related kidney disease/impairment is very common in ART-naïve populations. However, in resource-limited settings longitudinal data on renal function and the long-term impact of ART on renal disease are rare, and the long-term nephrotoxicity of tenofovir has not been studied.

Objective: to estimate prevalence and incidence of GFR reduction, renal serious adverse events (SAEs) and mortality where renal impairment was a contributing factor, together with associated risk factors, through 4-5 years after initiation of ART.

DART trial design & Methods

DART was a randomised trial of management strategies in 3316 symptomatic ART-naïve adults with CD4<200 cells/mm³ initiating triple drug ART in 3 centres in Uganda and Zimbabwe.

- Participants were randomised to Laboratory and Clinical Monitoring (LCM) or Clinically Driven Monitoring (CDM)
- All participants initiated co-formulated zidovudine/lamivudine plus a third drug: 600 participants were randomised between abacavir and nevirapine in a substudy, others received open-label (non-randomized) tenofovir DF or nevirapine, based on availability at that time and other concomitant medications (e.g. anti-TB).

Exclusion criteria for DART enrolment included creatinine >360 µmol/l (4.1 mg/dl) and/or urea >5xULN. GFR was not automatically calculated at screening.

Creatinine, full blood count and other biochemistry (urea, bilirubin, ALT/AST) were assessed in LCM and CDM patients at baseline, weeks 4 and 12, then every 12 weeks, body weight every 4 weeks. Urinalysis was not routinely performed. Serum creatinine was measured locally using a modified Jaffe method. No specific calibration was undertaken across centres.

In DART, results were returned to the treating clinicians for LCM but not CDM participants unless tests were requested for a clinical reason or there was grade 4 toxicity. Laboratory tests could also be requested outside scheduled assessments for clinical reasons in any participant.

Causes of death and SAEs were reviewed by an independent Review Committee. SAEs considered for this analysis included renal events as well as bone fractures which theoretically could have been a long-term consequence of renal damage.

GFR was estimated from serum creatinine using the Cockcroft-Gault formula, normalised per 1.73m² body surface area (using the DuBois formula), and classified according to the National Kidney Foundation (NKF) and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT):

- GFR decrease (single value):** mild: 60-90, moderate: 30-60, severe: 15-30, kidney failure: <15 ml/min/1.73m²
- Chronic kidney disease (CKD):** GFR <60 ml/min/1.73m² present on at least 2 occasions for >3 months (>80 days used in this analysis due to 12 weekly DART visit schedule) or confirmed 25% decline if <60 ml/min/1.73m² at baseline (the latter from INSIGHT). An alternative definition of CKD used a confirmed 25% decline from baseline for all participants.

Cumulative incidence was calculated considering deaths from non-renal causes as competing risks. Time to event analyses used Kaplan-Meier and log-rank tests.

No adjustments to p values were made for multiple comparisons.

Baseline characteristics & Follow-up

Baseline Characteristics	Description ^a
Serum Creatinine (mg/dl)	0.9 (0.8-1.0)
≤ 1.0 x ULN	3162 (95%)
> 1.0-1.5 x ULN (grade 1)	138 (4%)
> 1.5-3.0 x ULN (grade 2)	16 (0.5%)
> 3.0 x ULN (grade 3/4)	0
eGFR (ml/min/1.73m ²) ^c	89 (75-106)
> 90	1580 (48%)
60 to <90 (grade 1)	1492 (45%)
<60 to 30 (grade 2)	237 (7%)
<30 (grade 3/4)	7 (0.2%)
Centre:	
Harare, Zimbabwe	999 (30%)
Entebbe, Uganda	1020 (31%)
Kampala, Uganda	997 (30%)
IDI, Uganda ^b	300 (9%)
Sex	
Male	1160 (35%)
Female	2156 (65%)
Age (years)	36.8 (32.0-42.2)
HIV WHO stage:	
2	673 (20%)
3	1864 (56%)
4	779 (23%)
CD4 (cells/mm ³)	86 (51-139)
Weight (kg)	56 (30-63.5)
BMI (kg/m ²)	21.1 (19.1-23.6)
Haemoglobin (g/dl)	11.4 (10.3-12.7)
Initiated ART with zidovudine + lamivudine + tenofovir DF	2469 (74%)
nevirapine	547 (17%)
abacavir	300 (9%)

Notes: ULN: upper limit of normal; ^a Values are number (%) or median (interquartile range); ^b IDI is a satellite site to the Kampala centre

Analysis included data from all 3316 DART participants with right-censoring after 216 weeks (4.1 years) from randomisation (duration of follow-up was similar for all baseline regimens until this time point)

- 12,806 years follow-up between January 2003 and December 2008 (censoring at 216 weeks)
- 353 deaths (censoring at 216 weeks)

Incidence of decreased GFR

	Ever CKD (confirmed <60 ml/min/1.73m ² or 25% drop if <60 ml/min/1.73m ² at baseline)		Total
	no	yes	
Ever severe GFR decrease (<15 ml/min/1.73m ²)	3079	144	3223 (97%)
	75	18	93 (3%)
Total	3154 (95%)	162 (5%)	3316

- 60/93 of patients with severe GFR decrease had only one value <30 ml/min/1.73m². All of the 75 patients who had severe GFR decrease but not CKD had decreased GFR for less than 80 days: 38 died before resolution, 6 died after resolution, and 31 resolved and did not die before 216 weeks.
- A similar lack of association was observed between severe GFR decrease and CKD defined as <60 ml/min/1.73m² and a 25% decline from baseline for all.

Cumulative incidence of renal outcomes and fractures

	Median (IQR) GFR at ART initiation	Mean adjusted GFR change (95% CI) to week 216 ¹	Death with renal contribution	Severe GFR decrease (at least one value < 30 ml/min/1.73m ²)	CKD (confirmed <60 ml/min/1.73m ² or 25% drop if <60 ml/min/1.73m ² at baseline)	CKD (confirmed 25% decrease from baseline for all participants) ²	Renal SAE ³	Fractures SAE
Overall	89 (75-106)	+3 (+2, +4)	n=16 0.5% (0.3-0.8%)	n=93 2.9% (2.3-3.5%)	n=162 5.0% (4.3-5.8%)	n=94 2.9% (2.4-3.5%)	n=20 0.6% (0.4-1.0%)	n=30 0.9% (0.7-1.3%)
By first-line ART:								
tenofovir DF	90 (75-107)	+2 (+1,+3)	0.7% (0.4-1.1%)	3.1% (2.5-3.9%)	5.9% (5.0-6.9%)	3.4% (2.7-4.2%)	0.8% (0.5-1.2%)	1.0% (0.7-1.5%)
nevirapine	89 (76-103)	+7 (+5,+9)	0	1.9% (1.0-3.4%)	1.1% (0.5-2.5%)	2.1% (0.5-2.5%)	0.2% (0-1.3%)	1.0% (0.4-2.3%)
abacavir	80 (70-98)	+6 (+3,+9) p=0.001	p=0.07	2.4% (1.2-5.0%)	3.1% (1.6-5.8%) p=0.0004	2.1% (0.9-5.4%) p=0.01	0	0
By tenofovir DF 1: never taken TDF on TDF now or previously			0 0.6% (0.4-1.0%) p=0.04	2.0% (1.3-3.3%) 3.1% (2.5-3.8%) p=0.13	2.0% (1.2-3.4%) 5.8% (4.9-6.7%) p=0.0001	1.1% (0.5-2.2%) 3.4% (2.7-4.1%) p=0.002	0 0.8% (0.5-1.2%) p=0.02	0.6% (0.2-1.7%) 1.0% (0.7-1.5%) p=0.35
By randomisation:								
LCM	88 (75-104)	+4 (+3,+5)	0.3% (0.1-0.7%)	2.3% (1.7-3.1%)	5.0% (4.0-6.2%)	2.7% (2.0-3.6%)	0.7% (0.4-1.2%)	0.8% (0.5-1.4%)
CDM	90 (75-107)	+3 (+1,+4) p=0.14	0.7% (0.4-1.2%) p=0.13	3.4% (2.4-4.5%) p=0.05	5.0% (4.0-6.2%) p=0.99	3.1% (2.4-3.1%) p=0.54	0.6% (0.3-1.1%) p=0.65	1.1% (0.7-1.7%) p=0.47

¹ Linear regression adjusted for baseline factors (monitoring strategy, third ART drug, sex, age, BMI, CD4, WHO stage, haemoglobin, systolic blood pressure, centre) and pregnancy; ² Kityo, F Sali, D Tumukunde, T Otim, H Hakim, J Akoo, H Kyomugisha, A Byamukama, J Sabiti, J Komugyeno, P Wavamunno, S Makibi, A Orach, R Byaruhanga, O Labeja, P Katundu, S Tumuge, P Awio, A Namazzi, GT Baleingya, H Katabira, D Abaine, J Tukumuhaba, W Anywar, W Ojiambo, E Awengwe S Murungi, W Haguma, S Atwine, J Kigozi, Infectious Diseases Institute (formerly the Academic Alliance) Makerere University, Mulago, Uganda; E Katabira, A Ronald, A Kambugu, F Lutwama, A Nanfuka, J Walusimbi, R Nalumenya, R Nalumenya, R Kulumu, I Namata, L Nyachwo, A Florence, A Kusima, E Lutwama, F Oketta, B Buluma, R Waita, H Ojiambo, F Sadiq, J Wanyama, P Nabongo, The AIDS Support Committee (TASO), Uganda; R Ochi, D Mulhwezi, Imperial College, London, UK; C Gilks, K Boockvar, D Wingon, J Bohannon, MRC Clinical Trials Unit, London, UK; J Darbyshire, M Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Bauchenberger, S Sheehan, L Peto, K Taylor, M Speyer, A Ferrer, B Naidoo, D Penn, R Goodall, DART Virology Group; P Kaleebu (Co-Chair), D Pillay (Co-Chair), V Robertson, D Virelli, S Tumuge, M Chiara, P Katundu, C Ndemba, F Lyagaba, D Durr, R Goodall, A McCormick, DART Health Economics Group; A Medina Lara (Chair), S Foster, J Amurwon, B Nyenzi Wakholi, J Kigozi, L Muchababu, M Musazuki, Independent DART Trial Monitors; R Katundu, C Mufuka-Kapuya, D Trim, S Research Committee; I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Basett, A Chogo Wapakhabulo, J Darbyshire, B Gazzardi, C Gilks, H Grosskurth, J Hakim, A Latif, C Mapuchere, O Mugurungu, P Mugenyi, Observers: C Burke, S Jones, C Newland, S Rahim, J Rooney, M Smith, W Snowden, J-M Steens, Data and Safety Monitoring Committee: A Breckenridge (Chair), A McLaren (Chair-deceased), C Hill, J Materoga, A Pozniak, D Serwadda, Endpoint Review Committee: T Peto (Chair), A Fairhead, M Brook, E Katabira. Funding: DART is funded by the UK Medical Research Council, the UK Department for International Development (DFID), and the Rockefeller Foundation. GlaxoSmithKline, Gilead and Boehringer-Ingelheim donated first-line drugs for DART.

Key points

Incidence of severe GFR decrease and CKD was low in all groups.

- Severe GFR decrease occurred more often in the CDM than in the LCM arm, but there was no difference in the incidence of CKD.
- Treatment with tenofovir DF was associated with a higher incidence of CKD. This was confirmed in Cox regression models adjusting for baseline factors such as GFR, age, body mass index, or blood pressure (not shown). However, there was no difference in the incidence of severe GFR decrease.
- Of note, dose reduction of tenofovir DF occurred rarely (NB in CDM, creatinine results were only returned if requested for clinical reasons or grade 4).
- Only 2/16 deaths with renal contribution were judged definitely/probably related to ART (tenofovir DF in both, one also zidovudine). 3 other deaths already had severely decreased GFR at baseline (all had tenofovir DF first-line).

Conclusions

- DART GFR impairment was infrequent on all regimens, chronic kidney disease was only slightly more common.
- The Clinically Driven Monitoring strategy was associated with the occurrence of severe GFR decrease but not with chronic kidney disease.
 - This may be due to more acute HIV-related events in CDM.
- Tenofovir DF was associated with minor impairments in kidney function as reported previously, with little clinical significance.
- Renal disease contributed to death in only a few patients and was generally related to intercurrent disease.
- Limitation of our analysis: tubular function was not examined in DART.

GENERAL ISSUES WITH THE RENAL OUTCOMES USED IN THIS ANALYSIS:

- Severe GFR decreases are likely to predominantly reflect acute intercurrent illnesses rather than ongoing toxicity.
- The INSIGHT definition of CKD requires a 25% decrease only if the baseline GFR was <60 ml/min/1.73m². In a population with a high proportion of participants with 60-90 ml/min/1.73m² at baseline (such as in DART), a number of events likely result from small decreases to just below the threshold - these probably have little clinical relevance.
- A definition of CKD based on a confirmed 25% decline in everyone assumes that the baseline GFR is known relatively precisely. In DART there was only a single creatinine measurement at baseline, and therefore regression to the mean may have a large impact on outcomes.
- SAEs have been reviewed but the Reviewers relied on physician reporting. As ART was open-label, there might have been a bias towards reporting more renal events on tenofovir DF or relationships to this drug (also for causes of death).
- Deaths with renal impairment were rare, so power was low.

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