Glomerular Dysfunction and associated risk factors following initiation of ART in Africa: A subanalysis in the DART Trial

AJC Reid

on behalf of the **DART** Trial Team

Impaired Renal Function in HIV-infected patients

1. HIV infection itself (eg HIVAN)
   - probably improved by HAART
2. Acute Renal Failure
   - eg septicaemia, acute diarrhoea
3. Drug related renal impairment
   - ARV and non-ARV drugs
4. Non-HIV causes of renal impairment
   - hypertension, diabetes, malaria, bilharzia, hepatitis
5. Complicated combinations of the above

DART trial design: main randomisation

3316 previously untreated HIV-infected patients in Uganda and Zimbabwe: stage WHO 2, 3 or 4 and CD4<200 cells/mm^3

randomise to initiate triple drug ART with

Clinical and Laboratory Monitoring (12 weekly biochemistry, FBC & CD4; no virology)

Clinical Monitoring Only (biochemistry and/or FBC if clinically indicated)

- First-line ART was ZDV+3TC (combivir) plus:
  - Tenofovir DF (TDF) 2469 (74%)
  - Abacavir (ABC) 300 (9%) *(all randomised in NORA substudy)*
  - Nevirapine (NVP) 547 (16%) *(300 randomised in NORA substudy)*
- Tenofovir DF is a relatively new NtRTI with most data on renal safety coming from well-resourced settings

Methods & Objectives

Glomerular filtration rate (GFR) gives best overall measure of kidney function

Objectives

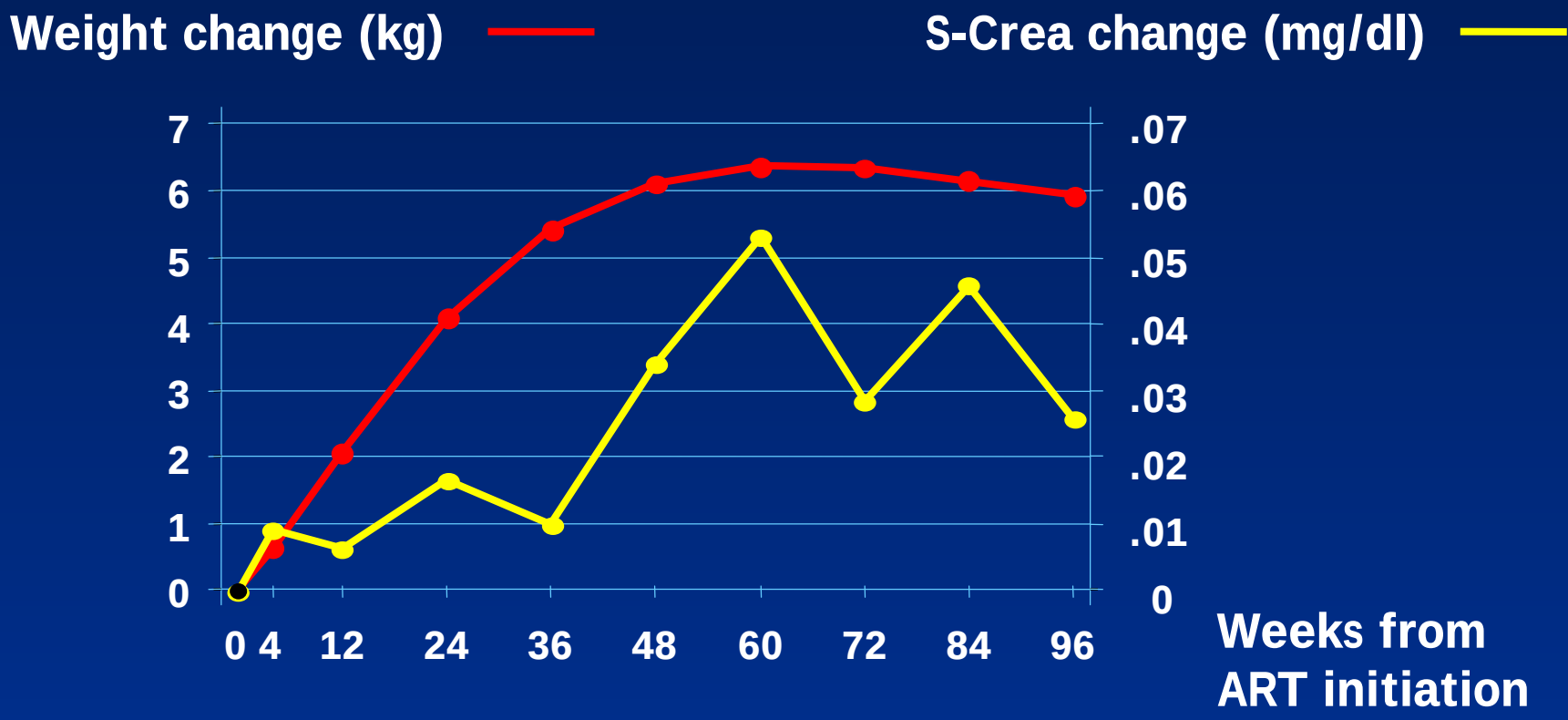
- To estimate prevalence and incidence of severe GFR reduction (grade 3 or 4; <30 ml/min/1.73m^2) up to week 96 using standard creatinine-based **Cockcroft-Gault** formula, adjusted for BSA
- To describe GFR changes over time & predictors
  - time split into 3 intervals: 0-4, 4-48, 48-96 weeks
  - demographics, regimen, baseline weight, CD4, haemoglobin
  - using random effects models

Baseline characteristics

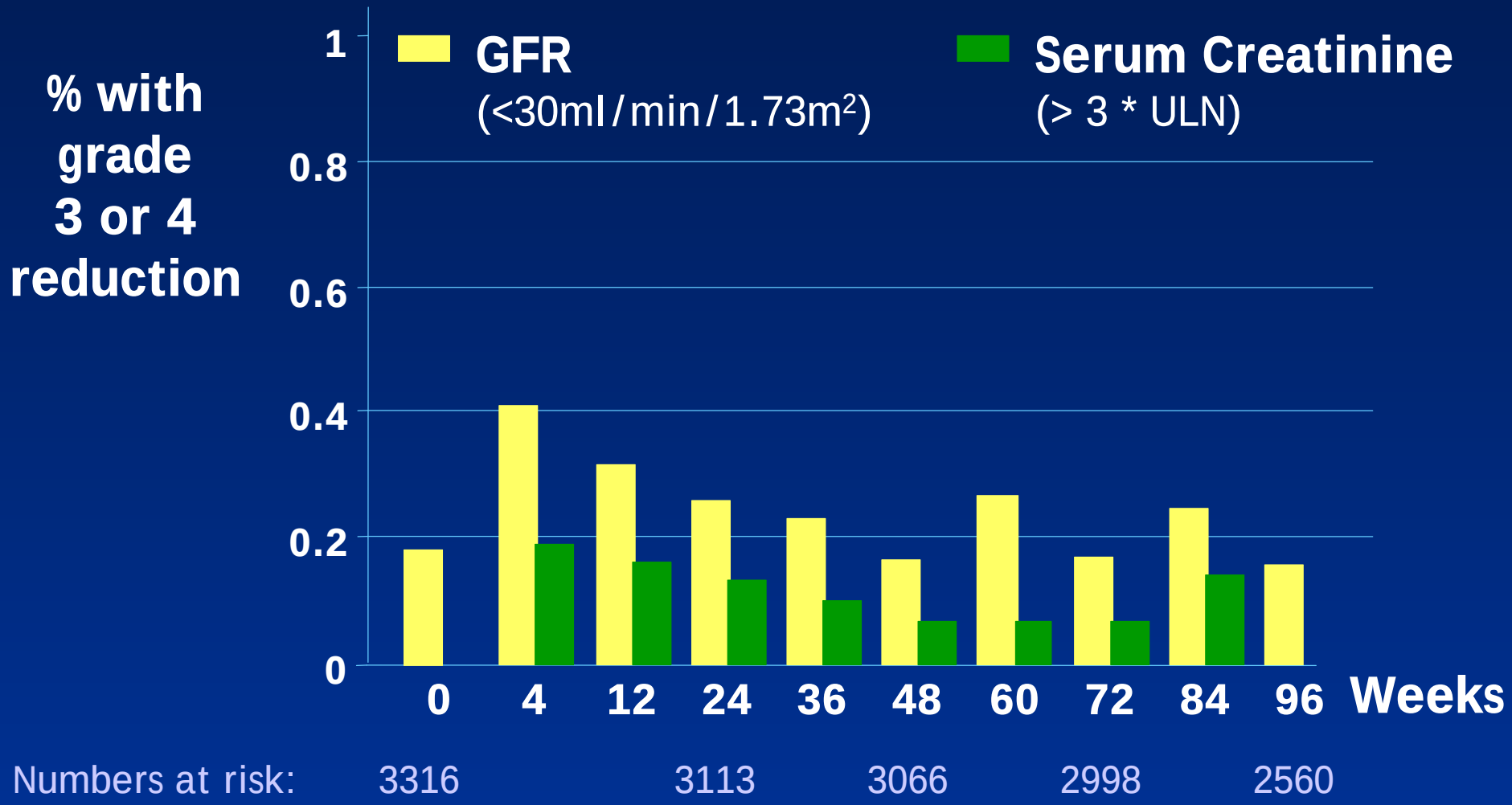
3316 participants in Uganda & Zimbabwe

- Sex 65% women
- Median age 37 years (IQR: 32-42)
- Median CD4 86 cells/mm^3 (IQR: 31-139)
- Median weight 57 kg (IQR: 50-64)
- WHO stage 56% WHO 3, 23% WHO 4
- Median GFR 89 ml/min/1.73m^2 (IQR: 75-106)
- Median follow-up 120 weeks
- Analysis to 96 weeks (~90% ≥ 72 weeks)

Weight and serum creatinine change after baseline



Prevalence of impaired GFR and raised Serum Creatinine (grade 3 or 4)

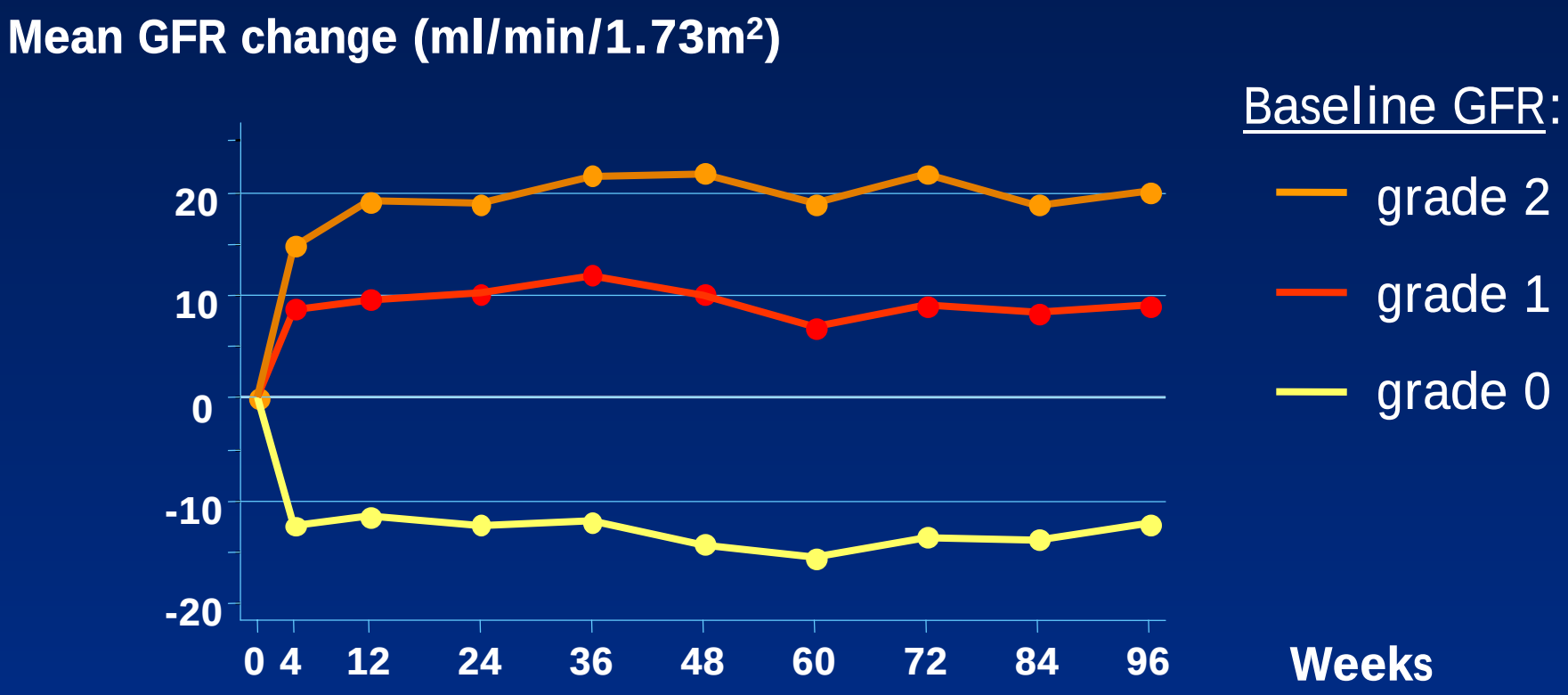


Incidence of severe GFR reduction

	up to 72 weeks		up to 96 weeks *	
NVP	3 / 247	1.2%	3 / 247	1.2%
NVP-NORA	4 / 299	1.3%	4 / 299	1.3%
ABC-NORA	3 / 300	1.0%	3 / 300	1.0%
TDF	33 / 2468	1.3%	40 / 2468	1.6%
Overall	43 / 3314	1.3%	50 / 3314	1.5%
	p = 0.98		p = 0.93	

* Proportion of participants with complete follow-up to 96 weeks larger in those initiating ART with TDF or NVP (~85%) than NORA (~43%)

GFR over time by baseline GFR
- unadjusted analysis -



- Patients with mild renal impairment at baseline showed greater improvements than those without impairment
  - changes were within the normal range in those without impairment

Predictors of GFR over time
- multivariable analysis -

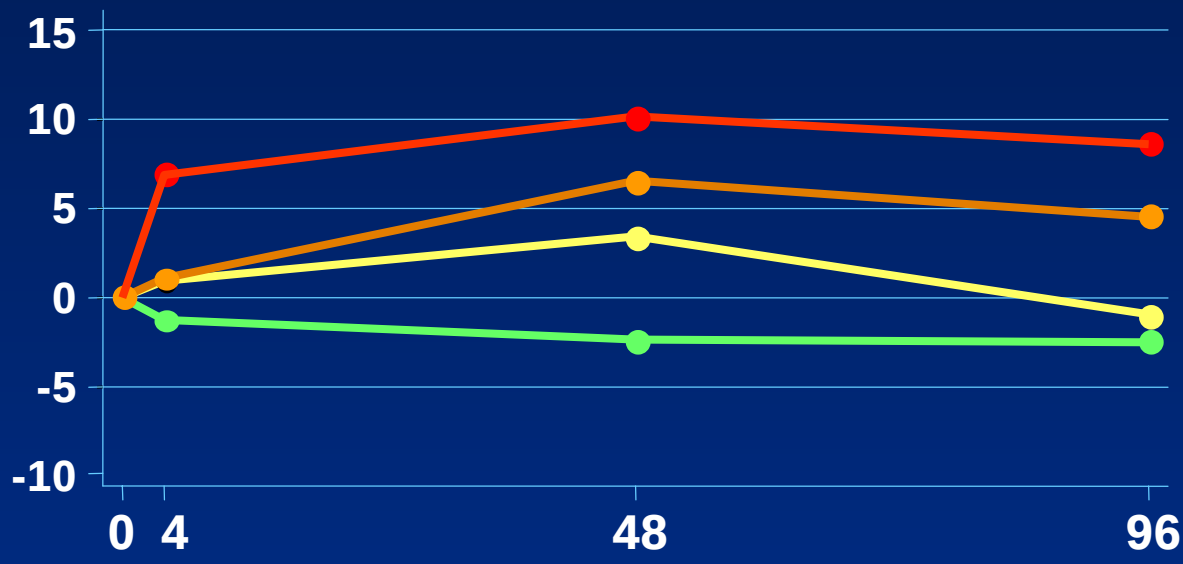
Factors independently modifying GFR changes over time*	p value	Better development in …
Sex	0.0006	women
Baseline haemoglobin	<0.0001	those with low values
Baseline weight	0.0027	those with low values
Baseline GFR	<0.0001	those with low values
Regimen	<0.0001	

– adjusted for effects of centre, age, baseline CD4 and WHO stage on baseline GFR

* Random effects model: significant interaction with time

Predicted GFR over time by regimen
- multivariable analysis -

Mean GFR change (ml/min/1.73m²)



Regimen:

- NVP-NORA
- ABC-NORA
- NVP
- TDF

NVP-N	+6.8	+10.1	+8.8
ABC-N	+1.2	+6.6	+4.8
NVP	+1.1	+3.4	-0.9
TDF	-1.2	-2.5	-2.2

GFR change from baseline

(global p value <0.0001)

Renal disease contributing to cause of death

- By 96 weeks, 11 (0.3%) patients had died with renal disease reported to contribute to cause of death
  - all had initiated ART with TDF (p=0.63 compared with other first-line regimens)
  - Endpoint Review Committee considered:
    - 3 HIV related, 2 not HIV or drug related, 1 unknown COD
    - 4 uncertain if primarily drug or HIV related (1 TDF; 1 TDF+gentamicin; 1 TDF+ZDV; 1 ZDV+cotox)
    - 1 definitely drug related (ZDV+TDF)
  - 4/11 had pre-existing GFR impairment (Grade 2 or higher) at baseline

Renal adverse events reported as clinical grade 3/4 AE by 96 weeks

	n	Drug relationship				
		def/prob TDF	uncertain TDF	uncertain ZDV/3TC	uncertain EFV	uncertain LPV/r
Clinical grade 3 or 4 AE	13	5	6	4	1	1

AE:

Acute renal failure: n = 9

Chronic renal failure: n = 3

Glomerulonephritis: n = 1

Incidence by first-line regimen:

ABC: 0% (0 / 300)

NVP: 0.2% (1 / 546)

TDF: 0.5% (12 / 2468)

p = 0.50

Conclusions

- Severe GFR impairment was infrequent on all regimens
- Patients with mild renal impairment at baseline showed greatest improvements
- Differences between regimens in GFR changes from baseline were small (albeit statistically significant) and within the normal range
- The majority of patients with renal disease contributing to death had multi-organ disease (sepsis) and/or pre-existing renal impairment
- Investigating the potential for longer-term nephrotoxicity of TDF requires further follow-up

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