



# The Development of AntiRetroviral Therapy in Africa (DART) trial

Design and  
key substudy results

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# Background & rationale



- In resource-rich countries, standard of care on ART includes routine laboratory monitoring for
  - toxicity (haematology, biochemistry)
  - efficacy (CD4 cell count, viral load)
- **The level of monitoring required has never been established**
- In Africa, laboratory monitoring
  - is not widely available (infrastructure, personnel etc)
  - is costly to maintain (reagents, quality control etc)
- **Question: can ART be given safely with clinically driven, rather than routine, laboratory monitoring?**



# Main objectives of DART



- To evaluate the need for routine laboratory monitoring of ART in African adults starting ART having fulfilled clinical and CD4 criteria for ART initiation
- *To evaluate 12 week cycles of structured treatment interruptions (STIs) in patients with CD4  $\geq 300$  cells/mm<sup>3</sup> at 48/72 weeks (stopped March 2006<sup>1</sup>)*
- Primary endpoints
  - *Efficacy:* new WHO stage 4 HIV event (AIDS) or death
  - *Safety:* any Serious Adverse Event which is not only HIV-related
- Cost-effectiveness analysis



# Trial Design

3316 ART-naive adults with stage WHO 2, 3 or 4 HIV disease,  
CD4 < 200 cells/mm<sup>3</sup> initiating ART

randomise

## Laboratory and Clinical Monitoring (LCM)

12 weekly biochemistry,  
FBC & CD4

Other investigations &  
concomitant medications if  
clinically indicated

Switch to second-line for  
• new/recurrent WHO 4  
(or multiple WHO 3)  
• CD4 < 100 cells/mm<sup>3</sup>

## Clinically Driven Monitoring (CDM)

12 weekly biochemistry,  
FBC & CD4;  
FBC & biochemistry only  
returned if clinically  
indicated (or grade 4 toxicity);  
CD4 never returned

Other investigations &  
concomitant medications if  
clinically indicated

Switch to second-line for  
• new/recurrent WHO 4  
(or multiple WHO 3)



# Why was DART so large and long?



- Designed with sufficient power to determine whether CDM was non-inferior to LCM
  - defined as no more than a very small increase in event rate from **10/100 PY in LCM to 11.8/100 PY in CDM**
  - this small difference was considered acceptable, given potential benefits of CDM in terms of costs, access to and ease of decentralised ART delivery and hence wider rollout
- Long follow-up was essential as any differences between laboratory and clinical monitoring may only emerge, or may become more apparent, over time
  - patients will be on ART for life, not just for 2-3 years



# ART regimens

- First-line regimens based on ZDV+3TC (as Combivir)

- 2469 (74%) ZDV+3TC+TDF

- 300 (9%) ZDV+3TC+bABC (open label after 24 weeks)

- 300 (9%) ZDV+3TC+bNVP (open label after 24 weeks)

- 247 (7%) ZDV+3TC+NVP

} randomised  
blinded  
NORA  
substudy  
in Uganda

- Different regimens increases generalisability

- Second-line regimens based on boosted PI

- LPV/r+NNRTI±NRTI if 3NRTIs as first-line

- LPV/r+2NRTIs if NNRTI+2NRTIs as first-line



# Wider contributions to the evidence base for ART in Africa



## DART is more than a trial - it has become a major research programme

- First-line NORA randomisation, and second-line pilot randomisations to optimise NRTIs and evaluate PI monotherapy
- HIV virology/resistance project (stored samples)
  - majority of laboratory work conducted in Africa
- Other projects in key clinical areas
  - 9 peer reviewed articles and 29 conference presentations with key findings for ART management in resource-limited settings:
    - very low levels of renal impairment with tenofovir DF to 2 years
    - safe strategies for stopping nevirapine (pharmacokinetics)
    - lower than expected rate of HSR with abacavir; absence of HLAB-5701
  - Other areas include toxicity, pharmacokinetics, adherence, health-related quality of life, clinical/immunological outcomes, including OIs and tuberculosis, pregnancy and infant follow-up, survival on ART vs pre-ART



# IAS poster presentations



- MOPEB003: Impact of different WHO 3/4 events on ART on subsequent survival
- MOPEB020: Impact of cotrimoxazole in patients on ART
- MOPEB057: 5 year follow-up of participants initiating ART with Combivir plus nevirapine or abacavir (randomised)
- TUPEB098: Assigning clinical endpoints in clinical trials in resource limited settings
- TUPDB104: Impact of ART on incidence of malaria in Uganda
- TUPEB184: 5 year follow-up of creatinine and estimated GFR in patients receiving and not receiving TDF first-line
- WEPEB261: Pregnancy outcomes in women in DART





# Impact of cotrimoxazole prophylaxis in patients on ART



## MOPEB020

### • Key findings (I)

- Cotrimoxazole prophylaxis (CTX) decreases mortality by 50% in the first 72 weeks on ART
  - independently of current CD4
  - no effect after 72 weeks

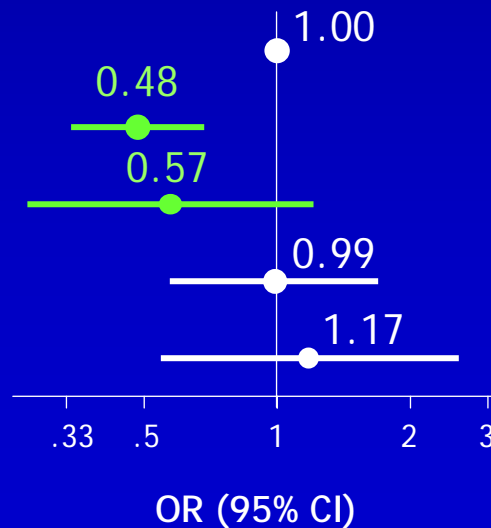
By current CD4: not on CTX

CD4 < 200, < 72 wks ART, on CTX

CD4 > 200, < 72 wks ART, on CTX

CD4 < 200, > 72 wks ART, on CTX

CD4 > 200, > 72 wks ART, on CTX



**Impact of daily cotrimoxazole prophylaxis in severely immunosuppressed adults in Africa started on combination ART in the DART trial**

**MOPEB020** CZ Gilber, D Ford, AS Walker, P Munday, J Harker, C Kityo, F Lubiano, H Grosskurth, A Beka, F Sanyal, P Muganyizi, De Groot, AG Redeker in the DART Trial Team

**Background**

Cotrimoxazole (trimethoprim-sulfamethoxazole) is a widely available, off-patent low cost antibiotic, used in resource limited settings to treat and prevent opportunistic infections. It also has antiproliferative activity.

Cotrimoxazole prophylaxis (CTX) significantly reduces mortality and morbidity in HIV positive HIV-infected adults and children in Africa.

Does the benefits of cotrimoxazole in individuals receiving ART are limited?

**DART trial design**

DART (Development of Antiretroviral Therapy) was a randomised trial of treatment strategies in 200 immunotolerant ART-naïve adults aged 18-50 years with CD4 counts between 100 and 350 cells/mm<sup>3</sup>.

Participants were randomised to either:

- Cotrimoxazole prophylaxis (CTP)
- Cotrimoxazole prophylaxis (CTP) + Zidovudine (ZDV)

**Patients, follow-up and data**

Analysis of the effects of cotrimoxazole included 21,970 (92%) DART participants (17,777 participants who took part in a pilot study of cotrimoxazole treatment) who were followed up for 11,112 (51%) person-years between January 2003 and December 2007.

2,916 deaths (13.3%) within 72 weeks of ART initiation.

**Table 1. Characteristics of the included DART cohort at randomisation**

ART initiation	ART-naïve (n=10,774)	on treatment (n=11,196)
Age (mean (SD))	35 (10)	35 (10)
Age range (median)	20-50	20-50
WHO stage		
I	1,000 (9.3%)	1,000 (9.0%)
II	2,000 (18.7%)	2,000 (18.0%)
III	5,000 (46.4%)	5,000 (45.5%)
IV	2,774 (25.7%)	2,774 (25.5%)
CD4 counts (mean, SD)	174 (57)	174 (57)
Trimethoprim-SDF treatment	11,196 (100%)	10,774 (100%)

**Statistical methods**

Intention-to-treat analysis was used to estimate the overall effects of cotrimoxazole prophylaxis on outcomes. These models adjust for time-dependent predictors of (1) use of cotrimoxazole prophylaxis, and (2) mortality, related to the baseline characteristics of the study population.

**The effect of cotrimoxazole prophylaxis on clinical outcomes**

**Table 2. Effect of cotrimoxazole prophylaxis (CTP) on outcomes**

Outcome	CTP	OR (95% CI)
Mortality in the first 72 weeks on ART	10,774	0.48 (0.43-0.54)
Mortality in the first 72 weeks on ART (not on CTP)	11,196	0.99 (0.78-1.26)
Mortality in the first 72 weeks on ART (not on CTP)	11,196	0.57 (0.47-0.69)
Mortality in the first 72 weeks on ART (not on CTP)	11,196	0.99 (0.77-1.27)
Mortality in the first 72 weeks on ART (not on CTP)	11,196	1.17 (0.80-1.71)

**Causes of death**

37% deaths were from causes likely to be directly affected by ART-related effects of cotrimoxazole (P22, opportunistic infections, HIV/AIDS, malaria).

Current cotrimoxazole prophylaxis reduced the risk of death from other causes by 32% (95% in the first 72 weeks on ART).

ART deaths were from other causes.

Current cotrimoxazole prophylaxis reduced the risk of death from other causes by 34% (95% in the first 72 weeks on ART).

**The effect of cotrimoxazole prophylaxis on CD4 counts and SMI**

**Table 3. Impact of cotrimoxazole prophylaxis (CTP) on CD4 count and SMI by time on ART**

Change from week 12 on ART	CTP	OR (95% CI)	Stat
Change from week 12 on ART	10,774	1.08 (1.04-1.12)	< .001
Change from week 12 on ART	11,196	1.00 (0.96-1.04)	> .05

**Conclusions**

Cotrimoxazole prophylaxis reduced mortality in HIV infected adults in the first 72 weeks on ART, an effect sustained for 72 weeks.

The impact of cotrimoxazole prophylaxis on mortality is significant and sustained beyond the impact on CD4 counts.

Cotrimoxazole prophylaxis should be provided in ART-naïve patients to maximize health benefits up to 72 weeks after the start of ART.

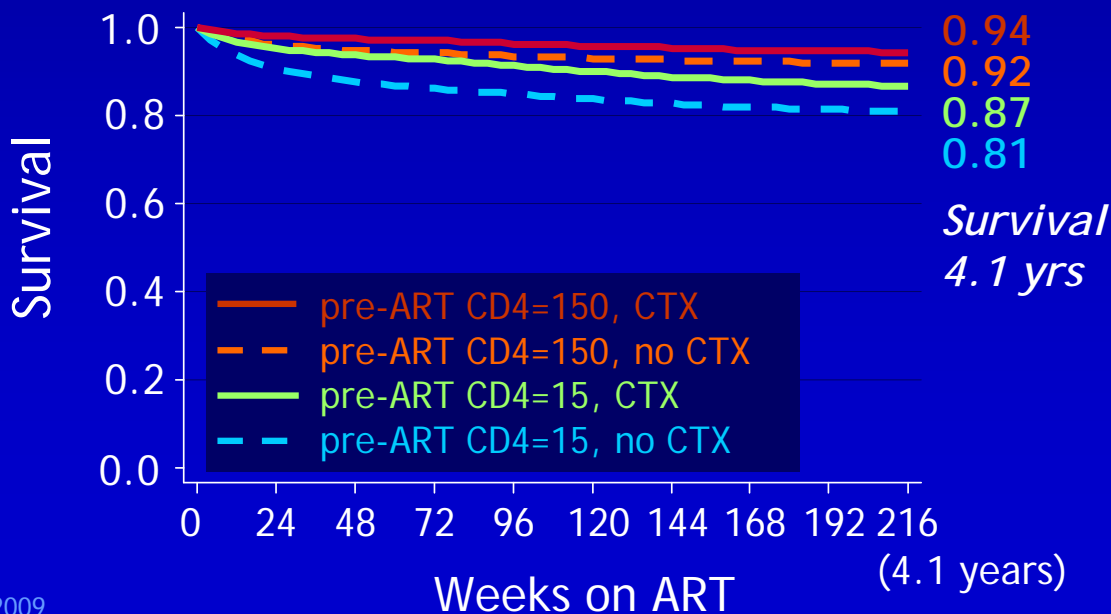


# Impact of cotrimoxazole prophylaxis in patients on ART

MOPEB020

- Key findings (II)

- 4 year survival for adults initiating ART and taking/not taking cotrimoxazole
  - 94% vs 92% with pre-ART CD4 150 cells/mm<sup>3</sup>
  - 87% vs 81% with pre-ART CD4 15 cells/mm<sup>3</sup>



**Impact of daily cotrimoxazole prophylaxis in severely immunosuppressed adults in Africa started on combination ART in the DART trial**

MOPEB020 CZ Gilber, D Ford, AS Walker, P Munday, J Hasker, C Kityo, F Laitanwa, H Grosskurth, A Beka, F Sanyal, P Muganyizi, De Groot, AG Rademers in the DART Trial Team

**Background**

Cotrimoxazole (trimethoprim-sulfamethoxazole) is a widely available, off-patent low cost antibiotic, used in resource limited settings to treat and prevent opportunistic bacterial infections. It also has antiparasitic activity. Cotrimoxazole prophylaxis (CTP) significantly reduces mortality and morbidity in HIV positive HIV-infected adults and children in Africa. The net benefits of cotrimoxazole in individuals receiving ART are limited.

**DART trial design**

MOPEB (Development of Antiretroviral Therapy) was a randomized trial of treatment strategies in 2006 compared ART in adults with CD4 counts below 350 cells/mm<sup>3</sup> initiating triple drug ART. Participants were randomized to either:
 

- Combination of Zidovudine, Zalcitabine, and Didanosine (ZZD)
- Combination of Zidovudine, Zalcitabine, and Stavudine (ZZS)
- Combination of Zidovudine, Zalcitabine, and Stavudine (ZZS) + Cotrimoxazole (ZZS+CTP)
- Combination of Zidovudine, Zalcitabine, and Stavudine (ZZS) + Cotrimoxazole (ZZS+CTP) + Cotrimoxazole (ZZS+CTP+CTP)

**Patients, follow-up and data**

Analysis of the effects of cotrimoxazole included 31,763/31,763 DART participants (17,777 participants who took part in a pilot study of cotrimoxazole treatment) who were followed up between January 2003 and December 2007. 21,763/31,763 (62%) were followed up for 4.1 years.

**Statistical methods**

Intentional treatment comparisons were made by comparing the effects of cotrimoxazole prophylaxis on outcomes. These models adjust for time-dependent confounding by age, sex, and CD4 count.

**The effect of cotrimoxazole prophylaxis on clinical outcomes**

Figure 3 Effect of current cotrimoxazole prophylaxis (CTP) on outcomes

Figure 3 shows the impact of cotrimoxazole prophylaxis (CTP) on mortality with patients on use, those on ART and current CD4 counts.

Figure 3 illustrates the effect of cotrimoxazole prophylaxis (CTP) on mortality in individuals on ART.

**Causes of death**

31% deaths were from causes likely to be directly affected by HIV related mortality. Cotrimoxazole prophylaxis (CTP) reduced the risk of death from these causes by 32% (95% CI 18-46%) in the first 72 weeks on ART.

40% deaths were from other causes.

**The effect of cotrimoxazole prophylaxis on CD4 counts and B66**

Table 1 Impact of cotrimoxazole prophylaxis (CTP) on CD4 count and B66 by time on ART

Table 2 Impact of cotrimoxazole prophylaxis (CTP) on CD4 count and B66 by time on ART

**Conclusions**

Cotrimoxazole prophylaxis reduced mortality in HIV infected adults in the first 72 weeks on ART, an effect sustained for 172 weeks.

There was no evidence that cotrimoxazole prophylaxis reduced the risk of death from other causes by 34% (95% CI 18-46%) in the first 72 weeks on ART.

Cotrimoxazole prophylaxis significantly reduced mortality in HIV infected adults in the first 72 weeks on ART, an effect sustained for 172 weeks.

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Cotrimoxazole prophylaxis significantly reduced mortality in HIV infected adults in the first 72 weeks on ART, an effect sustained for 172 weeks.

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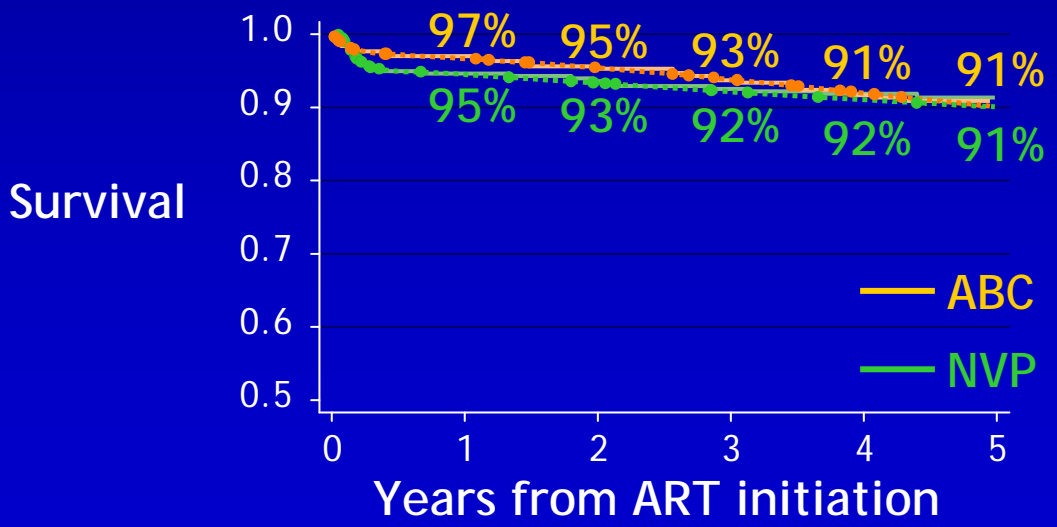


# 5 year follow-up of Combivir plus nevirapine or abacavir (randomised)

## MOPEB057

### Key findings:

- At 5 years, 91% participants alive in both groups (81% alive without new WHO 4 events)
- Clear VL and CD4 advantages to NVP



**Long-term randomised comparison of clinical outcomes following ART initiation with triple-nucleoside (Combivir/Abacavir) or NNRTI-based (Combivir/Nevirapine) therapy in Africa: the NORA substudy of the DART trial**  
 A Reid<sup>1</sup>, H Grosskurter<sup>2</sup>, P Mugenyi<sup>3</sup>, DM Gibis<sup>4</sup>, CF Gilks<sup>5</sup> & the DART Trial Team

**Background: NORA trial design**

**Cotrimoxazole prophylaxis and mortality**

**Death**

**New/recurrent WHO 4 or death**

**Conclusions**

**Table 1: NORA patient characteristics**

	ABC	NVP	Total
Mean age (SD)	37 (10)	37 (10)	37 (10)
Female (%)	52	52	52
Median CD4 pre-ART (IQR)	350 (250-450)	350 (250-450)	350 (250-450)
Median VL pre-ART log <sub>10</sub> copies/mL	5.2 (4.8-5.6)	5.2 (4.8-5.6)	5.2 (4.8-5.6)
Median WHO stage	2	2	2
Median time to ART initiation (days)	10	10	10
Median time to first WHO 4 or death (days)	100	100	100



# 5 year follow-up of estimated GFR in patients initiating ART



## TUPEB184

### • Key findings

- Low incidence of renal impairment on all regimens (TDF and non-TDF): overall
  - 2.9% eGFR ever <30 ml/min/1.73m<sup>2</sup>
  - 5.0% confirmed eGFR <60 ml/min/1.73m<sup>2</sup>
  - 2.9% confirmed 25% decrease from baseline eGFR
- No difference between LCM and CDM in incidence of confirmed eGFR decrease
- Renal disease contributed to death in a minority of patients (n=16, 0.5%) and was generally related to intercurrent disease

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

A Redf, W Sibole, AS Walker, J Haskin, P Sault, P Munder, F Lubiano, C Kityo, H Grossman, C Gillet, D Gani and the DART Trial Team

**Background**  
HIV infection is associated with several types of renal disease. Causes are multifactorial and include HIV itself, co-infections, comorbidities and their treatments. Recent data from sub-Saharan Africa suggest that HIV-related kidney disease may be more common in ART-naïve populations. However, it remains unclear whether longitudinal data on renal function and the long-term impact of ART on renal disease exist, and the African continent has no data on this topic.

**Objectives** To estimate prevalence and incidence of GFR reduction, renal disease adverse events (RAE) and mortality when renal impairment was a contributing factor, together with associated risk factors, through 4 years after initiation of ART.

**DART trial design & Methods**  
• DART is a randomised trial of management strategies in 2000 symptomatic, HIV-naïve adults with CD4-200 cells/mm<sup>3</sup> initiating triple drug ART in 5 centres in Uganda and Tanzania.  
• Participants were randomised to lamivudine and didanosine (Lam/Did) or Zidovudine and Didanosine (Zid/Did).  
• All participants received a baseline serum biochemistry panel and drug adherence was monitored through pill counts and self-reports. Urinary albumin excretion was measured at baseline and 4, 8 and 12 months. If at any time after randomisation eGFR < 60 ml/min/1.73m<sup>2</sup> was confirmed, a renal biopsy was performed. Serum creatinine, microalbuminuria and a modified Jaffe method for specific creatinine were used to estimate renal function.  
• Co-infections, full blood count and other laboratory tests, including ACT, AST, urea, creatinine, CD4 and CD8 counts at baseline, week 4 and 12, were performed. Urinary albumin excretion was measured at baseline and 4, 8 and 12 months. Urinary albumin excretion was measured at baseline and 4, 8 and 12 months. Urinary albumin excretion was measured at baseline and 4, 8 and 12 months.  
• Causes of death and SAEs were reviewed by an independent Review Committee. Subanalyses for this analysis included renal events and those patients with chronic kidney disease (CKD) who were included in the study. eGFR was estimated using the Cockcroft-Gault formula, and compared using the Wilcoxon-Mann-Whitney U test. The intercurrent network for fracture outcomes is based on the Fracture Risk Assessment Tool (FRAX).  
• GFR decrease (single values) were defined as: moderate 30-50% decrease (eGFR 15-59 ml/min/1.73m<sup>2</sup>); severe 50-75% decrease (eGFR 10-14 ml/min/1.73m<sup>2</sup>); and end-stage renal disease (eGFR < 10 ml/min/1.73m<sup>2</sup>).  
• Cumulative incidence was calculated considering deaths from non-renal causes as competing risks. This was done using a life table method and the log-rank test. All adjustments by values were made for multiple comparisons.

**Incidence of decreased GFR**

eGFR category	Lam/Did		Zid/Did		P-value
	n	%	n	%	
Ever	10	0.5	12	0.6	0.92
Confirmed	10	0.5	12	0.6	0.92
25% decrease	10	0.5	12	0.6	0.92

**Cumulative Incidence of renal outcomes and fractures**

Outcome	Time (years)	Lam/Did	Zid/Did	P-value
eGFR < 60 ml/min/1.73m <sup>2</sup>	0-4	0.00	0.00	0.99
	0-8	0.01	0.01	0.99
eGFR < 30 ml/min/1.73m <sup>2</sup>	0-4	0.00	0.00	0.99
	0-8	0.00	0.00	0.99
RAE	0-4	0.00	0.00	0.99
	0-8	0.00	0.00	0.99

**Key points**  
• Incidence of severe GFR decrease and CKD was low in all groups.  
• Severe GFR decrease occurred more often in the Zid/Did arm, but there was no difference in the incidence of CKD.  
• Treatment with lamivudine Zid/Did was associated with a higher incidence of CKD. This was not seen in the Lam/Did arm.  
• Only 17% of patients with severe GFR decrease had only one value < 30 ml/min/1.73m<sup>2</sup>. All other patients with severe GFR decrease had at least two values < 30 ml/min/1.73m<sup>2</sup>.  
• Only 17% of patients with severe GFR decrease had only one value < 30 ml/min/1.73m<sup>2</sup>. All other patients with severe GFR decrease had at least two values < 30 ml/min/1.73m<sup>2</sup>.  
• Only 17% of patients with severe GFR decrease had only one value < 30 ml/min/1.73m<sup>2</sup>. All other patients with severe GFR decrease had at least two values < 30 ml/min/1.73m<sup>2</sup>.

**CONCLUSIONS**  
• Severe GFR impairment was infrequent in all regimens, chronic kidney disease was rare (0.5% overall).  
• Treatment with lamivudine Zid/Did was associated with the occurrence of severe GFR decrease but not with severe CKD.  
• Only 17% of patients with severe GFR decrease had only one value < 30 ml/min/1.73m<sup>2</sup>. All other patients with severe GFR decrease had at least two values < 30 ml/min/1.73m<sup>2</sup>.  
• 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.

## WEPEB261

### Key findings

➤ 378 pregnancies in 299/1867 (16%) women of child-bearing age at ART initiation

– 4.83/100 woman-years

– 60% on combivir+tenofovir DF

➤ 57% livebirths, 6% stillbirths and 36% terminations/miscarriage

➤ No excess congenital abnormalities vs pregnancy register – 3.0%

– 3 club foot, 1 skin tag, 1 undescended testes, 1 hydrocephalus, 1 cardiac (PDA & ASD)

➤ No reported HIV-infected babies to date

**WEPEB261**  
Pregnancy rates & Outcomes among women on triple-drug antiretroviral therapy in the DART trial

**BACKGROUND**  
Epidemiologic data on the occurrence of pregnancy and outcome of pregnancy among African women on combination antiretroviral therapy (ART) are scarce. 2376 of women were enrolled in the Uganda 2 (Distal) DART trial of whom 1867 (80%) were of child-bearing age (<40 years at enrollment, median age 25 years). 161 women were pregnant at enrollment into the trial.

**INCIDENCE OF PREGNANCY BY AGE & TIME SINCE ENROLLMENT**  
Line graph showing incidence rates per 100 woman-years for different age groups (15-19, 20-24, 25-29, 30-34, 35-39, 40-44) over time since enrollment (0-12, 13-24, 25-36, 37-48, 49-60 months).

**FOETAL & INFANT OUTCOMES**  
299 live births and 24 stillbirths. Any congenital abnormality reported: 2 (3.0%).  
• Congenital hydrocephalus: 1 (3.0%)  
• Cardiac (PDA and ASD): 1 (3.0%)  
• Undescended testes: 1 (3.0%)  
• Club foot: 3 (3.0%)  
• Skin tag: 1 (3.0%)  
• HIV infection: 0 (0%)  
• Mean birth weight: 3.6 kg  
• Mean length: 47.5 cm  
• Mean head circumference: 33.5 cm  
• Mean gestational age at birth: 37 weeks + 3 days  
• 1 neonatal death was reported by 2 weeks postpartum.  
• Stillbirths: 24 (9.7%)  
• Miscarriages: 21 (8.4%)  
• Termination: 1 (0.4%)  
• 1 of 24 neonatal deaths occurred within 24 hours of birth.  
• 19 were HIV DNA PCR antibody negative, 4 were HIV DNA PCR antibody positive at the time of birth.  
• 100% (24/24) of the neonatal deaths were HIV DNA PCR antibody positive at the time of birth.  
• 19 (79%) had been tested by the DART assessment and all were HIV DNA PCR antibody negative at the time of death.

**EFFECT OF BASELINE CD4 COUNT & WHO STAGE ON PREGNANCY RATES**  
Table showing pregnancy rates by baseline CD4 count and WHO stage.

WHO Stage	Median CD4 count (range)	Mean CD4 count (SD)	Ever pregnant (n/N)	All women (n/N)	P value
WHO Stage I (n=26)	67 (21-116)	53 (21)	14 (54%)	12 (46%)	0.81
WHO Stage II (n=26)	320 (236-414)	182 (81)	142 (54%)	134 (51%)	0.81
WHO Stage III (n=26)	83 (23-132)	142 (81)	142 (54%)	134 (51%)	0.81
WHO Stage IV (n=26)	413 (248-578)	49 (18)	48 (18%)	48 (18%)	0.001

**PREGNANCY OUTCOMES OVER TIME ON ART**  
Stacked bar chart showing pregnancy outcomes over time on ART (0-12, 13-24, 25-36, 37-48, 49-60 months).

**MATERNAL AND INFANT ART**  
Pie chart showing mothers' ART regimens: 74% ZDV+3TC, 17% ZDV+3TC+FTC, 7% ZDV+3TC+FTC+FTD, 2% ZDV+3TC+FTC+FTD+FTD.

**RESULTS**  
378 pregnancies in 299 women.  
• 1 pregnancy: 225 (59%)  
• 2 pregnancies: 36 (9%)  
• 3 pregnancies: 13 (3%)  
• 4 pregnancies: 1 (0.3%)  
One of those pregnancies to:  
• 161 women aged <30 years  
• 138 women aged >30 years  
• 100% (378/378) women were on ART at the time of pregnancy.

**CONCLUSIONS & RECOMMENDATIONS**  
• Pregnancy rates in this population of HIV-infected African women increased after 12 years on ART and declined from the 48th month on ART.  
• Rates of pregnancy were higher among the younger age group and among women with less severe HIV clinical disease.  
• High rates of foetal loss were observed and are consistent over time. This may be due to increased reporting to the site of death following pregnancy, increased foetal loss in HIV-infected women but has not been reported in other studies.  
• Rates of congenital abnormalities in this study are low and similar to those previously reported.  
• 2.0/100 (2.4-3.5) HIV-infected women with first trimester ART in the Antiretroviral Pregnancy Register.  
• 2.7/100 live births in the CDC birth defect register.  
• Few women in DART chose to breastfeed.  
• No data from this cohort is known to be HIV-infected.  
• Continued documentation and outcome event monitoring from similar treatment cohorts is necessary to help contribute to the knowledge base on the effects of antiretroviral therapy on pregnancy, the neonatal period, early infancy & childhood.

**ACKNOWLEDGEMENTS**  
The work of the authors and staff was of immense importance to the DART trial.

**MATERIAL OUTCOMES**  
• 2 pregnant women were unable to give birth due to:  
• 2 miscarriages: 1 (3.0%)  
• 1 stillbirth: 1 (3.0%)  
• 1 termination: 1 (3.0%)  
• 1 neonatal death: 1 (3.0%)



# Looking forward



- Second-line studies - ART (OHFS) & bPI monotherapy (SARA)
- HIV virology/resistance project (stored samples)
- Hepatitis B virology project (stored samples)
- Follow-up of infants born to mothers in DART
- Impact of ART on disclosure and sexual behaviour
- Toxicity on first- and second-line ART
- Non-randomised comparison of first-line regimens
- Prevalence and impact of immunological non-response
- Optimising “when to switch” (using causal models)
- Relationship between (minor) symptoms and ART failure
  
- Maintenance of the DART cohort long-term
- EARNEST: a large (1200 participant) RCT of second-line ART





# DART partners

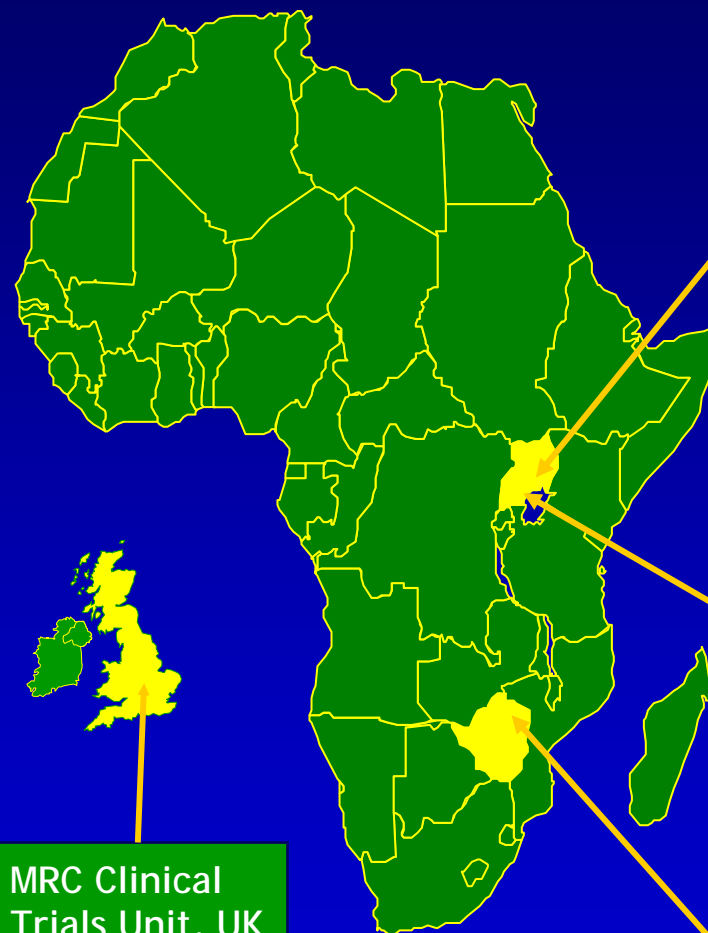
## Support:

MRC, UK

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GlaxoSmithKline  
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Joint Clinical Research  
Centre, Kampala, Uganda

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