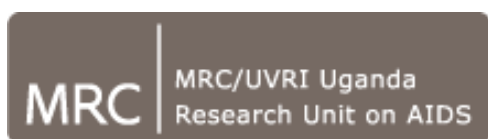




The Development of AntiRetroviral Therapy in Africa (DART) trial

Design and
key substudy results

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*on behalf of the **DART** Trial Team*



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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 ≥ 300 cells/mm³ at 48/72 weeks (stopped March 2006¹)*
- 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/mm³ 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/mm³

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)

- 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

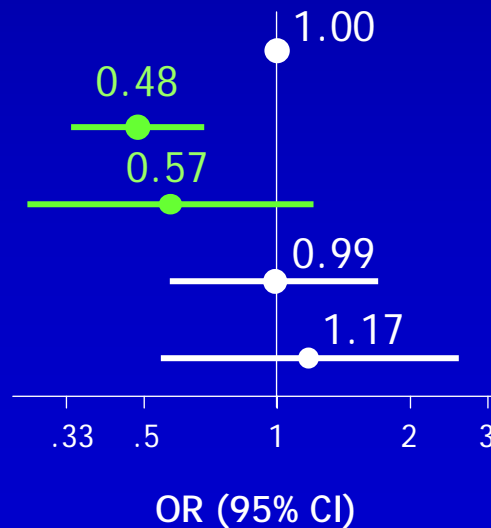
By current CD4: not on CTX

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 Gilbr, D Ford, AS Walker, P Munday, J Harker, C Kityo, F Lubiano, H Grosskurth, A Beka, F Sanyal, P Muganyizi, De Groot, AG Rademan 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 antiparasitic 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/mm³.

Participants were randomised to either:

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

DART was a 1:1 randomised trial, using a parallel design, in 200 immunotolerant HIV-infected adults, not receiving ART, at the start of the study.

Patients, follow-up and data

Analysis of the effects of cotrimoxazole included 21,970 (92%) DART participants (177 participants who took part in a pilot study of cotrimoxazole treatment immunotolerance of HIV were excluded).

11,122 participants followed up between January 2003 and December 2007.

2,916 deaths (19.2%) within 72 weeks of ART initiation.

Table 1. Characteristics of the included DART participants on randomisation to ART initiation (N=21,970) (including 177 pilot participants)

Characteristic	CTP (n=10,985)	CTP+ZDV (n=10,985)
Age (mean (SD))	35 (10)	35 (10)
Age range (years)	18-70	18-70
WHO stage		
I	1,000 (9.1%)	1,000 (9.1%)
II	1,000 (9.1%)	1,000 (9.1%)
III	1,000 (9.1%)	1,000 (9.1%)
IV	1,000 (9.1%)	1,000 (9.1%)
V	1,000 (9.1%)	1,000 (9.1%)
VI	1,000 (9.1%)	1,000 (9.1%)
VII	1,000 (9.1%)	1,000 (9.1%)
VIII	1,000 (9.1%)	1,000 (9.1%)
IX	1,000 (9.1%)	1,000 (9.1%)
X	1,000 (9.1%)	1,000 (9.1%)
XI	1,000 (9.1%)	1,000 (9.1%)
XII	1,000 (9.1%)	1,000 (9.1%)
XIII	1,000 (9.1%)	1,000 (9.1%)
XIV	1,000 (9.1%)	1,000 (9.1%)
XV	1,000 (9.1%)	1,000 (9.1%)
XVI	1,000 (9.1%)	1,000 (9.1%)
XVII	1,000 (9.1%)	1,000 (9.1%)
XVIII	1,000 (9.1%)	1,000 (9.1%)
XIX	1,000 (9.1%)	1,000 (9.1%)
XX	1,000 (9.1%)	1,000 (9.1%)
XXI	1,000 (9.1%)	1,000 (9.1%)
XXII	1,000 (9.1%)	1,000 (9.1%)
XXIII	1,000 (9.1%)	1,000 (9.1%)
XXIV	1,000 (9.1%)	1,000 (9.1%)
XXV	1,000 (9.1%)	1,000 (9.1%)
XXVI	1,000 (9.1%)	1,000 (9.1%)
XXVII	1,000 (9.1%)	1,000 (9.1%)
XXVIII	1,000 (9.1%)	1,000 (9.1%)
XXIX	1,000 (9.1%)	1,000 (9.1%)
XXX	1,000 (9.1%)	1,000 (9.1%)

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 all-cause mortality, and (ii) randomised, adjusted for the probability of treatment receipt. We included:

- Current cotrimoxazole prophylaxis
- WHO stage at the last 4 week period or earlier (if not randomised)
- Interactions between on/off cotrimoxazole in the last 4 week period and time-dependent predictors (see above).

Where adjusted marginal structural models were used to investigate whether the effect of cotrimoxazole on mortality differed with current CD4, WHO stage at randomisation was used as a time-varying covariate.

The effect of cotrimoxazole prophylaxis on clinical outcomes

Figure 1. Effect of current cotrimoxazole prophylaxis (CTP) on outcomes

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

Change from week 12 on ART	CTP (n=10,985)	B66 (n=10,985)
Change from week 12 on ART	10.4 (9.4-11.4)	10.4 (9.4-11.4)
Change from week 12 on ART	10.4 (9.4-11.4)	10.4 (9.4-11.4)
Change from week 12 on ART	10.4 (9.4-11.4)	10.4 (9.4-11.4)

Causes of death

21% deaths were from causes likely to be directly affected by ART resistance. The impact of cotrimoxazole prophylaxis on mortality was similar in individuals who were not on ART.

The effect of cotrimoxazole prophylaxis on CD4 counts and B66

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 72 weeks.

The impact of cotrimoxazole prophylaxis on mortality was similar in individuals who were not on ART.

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

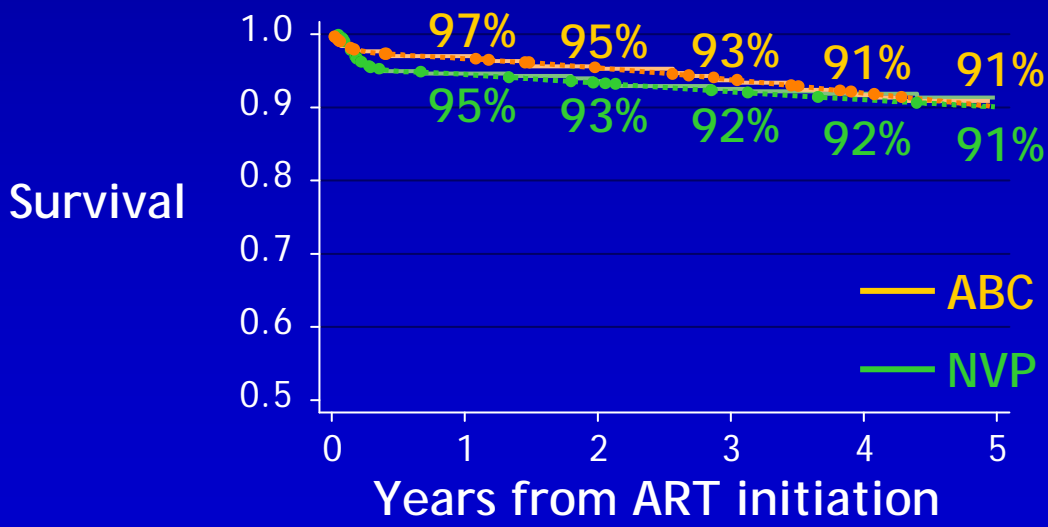


5 year follow-up of Combivir plus nevirapine or abacavir (randomised)

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*, H Grosskurter*, P Mugenyi*, DM Gibis*, CF Gilks* & 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)
Median CD4 pre-ART (IQR)	190 (100-250)	190 (100-250)	190 (100-250)
Median VL pre-ART log ₁₀ copies/mL (IQR)	4.8 (4.5-5.2)	4.8 (4.5-5.2)	4.8 (4.5-5.2)
Median WHO stage (IQR)	2 (1-3)	2 (1-3)	2 (1-3)
Median time to ART (days) (IQR)	10 (0-30)	10 (0-30)	10 (0-30)
Median time to CTXT (days) (IQR)	10 (0-30)	10 (0-30)	10 (0-30)
Median time to CTXT (days) (IQR)	10 (0-30)	10 (0-30)	10 (0-30)



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/1.73m²
 - 5.0% confirmed eGFR <60 ml/min/1.73m²
 - 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 Sibber, AS Walker, J Haskin, P Sault, P Munder, F Lubiano, C Kityo, H Grossman, C Gilst, D Gao 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 an randomised trial of treatment strategies in 2000 symptomatic, HIV-naïve adults with CD4-200 cells/mm³ initiating triple drug ART in 3 centres in Uganda and Tanzania.
- Participants were randomised to lamivudine and didanosine (Lam/3TC) or zidovudine and didanosine (ZDV/3TC).
- All participants received a baseline renal function test as a part of drug safety monitoring and were followed up for 4 years. At baseline, renal function was assessed using a single-shot 125I-iothalamate GFR study. If at two time points consecutive measurements were 15% or more different, a second GFR study was performed. Serum creatinine, microalbuminuria and a modified Jaffe method for specific creatinine were also measured.
- Creatinine, full blood count and other laboratory tests, including ACT, CCI, were repeated 12, 24 and 36 months after baseline, week 4 and 12, the latter two only in the Lam/3TC arm.
- At baseline, 125I-iothalamate GFR studies were performed. Some consecutive measurements were also performed. Some consecutive measurements were also performed.
- 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) were also included in the analysis. GFR was estimated from 125I-iothalamate using the modified Jaffe method, and compared against the reference method using the Cockcroft-Gault formula, and compared against the reference method using the Cockcroft-Gault formula, and compared against the reference method using the Cockcroft-Gault formula.
- GFR decrease (single values only) were defined as: 25-30% decrease, 30-35% decrease, 35-40% decrease, 40-45% decrease, 45-50% decrease, 50-55% decrease, 55-60% decrease, 60-65% decrease, 65-70% decrease, 70-75% decrease, 75-80% decrease, 80-85% decrease, 85-90% decrease, 90-95% decrease, 95-100% decrease, 100-105% decrease, 105-110% decrease, 110-115% decrease, 115-120% decrease, 120-125% decrease, 125-130% decrease, 130-135% decrease, 135-140% decrease, 140-145% decrease, 145-150% decrease, 150-155% decrease, 155-160% decrease, 160-165% decrease, 165-170% decrease, 170-175% decrease, 175-180% decrease, 180-185% decrease, 185-190% decrease, 190-195% decrease, 195-200% decrease, 200-205% decrease, 205-210% decrease, 210-215% decrease, 215-220% decrease, 220-225% decrease, 225-230% decrease, 230-235% decrease, 235-240% decrease, 240-245% decrease, 245-250% decrease, 250-255% decrease, 255-260% decrease, 260-265% decrease, 265-270% decrease, 270-275% decrease, 275-280% decrease, 280-285% decrease, 285-290% decrease, 290-295% decrease, 295-300% decrease, 300-305% decrease, 305-310% decrease, 310-315% decrease, 315-320% decrease, 320-325% decrease, 325-330% decrease, 330-335% decrease, 335-340% decrease, 340-345% decrease, 345-350% decrease, 350-355% decrease, 355-360% decrease, 360-365% decrease, 365-370% decrease, 370-375% decrease, 375-380% decrease, 380-385% decrease, 385-390% decrease, 390-395% decrease, 395-400% decrease, 400-405% decrease, 405-410% decrease, 410-415% decrease, 415-420% decrease, 420-425% decrease, 425-430% decrease, 430-435% decrease, 435-440% decrease, 440-445% decrease, 445-450% decrease, 450-455% decrease, 455-460% decrease, 460-465% decrease, 465-470% decrease, 470-475% decrease, 475-480% decrease, 480-485% decrease, 485-490% decrease, 490-495% decrease, 495-500% decrease, 500-505% decrease, 505-510% decrease, 510-515% decrease, 515-520% decrease, 520-525% decrease, 525-530% decrease, 530-535% decrease, 535-540% decrease, 540-545% decrease, 545-550% decrease, 550-555% decrease, 555-560% decrease, 560-565% decrease, 565-570% decrease, 570-575% decrease, 575-580% decrease, 580-585% decrease, 585-590% decrease, 590-595% decrease, 595-600% decrease, 600-605% decrease, 605-610% decrease, 610-615% decrease, 615-620% decrease, 620-625% decrease, 625-630% decrease, 630-635% decrease, 635-640% decrease, 640-645% decrease, 645-650% decrease, 650-655% decrease, 655-660% decrease, 660-665% decrease, 665-670% decrease, 670-675% decrease, 675-680% decrease, 680-685% decrease, 685-690% decrease, 690-695% decrease, 695-700% decrease, 700-705% decrease, 705-710% decrease, 710-715% decrease, 715-720% decrease, 720-725% decrease, 725-730% decrease, 730-735% decrease, 735-740% decrease, 740-745% decrease, 745-750% decrease, 750-755% decrease, 755-760% decrease, 760-765% decrease, 765-770% decrease, 770-775% decrease, 775-780% decrease, 780-785% decrease, 785-790% decrease, 790-795% decrease, 795-800% decrease, 800-805% decrease, 805-810% decrease, 810-815% decrease, 815-820% decrease, 820-825% decrease, 825-830% decrease, 830-835% decrease, 835-840% decrease, 840-845% decrease, 845-850% decrease, 850-855% decrease, 855-860% decrease, 860-865% decrease, 865-870% decrease, 870-875% decrease, 875-880% decrease, 880-885% decrease, 885-890% decrease, 890-895% decrease, 895-900% decrease, 900-905% decrease, 905-910% decrease, 910-915% decrease, 915-920% decrease, 920-925% decrease, 925-930% decrease, 930-935% decrease, 935-940% decrease, 940-945% decrease, 945-950% decrease, 950-955% decrease, 955-960% decrease, 960-965% decrease, 965-970% decrease, 970-975% decrease, 975-980% decrease, 980-985% decrease, 985-990% decrease, 990-995% decrease, 995-1000% decrease.

Incidence of decreased GFR

GFR decrease (single values only)	Lam/3TC		ZDV/3TC		Total
	n	%	n	%	
≥25%	10	1.0	10	1.0	20 (2.0)
≥30%	10	1.0	10	1.0	20 (2.0)
≥35%	10	1.0	10	1.0	20 (2.0)
≥40%	10	1.0	10	1.0	20 (2.0)
≥45%	10	1.0	10	1.0	20 (2.0)
≥50%	10	1.0	10	1.0	20 (2.0)
≥55%	10	1.0	10	1.0	20 (2.0)
≥60%	10	1.0	10	1.0	20 (2.0)
≥65%	10	1.0	10	1.0	20 (2.0)
≥70%	10	1.0	10	1.0	20 (2.0)
≥75%	10	1.0	10	1.0	20 (2.0)
≥80%	10	1.0	10	1.0	20 (2.0)
≥85%	10	1.0	10	1.0	20 (2.0)
≥90%	10	1.0	10	1.0	20 (2.0)
≥95%	10	1.0	10	1.0	20 (2.0)
≥100%	10	1.0	10	1.0	20 (2.0)

Cumulative Incidence of renal outcomes and fractures

Outcome	Lam/3TC		ZDV/3TC		Total
	n	%	n	%	
Renal RAE	10	1.0	10	1.0	20 (2.0)
Fractures	10	1.0	10	1.0	20 (2.0)
RAE + Fractures	10	1.0	10	1.0	20 (2.0)

Key points

- Incidence of severe GFR decrease and CKD was low in all groups.
- Treatment with lamivudine or zidovudine was not associated with a higher incidence of CKD.
- Incidence of renal RAE was similar between groups.
- Only 176 deaths with renal contribution were judged attributable to intercurrent disease.
- Renal disease contributed to death in only a minority of patients and was generally related to intercurrent disease.

Conclusions

- Severe GFR impairment was infrequent in all regimens, chronic kidney disease was very infrequent.
- Treatment with lamivudine or zidovudine was not associated with the occurrence of severe GFR decrease or with renal RAE.
- Only 176 deaths with renal contribution were judged attributable to intercurrent disease.
- Renal disease contributed to death in only a minority of patients and was generally related to intercurrent disease.
- Limitation of our analysis: tubular function was not examined in DART.



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

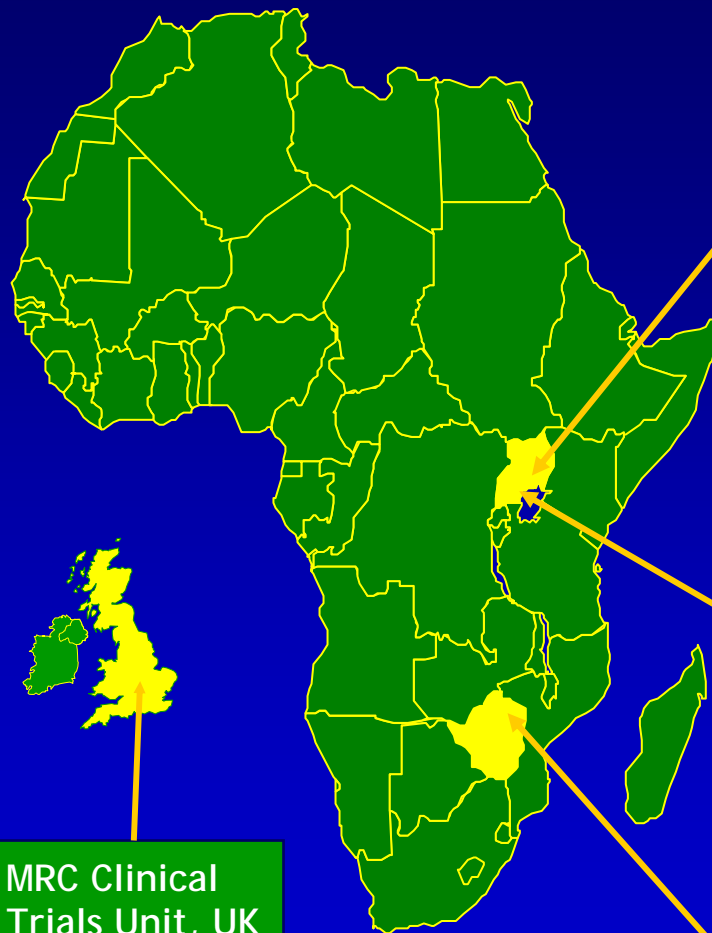
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