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

ISCRTN 13968779

MOPEB020

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Background

- Cotrimoxazole (trimethoprim-sulfamethoxazole) is a widely available, off-patent low-cost antibiotic, used in resource-limited settings to treat and prevent community-acquired infections. It also has antimalarial activity.
- Cotrimoxazole prophylaxis (CTX) significantly reduces mortality and morbidity in ART-naive HIV-infected adults and children in Africa
- Data on benefits of cotrimoxazole in individuals receiving ART are limited

DART trial design

- DART (Development of AntiRetroviral Therapy) was a randomised trial of management strategies in 3316 symptomatic ART-naive adults with CD4<200 cells/mm^3 initiating triple drug ART
- Participants were randomised to either
  - Laboratory and Clinical Monitoring (LCM) or
  - Clinically Driven Monitoring (CDM)
- DART ran in 3 centres, 2 in Uganda (plus 1 satellite site), 1 in Zimbabwe
- Cotrimoxazole was not routinely used, but prescribed at the discretion of the treating clinician

Patients, follow-up and data

- **Analysis of the effects of cotrimoxazole included 3179/3316 DART participants (137 participants who took part in a pilot study of structured treatment interruptions of ART were excluded)**
  - 11233 years follow-up between January 2003 and December 2007
  - 293 deaths; 85 within 12 weeks of ART initiation

Table 1: Characteristics of the included DART cohort at randomisation

At ART initiation	DART N=3179 (excluding STI pilot)	
Sex: female	2057	(65%)
Age (years) (median, IQR)	36	(32-42)
WHO stage: 2	644	(20%)
3	1794	(56%)
4	741	(23%)
CD4 (cells/mm^3) (median, IQR)	83	(29-137)
Haemoglobin (g/dl) (median, IQR)	11.4	(10.3-12.7)

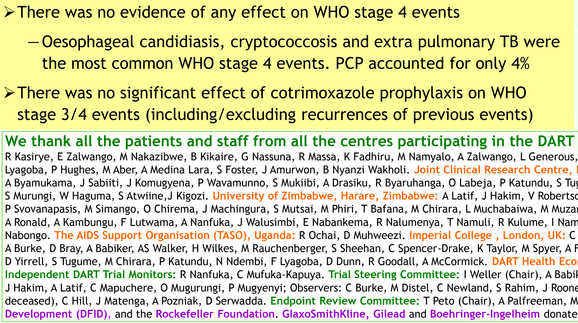
- Exposure to cotrimoxazole prophylaxis was variable
  - 12% participants did not use it at all
  - 60% were using it at ART initiation
  - 27% started it whilst on ART
  - Use often not continuous once started (individuals started, stopped)
- 57% of person-years follow-up was spent on cotrimoxazole prophylaxis

Statistical methods

- **Marginal structural models** were used to estimate the causal effects of cotrimoxazole prophylaxis on outcomes. These models adjust for time-dependent confounders by weights.
- Time dependent predictors of (i) use of cotrimoxazole prophylaxis, and (ii) outcomes (adjusted for by inverse probability of treatment weights, IPTW) included:
  - Current CD4
  - Current haemoglobin
  - WHO 3/4 event in the last 4 week period or earlier but after randomisation
  - Interactions between on/off cotrimoxazole in the last 4 week period and time-dependent predictors (as above).
- History-adjusted marginal structural models were used to investigate whether the effect of cotrimoxazole on mortality differed with current CD4.

The effect of cotrimoxazole prophylaxis on clinical outcomes

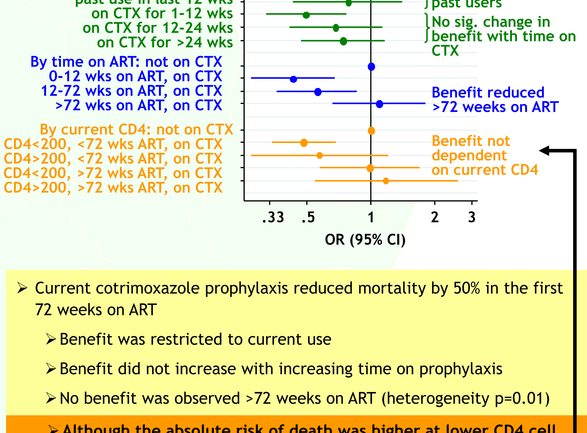
Figure 1: Effect of current cotrimoxazole prophylaxis (CTX) on outcomes



- Current cotrimoxazole prophylaxis significantly reduced mortality and malaria episodes
  - Impact on malaria was maintained throughout follow-up (not shown)
- There was no evidence of any effect on WHO stage 4 events
  - Oesophageal candidiasis, cryptococcosis and extra pulmonary TB were the most common WHO stage 4 events. PCP accounted for only 4%
- There was no significant effect of cotrimoxazole prophylaxis on WHO stage 3/4 events (including/excluding recurrences of previous events)

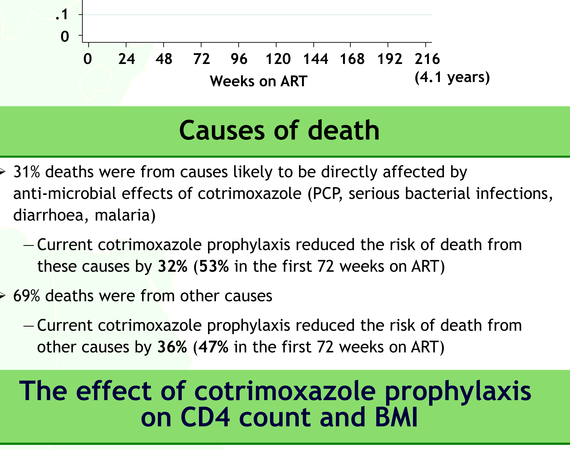
Cotrimoxazole prophylaxis and mortality

Figure 2: Variation in the impact of cotrimoxazole prophylaxis (CTX) on mortality with pattern of use, time on ART and current CD4



- Current cotrimoxazole prophylaxis reduced mortality by 50% in the first 72 weeks on ART
  - Benefit was restricted to current use
  - Benefit did not increase with increasing time on prophylaxis
  - No benefit was observed >72 weeks on ART (heterogeneity p=0.01)
- **Although the absolute risk of death was higher at lower CD4 cell counts, similar relative mortality risk reductions were seen in participants with current CD4<200 or CD4≥200 cells/mm^3**

Figure 3: Estimated effect of continuous cotrimoxazole prophylaxis (CTX) on survival of an individual on ART



Causes of death

- 31% deaths were from causes likely to be directly affected by anti-microbial effects of cotrimoxazole (PCP, serious bacterial infections, diarrhoea, malaria)
  - Current cotrimoxazole prophylaxis reduced the risk of death from these causes by **32%** (**53%** in the first 72 weeks on ART)
- 69% deaths were from other causes
  - Current cotrimoxazole prophylaxis reduced the risk of death from other causes by **36%** (**47%** in the first 72 weeks on ART)

The effect of cotrimoxazole prophylaxis on CD4 count and BMI

Table 2: Impact of cotrimoxazole prophylaxis (CTX) on CD4 count and BMI by time on ART

	CD4 count cells/mm^3	BMI kg/m^2
Change between weeks 0-12 on ART Current user of CTX vs not on CTX	-2 (-9,+4)	-.09 (-.20,+.03)
Change from week 12 on ART Current user of CTX vs not on CTX	-5 (-14,+3)	-.08 (-.25,+.08)

- In the first 12 weeks on ART CD4 count increased by a mean of 87 cells/mm^3 and BMI by 0.78 kg/m^2 but increases were similar in participants taking cotrimoxazole prophylaxis and those not taking it
- There was no evidence that cotrimoxazole prophylaxis directly increased CD4 or BMI after >12 weeks on ART

Conclusions

- **Cotrimoxazole prophylaxis halved mortality in HIV-infected adults in the first 12 weeks on ART, an effect sustained to 72 weeks**
  - We were unable to identify how the benefits of cotrimoxazole prophylaxis were achieved or to draw any conclusions about mechanism of action
  - No significant effects of cotrimoxazole prophylaxis were observed on WHO stage 3 or 4 events, CD4 counts or BMI
- **The impact of cotrimoxazole prophylaxis on malaria in Uganda was significant and sustained beyond the impact on survival**
- **Cotrimoxazole prophylaxis should be provided in ART rollout programs in resource-limited settings for up to 72 weeks; after this it may reasonable to stop**

We thank all the patients and staff from all the centres participating in the DART trial. MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda: H Grosskurth, P Munderi, G Kabuye, D Nsibambi, R Kasirye, E Zalwango, M Nakazibwe, B Kikaire, G Nassuna, R Massa, K Fadhiru, M Namyalo, A Zalwango, L Generous, P Khauka, N Rutikarayo, W Nakahima, A Mugisha, J Todd, J Levin, S Muyingo, A Ruberantwari, P Kaleebu, D Yirrell, N Ndembi, F Lyagoba, P Hughes, M Aber, A Medina Lara, S Foster, J Amurwon, B Nyanzi Wakholi. Joint Clinical Research Centre, Kampala, Uganda: P Mugyenyi, C Kityo, F Ssali, D Tumukunde, T Otim, J Kabanda, H Musana, J Akao, , H Kyomugisha, A Byamukama, J Sabiiti, J Komugyena, P Wavamunno, S Mukiibi, A Drasiku, R Byaruhanga, O Labeja, P Katundu, S Tugume, P Awio, A Namazzi, GT Bakeinyaga, H Katabira, D Abaine,J Tukamushaba, W Anywar, W Ojiambo, E Angweng, S Murungi, W Haguma, S Atwiine,J Kigozi. University of Zimbabwe, Harare, Zimbabwe: A Latif, J Hakim, V Robertson, A Reid, E Chidziva, R Bulaya-Tembo, G Musoro, F Taziwa, C Chimbetete, L Chakonza, A Mawora, C Muvirimi, G Tinago, P Svovanapasis, M Simango, O Chirema, J Machingura, S Mutsai, M Phiri, T Bafana, M Chirara, L Muchabaiwa, M Muzambi. Infectious Diseases Institute (formerly the Academic Alliance) Makerere University, Mulago, Uganda: E Katabira, A Ronald, A Kambungu, F Lutwama, A Nanfuka, J Walusimbi, E Nabankema, R Nalumenya, T Namuli, R Kulume, I Namata, L Nyachwo, A Florence, A Kusiima, E Lubwama, R Nairuba, F Oketta, E Buluma, R Waita, H Ojiambo, F Sadik, J Wanyama, P Nabongo. The AIDS Support Organisation (TASO), Uganda: R Ochai, D Muhweezi. Imperial College , London, UK: C Gilks, K Boocock, C Puddephatt, C Grundy, J Bohannon. MRC Clinical Trials Unit, London, UK: J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Rauchenberger, S Sheehan, C Spencer-Drake, K Taylor, M Spyer, A Ferrier, B Naidoo, D Dunn, R Goodall. DART Virology Group: P Kaleebu (Co-Chair), D Pillay (Co-Chair), V Robertson, D Yirrell, S Tugume, M Chirara, P Katundu, N Ndembi, F Lyagoba, D Dunn, R Goodall, A McCormick. DART Health Economics Group: A Medina Lara (Chair), S Foster, J Amurwon, B Nyanzi Wakholi, J Kigozi, L Muchabaiwa, M Muzambi. Independent DART Trial Monitors: R Nanfuka, C Mufuka-Kapuya. Trial Steering Committee: I Weller (Chair), A Babiker (Trial Statistician), S Bahendeka, M Bassett, A Chogo Wapakhabulo, J Darbyshire, B Gazzard, C Gilks, H Grosskurth, J Hakim, A Latif, C Mapuchere, O Mugurungi, P Mugyenyi; Observers: C Burke, M Distel, 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 Matenga, A Pozniak, D Serwadda. Endpoint Review Committee: T Peto (Chair), A Palfreeman, M Borok, 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, and Abbott provided Kaletra/Aluvia as part of the second-line regimen.