



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



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-naïve** 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-naïve adults with CD4<200 cells/mm³ 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

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)

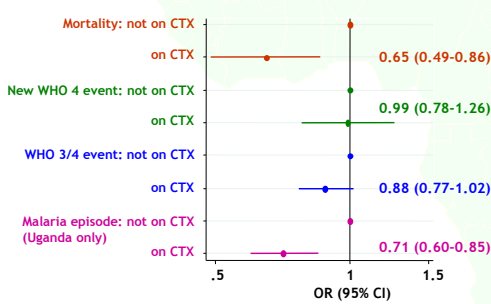
- Exposure to cotrimoxazole prophylaxis was variable
 - 12% participants did not use it at all
 - 60% were using it at ART initiation
 - 27% started it whilst on ART
 - Use often not continuous once started (individuals started, stopped)
- 57% of person-years follow-up was spent on cotrimoxazole prophylaxis

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

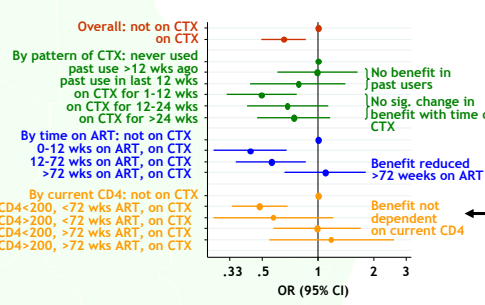


- Current cotrimoxazole prophylaxis significantly reduced mortality and malaria episodes
 - Impact on malaria was maintained throughout follow-up (not shown)
- There was no evidence of any effect on WHO stage 4 events
 - Oesophageal candidiasis, cryptococcosis and extra pulmonary TB were the most common 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)

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Cotrimoxazole prophylaxis and mortality

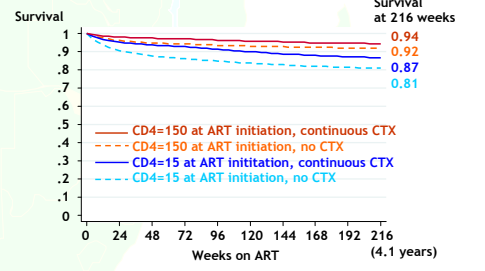
Figure 2: Variation in the impact of cotrimoxazole prophylaxis (CTX) on mortality with pattern of use, time on ART and current CD4



- 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/mm³

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)	-0.09 (-0.20,+0.03)
Change from week 12 on ART		
Current user of CTX vs not on CTX	-5 (-14,+3)	-0.08 (-0.25,+0.08)

- In the first 12 weeks on ART CD4 count increased by a mean of 87 cells/mm³ and BMI by 0.78 kg/m² 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