Does cotrimoxazole prophylaxis improve outcomes after ART initiation in HIV-infected African adults? A causal analysis using marginal structural models

AS Walker[1], D Ford[1], F Ssali[2], P Munderi[3], A Reid[4], A Kambugu[5], CF Gilks[6], AG Babiker[1] and the DART Trial Team

[1]MRC Clinical Trials Unit, London, UK; [2]Joint Clinical Research Centre, Kampala, Uganda; [3]MRCUVRI Program on AIDS, Entebbe, Uganda; [4]University of Zimbabwe, Harare, Zimbabwe; [5]Infectious Diseases Institute, Mulago, Uganda; [6]Imperial College, London, UK

ISCRTN 13968779

Poster #846b

www.ctu.mrc.ac.uk/dart
Email: dart@ctu.mrc.ac.uk

Abstract

Background: Randomised trials have shown that cotrimoxazole prophylaxis significantly reduces mortality in untreated HIV infection in resource-limited settings, but no trial has assessed whether benefits also occur on ART. Addressing this question outside of a trial requires causal models as use of cotrimoxazole prophylaxis after ART initiation is likely to influence and be influenced by underlying prognosis.

Methods: DART is a randomised trial of management strategies in symptomatic ART-naive adults with CD4<200 cells/mm^3 initiating triple drug ART in 4 centres (3 Uganda including one satellite, 1 Zimbabwe). In each centre, cotrimoxazole prophylaxis was prescribed at the treating physician's discretion. Marginal structural models with stabilized time-dependent inverse probability treatment weights were used to estimate the causal effect of cotrimoxazole prophylaxis (excluding 137 patients in a pilot STI study) splitting follow-up into 4-week periods (stratifying by centre and randomised monitoring strategy to compute weights).

Results: By March 2007, 3179 patients contributed 9214 years follow-up (median 3 years) and 267 deaths. Cotrimoxazole use differed by centre (12%, 77%, 71% and 72% of follow-up). Time-dependent predictors of cotrimoxazole use included lower CD4 and haemoglobin (last and last-but-one), WHO stage 3/4 event in the previous 4 weeks or earlier, and STI randomisation (not randomised, randomised to continuous ART or STIs). In the first 12 weeks after randomisation when use depended only on baseline factors, cotrimoxazole prophylaxis was associated with a significant reduction in mortality (OR=0.51 [95%CI 0.32-0.83] p=0.007), but less evidence of reductions in malaria (0.82 [0.63-1.05], p=0.12) and WHO 4 events (0.84 [0.54-1.20] p=0.34). After 12 weeks cotrimoxazole was associated with a smaller reduction in mortality (0.72 [0.51-1.02] p=0.07), a similar reduction in malaria (0.76 [0.62-0.94] p=0.01) and no effect on WHO 4 events (1.03 [0.73-1.46] p=0.87).

Discussion: Marginal structural models applied to observational data where cotrimoxazole prophylaxis was not used continuously and depended on time-varying confounders (which could be influenced by previous use) suggest that current cotrimoxazole prophylaxis reduces risk of mortality and malaria, but not WHO 4 events, in patients receiving ART. Mortality benefits appear to be greater during the first 12 weeks, which could be due to greater effects at ART initiation or in sicker patients.

DART trial design

- DART (Development of AntiRetroviral Therapy) is a randomised trial of management strategies in symptomatic ART-naive adults with CD4<200 cells/mm^3 initiating triple drug ART. 3316 participants have been randomised to
  - **Laboratory and Clinical Monitoring (LCM):** 12 weekly biochemistry and FBC, CD4 with all laboratory results returned to treating clinicians
  - **Clinical Monitoring Only (CMO):** 12 weekly biochemistry and FBC, with results only returned to treating clinicians if requested for clinical reasons or a grade 4 toxicity; 12 weekly CD4, with no results returned to treating clinicians
- Following a pilot study in 137 patients, 813 patients who achieved CD4≥300 cells/mm^3 after 48 or 72 weeks on ART entered a second randomisation comparing continuous therapy with structured treatment interruptions ((STI) 12 weeks on, 12 weeks off ART). The STI randomisation was terminated early on recommendation of DSMC in March 2006; all patients are now on continuous ART, or off ART for other reasons
- DART is running in 3 centres, 2 in Uganda (plus 1 satellite site), 1 in Zimbabwe
- **Cotrimoxazole is prescribed at the discretion of the treating clinician**

Methods: Patients, follow-up, data

- 3179 patients in DART were included (137 patients who took part in a pilot study of structured treatment interruptions of ART were excluded)
- 9214 years follow-up between January 2003 and March 2007
- 267 deaths; 84 (31%) within 12 weeks of ART initiation
- 369 first WHO 4 events and 1149 first diagnoses of malaria after entry

Table 1: Characteristics of the included DART cohort at randomisation

At ART initiation	DART N=3179	
Sex: female	2057	(65%)
Age (years) (median, IQR)	36	(31-42)
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)

- Information on current medication (other than ART) including drug, start date and indication was collected at 12-weekly visits
- We distinguished between cotrimoxazole prophylaxis and cotrimoxazole treatment by duration of use (usually ≤14 days for treatment) and reason for use
- **All analyses compare cotrimoxazole prophylaxis with no prophylaxis**

Methods: Marginal Structural Models

- Marginal structural models are causal models which can be applied to observational data which include time dependent confounders, which may themselves be affected by previous exposure
  - They are fitted in two stages: firstly each subject's probability of having their own treatment history for each time period given their covariate history is estimated. Then the effect of treatment on outcome is estimated in a weighted regression model, with weights for a subject in a time period inversely proportional to probability of their observed treatment history
- Data were split into 4-weekly intervals from DART randomisation. Cotrimoxazole prophylaxis use within any 4-week interval was defined as use for at least 7 days
- Use of cotrimoxazole in the first 12 weeks after DART randomisation was assumed to depend only on baseline covariates
- Logistic regression models were used to estimate the probability of cotrimoxazole in any 4-week interval >12 weeks after randomisation adjusting for previous cotrimoxazole prophylaxis (in the last six 4-week intervals for intervals >24 weeks after randomisation; and in the last three 4-week intervals for intervals 12-24 weeks after randomisation), time since randomisation (as a fractional polynomial) and baseline covariates (age, sex, stage, CD4, haemoglobin at trial entry, recruitment year). Time dependent covariates considered were: current and lagged CD4, current and lagged haemoglobin, history of WHO stage 3/4 events since randomisation and entry into the structured treatment interruption randomisation
  - Models were fitted within each centre (denoted A/B/C/D) and trial arm (LCM/CMO) and separately for intervals >24 weeks after randomisation and 12-24 weeks after randomisation. Backward elimination using p<0.1 was used. We fitted all predictors identified in any of the models in a final model within centre and arm to compute inverse-probability treatment weights for each period
- To adjust for censoring by loss to follow-up/end of follow-up the inverse probability of remaining uncensored was also estimated for each time period dependent on baseline and time-dependent covariates and cotrimoxazole history and included in the final weight
- The effect of cotrimoxazole on outcome was estimated by weighted logistic regression model adjusting for baseline covariates and time since randomisation. Weights adjusted appropriately for time-dependent confounders. We combined estimates for ≤12 weeks and >12 weeks by including intervals ≤12 weeks with unit weight

Use of cotrimoxazole prophylaxis

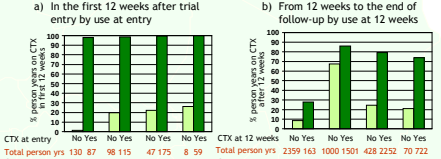
Table 2: Proportion of total follow-up time spent on cotrimoxazole prophylaxis by centre

Centre	A	B	C	D
Total patients (n)	(n=964)	(n=942)	(n=979)	(n=294)
On cotrimoxazole				
% person years	**12%**	**77%**	**72%**	**71%**
Person years follow-up	2739	2714	2902	858

Figure 1: Proportion of follow-up time spent on cotrimoxazole prophylaxis

a) In the first 12 weeks after trial entry by use at entry

b) From 12 weeks to the end of follow-up by use at 12 weeks



- **Cotrimoxazole prophylaxis was often not continuous if started (patients stopped and started during follow-up); patterns of use differed by centre**

Use of cotrimoxazole prophylaxis by time since randomisation and calendar time

Figure 2: Proportion of follow-up spent on cotrimoxazole prophylaxis by time since randomisation in patients who were not on prophylaxis at 12 weeks

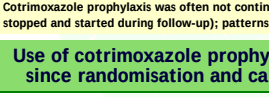
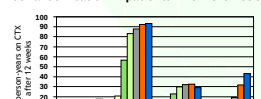


Figure 3: Proportion of follow-up spent on cotrimoxazole prophylaxis by calendar time in patients who were not on prophylaxis at 12 weeks



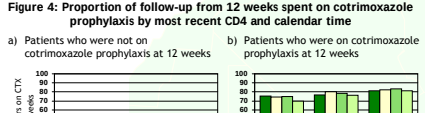
- **Use of cotrimoxazole prophylaxis (in those not on it at 12 weeks) increased with time since randomisation and with calendar time**
  - but effects differed by centre

Time-dependent predictors of use of cotrimoxazole prophylaxis

Figure 4: Proportion of follow-up from 12 weeks spent on cotrimoxazole prophylaxis by most recent CD4 and calendar time

a) Patients who were not on cotrimoxazole prophylaxis at 12 weeks

b) Patients who were on cotrimoxazole prophylaxis at 12 weeks

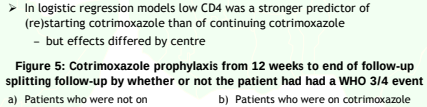


- Recent low CD4 was a time-dependent predictor of use of cotrimoxazole prophylaxis in both trial arms (LCM/CMO)
- In logistic regression models low CD4 was a stronger predictor of (re)starting cotrimoxazole than of continuing cotrimoxazole
  - but effects differed by centre

Figure 5: Cotrimoxazole prophylaxis from 12 weeks to end of follow-up splitting follow-up by whether or not the patient had had a WHO 3/4 event

a) Patients who were not on cotrimoxazole prophylaxis at 12 weeks

b) Patients who were on cotrimoxazole prophylaxis at 12 weeks



- A WHO 3/4 event since randomisation predicted subsequent use of cotrimoxazole prophylaxis
- In logistic regression models a recent event was a significant predictor of (re)starting cotrimoxazole; the effect on continuing was less consistent
  - but effects differed by centre

Regression models for use of cotrimoxazole prophylaxis

Time dependent predictors of use of cotrimoxazole were:
- Last and last-but one CD4
- Last and last-but one haemoglobin
- WHO 3/4 event in the last 4 week period or earlier but after randomisation
- Randomisation into the structured treatment interruption (STI) study (not randomised, randomised to continuous therapy or randomised to STI)
- Interactions between on/off cotrimoxazole in the last 4 week period and
  - last CD4, last haemoglobin, WHO 3/4 event in the last 4 week period, STI randomisation

The effect of cotrimoxazole prophylaxis on clinical outcomes

Table 3: The effect of cotrimoxazole prophylaxis on mortality after 12 weeks on ART: unweighted and weighted models

	OR	(95% CI)	heterogeneity between centres
Unweighted model adjusted for baseline covariates	0.78	(0.55-1.10)	het p=0.07
Unweighted model adjusted for baseline and time-dependent covariates	0.69	(0.49-0.96)	het p=0.94
Weighted MSM adjusted for baseline covariates[1]	0.72	(0.51-1.02)	het p=0.80

[1]Weights adjust for confounding due to time-dependent covariates

- Use of cotrimoxazole prophylaxis after 12 weeks on ART reduced the risk of death by an estimated 28%
- The estimated benefit from an unweighted model adjusting for baseline covariates only was similar but differed between centres (p=0.07); the heterogeneity reflects the difference between centres in the association between use and time-dependent covariates (CD4 etc)

Table 4: The effect of cotrimoxazole prophylaxis on clinical outcomes in the first 12 weeks on ART and after 12 weeks

Outcome	Unweighted model[1]	Weighted MSM model[1,2]		
	0-12 weeks OR (95% CI)	>12 weeks OR	(95% CI)	All weeks OR (95% CI)
Death	0.51 (0.32-0.83)	0.72	(0.51-1.02)	0.66 (0.49-0.88)
First WHO 4 event	0.84 (0.54-1.20)	1.03	(0.73-1.46)	0.93 (0.72-1.18)
First malaria diagnosis	0.82 (0.63-1.05)	0.76	(0.62-0.94)	0.77 (0.66-0.90)

[1]Adjusted for baseline covariates only [2]Weighted for time dependent covariates

- The benefit of cotrimoxazole prophylaxis on mortality was greater in the first 12 weeks than later; this may reflect a greater benefit during early ART or it may be that sicker patients benefit most from cotrimoxazole
- There was no evidence for any additional benefit of taking cotrimoxazole prophylaxis before the current period

Conclusions

- Marginal structural models applied to observational data where cotrimoxazole prophylaxis was not used continuously and depended on time-varying confounders (which could be influenced by previous use) suggest that current cotrimoxazole prophylaxis reduces risk of mortality and malaria, but not WHO 4 events, in patients receiving ART
- Results of ongoing randomised trials assessing the benefit of continuing cotrimoxazole with ART are awaited with interest

We thank all the patients and staff from all the centres participating in the DART trial.

MRC Programme on AIDS/Uganda Virus Research Institute, 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, A Ruberantwari, P Hughes, M Aber. **Joint Clinical Research Centre, Kampala, Uganda:** P Mugyenyi, C Kityo, D Tumukunde, F Ssali, D Atwine, G Mulindwa, R Byaruhanga, T Bakeimyaga-Grace, H Katabira, E Nimwesiga, G Barungi, S Atwiine, F Ahimbisibwe, S Tugume, T Otim, J Takubwa, M Mulindwa, S Murungi, J Tukamushaba, D Muebesa, H Kyomugisha, J Kagina, P Katundu, O Labeja. **University of Zimbabwe, Harare, Zimbabwe:** A Latif, J Hakim, V Robertson, A Reid, E Chidziva, A Jamu, S Makota, R Bulaya-Tembo, G Musoro, N Ngorima, F Taziwa, L Chakonza, H Chirairo, S Chitsungo, F Mapinge, A Mawora, C Muvirimi, G Tinago, J Chimanzi, J Machingura, C Maweni, S Mutsai, R Warara, M Matongo, S Mudzingwa, M Jangano, K Moyo, L Vere, M Phiri, Bafana T. **Academic Alliance, Mulago Hospital, Uganda:** E Katabira, J Oyugi, A Ronald, A Kambungu, R Ndumenya, F Sematala, R Nairudi, E Bulume, M Teopista, C Twijukye, Lubwana E. **The AIDS Support Organisation (TASO), Uganda:** A Coutinho, B Etukoit. **Imperial College, London, UK:** C Gilks, K Boocock, C Puddephatt, D Winogron. **MRC Clinical Trials Unit, London, UK:** J Darbyshire, DM Gibb, A Burke, D Bray, A Babiker, AS Walker, H Wilkes, M Rauchenberger, L Peto, K Taylor, M Speyer, A Ferrier, B Naidoo. **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, S Jones, 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 LPV/r (Kaletra/Aluvia) as part of the second-line regimen for DART.