Effect of WHO stage 3/4 events after ART initiation on survival of HIV-infected African adults in the DART trial

C Kityo[1], D Ford[2], AS Walker[2], J Hakim[3], P Munderi[4], F Lutwama[5], F Ssali[1], A Reid[3], H Grosskurth[4], DM Gibb[2], CF Gilks[6], AG Babiker[2] & the DART Trial Team

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

ISCRTN 13968779

MOPEB003

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

Background and objective

- **Background:** In middle/low-income settings, where access to laboratory measurements is limited, WHO stage 3/4 events are often used to determine success/failure of ART. However, mortality associated with different WHO 3/4 events is likely to vary.
- **Objective: To estimate mortality risks following a WHO 3/4 event according to diagnosis in individuals starting triple drug ART in Africa**

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

Patients, follow-up and data

- **Analysis of the effects of WHO 3/4 events on mortality included 3179/3316 DART participants (137 patients who took part in a pilot study of structured treatment interruptions of ART were excluded)**

Table 1: Characteristics of the included DART cohort at randomisation

At ART initiation	DART N=3179 (exc 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)

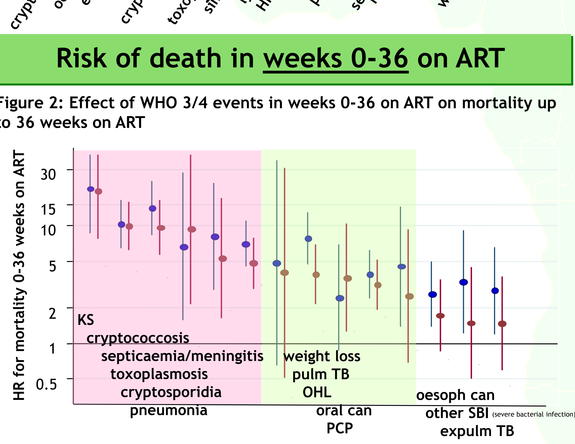
- 13,839 years follow-up between Jan 2003 and Dec 2008; median 4.8 years
- 1386 (44%) participants had a WHO 3/4 event after starting ART
- 359 deaths (156 (43%) in first 36 weeks on ART)
- 630 participants switched to second-line, all >36 weeks after starting ART; 7.5% of follow-up on second-line

Methods

- **Follow-up was divided by time on ART. We looked at the first 36 weeks on ART and >36 weeks on ART separately**
  - 0-36 weeks: high death rate, deaths may be related to late start of ART, events may be different to later (e.g. IRIS)
  - >36 weeks: events more likely to reflect ART failure, patients may switch to second-line therapy, which may reduce the risk of death
- **Cox proportional hazards models** were used to estimate the Hazard Ratio for mortality after a WHO 3/4 event
- **Marginal structural models** were used to estimate the causal Odds Ratio for mortality after a WHO 3/4 event

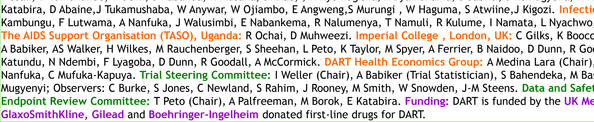
WHO 3/4 events after ART initiation

Figure 1: Number of events by type and time on ART



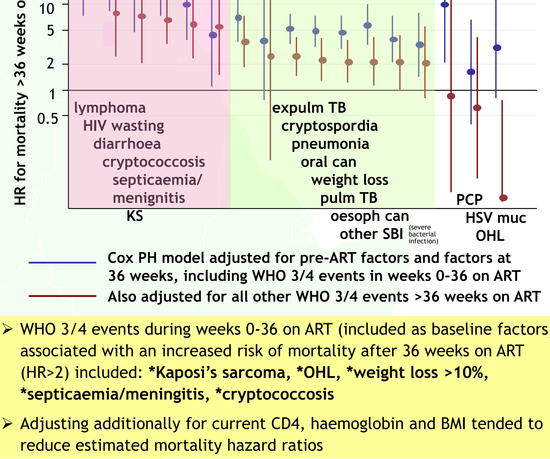
Risk of death in weeks 0-36 on ART

Figure 2: Effect of WHO 3/4 events in weeks 0-36 on ART on mortality up to 36 weeks on ART



Risk of death after 36 weeks on ART

Figure 3: Effect of WHO 3/4 event >36 weeks on ART on mortality >36 weeks on ART

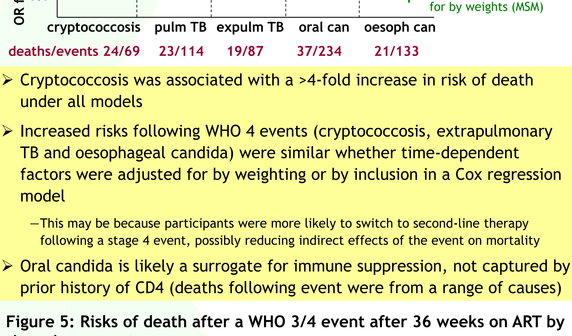


- WHO 3/4 events during weeks 0-36 on ART (included as baseline factors) associated with an increased risk of mortality after 36 weeks on ART (HR>2) included: ***Kaposi's sarcoma, *OHL, *weight loss >10%, *septicaemia/meningitis, *cryptococcosis**
- Adjusting additionally for current CD4, haemoglobin and BMI tended to reduce estimated mortality hazard ratios

Estimated causal risks of death after a WHO 3/4 event after 36 weeks on ART

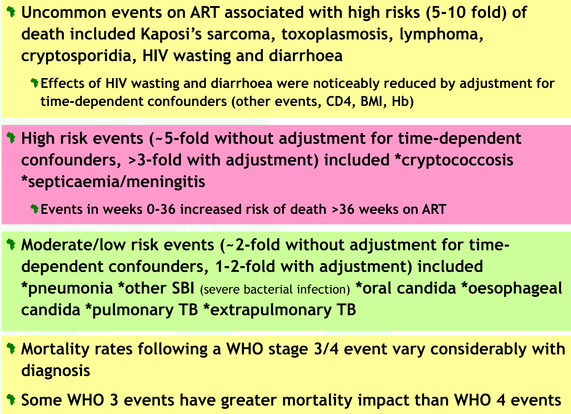
- Marginal structural models (MSM) were used to estimate the **direct and indirect effects** of an event on mortality. Pre-ART factors and factors at 36 weeks were adjusted for in the regression model. Weights were used to adjust for time-dependent confounders (e.g. CD4 which is likely to influence the probability of having a WHO event and may be influenced subsequently by the event).

Figure 4: Risks of death after a WHO 3/4 event after 36 weeks on ART



- Cryptococcosis was associated with a >4-fold increase in risk of death under all models
- Increased risks following WHO 4 events (cryptococcosis, extrapulmonary TB and oesophageal candida) were similar whether time-dependent factors were adjusted for by weighting or by inclusion in a Cox regression model
  - This may be because participants were more likely to switch to second-line therapy following a stage 4 event, possibly reducing indirect effects of the event on mortality
- Oral candida is likely a surrogate for immune suppression, not captured by prior history of CD4 (deaths following event were from a range of causes)

Figure 5: Risks of death after a WHO 3/4 event after 36 weeks on ART by time since event



Conclusions

- **Uncommon events on ART associated with high risks (5-10 fold) of death included Kaposi's sarcoma, toxoplasmosis, lymphoma, cryptosporidia, HIV wasting and diarrhoea**
  - Effects of HIV wasting and diarrhoea were noticeably reduced by adjustment for time-dependent confounders (other events, CD4, BMI, Hb)
- **High risk events (~5-fold without adjustment for time-dependent confounders, >3-fold with adjustment) included *cryptococcosis *septicaemia/meningitis**
  - Events in weeks 0-36 increased risk of death >36 weeks on ART
- **Moderate/low risk events (~2-fold without adjustment for time-dependent confounders, 1-2-fold with adjustment) included *pneumonia *other SBI** (severe bacterial infection) ***oral candida *oesophageal candida *pulmonary TB *extrapulmonary TB**
- **Mortality rates following a WHO stage 3/4 event vary considerably with diagnosis**
- **Some WHO 3 events have greater mortality impact than WHO 4 events**

We thank all the patients and staff from all the centres participating in the DART trial. 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. 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, 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. 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 Mulweezi. Imperial College , London, UK: C Gilks, K Boocock, C Puddephatt, D Winogron, 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, L Peto, 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, 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.