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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-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

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)

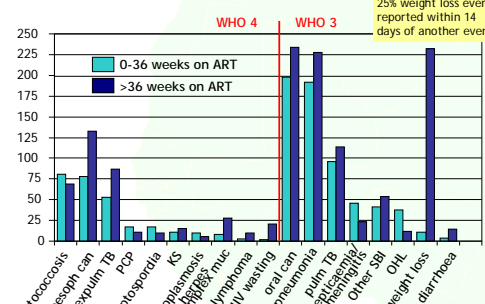
- 13,839 years follow-up between Jan 2003 and Dec 2008: median 4.8 years
- 1386 (44%) participants had a WHO 3/4 event after starting ART
- 359 deaths (156 (43%) in first 36 weeks on ART)
- 630 participants switched to second-line, all >36 weeks after starting ART; 7.5% of follow-up on second-line

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

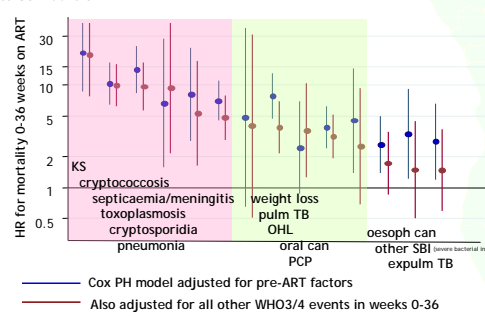
WHO 3/4 events after ART initiation

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



Risk of death in weeks 0-36 on ART

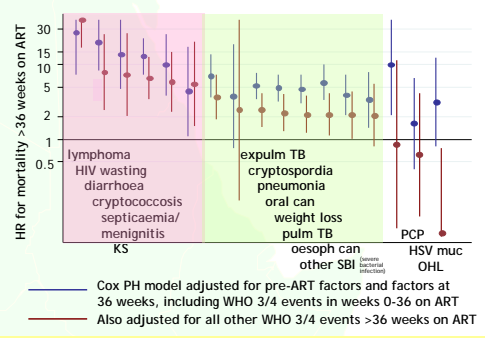
Figure 2: Effect of WHO 3/4 events in weeks 0-36 on ART on mortality up to 36 weeks on ART



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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

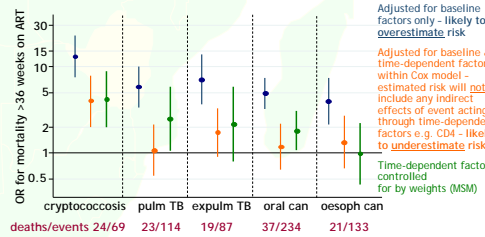


- WHO 3/4 events during weeks 0-36 on ART (included as baseline factors) associated with an increased risk of mortality after 36 weeks on ART (HR>2) included: *Kaposi's sarcoma, *OHL, *weight loss >10%, *septicaemia/meningitis, *cryptococcosis
- Adjusting additionally for current CD4, haemoglobin and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

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

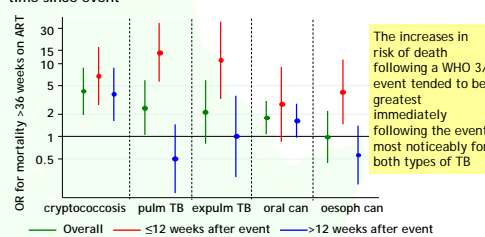
- Marginal structural models (MSM) were used to estimate the direct and indirect effects of an event on mortality. Pre-ART factors and factors at 36 weeks were adjusted for in the regression model. Weights were used to adjust for time-dependent confounders (e.g. CD4 which is likely to influence the probability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