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

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Background and objective

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

DART trial design

- DART (Development of Antiretroviral Therapy) was a randomised trial of management strategies in 2016 symptomatic ART-naive 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 can 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 377/3434 DART participants (127 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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>WHO 0</th>
<th>WHO 1</th>
<th>WHO 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (median, IQR)</td>
<td>35 (25-45)</td>
<td>36 (25-45)</td>
<td>36 (25-45)</td>
</tr>
<tr>
<td>CD4 (cells/mm³) (median, IQR)</td>
<td>179 (64-275)</td>
<td>179 (64-275)</td>
<td>179 (64-275)</td>
</tr>
<tr>
<td>WHO stage</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>26%</td>
<td>43%</td>
<td>38%</td>
</tr>
<tr>
<td>Oral candida</td>
<td>36%</td>
<td>38%</td>
<td>38%</td>
</tr>
</tbody>
</table>

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-risk events, deaths may be related to start of ART events may be different to later (e.g. IRIS)
  - >36 weeks: events may likely reflect true mortality, 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 in a time-dependent way
- Marginal structural models were used to estimate the causal Odds Ratio for mortality after a WHO 3/4 event

WHO 3/4 events post ART initiation

- 13,839 patients follow-up between Jan 2003 and Dec 2008; median 4.8 years
- 1368 (4%) patients had a WHO 3/4 event after starting ART
- 359 deaths (15%) in 1st 36 weeks on ART
- 630 participants switched to second-line, all >36 weeks after ART, 7.5% of follow-up on second-line

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

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

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

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

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

Figure 6: Mortality risk following a WHO stage 3/4 event is markedly increased and independent of co-morbidity

Conclusions

- Uncommon events on ART associated with high risks (5–10 fold) of death included Kaposi’s sarcoma, toxoplasmosis, lymphoma, HCMV, HIV wasting and diarrhoea
- Effects of HIV wasting and diarrhoea were noticeably reduced by adjustment 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)
- Cox PH model adjusted for pre-ART factors and factors at 36 weeks, including WHO 3/4 events in 0–36 on ART
- Also adjusted for all other WHO3/4 events in 0–36 weeks

- 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 (OR 2.82; 95% CI: Kaposi’s sarcoma, ORM: 4.0% weight loss >10%; *septicaemia/meningitis, +cryptococcosis
- Adjusting additionally for current CD4, haemoglobin and BMI tended to reduce estimated mortality hazard ratios

Estimated causals 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).

- The increases in risk of death following a WHO 3/4 event tended to be proportional immediately, the most noticeable for both types of TB

- Some WHO 3/4 events have greater mortality impact than WHO 4 events