**BACKGROUND**

DART was one of the first large randomised clinical trials of ART in Africa, comparing management strategies in 3166 adults initiating first-line ART in Uganda and Zimbabwe.

- Participants were randomised into two arms: a CLINICAL DRUG-GAMING (CDG) arm and a CLINICAL DRUG-GAMING (CDG) arm. Enrollment started in January 2003 and follow-up was continued until December 2006.

A large number of endpoints were initially reported, reflecting the relatively advanced HIV disease and severe comorbidities in participants enrolled in clinical trials. This resulted in a large number of events being reported, most of which were drug-related or related to treatment toxicities. The endpoints were reviewed by an independent endpoint review committee, the DART Events Committee (DEC), which was responsible for determining whether a given event was related to the study treatment or not.

**OBJECTIVE**

To devise a set of reproducible reliable criteria to supplement WHO 4 criteria to evaluate endpoints in clinical trials

**METHODS**

- Reported endpoints were reviewed using a standardised form, blinded to randomised arm, and classified using WHO criteria for stage 1 and 4 events (as modified in 2000).

The process of classifying endpoints was complex and time-consuming. WHO criteria were determined based on the DART protocol.

- WHO 4 events were reported by sites after enrolment and before 31 December 2008.

- Events were classified as either fatal or non-fatal, and as either WHO 4 or non-acute. The WHO 4 criteria were defined as events that were: 1. Life-threatening, 2. Required hospitalisation, 3. Resulted in death, or 4. Resulted in severe residual disability.

- The decision to classify an event as a WHO 4 event was based on clinical judgment, taking into account the patient's overall clinical status, the severity of the event, and the course of the disease.

- The classification of WHO 4 events was done by an independent endpoint review committee, the DART Events Committee (DEC), which was responsible for determining whether a given event was related to the study treatment or not.

- The classification was based on a consensus of the DEC members, with any disagreements resolved by a second review.

**RESULTS**

- **Depression**
  - Report rate: 9%
  - Severity: WHO 4 events (9%)

- **HIV wasting**
  - Report rate: 6%
  - Severity: WHO 4 events (6%)

- **Cryptococcal meningitis**
  - Report rate: 4%
  - Severity: WHO 4 events (4%)

- **CMV oesophagitis**
  - Report rate: 3%
  - Severity: WHO 4 events (3%)

- **Tuberculosis, extrapulmonary**
  - Report rate: 2%
  - Severity: WHO 4 events (2%)

**DISCUSSION**

- Most HIV clinical trials published and presented in recent years have used surrogates markers as endpoints. The change from using clinical to surrogate endpoints has been driven by the reduction in events due to the effectiveness of therapy, and by the evidence of clinical events that are no longer relevant as drug development endpoints.

- The availability of effective ART has led to a shift in focus from clinical endpoints to surrogate endpoints, such as CD4 cell count and viral load. However, clinical endpoints remain important in evaluating the safety and efficacy of new treatments.

- The vast majority of these studies have been in populations with resource-rich settings.

- The 43% of the 21 million people who are living with HIV do not have access either to ART or to the laboratory measurements on which trials in resource-rich settings depend.

- In most cases, it is not possible to use surrogate endpoints or clinical events to measure treatment outcome in resource-limited settings.

- An opportunity exists to undertake trials based on clinical outcomes to answer crucial scientific questions about HIV management.