# Mortality/morbidity after initiating ART with CD4 <100 cells/μL in the REALITY trial

**Poster 490**

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ISRCTN43622374


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## ABSTRACT (updated)


**Background:** In sub-Saharan Africa, 20-25% of those starting ART have CD4<100 cells/μL; ~10% die within 3 months. We investigated the contribution and timing of different causes of mortality/morbidity in the REALITY trial (ISRCTN43622374).

**Methods:** Patients starting ART were randomised to enhanced-prophylaxis against infections (co-trimoxazole [CTX] plus 12 weeks isoniazid+fluconazole, single-dose albendazole, 5-days azithromycin (AZ); Px+) vs CTX alone. Events and causes of death were adjudicated by an endpoint review committee blind to randomization, as (non-mutually exclusively) TB, cryptococcosis, severe bacterial infection (SBI; septicaemia, meningitis, pneumonia), other infections potentially responsive to AZ (eg diarrhoea, malaria, encephalitis, toxoplasmosis), other events, and unknown (deaths only).

**Results:** Median pre-ART CD4 was 37 cells/μL. 225(12.7%) of 1805 patients died by week-48. Most fatal/non-fatal events occurred early (median 4.0 (IQR 2.0-11.7) weeks) after ART initiation, then rates declined exponentially. 154 deaths were adjudicated as having single and 71 multiple causes, which included TB in 80(4.5%) patients, cryptococcosis 20(1.1%), SBI 33(1.9%), other potentially-AZ-responsive infections 23(1.3%), other causes 63(3.6%) and unknown causes 88(5.0%). Considering the incidence of first fatal/non-fatal events through week-48, TB was diagnosed in 10.9%, cryptococcosis 2.5%, SBI 5.1%, other potentially-AZ-responsive infections 3.6% and other events 27.0%. Px+ reduced deaths from cryptococcosis (p=0.03) and unknown causes (p=0.03) but not deaths from TB (p=0.34), SBI (p=0.90), other potentially-AZ-responsive infections (p=0.31) or other causes (p=0.66). Px+ reduced the incidence of non-fatal/fatal TB (p=0.007) and cryptococcosis (p=0.03) but not SBI (p=0.26), other potentially-AZ-responsive infections (p=0.34) or other events (p=0.81). By 48 weeks, event rates were lowest (<1 per 100 person-years [PY]) for cryptococcosis, moderate (1–5 per 100 PY) for TB, SBI, potentially AZ-responsive infections and unknown deaths, and highest (>5 per 100PY) for other events. Median last post-baseline VL before death was 95 c/ml (N=140); CD4 was 59 cells/μL.

**Conclusions: Enhanced prophylaxis reduced mortality and the incidence of TB and cryptococcosis in those with CD4 <100 cells/μL. The high early incidence of both opportunistic and non-opportunistic infections highlights the need for a broad Px+ bundle at the same time as ART initiation in those with advanced HIV disease.**


## BACKGROUND

- ~20-25% of people starting ART in Africa have CD4 <100 cells/μL
  - ~10% die within three months of starting treatment
- In the REALITY randomised trial, a broad enhanced anti-infection prophylaxis bundle reduced all-cause mortality versus co-trimoxazole alone in adults and children aged over 5 years initiating ART with CD4<100 cells/μL (Hakim *et al*., NEJM 2017)
- Here we investigate in detail:
  - Timing of different causes of mortality/morbidity
  - Relative importance of different causes of mortality and morbidity

## METHODS

- REALITY (ISRCTN43622374) recruited 1805 HIV-infected ART-naïve adults and children ≥5 years (98% aged ≥13 years) from Zimbabwe, Uganda, Malawi and Kenya with CD4<100 cells/μL
- Patients were randomized to enhanced-prophylaxis against infections vs standard-prophylaxis (co-trimoxazole), with World Health Organization (WHO)-recommended ART (2NRTI+NNRTI)
  - Enhanced-prophylaxis comprised single-dose albendazole, 5-days azithromycin, 12 weeks fluconazole, and 12 weeks fixed-dose-combination (FDC) of co-trimoxazole/isoniazid/pyridoxine
- Causes of death and non-fatal events (grade 3/4 AEs, SAEs, WHO 3/4 events) were adjudicated by an independent endpoint review committee blinded to randomised group, as (non-mutually exclusively):
  - Tuberculosis (TB)
  - Cryptococcosis
  - Severe bacterial infection (SBI; septicaemia, meningitis, pneumonia)
  - Other infections potentially responsive to azithromycin (eg diarrhoea, malaria, encephalitis, toxoplasmosis)
  - Other events
  - Unknown (deaths only; many died at home)
- Events were also assessed for compatibility with IRIS

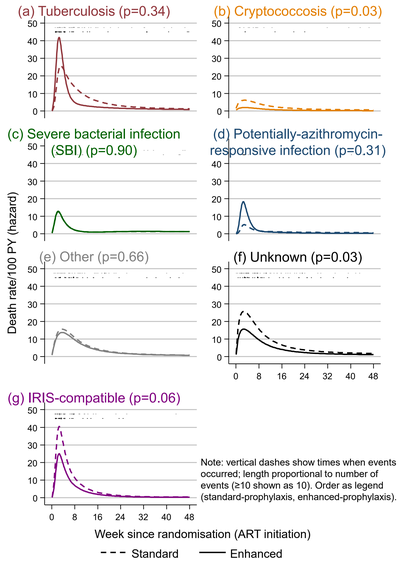
**Table 1: Baseline characteristics**

| | Total (n=1805) |
|---|---|
| Male | 961 (53.2%) |
| Age (years)<br>5-17 years | 36 (29-42)<br>72 (4.0%) |
| WHO stage<br>1/2<br>3/4 | <br>854 (47.3%)<br>951 (52.7%) |
| CD4 (cells/μL) | 37 (16-63) |
| HIV viral load (copies/ml) (N=1804) | 249770 (95280, 606360) |
| Weight (kg) | 7.8 (6.1-9.5) |
| Country of enrolment<br>Uganda<br>Zimbabwe<br>Kenya<br>Malawi | <br>630 (34.9%)<br>569 (31.5%)<br>351 (19.4%)<br>255 (14.1%) |

Note: values are n (%) or median (IQR)

## RESULTS

**Figure 1:**
**Rates of fatal events over time from ART initiation**



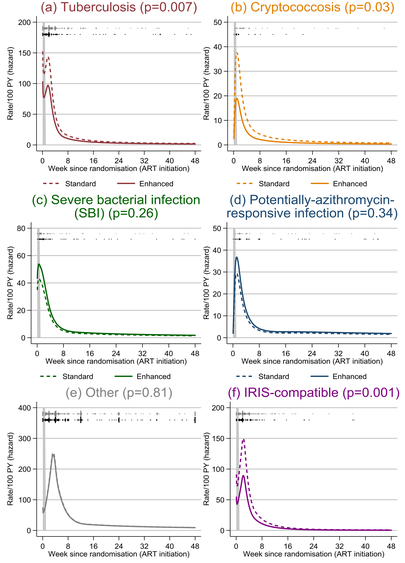

Note: vertical dashes show times when events occurred; length proportional to number of events (≥10 shown as 10). Order as legend (standard-prophylaxis, enhanced-prophylaxis).

- 225 (12.7%) of 1805 patients died by week-48
- Most fatal/non-fatal events occurred early after ART initiation, then rates declined exponentially (Figure 1) (Figure 2)
- 154 deaths were adjudicated as having single and 71 multiple causes, which included TB in 80 (4.5%) patients, cryptococcosis 20 (1.1%), SBI 33 (1.9%), other potentially-azithromycin-responsive infections 23 (1.3%), other 63 (3.6%) and unknown 88 (5.0%)
  - 67/225 (29.8%) deaths were compatible with IRIS
- Enhanced-prophylaxis reduced deaths from cryptococcosis (p=0.03) and unknown causes (p=0.03) but not deaths from TB (p=0.34), SBI (p=0.90), other potentially-azithromycin-responsive infections (p=0.31) or other causes (p=0.66) (Figure 1)
  - Similar trend in IRIS-compatible deaths (p=0.06)
- Enhanced-prophylaxis reduced the incidence of non-fatal/fatal TB (p=0.007), cryptococcus (p=0.03) and IRIS-compatible events (p=0.001) but not SBI (p=0.26), other potentially-azithromycin-responsive infections (p=0.34) or other events (p=0.81) (Figure 2)
- Median (IQR) last post-baseline VL before death was 95 (<50-522) copies/ml (N=140), with little variation between causes
- CD4 was 59 (32-101) cells/μL, also with little variation (Table 2):

**Table 2: Last post-baseline CD4 and viral load before death**

| Cause of death | CD4 | Viral load |
|---|---|---|
| Tuberculosis | 53 (32-108) | 125 (<50-314) |
| Cryptococcosis | 46 (14-59) | <50 (<50-212) |
| Severe bacterial infection | 53 (14-91) | 70 (<50-522) |
| Potentially-azithromycin-responsive infection | 50 (32-115) | 309 (118-637) |
| Other event | 66 (36-111) | 99 (<50-322) |
| **Unknown cause** | **67 (32-99)** | **70 (<50-724)** |

**Figure 2: Rates of combined fatal plus non-fatal events over time from ART initiation**




## CONCLUSIONS

- **In Africans who initiated ART with CD4 <100 cells/μL, enhanced prophylaxis reduced the mortality from cryptococcosis and unknown cases, and the incidence of TB, cryptococcosis and IRIS-compatible events**
- **The high early incidence of both opportunistic and non-opportunistic infections highlights the need for a broad enhanced-prophylaxis bundle at the same time as ART initiation in those with advanced HIV disease**


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