High rate of viral suppression in late deaths on first-line ART in resource-limited settings

David Dolling[1], Moira Spyer[1], Peter Nkurunziza[2], Pontiano Kaleebu[2], Cissy Kityo[3], James Hakim[4], Charles Gilks[5], Deenan Pillay[6], Ruth Goodall[1] on behalf of the DART Virology Group

[1]MRC Clinical Trials Unit at UCL, London, UK; [2]MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda; [3]Joint Clinical Research Centre, Kampala, Uganda; [4]University of Zimbabwe, Harare, Zimbabwe; [5]School of Population Health, University of Queensland, Brisbane, Australia, [6]Africa Centre for Health and Population Studies, University of KwaZulu Natal, Durban, South Africa

1027

Email: d.dolling@ucl.ac.uk

Background

- Early deaths (<48 weeks) after ART initiation in resource-limited settings are well recognised and have been shown to be related to patients starting ART severely immunocompromised.
- Late deaths are widely assumed to be due to virological failure or to non-adherence.
- **Objective:** To determine risk factors for late deaths with suppressed viral load.

DART virology study

- DART compared management strategies in 3,316 ART-naive adults initiating a triple drug regimen in Uganda and Zimbabwe containing ZDV+3TC and either TDF, ABC or NVP.
- CD4 cell counts, haematology and biochemistry tests every 12 weeks and participants were randomised to either:
  - **L**aboratory and **C**linical **M**onitoring (LCM): Test results returned to clinicians
  - **C**linically **D**riven **M**onitoring (CDM): Test results not returned.
- Plasma was stored at screening, enrolment and every 12 weeks.

Methods

- Retrospectively conducted viral load testing on all patients who died after 48 weeks on first-line ART. Viral was tested at the time of death and at week 48.
- Reported causes of death were adjudicated by an Independent Review Committee.
- Logistic regression models determined predictors of death with virological suppression (<200 copies/mL) among patients who died.
- In the multivariate logistic regression model, variables were selected using backward elimination with a p-value of 0.1.
- Fractional polynomials were used for continuous variables.
- A linear mixed model investigated CD4 trajectory on the square root scale in the 48 weeks prior to death. CD4 cell count trajectories were back-transformed using a smearing estimate.
- Cause-specific (CSH) and subdistribution hazard (SH) ratios were examined to determine if variables had a direct or indirect effect on death.

Virological status at death

- Viral load measurements available a median (IQR) of 10 (6-13) weeks prior to death.
- 45/105 (41%) patients were virologically suppressed at death on first-line ART.
- Deaths with virological suppression were more likely to be gastrointestinal (12% vs 2%; p=0.04) or HIV-related malignancies (12% vs 2%; p=0.04).
- Deaths with virological failure more often cryptococcus (8% vs 0%; p=0.08).
- No difference in other causes of death (Neurological, Tuberculosis, Renal, Lung, Septicaemia/Neutropenia, Trauma/Suicide, Cardiovascular Disease, Hepatic, Malaria/Cholera, Anemia/neutropenia/thrombocytopenia, Other Cancers, Lactic acidosis, Wasting/Diarrhoea, Unknown).

Variable	N (% with VS)	Univariate OR (95% CI)	Multivariate OR (95% CI)	p-value
Trial Arm				
LCM	45 (58%)	1.00	1.00	<0.01
CDM	60 (28%)	0.29 (0.13 – 0.65)	0.28 (0.11 – 0.68)	-
Gender				
Male	42 (31%)	1.00	-	-
Female	63 (48%)	2.03 (0.89 – 4.60)	-	-
Initial ART				
TDF	84 (37%)	1.00	-	-
NVP	11 (55%)	2.05 (0.58 – 7.28)	-	-
ABC	10 (60%)	2.56 (0.67 – 9.80)	-	-
TB at enrolment	26 (42%)	1.08 (0.44 – 2.64)	-	-
Centre				
Entebbe	33 (52%)	1.00	1.00	0.06
JCRC	40 (45%)	0.77 (0.31 – 1.94)	1.07 (0.37 – 3.04)	
Harare	32 (25%)	0.31 (0.11 – 0.90)	0.30 (0.09 – 0.98)	
Opportunistic Infections	21 (24%)	0.38 (0.13 – 1.13)	-	-
Variable	**Median with VS (IQR)**	**Univariate OR (95% CI)**	**Multivariate OR (95% CI)**	**p-value**
Age (Decades)	4.0 (3.4 – 4.3)	1.42 (0.86 – 2.34)	-	-
Baseline (week 0) CD4 Cell Count (per 100 Cells/mm^3)	1.07 (0.56 – 1.42)	3.42 (1.65 – 7.10)	3.83 (1.69 – 8.69)	<0.01
Baseline (week 0) Viral Load (log_{10} copies/mL)	5.47 (5.01 – 5.66)	1.52 (0.84 – 2.76)	-	-

Table 1: Predictors of death with virological suppression among patients who died

- Deaths with virological suppression were significantly more likely in the LCM arm.
- Patients with higher baseline CD4 cell count more likely to die virologically suppressed.

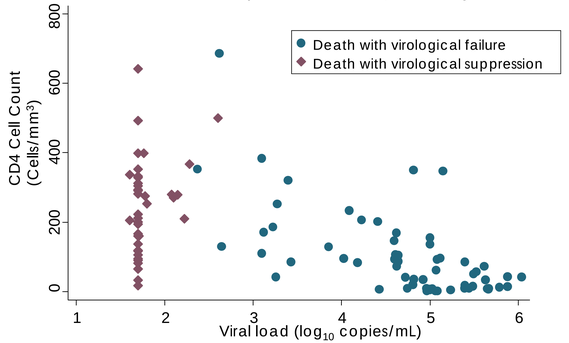


Figure 1: Viral load and CD4 cell count at death

- CD4 was significantly lower at death in patients with virological failure (Median: 62 vs 238 cells/mm^3; p<0.01).

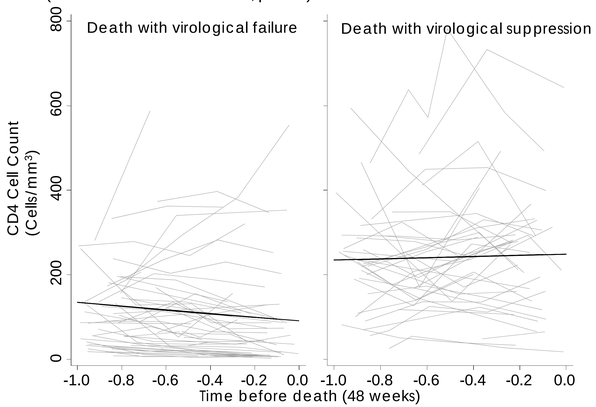


Figure 2: CD4 trajectory prior to death

- Clear decline of 44 CD4 cells/mm^3 in the 48 weeks (p<0.001) prior to death in patients with virological failure, while patients who died with virological suppression had an increase of 14 CD4 cells/mm^3 per 48 weeks (p=0.54).

Predictors of death by virological status

Variable	Death with virological failure aCSH	p-value	aSH	p-value	Death with virological suppression aCSH	p-value	aSH	p-value
Trial Arm								
LCM	1.00	<0.01	1.00	<0.01	1.00	0.06	1.00	0.08
CDM	2.27	-	2.39	-	0.55	-	0.57	-
Centre								
Entebbe, Uganda	1.00	0.48	1.00	0.42	1.00	0.17	1.00	0.25
Kampala, Uganda	0.97	-	1.04	-	0.91	-	0.99	-
Harare, Zimbabwe	1.36	-	1.46	-	0.44	-	0.49	-
Age (10 years)	0.98	0.91	1.00	0.99	1.37	0.10	1.38	0.09
Baseline BMI (kg/m^2)	0.99	0.81	0.99	0.98	0.87	<0.01	0.88	0.06
Baseline CD4 cell count (100 Cells/mm^3)	0.48	<0.01	0.47	<0.01	1.63	0.07	1.52	0.10

Table 2: Cause-specific (aCSH) and subdistribution (aSH) hazard ratio for all patients

- Similar covariate effects for both models implies direct rather than indirect causality.
- Patients in the CDM arm had a more than 2-fold higher rate of death with virological failure and a higher cumulative incidence of death with virological failure.
- A 100 cell/mm^3 increase in baseline CD4 cell count was associated with a more than 2-fold reduction in the rate of death with virological failure.
- Our data suggests that patients in the CDM arm had a lower risk of death with virological suppression (p=0.08).
- Patients with a lower baseline BMI and older patients had a higher rate of death with virological suppression.
- There was potentially an increased rate of death with virological suppression for higher baseline CD4 cell count (p=0.10).

Conclusions

- A surprisingly high number of late deaths on ART occurred without virological criteria for treatment switch being met.
- Returning test results to clinicians reduced the rate of death with virological failure.
- Deaths with virological suppression were unlikely to be directly related to HIV and, as shown in other studies, there was an increased risk with older age and lower BMI.
- As expected, deaths with virological failure occurred more in those with lower baseline CD4 cell count.
- The relationship between trial arm and deaths with virological suppression is unexplained.

DART Virology Group: P. Kaleebu (Co-Chair), D. Pillay (Co-Chair), P. Awio , M. Chirara, D. Dunn, D. M. Gibb, C. Gilks, R. Goodall, A. Kapaata, M. Katuramur, F. Lyagoba, B. Magambo, K. Mataruka, L. Mugarura , T. Musunga, M. Nabankkema, J. Nkalubo, P. Nkurunziza, C. Parry, V. Robertson, M. Spyer, D. Mulima, D.E. Williams, I. Nankya, S. Nassimbwa, E. Ndashimye, E. Nabulime, M. Phiri, K. Mutasa, S. Mukasa.

Funding: DART is funded by the **UK Medical Research Council**, the **UK Department for International Development (DFID)**, and the **Rockefeller Foundation**. **GlaxoSmithKline/ViiV Healthcare, Gilead** and **Boehringer-Ingelheim** donated first-line drugs for DART.