Poster 00234

Association of plasma biomarkers with early mortality in advanced HIV infection

Victor Riitho[1], Roisin Connon[2], Agnes Gwela[3], Josephine Namusanje[4], Ruth Nhema[5], Abraham Siika[6], James Hakim[5], Victor Musiime[4], James A. Berkley[3], Alexander Szubert[2], Nigel Klein[7], A S. Walker[2], Diana Gibb[2], Andrew J Prendergast[1], for REALITY Trial Team

email: vriitho@gmail.com / v.riitho@qmul.ac.uk

[1]Queen Mary University of London, London, United Kingdom, [2]MRC Clinical Trials Unit at UCL, Institute of Clinical Trials and Methodology, UCL, London, United Kingdom, [3]KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya, [4]Joint Clinical Research Centre, Kampala, Uganda, [5]University of Zimbabwe, Harare, Zimbabwe, [6]Moi University, Eldoret, Kenya, [7]UCL Great Ormond Street Institute of Child Health, London, United Kingdom

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BACKGROUND

- One-third of people living with HIV in Sub-Saharan Africa start treatment with advanced HIV (CD4 count <200/mm^3 or WHO stage 3/4 disease), of whom 10% die within three months of initiating ART.
- In the REALITY trial (ISRCTN43622374), 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).
- In this study, we explored the contribution of soluble immune and inflammatory markers to early mortality in advanced HIV in Kenya (Kilifi and Eldoret), Uganda (Fort Portal, Mbale, Mbarara and Gulu) and Zimbabwe (Harare).

METHODS

- A case-cohort sub-study of the REALITY) trial included 599 patients aged ≥13 years with CD4 <100 cells/mm^3 starting first-line ART (2NRTI+NNRTI +/- additional INSTI for 12 weeks).
- Patients were randomised to standard-of-care (SOC) prophylaxis (cotrimoxazole) or enhanced prophylaxis (EP) [additional isoniazid/pyridoxine (≥12 weeks), fluconazole (12 weeks), azithromycin (5 days) and albendazole (one dose)].
- Cases were all deaths ≤24 weeks post-starting ART and controls were a sample of those alive at week 48. Biomarkers were assayed using ELISA and Luminex.
- Associations of baseline values with all-cause mortality at 24 weeks were analysed using a Cox model (backward elimination, exit p=0.1). Similarly, cause-specific mortality was analysed for TB, cryptococcosis, severe bacterial infection (SBI), other and unknown (deaths could be from multiple causes) using Fine & Gray models (death for another cause a competing risk). Models adjusted for prophylaxis randomisation, VL, CD4, WHO stage, age and BMI at enrolment, and centre; and weighted according to inverse probability of selection into the substudy.

RESULTS

Table 1: Baseline characteristics

Variable	Overall	Deaths	Controls
Baseline clinical characteristics: median (IQR) or n (%)			
Age, years	37 (30-43)	38 (30-44)	36 (30-43)
CD4 count, cells/uL	34 (15-64)	24 (10-46)	38 (16-67)
BMI, kg/m2	19 (17-21)	18 (16-19)	19 (17-21)
WHO Stage at enrolment: 3-4	351 (59%)	130 (77%)	221 (51%)
Enhanced prophylaxis	295 (49%)	69 (41%)	226 (53%)
Plasma HIV RNA, log 10 copies/mL	5.43 (5.04-5.79)	5.55 (5.14-5.96)	5.40 (4.97-5.71)

CAUSES OF DEATH

Causes of death were adjudicated by an independent endpoint review committee blinded to randomised group, and categorised as (non-mutually exclusively):

- Tuberculosis (TB)
- Cryptococcosis
- Severe bacterial infection (SBI; septicaemia, meningitis, pneumonia)
- Other infections potentially responsive to azithromycin (e.g. diarrhoea, malaria, encephalitis, toxoplasmosis)
- Unknown (many died at home)

References:

Hakim *et al.*, Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa, NEJM 2017

Post *et al.*, Causes and Timing of Mortality and Morbidity Among Late Presenters Starting Antiretroviral Therapy in the REALITY Trial, CID 2018

Table 2: Associations with all cause mortality

Variable	Univariable[1] HR (95% CI)	Multivariable HR (95% CI)	Multi-variable p-value
CRP (log 10)	2.46 (1.92-3.15)	1.98 (1.51-2.59)	<0.001
IFN-gamma (log 10)	3.66 (2.06-6.50)	3.09 (1.55-6.16)	0.001
IL23 (log 10)	0.85 (0.60-1.19)	0.50 (0.32-0.80)	0.004
IL2 (log 10)	0.72 (0.32-1.61)	0.20 (0.06-0.67)	0.009
IL6 (log 10)	1.75 (1.09-2.80)	2.84 (1.00-8.06)	0.05
IP10 (log 10)	1.25 (0.89-1.76)	2.29 (1.39-3.75)	0.001
Rantes (log 10)	0.52 (0.33-0.81)	0.32 (0.17-0.60)	<0.001
Covariates[2]			
OI randomisation: SOC		1.00	0.008
Enhanced prophylaxis		0.58 (0.39-0.87)	
Stage at enrolment: 1-2		1.00	0.004
3-4		2.13 (1.27-3.57)	
Age (per 5 years)		1.13 (1.03-1.24)	0.009
CD4 (per 10 cells/mm3)		0.89 (0.83-0.95)	0.001
BMI		0.92 (0.85-1.01)	0.07
RNA VL (log 10)		1.12 (0.78-1.61)	0.53

[1]Univariable models were adjusted for same covariates as the multivariable model.
[2]Models also adjusted for centre.

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Table 3: Association between biomarkers and all-cause and cause-specific mortality

Risk Factors	All-cause Hazard ratio	TB	Cryptococcosis	SBI	Other deaths	Unknown
	Subhazard Ratio per log10 increase (95% CI), p values, * <0.05, ** <0.01, [2] log2 increase					
IL-2	0.20 (0.06-0.67)**					
RANTES	0.32 (0.17-0.60)**					0.42 (0.20-0.86)*
IL-23	0.50 (0.32-0.80)**					
CRP	1.98 (1.51-2.59)**	2.01 (1.20-3.39)**		2.20 (1.10-4.37)*		
IP-10	2.29 (1.39-3.75)**					
IL-6	2.84 (1.00-8.06)*					
IFNγ	3.09 (1.55-6.16)**				5.90 (1.97-17.66)**	
sST2		1.59 (1.09-2.31)*,[2]				
IL-8			0.23 (0.06-0.95)*			
IL-4			8.28 (1.90-36.06)**			
sCD163				0.79 (0.63-0.98)*,[2]		
IL-9					0.29 (0.16-0.52)**	
TNFα						0.32 (0.12-0.90)*
sCD14					1.98 (1.17-3.34)*	1.81 (1.22-2.70)**,[2]
I-FABP						0.76 (0.61-0.95)*,[2]
IL-18						4.51 (1.57-12.97)**

<1 >1

DISCUSSION AND CONCLUSION

- Levels of expression of immune cell-derived soluble factors prior to ART initiation were associated with mortality in adults and adolescents with advanced HIV in sub-Saharan Africa.
- Inflammatory biomarkers (CRP, IFNγ, IL-6 and IP-10) were associated with increased all-cause mortality.
- Homeostatic and adaptive markers (IL-2, IL-23 and RANTES) were associated with reduced all-cause mortality.
- We identified distinct biomarker patterns depending on the cause of death.

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