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Please also see abstract #295

Immunologic Pathways That Predict Mortality in HIV+ Ugandans Initiating ART

Sulggi Lee[1], Helen Byakwaga[2], Yap Boum[2], Tricia H. Burdo[3], Yong Huang[1], Jessica E. Haberer[4], Russell P. Tracy[5], Huyen Cao[6], Annet Kembabazi[2], David R. Bangsberg[4], Jeffrey N. Martin[1], and Peter W. Hunt[1]

[1] University of California San Francisco, CA, USA; [2] Mbarara University of Science and Technology, Mbarara, Uganda; [3] Boston College, Boston, MA, USA; [4] Massachusetts General Hospital and Harvard University, Boston, MA, USA; [5] University of Vermont, Burlington, VT, USA; [6]California Department of Public Health, Richmond, CA, USA

Sulggi Lee, MD PhD
SFGH Blg 80, Ward 84
995 Potrero Avenue
San Francisco, CA 94110
(415) 735-5127
sulggi.lee@ucsf.edu

Background

- Abnormal immune activation persists in most HIV-infected individuals despite prolonged antiretroviral therapy (ART)-mediated viral suppression.
- The specific immunologic pathways predicting disease remain incompletely defined, particularly in resource-limited settings.
- Plasma kynurenine/tryptophan (KT) ratio, a marker of indoleamine 2,3-dioxygenase-1 (IDO) activity, predicts mortality more strongly than T cell activation in HIV+ ART-suppressed Ugandans (Byakwaga JID 2014).
- It is unclear whether KT ratio is simply a marker for innate immune activation or an independent predictor of disease.
- IL-6 and D-dimer are stronger predictors of morbidity and mortality than KT ratio and T cell activation among ART-suppressed individuals in resource-rich settings (Tenorio JID 2014, Hunt JID 2014).
- The relative prognostic importance of these biomarkers in resource-limited settings – where infectious causes of death are more common - is less well defined (Balagopol, CROI 2013, #785).

Methods

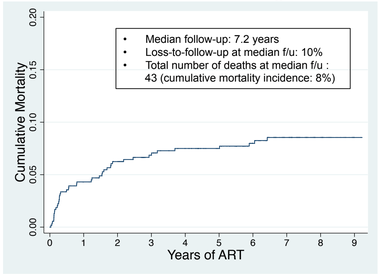
- We sampled the first 542 HIV-infected Ugandans initiating ART in the UARTO cohort.
- The following biomarkers were assessed at baseline and month 6 of ART-mediated viral suppression (VL<400):
  - Plasma KT ratio (by LC-MS)
  - D-dimer, IL-6, sCD163, sCD14 (by ELISA)
  - CD4+ and CD8+ T cell activation (%HLA-DR+CD38+ on freshly collected whole blood)
- Predictors of mortality were assessed with Cox proportional hazards models adjusted for age, body mass index, and pre-ART CD4+T cell count.
  - Further adjustment for other biomarkers was performed to assess possible confounding and/or mediation.

Results

Descriptive Statistics of Study Participants

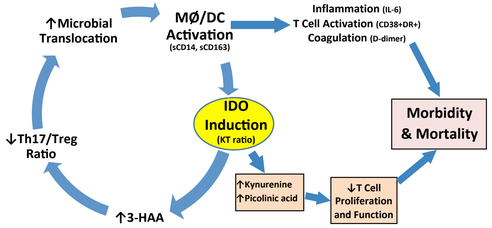
Characteristics	(N=542)
Age	34 (29 - 40)
Female	376 (70%)
Pre-ART CD4+ Count (cells/mm^3)	140 (79 - 219)
Pre-ART HIV RNA ($\log_{10}$ copies/mL)	5.0 (4.6 – 5.5)
Pre-ART body mass index (kg/m^2)	21 (19 – 24)

Mortality Risk Following ART

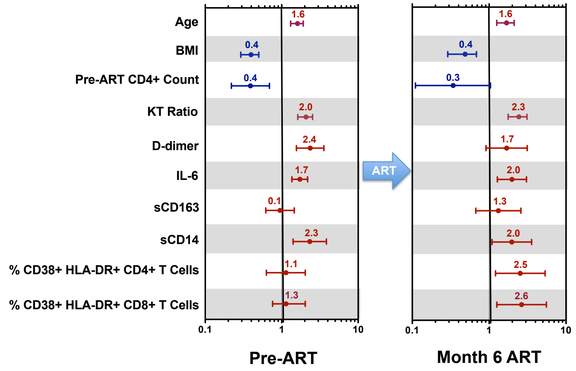


- *Kaplan-Meier failure estimates. Deaths from trauma or suicide were excluded from the analysis.*

IDO May Contribute to the Increased Morbidity & Mortality in Chronic HIV Infection



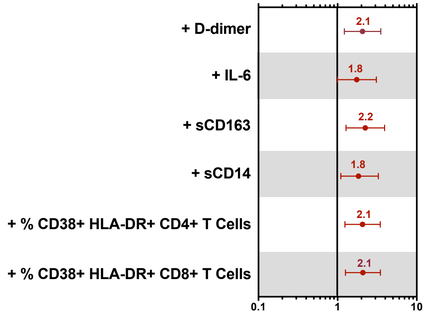
Biomarkers Measured Pre-ART and at Month 6 of ART-mediated Viral Suppression Predict Mortality



Hazards of Mortality
(Adjusted HR Per Interquartile Range Increase)

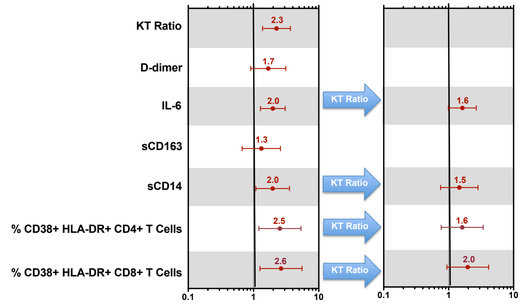
- *All aHRs are adjusted for pre-ART age, BMI, and CD4+ T cell count*
- *Biomarkers were modeled on a $\log_{10}$ scale*

Month 6 KT Ratio Remains a Strong Predictor of Mortality Even After Further Adjustment for Other Biomarkers



Hazards of Mortality at Month 6 ART
(Adjusted HR Per Interquartile Range Increase)

Mortality Associations of Other Biomarkers at Month 6 of ART No Longer Significant After Adjustment for KT Ratio



Hazards of Mortality at Month 6 ART
(Adjusted HR Per Interquartile Range Increase)

- *All aHRs are adjusted for pre-ART age, BMI, and CD4+ T cell count*
- *Biomarkers were modeled on a $\log_{10}$ scale*

Conclusions / Implications

- KT ratio is a strong independent predictor of mortality in HIV-infected Ugandans starting ART.
- The immunologic pathways most important in driving mortality in treated HIV infection may be different in resource-limited vs. resource-rich settings.
- Adaptive immune defects from IDO and T cell activation may have a greater impact in resource-limited settings where infections remain important causes of death.

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