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BRIEF REPORT

Immunologic Pathways That Predict Mortality in HIV-Infected Ugandans Initiating Antiretroviral Therapy

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The plasma kynurenine/tryptophan (KT) ratio, a marker of adaptive immune defects, strongly predicts mortality during treated human immunodeficiency virus (HIV) disease in Ugandans as compared to US-based populations. Here, the KT ratio and T-cell and plasma biomarkers of immune activation were measured among 535 HIV-infected Ugandans prior to ART initiation and at month 6 of viral suppression. The month 6 KT ratio (adjusted hazard ratio [aHR], 2.74), soluble CD14 level (aHR, 2.32), interleukin 6 level (aHR, 2.34), and D-dimer level (aHR, 1.95) were associated with mortality occurring ≥6 months after ART initiation. The KT ratio remained significantly predictive of mortality even after adjustment for the additional biomarkers, suggesting an independent contribution to clinical outcomes in resource-limited settings.

Keywords. HIV; kynurenine; tryptophan; D-dimer; IL-6; sCD14; mortality; antiretroviral therapy; Africa.

Abnormal immune activation persists in human immunodeficiency virus (HIV)–infected individuals despite antiretroviral therapy (ART) and strongly predicts morbidity and mortality [1]. The majority of this research has been conducted in high-income countries and suggests that markers of inflammation (eg, interleukin 6 [IL-6]), coagulation (eg, D-dimer), and innate immune activation (eg, soluble CD14 [sCD14] and sCD163) are stronger predictors of mortality than T-cell activation or plasma kynurenine/tryptophan (KT) ratio, a marker of indoleamine 2,3-dioxygenase-1 (IDO), a pathway conferring adaptive immune defects [1]. Nevertheless, the majority of HIV-infected individuals currently live in resource-limited regions where infectious complications remain considerable determinants of morbidity and mortality, even among individuals initiating ART at high CD4$^+$ T-cell counts [2]. Thus, it is important to assess which immunologic pathways predict mortality in resource-limited settings, as they may differ from those in resource-rich settings.

IL-6 was less predictive of mortality than pre-ART T-cell activation in the international PEARLS study [3]. Our group recently reported that the KT ratio predicts mortality more strongly than T-cell activation in Ugandans with ART-suppressed HIV infection [4] and to a greater degree than observed in North American studies [5, 6]. Nevertheless, it is unclear whether the KT ratio is simply a marker for innate immune activation and inflammation or an independent predictor of disease. Here, we evaluated the relative prognostic strength for mortality of these and other markers in 535 treatment-naive HIV-infected participants; this sample includes an additional 100 individuals and a median 2 years of follow-up added to our prior study [4].

MATERIALS AND METHODS

Participants

Ugandans living with HIV and enrolled in the UARTO cohort between 2005 and 2013 were seen prior to ART initiation and followed every 3 months during therapy; 435 participants were included in a prior report [4]. The primary ART regimens included zidovudine/lamivudine, stavudine/lamivudine, or tenofovir/emtricitabine, plus nevirapine or efavirenz. Participants with documented viral suppression (<400 copies/mL) at month 6 were included in the mortality analyses of individuals with ART-suppressed infection. Longitudinal follow-up and deaths were assessed using an active vital status ascertainment program [7]. Cause of death was recorded under broad categories (eg, "illness/disease," "trauma," "suicide," or "related to childbirth") and adjudicated through interview of participants' family/caregivers and, where available, medical record review. Deaths due to trauma, injury, suicide, or childbirth were excluded. All participants provided written informed consent. The institutional review boards of Mbarara University and the University of California–San Francisco approved this research.

Laboratory Methods

Before ART initiation and at month 6 of viral suppression, participants underwent measurement of the KT ratio [4], D-dimer level (Diagnostico Stago), IL-6 level (Meso Scale Diagnostics), sCD14 level (R&D Systems), sCD163 level (Trillium Diagnostics), and intestinal fatty acid binding protein (I-FABP)

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level (R&D Systems), using cryopreserved plasma specimens; the ratio of $CD4^+$ to $CD8^+$ T cells (hereafter, the "$CD4^+/CD8^+$ ratio) and T-cell activation (calculated as the percentage of $HLA\text{-}DR^+CD38^+$ cells among $CD4^+$ and $CD8^+$ T cells) were assessed using fresh whole-blood specimens [8]. Participants also underwent pre-ART measurements of the plasma sCD27 level (eBioscience) and the CXCL10 (also known as "inducible protein 10") level (R&D Systems). Approximately 98% of plasma samples were obtained in ACD tubes, with the remainder collected in ethylenediaminetetraacetic acid–containing tubes. To account for differences in diluent volume, values obtained from specimens in ACD tubes were multiplied by an adjustment factor of 1.276. HIV-1 RNA testing was assessed with the Roche Amplicor assay (lower limit of detection, <400 copies/mL) or the Roche Cobas Taqman v1.0 assay (lower limit of detection, <40 copies/mL). $CD4^+$ and $CD8^+$ T-cell counts were measured using the FACSCalibur system (Becton Dickinson).

Statistical Methods

The relationships between biomarkers were evaluated using Spearman rank correlations. Hazards of death per change in interquartile range (IQR) of the level of each $\log_{10}$-transformed biomarker were modeled using Cox regression. This standardization allowed comparison of the relative strength of mortality associations between different markers of immune activation and inflammation. Multivariable models were adjusted for age, sex, body mass index, and pre-ART HIV RNA load and $CD4^+$ T-cell count [4]. We also performed sensitivity analyses, excluding participants with suspected *Mycobacterium tuberculosis* infection, to evaluate the potential effect of coinfection on mortality associations. Suspected cases of *M. tuberculosis* infection were defined as the presence of positive laboratory (sputum acid-fast bacillus smear) results and/or documented use of tuberculosis medications within the first 9 months of ART initiation. Sensitivity analyses were also performed using limited self-reported smoking data [9]. Statistical analyses were performed using Stata, version 14 (StataCorp, College Station, TX).

RESULTS

The 535 study participants were mostly female with a median age of 34 years, pre-ART $CD4^+$ T-cell count of 139 cells/mm^3, and pre-ART HIV RNA of 5.0 $\log_{10}$ copies/mL (Supplemental Table 1). A total of 457 participants achieved viral suppression by month 6 of ART, with a median $CD4^+$ T-cell count of 242 cells/mm^3. Forty-four deaths occurred during a median of 7 years of follow-up; 36 were due to illness/disease, while 8 were due to unknown causes (but not trauma/injury, suicide, or a cause related to childbirth). Nineteen deaths occurred ≤6 months after initiation of ART (14 were due to illness/disease, and 5 were due to an unknown cause). Approximately 5% of participants were lost to follow-up at year 2, and 9% were lost to follow-up at year 7. Among clinical predictors, only age was predictive of (late) mortality (Supplementary Table 2). The pre-ART biomarkers were measured a median of 2.1 months (IQR, 1.4–3.3 months) prior to death, whereas deaths in the late-mortality analysis occurred a median of 1.8 years (IQR, 1.4–3.2 years) after biomarker measurement.

The pre-ART KT ratio was moderately correlated with CXCL10, sCD14, and sCD27 levels (Spearman R ≥0.52; Supplementary Figure 1; distributions are in Supplementary Table 3). In addition, there were moderate correlations between pre-ART sCD14 and IL-6 levels, CXCL10 and sCD27 levels, $CD4^+$ T-cell activation and $CD8^+$ T-cell activation, and $CD4^+$ T-cell activation and the $CD4^+/CD8^+$ ratio (Spearman R ≥0.50 for all). Pre-ART biomarkers associated with early mortality were D-dimer (hazard ratio [HR], 2.53), IL-6 (HR, 2.13), sCD14 (HR, 3.88), and $CD4^+/CD8^+$ ratio (HR, 0.48); all associations except $CD4^+/CD8^+$ ratio remained statistically significant in multivariable models (Table 1). The plasma KT ratio was also statistically significantly associated with early mortality (HR, 1.91) but not after multivariable adjustment (Table 1). A much broader set of pre-ART biomarkers predicted late deaths, with the following remaining predictive in multivariable models: sCD27 (adjusted HR [aHR], 2.48), sCD14 (aHR, 2.40), KT ratio (aHR, 2.37), D-dimer (aHR, 2. 32), and IL-6 (aHR, 1.60).

Among 457 participants with virological suppression, the associations between month 6 biomarkers were generally less strong than the correlations at baseline (Supplemental Figure 2). During the first 6 months of ART suppression, the $CD4^+/CD8^+$ ratio increased by 69% ($P < .0001$), and levels of all other biomarkers except I-FABP declined significantly. by 5%–43% ($P < .0024$ for all). Month 6 biomarkers associated with late mortality included the KT ratio (HR, 2.43), sCD14 (HR, 2.19), IL-6 (HR, 2.16), $CD4^+$ T-cell activation (HR, 1.95), and D-dimer (HR, 1.87; Table 2 and Supplementary Figure 3). The month 6 KT ratio (aHR, 2.72), sCD14 (aHR, 2.29), IL-6 (aHR, 2.10), and D-dimer (aHR, 1.95) but not $CD4^+$ T-cell activation remained statistically significant in multivariable models (Table 2). Further adjustment of each biomarker for the month 6 KT ratio attenuated the associations, with only IL-6 remaining statistically significant after additional KT ratio adjustment (aHR, 1.84; Table 2). Conversely, while there was modest attenuation of the association between the month 6 KT ratio and mortality after adjustment for each of the other biomarkers (particularly IL-6 and sCD14), the KT ratio remained a statistically significant and independent predictor of mortality (Table 2).

Exclusion of 46 participants (9%) with suspected tuberculosis resulted in reduced statistical power, but the associations between biomarkers and mortality were largely unchanged (Supplementary Tables 4–5). Smoking data were only available

Table 1. Associations With Early and Late Mortality Among Biomarkers Measured Before Antiretroviral Therapy (ART) Initiation Among 535 Human Immunodeficiency Virus–Infected Ugandans

	Early Mortality (n = 19)		Late Mortality (n = 25)	
Biomarker (Units)	Univariate HR (95% CI)[a]	Multivariate aHR (95% CI)[b]	Univariate HR (95% CI)[a]	Multivariate aHR (95% CI)[b]
KT ratio[c]	1.91 (1.14–3.19)	1.57 (.82–3.00)	2.39 (1.57–3.63)	2.37 (1.48–3.80)
D-dimer (μg/mL)	2.53 (1.56–4.11)	2.50 (1.41–4.44)	2.03 (1.29–3.21)	2.32 (1.27–4.24)
IL-6 (pg/mL)	2.13 (1.68–2.71)	1.89 (1.38–2.58)	1.78 (1.34–2.37)	1.60 (1.10–2.33)
sCD163 (μg/L)	1.23 (.71–2.12)	0.99 (.53–1.86)	1.16 (.71–1.89)	0.82 (.47–1.43)
sCD14 (μg/L)	3.88 (1.90–7.90)	3.04 (1.34–6.90)	2.76 (1.51–5.06)	2.40 (1.21–4.75)
sCD27 (μg/mL)	0.82 (.59–1.15)	0.73 (.55–.95)	2.45 (1.53–3.92)	2.48 (1.43–4.30)
CXCL10 (pg/mL)	1.19 (.68–2.10)	0.64 (.32–1.28)	1.62 (1.02–2.56)	1.72 (.92–3.23)
I-FABP (pg/mL)	1.07 (.55–2.10)	1.05 (.58–1.91)	1.61 (.86–3.01)	1.75 (.89–3.40)
$CD4^+$ T-cell activation[d]	0.94 (.47–1.89)	0.61 (.26–1.41)	1.87 (.95–3.67)	1.51 (.68–3.37)
$CD8^+$ T-cell activation[e]	0.68 (.39–1.21)	0.65 (.35–1.23)	2.01 (1.00–4.02)	1.95 (.92–4.13)
$CD4^+/CD8^+$ ratio[f]	0.48 (.29–.79)	0.86 (.40–1.83)	0.70 (.45–1.10)	0.98 (.51–1.88)

The early mortality group comprised participants who died ≤6 months after ART initiation, and the late mortality comprised those who died >6 months after ART initiation. HRs falling within 95% CIs are considered statistically significant.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; I-FABP, intestinal fatty acid-binding protein; IL-6, interleukin 6; sCD14, soluble CD14; sCD27, soluble CD27; sCD163, soluble CD163.

[a]Cox regressions modeled as the increase in mortality per increase in interquartile range for each $\log_{10}$biomarker.

[b]Adjusted for age, sex, body mass index, the pre-ART HIV RNA load, and the pre-ART $CD4^+$ T-cell count.

[c]Ratio of the kynurenine level (in nM) to the tryptophan level (in μM).

[d]Calculated as the percentage of $CD38^+HLA\text{-}DR^+$ cells among $CD4^+$ T cells.

[e]Calculated as the percentage of $CD38^+HLA\text{-}DR^+$ cells among $CD8^+$ T cells.

[f]Ratio of the absolute $CD4^+$ T-cell count (in cells/mm^3) to the absolute $CD8^+$ T-cell count (in cells/mm^3).

Table 2. Predictors of Late Mortality Among 457 Human Immunodeficiency Virus (HIV)–Infected Ugandans With a Plasma HIV RNA Load <400 copies/mL by Month 6 of Antiretroviral Therapy (ART)

Biomarker (Units)	Univariate HR (95% CI)[a]	Multivariate aHR I (95% CI)[b]	Multivariate aHR II (95% CI)[c]
KT ratio[d,e]	2.43 (1.62–3.65)	2.74 (1.63–4.60)	…
D-dimer (μg/mL)	1.87 (1.00–3.53)	1.95 (1.00–3.80)	1.83 (.82–4.11)
IL-6 (pg/mL)	2.16 (1.51–3.08)	2.34 (1.51–3.63)	1.84 (1.10–3.05)
sCD163 (μg/L)	1.92 (.98–3.76)	1.52 (.73–3.19)	0.97 (.43–2.22)
sCD14 (μg/L)	2.19 (1.28–3.75)	2.32 (1.25–4.31)	1.54 (.76–3.12)
I-FABP (pg/mL)	1.01 (.51–2.02)	0.89 (.44–1.79)	0.73 (.36–1.50)
$CD4^+$ T-cell activation[f]	1.95 (1.07–3.56)	2.04 (.95–4.42)	1.64 (.75–3.57)
$CD8^+$ T-cell activation[g]	1.96 (.99–3.87)	2.09 (.93–4.68)	1.79 (.80–3.99)
$CD4^+/CD8^+$ ratio[h]	0.63 (.39–1.04)	1.08 (.55–2.12)	1.03 (.46–2.27)

The late mortality group comprised 25 participants who died >6 months after ART initiation. HRs falling within 95% CIs are considered statistically significant.

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; I-FABP, intestinal fatty acid-binding protein; IL-6, interleukin 6; sCD14, soluble CD14; sCD163, soluble CD163.

[a]Cox regressions modeled as the increase in mortality per increase in interquartile range for each $\log_{10}$ biomarker level.

[b]Adjusted for age, sex, body mass index, the pre-ART HIV RNA load, and the pre-ART $CD4^+$ T-cell count.

[c]Adjusted for the KT ratio at month 6 of ART, sex, body mass index, the pre-ART HIV RNA load, and the pre-ART $CD4^+$ T-cell count.

[d]Ratio of the kynurenine level (in nM) to the tryptophan level (in μM).

[e]HRs for the KT ratio after adjustment for the following biomarkers, as well as for age, sex, body mass index, the pre-ART HIV RNA load, and the pre-ART $CD4^+$ T-cell count, were as follows: 2.48 (95% CI, 1.42–4.33), after adjustment for D-dimer; 1.90 (95% CI, 1.04–3.49), after adjustment for IL-6; 2.69 (95% CI, 1.52–4.75), after adjustment for sCD163; 2.15 (95% CI, 1.16–3.97), after adjustment for sCD14; 2.64 (95% CI, 1.47–4.73), after adjustment for I-FABP; 2.50 (95% CI, 1.45–4.31), after adjustment for $CD4^+$ T-cell activation; 2.56 (95% CI, 1.50–4.35), after adjustment for $CD8^+$ T-cell activation; 2.56 (95% CI, 1.50–4.38), after adjustment for the $CD4^+/CD8^+$ ratio.

[f]Calculated as the percentage of $CD38^+HLA\text{-}DR^+$ cells among $CD4^+$ T cells.

[g]Calculated as the percentage of $CD38^+HLA\text{-}DR^+$ cells among $CD8^+$ T cells.

[h]Ratio of the absolute $CD4^+$ T-cell count (in cells/mm^3) to the absolute $CD8^+$ T-cell count (in cells/mm^3).

for 381 of 535 participants (and just 28 of 44 deaths), limiting the feasibility of multivariable adjustment; however, adjustment for smoking did not substantively change any of the key inferences (Supplementary Table 6).

DISCUSSION

In this study of 535 HIV-infected individuals initiating ART in Uganda, deaths during the first 6 months of ART were predicted by IL-6, D-dimer, and sCD14 levels. Deaths occurring after longer periods of ART suppression were most strongly predicted by the KT ratio—a marker of IDO activity. In further adjusted analyses, the KT ratio was an independent predictor of mortality among Ugandans with ART suppression, highlighting the potential importance of this pathway in resource-limited settings where the immunologic predictors of mortality during treated HIV infection have been incompletely defined.

IDO is induced by bacterial lipopolysaccharide and by cytokines such as interferon γ, tumor necrosis factor α, and transforming growth factor β [10], which may contribute to further microbial translocation (via suppression of T-helper type 17 and T-helper type 22 cells) and innate immune activation. IDO catabolites promote regulatory T-cell expansion and suppression of lymphocyte proliferation [11] and may be an important link between the innate and adaptive immune defects during treated HIV disease. In 2 US-based cohorts of ART-suppressed HIV-infected participants [5, 6], including individuals with advanced HIV disease (median nadir $CD4^+$ T-cell count, 30 cells/mm^3) [5], IL-6 was a much stronger predictor of mortality than D-dimer or the KT ratio, whereas in our Ugandan cohort, the KT ratio was a stronger predictor of mortality than IL-6 or D-dimer levels. The adaptive immune defects from IDO may have greater impact in low-income countries, where infections remain important causes of death even during viral suppression, whereas in high-income countries, markers of inflammation and coagulation may reflect the greater contribution of cardiovascular complications to deaths [1].

Limitations of the study include the small number of deaths and the inability to evaluate whether the cause of death (measured as only broad categories) influenced results. We also had limited data on comorbidities (except *M. tuberculosis* coinfection) and smoking. Nonetheless, the relative strength of associations in the current study appeared to follow a different pattern than those observed in studies from high-income countries, and sensitivity analyses controlling for suspected *M. tuberculosis* infection or smoking did not change results.

The pre-ART KT ratio appeared to be a less robust predictor of early mortality as compared to the other biomarkers. While the number of deaths in our study precludes drawing definitive conclusions, one possibility is that the early deaths might represent a mixture of immunodeficiency-related pathologies or an immune reconstitution inflammatory response to underlying coinfections. Furthermore, pre-ART levels of biomarkers were measured within a few months of the event, whereas events in the late mortality analysis occurred almost 2 years after biomarker measurement. However, results were unchanged after exclusion of suspected *M. tuberculosis*–infected participants, suggesting a relatively minor effect of coinfection in this analysis.

We observed a statistically significant association between month 6 $CD4^+$ T-cell activation and late mortality, but this association was no longer statistically significant in a multivariable model including $CD4^+$ T-cell count. Similar trends, while not statistically significant, were also observed for $CD8^+$ T-cell activation. Lower $CD4^+$ T-cell counts may potentially confound the association between T-cell activation and mortality or could represent a true causal association between T-cell activation and mortality, which would largely be mediated by greater $CD4^+$ T-cell depletion. This latter interpretation would be consistent with findings from the recent ACTG PEARLS study, conducted in low-income and middle-income countries, in which pre-ART $CD4^+$ T-cell immune activation predicted early clinical progression, even after adjustment for $CD4^+$ T-cell count [3].

There was a notable lack of association between certain biomarkers and mortality in our cohort. We did not observe a statistically significant association between I-FABP, a marker of enterocyte turnover, and mortality, as previously reported [5, 12], nor between sCD163 and mortality, in contrast to a Danish study [13]. D-dimer levels were also less predictive of mortality in our study than in studies conducted in high-income countries [5, 6]; these findings may reflect differences in baseline inflammatory markers and/or a relatively smaller contribution of cardiovascular complications to mortality in our relatively young, predominantly female Ugandan cohort which may change as the population ages and becomes at higher risk for cardiovascular complications. Notably, I-FABP and sCD163 levels were lower and D-dimer levels higher in our Ugandan cohort, compared with those in prior studies [5, 6, 12, 13] (Supplementary Tables 4–5). Further studies are needed to determine whether differences in baseline inflammatory markers, host genetics [14], or coinfections may contribute to these differences.

In summary, the immunologic factors that predict mortality in Ugandans with ART-suppressed HIV infection may differ from those previously reported in individuals from high-income countries with ART-suppressed infection. Whether these differences are influenced by dissimilarities in causes of death (eg, infectious versus cardiovascular) or environmental or host differences requires further study. Nonetheless, the KT ratio appears to be a strong and independent predictor of mortality risk in Ugandans with ART-suppressed infection and a potentially attractive interventional target that could be explored in future clinical trials as IDO inhibitors become clinically available [15].

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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