Evaluating Biomarkers and Mortality by Sex in People With Late HIV Starting Antiretroviral Therapy

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BACKGROUND

- In people with HIV (PWH) with low CD4 counts at antiretroviral therapy (ART) initiation (CD4<100 cells/μL), are there biomarker differences between males and females that could be associated with the increased risk of mortality previously seen in females?

In a large international study, we previously demonstrated a link between female sex and increased risk of mortality in people with HIV (PWH) with CD4<100 cells/μL who were initiating antiretroviral therapy (ART). Our understanding of the factors underlying these differences remains incomplete. In this study, we sought to assess if there are biomarker differences between males and females that could provide insight on this disparity.

METHODS

- Secondary analysis of clinical and biomarker data from a prospective study (NCT00286767) that included ART-naïve PWH with CD4<100 cells/μL in the U.S., Kenya, and Thailand, who initiated ART between December 2006-March 2013 and were followed for 48 weeks.
- We assessed 506 PWH, 39.3% of whom were female (assigned sex at birth, N=199), with a median follow-up of 48 weeks.
- We assessed for differences in the following by sex:
  - Baseline biomarkers: C-reactive protein (CRP), IP-10, D-dimer, hyaluronic acid (HA), hepcidin, soluble tissue factor (TF), tumor necrosis factor (TNF), IL-2, -6, -8, -10, -17, IFN-γ, myeloperoxidase (MPO), sCD14, and sCD163.
  - Associations between the odds of death and baseline biomarkers.
  - Hazards of death.

Using data previously collected in a large international study of ART-naïve people with advanced HIV initiating ART, we retrospectively analyzed the participants' clinical and biomarker data for differences between males and females and to assess for differences between odds of mortality risk by sex.

Female sex was associated with *increased mortality* in people with advanced HIV starting ART, and was characterized by ***a distinct biomarker risk profile for death*** compared to males.

RESULTS

	Female (N=199)	Male (N=307)	P value
Baseline			
Age (years)	37.0 [32.0-43.0]	37.0 [31.0-46.0]	0.620
Platelets (K/μL)	238 [166-313]	212 [161-268]	**0.027**
Hemoglobin (g/dL)	10.4 [9.30-11.3]	11.5 [9.95-13.1]	**<0.001**
CD4 count (cells/μL)	27 [12-57]	29 [11-54]	0.394
BMI (kg/m^2)	19.7 [17.7-23.4]	20.6 [18.1-23.5]	**0.010**
Plasma HIV-1 viral load (log_{10} cp/mL)	5.36 [4.95-5.80]	5.27 [4.87-5.65]	0.836
CRP (mg/L)	4.62 [1.14-14.9]	5.74 [1.55-19.3]	0.066
D-dimer (mg/L)	1.04 [0.64-2.14]	1.05 [0.61-2.09]	0.960
HA (ng/mL)	88.9 [40.8-145]	108 [57.8-183]	0.035*
Hepcidin (ng/mL)	300 [278-446]	300 [253-474]	0.840
IFN-γ (pg/mL)	4.34 [2.22-10.2]	3.30 [1.37-8.58]	0.161
IL-2 (pg/mL)	0.71 [0.31-1.28]	0.305 [0.31-1.10]	0.262
IL-6 (pg/mL)	2.71 [1.37-7.10]	2.20 [1.19-5.14]	0.957
IL-8 (pg/mL)	12.0 [6.86-25.1]	10.2 [5.64-17.9]	0.328
IL-10 (pg/mL)	10.4 [5.38-19.1]	9.57 [5.68-17.0]	0.320
IL-27 (pg/mL)	525 [339-781]	467 [310-730]	0.359
IP-10 (pg/mL)	2410 [1570-3780]	2370 [1460-3870]	0.283
MPO (ng/mL)	16.5 [9.78-27.7]	15.7 [10.9-24.3]	0.288
sCD14 (ng/mL)	2470 [2000-3230]	2230 [1790-3000]	0.020*
sCD163 (pg/mL)	518 [175-913]	362 [89.5-738]	0.054
TF (pg/mL)	75.0 [56.7-107]	79.5 [59.7-103]	0.770
TNF (pg/mL)	13.0 [8.68-18.0]	11.3 [7.82-16.6]	0.298
Post-ART Initiation			
CD4 recovery rate (cells/μL/wk)	3.01	2.61	**0.045**
Hazard ratio for mortality by day 30	3.34	(Reference group)	**0.038**

Table: Baseline clinical and biomarker data, rate of CD4 recovery, and survival hazard ratio. *: after adjusting for multiple comparisons and clinical site, there were no statistically significant differences between these biomarkers.

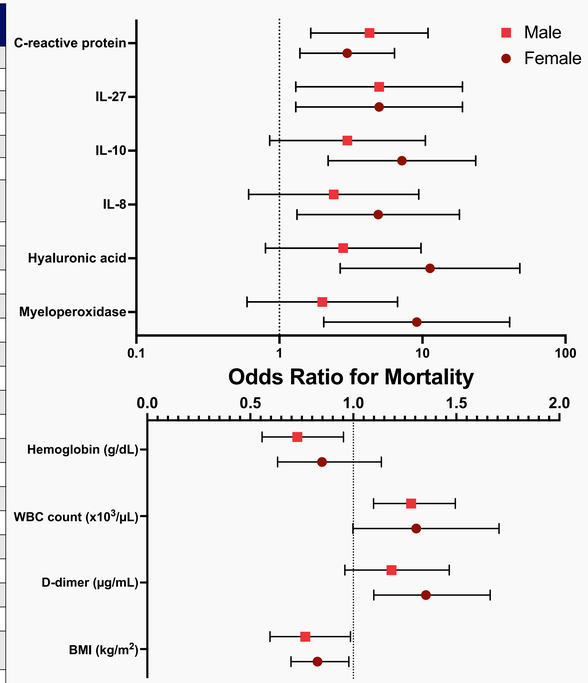

Figure: Multivariable logistic regression models for odds of mortality by biomarker stratified by sex. C-reactive protein, IL-27, IL-10, IL-8, hyaluronic acid, and myeloperoxidase were transformed from pg/mL to a log10 scale.

CONCLUSIONS

- At ART initiation, there were no significant differences by sex in CD4 count, HIV-1 viral load, or in any measured biomarkers in PWH with CD4 <100 cells/μL.
- Female sex was associated with a **slightly higher rate of CD4 recovery** after ART initiation.
- Female sex was associated with an **increased risk of mortality**, particularly **within the first 30 days**, after ART initiation.
- The biomarkers associated with increased odds of mortality were **different between females and males**:
  - Increased **CRP**, increased **IL-27**, and decreased **body mass index** were associated with increased odds of death in **both sexes**;
  - Increased **IL-8**, **IL-10**, **HA**, **MPO**, and **D-dimer** were associated with increased odds of death in **females but not males**;
  - Elevated **white blood cell count** and decreased **hemoglobin** were associated with increased odds in **males but not females**.
- There may be distinct pathophysiologic mechanisms that account for the observed increased risk of death seen in female PWH that warrant further investigation.

Despite similar baseline biomarker profiles, CD4 count, and viral load, along with a slightly higher rate of CD4 recovery, females demonstrated an increased mortality rate within 30 days of ART initiation compared to males. The biomarkers that were most strongly associated with mortality risk differed between males and females, suggesting there may be distinct pathophysiologic mechanisms contributing to this difference.

ADDITIONAL KEY INFORMATION

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