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Indoleamine 2,3-dioxygenase-1 (IDO) Activity as a Determinant of AIDS-associated Kaposi's Sarcoma in Africa

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Background

- Kaposi's sarcoma (KS) remains a leading cause of cancer in HIV-infected individuals in resource-limited settings.
- Other than human herpesvirus 8 (HHV-8) and CD4+ T cell lymphopenia, the mechanisms responsible for KS are poorly understood.
- Additional mechanisms must exist in sub-Saharan Africa given how relatively few HIV-infected patients develop KS despite the high prevalence of both HHV-8 infection and low CD4+ T cell count.
- A recently explored pathway of HIV pathogenesis involves the induction of indoleamine 2,3-dioxygenase-1 (IDO) in activated myeloid cells
  - Catalyzes tryptophan into kynurenine and other immunologically active catabolites that suppress T cell proliferation.
  - IDO activity can be quantified by the ratio of kynurenine/tryptophan (KT ratio) in plasma (higher values = greater IDO activity).
  - Higher plasma KT ratio predicts blunted CD4+ T cell recovery and increased mortality in HIV+ Ugandans starting antiretroviral therapy (ART) (Byakwaga, JID, in press).
- IDO-induced inhibition of T cell proliferation plays a role in;
  - maternal tolerance of fetal antigens during pregnancy
  - evasion of immune responses by several cancers
- Higher IDO activity might:
  - Promote KS by decreasing immune surveillance, or
  - Inhibit emergence of KS by suppressing inflammatory milieu needed for KS development.

Objective

To assess whether IDO activity has a role in the development of KS in untreated HIV-infected African adults..

Participants

HIV-infected Ugandan adults, identified just prior to start of ART. Pregnant women were excluded.

Cases: Mild-moderate biopsy-confirmed KS and no urgent indications for chemotherapy, seen in preparation for the Antiretrovirals for Kaposi's Sarcoma (ARKS) clinical trial, based at the Infectious Diseases Institute in Kampala, Uganda.

Controls: No KS, derived from Uganda AIDS Rural Treatment Outcomes (UARTO), a clinic-based cohort of HIV-infected adults initiating ART in Mbarara, Uganda

Measurements

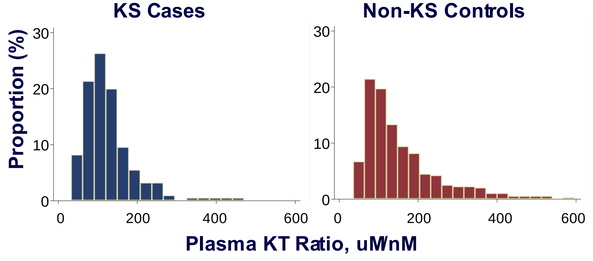
- Both ARKS and UARTO studies used the same instruments and labs for all study measurements.
- IDO activity was captured by tryptophan (uM) and kynurenine (nM) levels measured in morning plasma by liquid chromatography tandem mass spectrometry

Characteristics of Participants

Characteristic	KS Cases (n=222)	Controls (n=409)
Age	34 (28-40)	35 (29-40)
Female Sex	44%	68%
BMI, kg/m^2	21.4 (19.4-23.1)	21.1 (19.4-23.4)
Hemoglobin, g/dL	11.6 (10.3-13.2)	12.2 (10.6-13.7)
Physical Health Status[a]	53.3 (36.4-58.2)	54.0 (45.0-58.6)
Mental Health Status[a]	48.6 (37.7-56.7)	52.6 (45.9-58.7)
Asset Index[b]	0.18 (-1.80-1.78)	-0.58 (-1.82-0.86)
HIV RNA, $\log_{10}$ copies/ml	5.3 (5.0-5.6)	5.1 (4.6-5.6)
CD4+ T cell, count/mm^3		
<50	35%	16%
51-100	11%	18%
101-200	23%	41%
201-350	18%	21%
>350	13%	3%
KT Ratio, nM/uM, by Quartile		
Q1 (34-89)	27%	24%
Q2 (90-120)	28%	23%
Q3 (21-179)	29%	23%
Q4 (180-1369)	16%	30%

All data as median (interquartile range) unless indicated
[a] Scores derived using the Medical Outcomes Study HIV survey
[b] Asset based measure of socioeconomic status (Pritchett et al)

Distribution of Plasma KT Ratio in Cases vs Controls

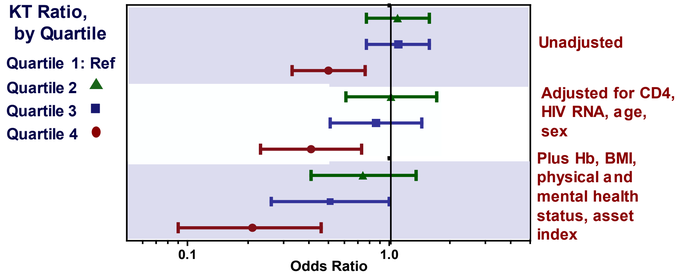


Multivariable Logistic Regression for Determinants of KS

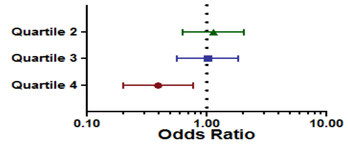
	Adjusted Model 1		Adjusted Model 2	
Characteristic	OR (95% CI)	P value	OR (95% CI)	P value
Plasma KT ratio, by quartile				
Q1 (34-89)	Ref		Ref	
Q2 (90-120)	1.02 (0.61-1.72)	0.93	0.74 (0.41-1.36)	0.34
Q3 (121-179)	0.86 (0.51-1.45)	0.58	0.51 (0.26-1.00)	0.049
Q4 (180-1369)	0.41 (0.23-0.73)	0.002	0.21 (0.09-0.46)	<0.001
HIV RNA, log10 copies/ml				
≤10,000	Ref		Ref	
10,001-50,000	2.6 (0.8-8.1)	0.096	2.4 (0.8-7.9)	0.14
50,001-100,000	4.1 (1.3-12.3)	0.013	4.1 (1.3-12.9)	0.018
100,001-500,000	9.6 (3.4-27.7)	<0.001	9.3 (3.1-27.8)	<0.001
>500,000	5.6 (1.8-17.1)	0.003	5.2 (1.6-16.8)	0.006
CD4+ T cell count, cells/mm^3				
<50	Ref		Ref	
51-100	0.30 (0.16-0.55)	<0.001	0.25 (0.13-0.49)	<0.001
101-200	0.33 (0.21-0.54)	<0.001	0.34 (0.20-0.57)	<0.001
201-350	0.54 (0.31-0.94)	0.029	0.52 (0.28-0.95)	0.033
>350	2.60 (1.15-5.87)	0.021	2.55 (1.08-7.04)	0.033
Sex				
Men	Ref		Ref	
Women	0.41 (0.28-0.61)	<0.001	0.22 (0.13-0.37)	<0.001
Age, per 10 years	0.79 (0.62-1.01)	0.059	0.84 (0.64-1.09)	0.19
Hemoglobin, g/dL			0.73 (0.60-0.89)	0.002
BMI, kg/m^2			1.11 (1.04-1.18)	0.002
Physical Health Status*			1.00 (0.98-1.03)	0.83
Mental Health Status*			0.97 (0.95-1.00)	0.041
Asset Index*			1.04 (0.95-1.14)	0.42

*Per unit increase in respective scale

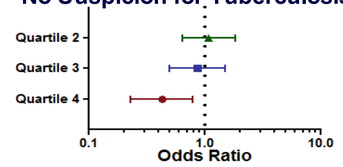
Plasma KT Ratio Inversely Associated with KS



Restricting to Participants from Low Malaria Endemic Areas



Restricting to Participants with No Suspicion for Tuberculosis



Adjusted for age, sex, CD4+ T cell count, HIV RNA level; quartile 1 is reference.

Conclusions

- Higher IDO activity, evidenced by **higher** plasma KT ratio, is associated with **lower** occurrence of KS.
- There is a strong independent positive association between plasma HIV RNA and KS.

Implications

- The inverse relationship between KT ratio and KS is consistent with hypothesis that lymphocyte proliferation is necessary for the development of KS and compatible with the inflammatory nature of KS lesions.
- Some consequences of immune activation in HIV might actually suppress or mask certain cancers.
- Independent role of plasma HIV RNA levels provides clinical augmentation of earlier biological research suggesting a causative role of HIV *per se* in KS etiology.

Acknowledgements

IeDEA ACSR AIDS and Cancer Specimen Resource
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CFAR Center for AIDS Research
UCSF University of California San Francisco advancing health worldwide