



Untreated HIV-infected Individuals in Uganda Have Higher CD8+ T cell Activation Levels than Untreated HIV-infected Individuals in North America

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Background

- Generalized T cell activation is an important mediator of immunodeficiency in HIV disease.
- HIV itself can cause T cell activation through both direct and indirect mechanisms.
- However, co-infections may further increase T cell activation in HIV-infected individuals.
- Several studies have reported higher T cell activation in HIV-infected patients from resource-limited settings, perhaps a result of prevalent co-infections (TB, malaria, parasites, etc).
- However, it remains unclear whether these observed increases were due to higher levels of viral replication, differences in disease stage, or variability between laboratories.

Research Questions

- Do untreated HIV-infected individuals in Uganda have higher T cell activation levels than untreated individuals in North America?
- Are these differences independent of the level of HIV replication?
- Do co-infections alter the association between HIV replication and T cell activation?

Methods

- Untreated HIV-infected patients were sampled from cohort studies in Uganda and US:**
 - Uganda Antiretroviral Treatment Outcomes (UARTO): A clinic-based cohort of over 200 treatment-naïve HIV-infected individuals beginning antiretroviral therapy in Mbarara, Uganda.
 - First 47 enrolled participants were included in this analysis prior to initiating therapy
 - Research in Access to Care for the Homeless Cohort (REACH): A community-based cohort of marginally-housed and homeless HIV-infected patients in San Francisco sampled from shelters, meal lines, and single-room-occupancy hotels.
- Inclusion criteria**
 - No antiretroviral therapy in past 6 months
 - CD4+ T cell count <250 cells/mm³ (based on the typical treatment threshold at the Uganda site)
- Cellular immunology laboratories established at both sites with standardized instruments, technician training, and specimen processing/analysis protocols.**
 - Validation of staining protocols, FACSCalibur settings, and gating analyses was performed using identical FACSCalibur machines at each site.
 - US HIV-seronegative samples and cryopreserved Ugandan PBMC samples were analyzed concomitantly, to ensure consistency of settings between sites.
- The % activated (CD38+ HLA-DR+) CD4+ and CD8+ T cells assessed by 4-color flow cytometry on freshly obtained whole blood specimens at each site.**
 - Preset gating applied to all samples, based on CD38/DR expression in HIV-uninfected Ugandans.
- Plasma Hepatitis C Virus RNA levels (Versant HCV RNA, v3.0, Bayer) were obtained on all HCV-seropositive (EIA v2.0, Abbott) and RIBA+ (v3.0, Chiron) REACH participants**
- We assessed whether HCV replication levels modified the association between plasma HIV RNA levels and T cell activation using linear regression models.**

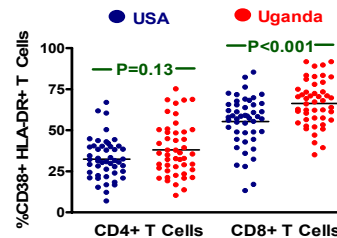
Results

Baseline Characteristics of the Untreated HIV-infected Participants

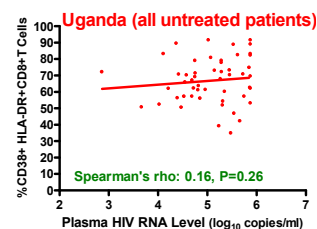
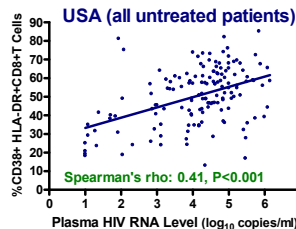
Characteristic	Country of Residence	
	USA Median, n=48	Uganda Median, n=47
Age, years	44	35
Female Gender, no. (%)	10 (21)	33 (70)
CD4+ T Cell Count, cells/mm ³	131	102
Plasma HIV RNA Level, log ₁₀ copies/ml	4.9	5.2
Antiretroviral Therapy-Naïve, no. (%)	23 (48)	47 (100)
Hepatitis C Virus Seropositive, no. (%)	34 (72)	Est. <5% prevalence

Higher T Cell Activation Levels in Ugandan vs. US Patients with Untreated HIV Infection.

Untreated HIV-infected Ugandans had a mean 11% more activated C8+ T cells even after adjustment for plasma HIV RNA level and CD4+ T cell count (P<0.001).

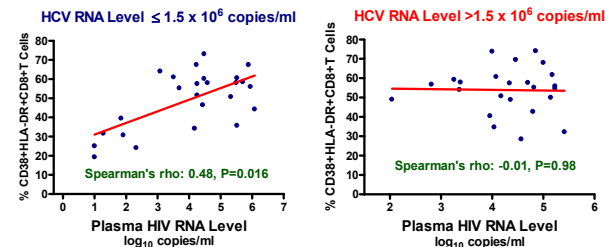


Relationship between Plasma HIV RNA Levels and T Cell Activation Might Be Weaker in HIV-infected Ugandans.



P for interaction=0.30

The Relationship Between Plasma HIV RNA Levels and T Cell Activation Appears Weaker at Higher Hepatitis C Virus Replication Levels



- Patients with higher HCV RNA levels experienced a smaller observed increase in the percentage of activated CD8+ T cells than for every unit increase in plasma HIV RNA level (P for interaction =0.038).

Conclusions/Implications

- Untreated HIV-infected Ugandans have higher CD8+ T cell activation levels than untreated North American HIV-infected patients, even after adjustment for plasma HIV RNA levels and CD4+ T cell count.
 - Higher T cell activation levels in Uganda might be explained by prevalent sub-clinical co-infections (TB, malaria, parasitic infections, etc.)
 - Alternatively differences in viral factors (clade, tropism, etc.) or other host factors may play a role.
- The relationship between viral replication and T cell activation appears weaker in Ugandan than North American patients with untreated HIV infection.
 - Additional data, particularly from untreated HIV-infected Ugandans with lower plasma HIV RNA levels, will be necessary to confirm this observation.
 - If this association is validated with more data, it might suggest that unmeasured co-infections in Ugandan patients confound the association between plasma HIV RNA levels and T cell activation.
- Hepatitis C virus replication appears to weaken the observed relationship between HIV replication and T cell activation.
 - Additional data, particularly from HCV co-infected individuals with high plasma HCV RNA levels but low plasma HIV RNA levels will be necessary to confirm this observation.
 - If validated with more data, might suggest the hypothesis that induction of regulatory T cell responses in chronic HCV disease suppress HIV-specific T cell responses, causing a paradoxical decrease in T cell activation despite increased HIV replication.
 - If co-infections modify the association between HIV replication and T cell activation, the relative prognostic value of plasma HIV RNA levels and T cell activation in predicting subsequent HIV disease progression may be altered in resource-limited settings.

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