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Sexually Transmitted Infections and Immune Activation among HIV-Infected but Virally Suppressed Youth on Antiretroviral Therapy

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Abstract

Background—Human immunodeficiency virus (HIV) infection is associated with chronic immune activation, and concurrent sexually transmitted infections (STIs) may increase immune activation.

Objectives—Because HIV-infected youth are at high risk of STIs and little is known about the impact of STIs on immune activation in HIV-infected youth, we conducted an exploratory study examining the association between STIs and systemic inflammation and immune activation among HIV-infected adolescents.

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Study Design—Forty-nine behaviorally infected U.S. youth ages 18–24 years with baseline CD4⁺ T-cells >350 who maintained viral suppression on therapy by week 48 were included. Evaluation for STIs (herpes simplex virus [HSV], *Chlamydia trachomatis*, syphilis, *Neisseria gonorrhoeae*) was conducted as standard of care and reported on case report forms. Measures of T-cell subsets, systemic immune activation, and soluble factors were examined at week 48 for differences between participants with an STI diagnosis during the 48 weeks compared to those without an STI.

Results—Forty-three participants (88%) were male; 57% had baseline CD4⁺ T-cell counts >500 cells/mm³. Eighteen youth were reported to have 1 STI. At week 48, participants with STIs demonstrated lower CD4⁺ T-cell counts (any STI vs. no STI, $p=0.024$; HSV vs. no STI, $p=0.022$) and evidence of increased systemic immune activation, including higher CD57 intensity, higher HLA-DR intensity, and lower CD28 percentage, when compared to those without STIs. There were no differences in soluble factors between STI groups.

Conclusions—Results indicate novel activation of CD4⁺ T-cells among HIV-infected youth who have STIs other than HSV, which may contribute to disease progression.

Keywords

HIV; Immune activation; Sexually transmitted infection; Youth; Adolescent

Background

Human immunodeficiency virus (HIV) infection is associated with chronic immune activation leading to loss of T-cells and HIV disease progression.¹ HIV replication in lymph nodes alters node structure, further decreasing CD4⁺ T-cells.^{2–4} Markers of immune activation are associated with declining CD4⁺ T-cell counts,⁵ HIV disease progression,⁶ and development of persistent inflammation that is not fully reversed by combination antiretroviral therapy (cART).^{7–9}

Sexually transmitted infections (STIs), which are common among HIV-infected youth,^{10,11} increase HIV transmission risk through increasing HIV shedding in genital secretions.^{12,13} However, STIs may have systemic effects. Herpes simplex virus (HSV) infection is associated with increased serum HIV viral load (VL).^{7,14} Cytomegalovirus (CMV),^{15,16} chronic HSV,¹⁷ human herpesvirus 8,¹⁸ and Epstein-Barr virus¹⁹ co-infections are associated with increased inflammation and immune activation, and STIs may impact systemic immune activation.²⁰

Objectives

Because STIs are common among HIV-infected youth^{11,21,22} and immune activation promotes HIV disease progression, this exploratory study examined the association between STIs and systemic inflammation and immune activation among a sample of HIV-infected adolescents who were virally suppressed on cART.

Study Design

Behaviorally HIV-infected 18–24 years-olds with CD4⁺ T-cell counts >350 cells/mm³ were recruited for the parent study and randomized to early cART with tenofovir/emtricitabine plus ritonavir-boosted atazanavir or standard care. Recruitment occurred at 23 U.S. sites of two HIV research networks from 2007–2010. Seventy-five youth were randomized to early cART and maintained on the regimen for 48 weeks.⁹ These analyses focused on the 49 youth who achieved viral suppression - VL<100 copies/ml by week 24 and maintained through week 48 - and included data through week 48. Subjects were evaluated for STIs according to standard of care and reported to the protocol team. STI diagnoses based on clinical or laboratory results obtained by clinical providers for HSV, *Chlamydia trachomatis*, syphilis, and *Neisseria gonorrhoeae* were reported at pre-entry, baseline, and week 12, 24, 36, and 48 visits. Week 48 measurements of T-cell subsets, fluorescent intensity of activation markers on CD4⁺ and CD8⁺ T-cells, and percentage of activation markers were analyzed. Methods for collection and analyses of T-cell subsets have been described.⁹ Each T-cell population was gated individually to determine the relative expression and mean fluorescent intensity (MFI) of CD28, CD38, HLA-DR⁹ and CD57 expression (BD Bioscience, San Jose, CA). Soluble markers of immune activation - sCD14, sCD27, sCD163 - were measured in plasma using ELISA at baseline, week 24, and week 48.⁹ This project was approved by each site's institutional review board.

STI diagnosis was defined as report of any STI before week 48. Because HSV-related immune activation may differ from that related to STIs that are eradicated with antibiotics, STIs were categorized as “HSV” and “STIs other than HSV.” We compared participants 1) with STIs vs. without STIs; 2) with HSV vs. STIs other than HSV; 3) without STIs vs. with STIs other than HSV; and 4) with HSV vs. without STIs. Descriptive statistics were performed. Wilcoxon Rank-Sum tests were used to compare overall T-cells and subsets, and MFI and percentage of activation markers on CD4⁺ and CD8⁺ T-cells at week 48 between different STI groups. Linear regression was utilized to compare soluble factors at week 48; multiple repeated measures were used to examine soluble factors across the 48 weeks of the study. Two-sided p-values were calculated. Statistical significance was p 0.05. Analyses were completed with SAS version 9.3 (Cary, NC).

Results

Characteristics for the 49 youth in this analysis are shown in Table 1.

Differences in T-cells were found between participants with and without STIs (Table 2). Participants with any STI and those with HSV had significantly lower CD4⁺ T-cell counts at week 48 versus participants without STIs. Participants with HSV (vs. without STIs) had lower CD4⁺ TemRA T-cell counts. There were no other significant differences in CD4⁺ or CD8⁺ T-cell counts or subsets between groups.

MFI and percentage of expression of activation markers on CD4⁺ and CD8⁺ T-cells differed between those with and without STIs at week 48 (Table 2). Participants with STIs vs. without STIs had significantly higher CD57 MFI on both CD4⁺ TCM T-cells and CD4⁺

TemRO T-cells. Participants with STIs other than HSV vs. those without STIs had significantly higher CD57 MFI on both CD4⁺ TCM and TemRO T-cells. Participants with STIs other than HSV, versus those without STIs, had significantly higher HLA-DR MFI on CD4⁺ naïve T-cells. Participants with any STIs, versus those without STIs, had significantly lower CD28 percentage on CD4⁺TCM and TemRO T-cells. Similarly, those with STIs other than HSV, versus those without STIs, had significantly lower CD28 percentages on CD4⁺ and TemRO T-cells.

There were no significant differences in soluble factors between groups (data not shown).

Discussion

This is the first study to demonstrate lower CD4⁺ T-cell counts and increased immune activation in the setting of STIs among virally suppressed HIV-infected youth. Although sex workers with STIs had increases in HIV VL and cytokines,²⁰ our study demonstrated novel markers of immune activation on CD4⁺ T-cells among youth with STIs other than HSV among a cohort consisting of youth optimally suppressed on cART and with normal CD4⁺ T-cell counts at entry.

STIs were reported throughout the study, suggesting that these youth participated in risky sexual behaviors despite receiving counseling during ongoing medical care. These findings are consistent with other studies of HIV-infected adolescents.^{21–23} Because STIs in HIV-infected youth are associated with HIV transmission and systemic inflammation, developing safer sex interventions specifically targeting HIV-infected youth is critical.

Virally suppressed youth with any STI and youth with HSV only had lower CD4⁺ T-cell counts at week 48 versus those with no STIs. Decreased CD4⁺ T-cell counts have been associated with cervical gonorrhea infection.²⁰ Although HSV-2 infection did not influence CD4⁺ T-cell counts in HIV-infected adults,²⁴ the youth in our study likely were more recently infected with HSV and thus may have more active disease, which may lead to lower CD4⁺ T-cells observed at week 48.

Youth with STIs had higher expression of CD57 and HLA-DR on CD4⁺ T-cells, indicating increased immune activation. This novel finding suggests that HIV-infected youth with STIs other than HSV have activation specific to CD4⁺ T-cells rather than activation of CD8⁺ T-cells commonly associated with HIV and other viral infections.²⁵ STIs other than HSV appear to directly activate CD4⁺ T-cells, increasing CD57, a known marker of T-cell activation and terminal cell differentiation.^{26,27} Increased HLA-DR on CD4⁺ T-cells validates STI-specific CD4⁺ T-cell activation as this marker is associated with high levels of HIV viral replication²⁸ and HIV disease progression.⁶ Although elevated CD4⁺HLA-DR expression persists among virally suppressed patients,²⁹ concomitant STI increased HLA-DR, indicating greater T-cell activation. Youth with STIs and those with STIs other than HSV had a lower CD4⁺CD28⁺ percentage. Because lower CD28 levels are associated with terminal differentiation³⁰ and disease progression,³¹ these findings further support that STIs may contribute to chronic immune activation among HIV-infected youth even when viral replication is controlled.⁹ Our findings expand upon prior work that demonstrated T-cell

activation among HIV-infected patients with co-infections other than STIs – even when patients were HIV virally suppressed - including visceral leishmaniasis (associated with increased CD4⁺CD38⁺HLA-DR and CD8⁺ CD38⁺HLA-DR T-cells³²; increased CD8⁺CD38⁺ T-cells³³) and active or latent tuberculosis (increased expression of CD38 and HLA-DR on CD4⁺ and CD8⁺ T-cells).³⁴

Our limitations include: 1) STI diagnoses are based on reported clinical diagnoses and contemporaneous laboratory results reported to site clinicians; 2) exact timing of STI diagnoses is unknown; we are unable to determine causality; 3) while number of participants limits power to detect small differences, increased inflammation among participants with STIs was evident; 4) because site of STI was not reported, differences in immune activation by site cannot be determined; 5) multiple comparisons performed might increase the possibility that findings are due to chance, although our findings are biologically plausible.

STIs among youth who were virally suppressed after 48 weeks of cART were associated with lower CD4⁺ T-cell counts and increased systemic immune activation, suggesting further investigation into the impact of STIs on systemic immune activation is warranted.

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Ethical approval: This project was approved by the institutional review board at each of the sites involved in the study (listed below).

The following ATN sites participated in this study: University of South Florida, Tampa (Emmanuel, Lujan-Zilberman, Julian), Children's Hospital of Los Angeles (Belzer, Flores, Tucker), University of Southern California at Los Angeles (Kovacs, Homans, Lozano), Children's National Medical Center (D'Angelo, Hagler, Trexler), Children's Hospital of Philadelphia (Douglas, Tanney, DiBenedetto), John H. Stroger Jr. Hospital of Cook County and the Ruth M. Rothstein CORE Center (Martinez, Bojan, Jackson), University of Puerto Rico (Febo, Ayala-Flores, Fuentes-Gomez), Montefiore Medical Center (Futterman, Enriquez-Bruce, Campos), Mount Sinai Medical

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Abbreviations

HIV	human immunodeficiency virus
cART	combination antiretroviral therapy
STIs	sexually transmitted infections
HSV	herpes simplex virus
CMV	cytomegalovirus
VL	viral load
CM	central memory
EM	effector memory
MFI	mean fluorescent intensity

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Highlights

- HIV-infected youth have high risk of acquiring sexually transmitted infections (STI).
- Virally suppressed youth with STIs had lower CD4+T-cell counts vs those without STIs.
- Youth with STIs showed evidence of increased markers of immune activation

Table 1Participant Characteristics (n=49)^a

Characteristic	Number (Percent)	Mean (SD)
Age		
18–20 years	21 (42.9)	
21– 24 years	28 (57.1)	
Birth Gender – Male	43 (87.8)	
Race-Ethnicity		
African-American	33 (67.3)	
Other	16 (32.7)	
Route of HIV transmission		
Man who has sex with men	40 (81.6)	
Heterosexual	8 (16.3)	
Unknown/other	1 (2.0)	
Baseline CD4+ T-cell count		
350–500	21 (42.9)	
>500	28 (57.1)	
Baseline HIV viral load (copies/ml)		21,331 (21,545)
Youth with 1 STI diagnosis	18 (37)	
Herpes simplex virus (HSV)	8 (16.3)	
Chlamydia	7 (14.3)	
Syphilis	4 (8.2)	
Gonorrhea	4 (8.2)	
Youth with > 1 STI reported	6 (12.2)	
Number of visits at which an STI was reported		2.6 (2.0)
Visits at which STI first reported		
Pre-entry	3 (6.1)	
Baseline	3 (6.1)	
Week 12	3 (6.1)	
Week 24	3 (6.1)	
Week 36	2 (4.1)	
Week 48	4 (8.2)	

SD: standard deviation; HIV: human immunodeficiency virus; STI: sexually transmitted infection; HSV: herpes simplex virus

^aThere were no differences in age, gender, or race/ethnicity between those with and without STIs (data not shown).

Table 2

Associations between Inflammatory Markers and Sexually Transmitted Infections (STIs) at Week 48^a.

Inflammatory Marker	Without STI (n = 29–31) ^b	With Any STI (n = 17–18) ^b	HSV Only (n = 7–8) ^b	STI other than HSV (n = 10)	P-value
Lymphocyte Count (cells/ μ l) ^c					
CD4 ⁺ T-cells, count, mean (SD)	878 (251)	725 (248)			0.024
CD4 ⁺ T-cells, count, mean (SD)	878 (251)		670 (105)		0.022
Lymphocyte Population (cells/ μ l) ^c					
CD4 ⁺ TemRA T-cells, mean (SD)	199 (87.3)		130 (59.6)		0.049
Activation Marker, Mean Fluorescent Intensity (MFI) ^d					
CD4 ⁺ TCM T-cells, CD57, mean (SD)	1424 (1244)	2663 (2882)			0.042
CD4 ⁺ TCM T-cells, CD57, mean (SD)	1424 (1244)			3202 (3444)	0.042
CD4 ⁺ TemRO T-cells, CD57, mean (SD)	4373 (4317)	8337 (7540)			0.029
CD4 ⁺ TemRO T-cells, CD57, mean (SD)	4373 (4317)			7814 (5751)	0.036
CD4 ⁺ naïve T-cells, HLA-DR, mean (SD)	63 (34)			89 (40)	0.014
Activation Marker, Percentage ^e					
CD4 ⁺ TCM T-cells, CD28 mean (SD)	98.5 (1.6)	97.0 (3.1)			0.021
CD4 ⁺ TCM T-cells, CD28 mean (SD)	99 (1.6)			96 (3.6)	0.019
CD4 ⁺ TemRO T-cells, CD28, mean (SD)	94.0 (7.1)	88.5 (9.1)			0.014
CD4 ⁺ TemRO T-cells, CD28, mean (SD)	94.0 (7.1)			88 (7.5)	0.019

STI: sexually transmitted infection; HSV: herpes simplex virus; SD: standard deviation; MFI: mean fluorescent intensity.

^aResults with $p < 0.05$ are shown.^bNumbers vary due to missing data.^cNo other significant differences in CD4⁺ or CD8⁺ T-cell counts or subsets between STI groups.^dNo other significant differences in MFI between those with and without STIs for other activation markers (CD28, CD38, HLA-DR) on CD4⁺ T-cells nor for any activation markers on CD8⁺ T-cells. No significant differences in MFI between those with STIs other than HSV and those without STIs for other activation markers (CD28, CD38) on CD4⁺ T-cells nor for any activation markers on CD8⁺ T-cells. No significant differences in CD4⁺ and CD8⁺ MFI between those with HSV and those with STIs other than HSV, nor between those with HSV and those without STIs.^eNo significant differences in percentage of activation markers between those with and without STIs for other activation markers (CD38, HLA-DR, CD57) on CD4⁺ T-cells nor for any activation markers on CD8⁺ T-cells. No significant differences in percentage of activation markers between those with STIs other than HSV and those without STIs for other activation markers (CD38, HLA-DR, CD57) on

CD4⁺ T-cells nor for any activation markers on CD8⁺ T-cells. No significant differences in CD4⁺ and CD8⁺ percentage of activation markers between those with HSV and those with STIs other than HSV, nor between those with HSV and those without STIs.

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