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Elevated Urinary Leukocyte Esterase as a Potential Surrogate Marker for HIV Sexual Transmission Risks in Men Receiving Antiretroviral Therapy

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Abstract

Background—Local genital tract inflammation stimulates Leukocyte activity and causes HIV shedding, potentially increasing HIV sexual infectiousness. Although there are available clinical markers for genital tract inflammation, such as urinary Leukocyte esterase, none have yet been examined in relation to HIV sexual risk behaviors.

Purpose—To examine the association between urinary Leukocyte esterase and sexual practices.

Methods—Sexually active men living with HIV and receiving antiretroviral therapy (ART, N = 290) provided urine specimens and completed behavioral health assessments. HIV RNA tests and CD4 cell counts were abstracted from medical records. Urine specimens were analyzed for Leukocyte esterase using a standard point of care dipstick test.

Results—Thirty-one (10.6%) participants tested positive for Leukocyte esterase. Logistic regression models did not indicate differences between men with elevated and un-elevated Leukocyte activity on demographic, health, recent STI symptoms and diagnoses, or substance use. However, men with elevated Leukocyte activity indicated significantly greater sexual behavior in the previous 3-months, including more recent unprotected sexual intercourse.

Discussion—A simple over-the-counter urine test may serve as an indicator of sexual HIV infectiousness to inform further evaluation and treatment of genital tract inflammation, as well as condom use decisions during times of increased genital tract inflammation.

Keywords

Genital tract inflammation; HIV transmission risks; Treatment as prevention

Antiretroviral therapies (ART) effectively suppress HIV replication and have the potential to reduce sexual infectiousness, forming the basis for using HIV treatments as prevention. Most ART regimens penetrate the urogenital compartment of the immune system and suppress HIV in genital secretions. (1) HIV RNA is typically undetectable in the semen of men who achieve blood plasma HIV suppression and do not have co-occurring genital tract inflammation. (2) The biological plausibility of using HIV treatments for prevention is well

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established (3), with the most compelling evidence coming from a clinical trial showing early treatment with ART can prevent HIV transmission in heterosexual couples. (4) Still, it is widely known that HIV shedding occurs even when peripheral blood plasma viral activity is suppressed and even in the absence of symptomatic genital infections. (5)

HIV suppression in blood plasma is often erroneously assumed to always correspond with HIV-1 RNA in genital secretions, and therefore mistakenly interpreted as an indicator of sexual infectiousness (6, 7). High concordance between blood plasma and semen HIV RNA has only occurred under controlled conditions that assure perfect adherence to a viral suppressive ART regimen and intensive screening, diagnosis, and treatment of co-occurring sexually transmitted infections (STI). (2, 8) Studies testing the association between HIV RNA in blood plasma and semen in typical clinical samples find a modest average correlation of .44. (5) One study demonstrated no relationship between blood plasma and semen HIV RNA; 53% of men with undetectable HIV RNA in blood plasma had detectable virus in semen and 31% of men with undetectable virus in semen had detectable blood plasma virus. (9)

Local inflammation of the genital tract activates HIV replication, shedding virus and therefore increasing HIV infectiousness. (10, 11) Genital tract inflammation can recreate magnitudes of infectiousness that are otherwise only seen in acute HIV infection. (12) Although HIV RNA in genital secretions tends to be lower than HIV RNA in blood plasma, this relationship can be inverted in the presence of genital tract inflammation. (13)

Genital tract HIV RNA is directly associated with the number of Leukocytes present. There is indeed a dose-relationship between Leukocyte activity in the genital tract and HIV shedding (14). In one prospective study, for example, the odds of detecting genital tract HIV RNA increased 1.36 for every 1000 cell increase in genital tract Leukocytes. (15) Past research has shown that urethritis is associated with an eightfold increase in HIV in the seminal plasma compartment (16). As much as 40% discordance is observed between seminal and blood viral populations and the complexity of viral populations differs between the two compartments, suggesting at least partial independence of the blood and genital compartments (16-18). An easily performed and inexpensive test for genital tract Leukocyte activity, may therefore serve as a marker for HIV infectiousness that could inform the practice of HIV treatment as prevention.

The current study is the first to report the association between urinary Leukocyte esterase and sexual behaviors in men living with HIV infection. Leukocyte activity is monitored by an easily performed urine test to detect Leukocyte esterase – an indicator of local lower urogenital tract inflammation. Leukocyte esterase in urine is detected using a simple over-the-counter dip-test and therefore offers a point of care or home test for genital tract inflammation. Research shows that elevated Leukocyte esterase is sensitive to detecting genital tract inflammation, with low specificity for detecting STI (19). Exposure to sexually transmitted pathogens, including re-exposure to HIV, as well as urogenital stimulation and other sources of inflammatory response that can result from HIV seroconcordant sexual relationships can increase HIV infectiousness and therefore increase risks to uninfected sex partners. In the current study, we hypothesized that elevated Leukocyte esterase in men

living with HIV infection and receiving ART would demonstrate greater recent sexual activity than their counterparts with un-elevated Leukocyte esterase. In addition, we predicted that the association between Leukocyte esterase and sexual behavior could be indicative of multiple sources of genital tract inflammation and would therefore occur in the context of low-rates of STI symptoms and diagnoses.

Methods

Participants

Men living with HIV/AIDS who were currently receiving ART (N = 290) were reached through community recruitment strategies. Individuals interested in participating contacted our research program to schedule an intake assessment appointment. The study entry criteria were (a) biologically male and 18 years of age or older, (b) HIV positive and prescribed ART, and (c) sexually active as defined by having at least one sex partner in the previous month.

Measures

Participants provided four sources of data. First, participants completed audio-computer assisted self-interviews (ACASI) to assess demographic, health and behavioral characteristics at the start of the study. Second, we assessed medication adherence using phone-based unannounced pill counts. Third, we collected HIV RNA (viral load) and CD4 cell counts using a participant assisted medical chart abstraction procedure. Finally, participants provided urine specimens for substance use screening and Leukocyte esterase (LE) testing.

Computerized Interviews

Demographic and health characteristics—Participants were asked their gender, age, years of education, income, ethnicity, and employment status. Participants also reported the year they first tested HIV positive and whether they had experienced 14 HIV-related symptoms of 2-weeks duration. To assess alcohol use we administered the Alcohol Use Disorders Identification Test (AUDIT), a 10-item scale designed to measure alcohol consumption and identify risks for alcohol abuse and dependence. (20) Scores on the AUDIT range from 0 – 40 and the AUDIT with scores greater than 8 indicating high-risk for alcohol use disorders and problem drinking.

Sexual health—Participants reported whether they had experienced three common STI symptoms and whether they had been diagnosed with any of eight non-HIV STI or sources of genital disease during the past 3-months (see Results for symptoms and diagnoses).

Sexual behavior—Participants responded to questions assessing their number of male and female sex partners and frequency of sexual behaviors (anal and vaginal intercourse) with seroconcordant (i.e., same HIV status) and serodiscordant (i.e., different HIV status) partners in the previous 3-months. Studies show that a 3-month retrospective timeframe yields reliable estimates of sexual behavior. (21) These data were collected specific to the participant's practices as the insertive or receptive partner during anal sex. In addition, we

assessed anal sex with male and female partners and combine these behaviors for insertive anal intercourse. We present sexual behavior data as composites (i.e., total intercourse, condom protected intercourse, unprotected intercourse) and for individual acts (i.e., unprotected anal intercourse as the insertive partner with HIV serodiscordant partners).

ART Adherence

Participants consented to three unannounced telephone-based pill counts over the course of 6-weeks constituting a prospective measure of adherence. Unannounced pill counts are reliable and valid in assessing medication adherence when conducted in homes (22) and on the telephone (23, 24). In this study we conducted unannounced cell-phone based pill counts. Participants were provided with a free cell phone for use in the study assessments. Following office-based training in the pill counting procedure, participants were called at unscheduled times by a phone assessor. Pill counts were unscheduled and occurred over 21 to 35 day intervals. Participants counted each of the antiretroviral medications they were taking. Pharmacy information from pill bottles was also collected to verify the number of pills dispensed between calls and whether there was a lapse in obtaining medications from the pharmacy. Adherence was calculated as the ratio of pills counted relative to pills prescribed, taking into account the number of pills dispensed, and averaged across pill counts to yield one-month adherence.

Chart Abstracted Viral Load and CD4 Cell Count

We used a participant assisted method for collecting chart abstracted HIV RNA viral load and CD4 cell counts from medical records. Participants were given a form that requested their doctor’s office to provide results and dates of their most recent viral load and CD4 cell counts. These data were therefore obtained directly by the participants from their primary HIV care providers. The form included a place for the provider's office stamp or signature to assure data authenticity.

Urinalysis and Drug Testing

Urine specimens were first tested for LE and nitrites. We performed a chemstrip test for the presence of Leukocyte esterase, an enzyme that is indicative of urinary tract inflammation. Granulocytic Leukocytes contain esterases that catalyze the hydrolysis of an indoxylcarbonic acid ester to indoxyl, which reacts with a diazonium salt to produce a purple color on the test strip. Specimens were taken with over-the-counter ‘urine dip’ Roche Chemstrips 2 LN (cost US$0.16 each) and read on-site at the research office. Although chemstrips can be visually read for color change at no cost, we processed the chemstrips using the Roche Urisys 1100 Urine Analyzer (cost $1200). Using the same chemstrips, we also tested for nitrites, indicative of an upper urinary tract infection or renal disease to differentiate potential upper and lower urogenital tract sources of inflammation.

Following LE and nitrite testing we used a multi-panel dip-test to detect illicit drug metabolites in participant’s urine specimens. Drug detection used a lateral flow chromatographic immunoassay for qualitative detection of 12 drugs and drug metabolites (Redwood Toxicology Labs - Reditest-12). The test is FDA approved and is sensitive and specific for initial drug screening.

Procedures

Men living with HIV were recruited through targeted community sampling. We used both venue recruitment and snowball sampling techniques. Recruitment relied on responses to brochures placed in waiting rooms of HIV service providers and infectious disease clinics throughout Atlanta, GA. We also implemented an explicit systematic approach to word-of-mouth chain recruitment. Specifically, participants were given brochures that described the study opportunity and were encouraged to use the brochures to refer their HIV positive friends to the study.

Participants provided informed consent and completed the computerized interviews. Participants were then instructed in procedures to conduct unannounced pill counts and how to obtain their most recent CD4 cell count and HIV RNA viral load test results from their medical provider. We also asked participants to provide a first catch urine specimen during this office visit. Participants who tested LE positive were informed of their test results and given a written explanation to take to their medical provider. Drug test results were provided to participants upon request. Participants received US$120 for completing all study measures and procedures. The university Institutional Review Board approved all procedures and protocol changes.

Data Analyses

Logistic regressions were performed to test for associations between men who did not (N = 259) and men who did (N = 31) test LE positive. Significance tests were performed on composite sexual behaviors (e.g., anal intercourse) to eliminate overlap and avoid statistical redundancy. Analyses of sexual behaviors controlled for participant age and years since testing HIV positive. Significance tests were not performed for sparse tables (cell sizes < 5). For all analyses we report odds ratios with 95% confidence intervals. Statistical significance was defined by $p < .05$.

Results

Among the 290 sexually active men living with HIV and receiving ART, 31 (10.6%) tested LE positive, of which 18 (58%) demonstrated trace levels and 13 (42%) showed significantly elevated LE.

Demographic and Health Characteristics

Table 1 shows the demographic and health characteristics for LE negative and LE positive participants. Logistic regressions did not indicate significant associations between elevated LE and participant demographic characteristics. There were also no significant associations between testing LE positive and heath indicators including ART adherence. In addition, only one participant had positive nitrite test results.

Substance Use

Drug screening results showed that marijuana was detected among 30% of participants, as was cocaine for 28%. More than half of the sample (56%) screened positive for at least one of the 12 illicit drugs, 15% tested positive for two drugs, and 4% were positive for three or

more drugs. Logistic regressions did not indicate any significant associations between elevated LE and substance use. (see Table 2)

Sexual Health History

Nearly every participant reported discussing sexual practices with their health care provider. Half (48%) of participants reported having been tested for STI in the previous 3-months and one in five had been diagnosed with an STI in that time period. The most commonly diagnosed STI were HSV (8%) and HPV (6%). There were no associations between LE test results and any of the sexual health indicators including STI symptoms and recent diagnoses. (see Table 3)

Sexual Behavior

Table 4 shows the sexual behaviors reported over the previous 3-months for the LE groups. Forty-seven percent of LE negative men reported two more sex partners, as did 36% of LE positive men, a non-significant difference. In addition, 27% of participants reported unprotected anal or vaginal intercourse with HIV serodiscordant or unknown HIV status partners. LE positive participants were significantly more likely to report their most recent sexual encounter had occurred within the previous week of the assessment.

Results showed that LE positive participants had significantly more total sexual acts and a trend toward greater total unprotected sexual intercourse compared to their LE negative counterparts. Examination of sexual behaviors by partner HIV status indicated that LE positive participants had higher rates of total sex and unprotected intercourse with HIV seroconcordant partners than the LE negative group. Both LE groups reported unprotected anal and vaginal intercourse with HIV uninfected partners, with no significant differences.

Discussion

More than one in five men living with HIV in this study reported having been diagnosed with an STI in the previous three months. Over 40% had two or more sex partners in that time period, and one in four reported unprotected anal or vaginal intercourse with HIV non-infected partners. In addition, ART adherence was suboptimal for many men, with an average of 85% of ART taken over the prospective month. These results therefore demonstrate considerable potential for HIV transmission to uninfected partners, with these risks significantly amplified by genital tract inflammation.

This is the first study that we are aware to examine sexual practices in association with any marker for genital tract inflammation in sexually active HIV positive men. We found that 10% of participants tested positive for elevated urinary Leukocyte esterase, indicating local genital tract inflammatory processes that likely correspond with increased HIV infectiousness. Elevated LE was not explained by recent STI symptoms or diagnoses. Consistent with past research, elevated LE was therefore not indicative of STI. (19) The prevalence of elevated LE in this sample is therefore likely to reflect inflammatory disease processes other than those caused by a current STI. Furthermore, we did not observe associations between LE and demographic, health or substance use characteristics. Thus, confirming our study hypothesis, only rates of recent sexual practices, particularly

unprotected anal and vaginal intercourse, were significantly associated with elevated LE. Our findings suggest higher rates of unprotected sex with HIV seroconcordant partners may contribute to increased infectiousness. Importantly, the resulting increased HIV infectiousness will translate to higher risks for HIV transmission during unprotected intercourse with HIV serodiscordant partners. Thus, while serosorting may be a useful risk reduction strategy for HIV positive men who restrict their sexual relationships to HIV positive partners, it may inadvertently increase HIV infectiousness and therefore increase risks to uninfected sexual partners.

HIV RNA concentrations in semen are elevated when inflammatory processes stimulate HIV shedding. Leukocyte esterase testing may offer a screening test for genital tract inflammation of potential value in clinical settings. Detecting genital tract inflammation with LE testing is particularly important in sexually active people living with HIV because evidence for inflammatory disease processes can indicate increased risks for HIV infectiousness. Although LE tests are commonly used to screen for potential STI (25, 26), other sources of inflammation would similarly increase HIV infectiousness. Genital tract inflammation resulting from incomplete STI treatment, urethritis, chronic prostatitis, viral pathogens including HSV, HPV, and re-exposure to HIV, as well as other non-specific causes including substance use are all putative candidates for explaining the elevated LE observed in the current study (27-32).

These findings should be interpreted in light of the study limitations. First, we relied on a convenience sample that cannot be considered representative of men living with HIV infection. The sample also came from a wide-range of providers that likely varied in sexual health services. Because the interpretation of elevated urinary leukocytes is interpreted different between genders, we did not include women in this study. Future research is therefore needed to replicate these results in women living with HIV. The study also relied on self-report instruments to assess sexual behaviors. Although we collected sexual behaviors using state of the science-computerized interviews, these data may still be subject to reporting biases. Socially sensitive behaviors such as sexual behaviors and STI assessed by self-report may be underreported, suggesting that rates of unprotected sex in this study should be considered lower-bound estimates. Another limitation of the current study is our assumption that elevated LE is associated with increased HIV infectiousness. However, studies of genital tract inflammation in relation to HIV RNA in semen support this assumption. (10, 15) Our cross-sectional study design precludes directional interpretations of the findings, such that the observed associations between sexual behaviors and elevated leukocyte activity may be the result of a third variable, such as substance use. Prospective research is therefore needed to rule out potential confounding variables.

We conclude that elevated LE is associated with unprotected sexual behaviors in men living with HIV infection and may serve as a surrogate marker for increased HIV transmission risks for sexually active men receiving ART. If confirmed by subsequent research, this inexpensive (US$0.16) and easily performed over-the-counter urine test could be integrated into the standard of care for using HIV treatments as prevention to inform clinical decisions for further evaluation and treatment of genital tract inflammation and behavioral decisions regarding the use of condoms during times of increased genital tract inflammation. Should

studies confirm these associations, the results may be used to design interventions. For example, HIV positive individuals may be counseled to refrain from unprotected sex when they have tested positive for elevated LE. In addition, counseling may counter compensator sexual activity that could accompany results of negative LE testing. These interventions will be especially warranted for persons who use home LE testing to inform them of their sexual infectiousness. Sexual health messages should therefore be developed to accompany the interpretation of both positive and negative LE testing among people living with HIV.

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Table1

Demographic and Health Characteristics of HIV Infected Men Testing Negative and Positive for Urinary Leukocyte Esterase (LE).

	LE Negative (N = 259)		LE Positive (N = 31)			
Characteristic	**M**	**SD**	**M**	**SD**	**OR**	**95%CI**
Age	45.22	10.01	47.64	9.18	1.02	0.98-1.06
Years education	12.85	1.81	13.13	1.71	1.09	0.87-1.37
Years since HIV diagnosis	14.13	8.34	17.22	9.31	1.05+	1.00-1.09
HIV symptoms	3.74	3.64	3.06	3.93	0.95	0.85-1.06
ART adherence	87.8	15.6	86.9	14.6	0.68	0.06-7.07
Log HIV RNA c/Ml	2.07	1.06	2.01	1.03	0.94	0.65-1.36
CD4 count	465.72	276.18	445.48	261.75	1.00	0.99-1.01
	N	%	N	%		
Caucasian	20	8	0			
African-American	239	92	31	100	NP	
Unemployed	67	26	10	32	Ref	
Employed/Student	43	17	4	13	0.52	0.95-2.87
Disability	151	55	17	55	0.33	0.50-2.12
Income < $10,000	154	60	19	61	1.06	0.49-2.29
AUDIT ≤ 7	100	39	11	35		
AUDIT ≥ 8	159	61	20	65	1.14	0.52-2.49
HIV RNA ≤ 400c/Ml	204	81	26	84		
HIV RNA > 400C/Ml	50	20	5	16	0.80	0.29-2.19
CD4 < 200	50	20	4	13		
CD4 ≥ 200	205	80	27	87	1.66	0.56-4.96
Elevated Nitrites	0			1	NP	
Diagnosed with renal disease	11	4	2	6	NP	

Note:

LE = Leukocyte Esterase; NP = not performed sparse or empty cells.

+ p < .10;

Table 2

Substance Use among HIV Infected Men Testing Negative and Positive for Urinary Leukocyte Esterase (LE).

	LE Negative (N = 259)		LE Positive (N = 31)			
Drug test	**N**	**%**	**N**	**%**	**OR**	**95%CI**
Opiates	8	3	1	3	NP	
Oxycodone	12	5	0		NP	
Phencyclidine	1		0		NP	
Buprenorphine	0		0		NP	
Benzodiazepines	21	8	2	7	NP	
Cocaine	78	30	5	16	0.46	0.16-1.20
Amphetamine	6	2	1	3		
Methamphetamine	5	2	1	3		
MTD	1	1	0			
Marijuana (THC)	77	30	11	36	1.30	0.59-2.84
Propoxyphene	1	1	0			
Barbiturates	0		0			
Methylenedioxymeth amphetamine (MDMA)	1	1	0			
No Drug Use	113	44	14	45	Ref	
One drug	94	36	14	45	1.36	0.16-11.36
Two Drugs	41	16	2	7	1.64	0.20-13.68
Poly-substance use	11	4	1	3	0.54	0.04-6.47

Note : LE = Leukocyte Esterase; NP = not performed due to sparse or empty cells.

Table 3

Sexual Health Characteristics of HIV Infected Men Testing Negative and Positive for Urinary Leukocyte Esterase (LE).

	LE Negative (N = 259)		LE Positive (N = 31)			
STI History	**N**	**%**	**N**	**%**	**OR**	**95%CI**
Discusses sexual health with a provider	249	96	30	97	0.83	1.03-6.71
STI tested	127	49	13	41	0.75	0.35-3.59
STI Symptoms past 3-months						
Genital discharge	10	4	2	7	NP	
Painful urination	17	7	1	3	NP	
Genital ulcers	13	5	2	7	NP	
STI Diagnoses past 3-months						
Gonorrhea	12	5	0		NP	
Chlamydia	5	2	1	3	NP	
Syphilis	23	9	2	6	NP	
HSV	22	9	3	10	NP	
Trichomoniasis	0		0		NP	
HPV	15	6	4	13	NP	
Any STI	58	22	7	23	1.01	0.41-2.46
NGU	3	1	0		NP	
UTI	4	1	1	3	NP	

Note : LE = Leukocyte Esterase; HSV = Herpes Simplex Virus; HPV Human Papilloma Virus; NGU = Non-gonorrheal Urethritis; UTI = Urinary Tract Infection; NP = not performed due to sparse or empty cells.

Table 4

Sexual Behaviors among HIV Infected Men Testing Negative and Positive for Urinary Leukocyte Esterase (LE).

	LE Negative (N = 259)		LE Positive (N = 31)			
Sex Behaviors Past 3-months	**N**	**%**	**N**	**%**	**OR**	**95% CI**
2+ Sex Partners	122	47	11	36	0.66	0.30-1.45
HIV+ Partners	175	68	20	65	0.98	0.44-2.20
HIV- Partners	73	28	7	23	0.95	0.45-2.03
Unprotected Insertive Serodiscordant Sex	73	28	7	23	0.74	0.30-1.80
Most recent sex > 1 Week	159	62	11	35	Ref	
Most recent sex < 1 Week	99	38	20	65	3.10**	1.41-6.83
	M	SD	M	SD		
Total Sexual Behaviors						
Total Intercourse	7.59	11.23	11.70	16.89	1.03*	1.01-1.05
Total Condom Protected Intercourse	4.23	9.24	6.12	11.42	1.02	0.99-1.05
Total Unprotected Intercourse	3.36	6.29	5.58	13.03	1.03+	1.00-1.07
Seroconcordant Sex						
Total intercourse	3.66	5.31	7.67	14.84	1.06**	1.01-1.10
Condom Protected intercourse	1.85	3.15	2.77	5.13	1.08	0.98-1.17
Total Unprotected intercourse	1.80	3.55	4.90	13.10	1.07*	0.01-1.13
Unprotected Anal Insertive	0.70	1.90	0.97	1.87		
Unprotected Anal Receptive	0.87	2.58	3.16	12.65		
Unprotected Vaginal	0.23	1.10	0.77	3.00		
Serodiscordant Sex						
Total intercourse	3.93	10.12	4.03	10.86	1.01	0.97-1.04
Condom Protected intercourse	2.38	8.55	3.35	10.83	1.01	0.98-1.05
Unprotected intercourse	1.55	5.31	0.67	1.42	0.92	0.76-1.11
Unprotected Anal Insertive	0.27	0.99	0.32	0.75		
Unprotected Anal Receptive	0.88	4.45	0.36	1.01		
Unprotected Vaginal	0.39	2.59	0			

Note:

LE = Leukocyte Esterase.

+ p < .10;

* p < .05;

** p <01;