Human Immunodeficiency Virus in Semen and Plasma: Investigation of Sexual Transmission Risk Behavioral Correlates

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ABSTRACT

Risks for sexually transmitted HIV may be related to concentrations of virus detected in semen and previous research shows a small to moderate association between viral load in blood and semen. This study examined the association between viral load in semen and plasma in a community sample of HIV-infected men and is the first study to examine semen viral load in relation to sexual transmission risk behaviors. A sample of 44 HIV-positive men recruited from community service agencies provided semen, blood, and urine samples and completed clinical interviews assessing health and behavior. We failed to find an association between viral load in semen and plasma, Spearman $\rho = 0.07, p > 0.1$. When restricted to participants with detectable virus in semen and plasma, the correlation remained nonsignificant, $\rho = -0.16, p > 0.1$. Men who had higher semen viral loads relative to their plasma viral load were distinguished by having engaged in significantly higher rates of unprotected intercourse as the insertive sex partner in the previous 3 months. Semen viral load was not, however, related to recent or current sexually transmitted infections (STIs). This study is among the first to examine sexual transmission risk behaviors as marker for HIV infectiousness. Results caution against inferring sexual transmission infectiousness based on plasma viral load and suggest that HIV-positive men who practice higher rates of insertive intercourse may be more infectious even in the absence of other STIs.

INTRODUCTION

STUDIES SHOW that approximately one in three people living with HIV/AIDS continues to practice unprotected sexual behaviors, potentially placing themselves and their sex partners at risk for exposure to HIV and other sexually transmitted pathogens.^{1,2} Among the factors associated with continued sexual transmission risk behaviors in HIV-infected people are the perceived benefits of medical advances in HIV treatments.^{3,4} Successful antiretroviral therapy suppresses HIV replication and can reduce the amount of HIV in peripheral blood to levels below detection, suggesting reduced infectivity. Thus, individuals with undetectable virus in peripheral blood may perceive themselves as less infectious and perceptions of reduced infectivity appear to influence sexual transmission risk behaviors in some HIV-infected and uninfected persons.^{3,5–7} There is also evidence that individuals with higher concentrations of plasma

HIV are more likely to transmit the virus to blood recipients, offspring, and sex partners.^{8–10} However, studies that correlate plasma levels of HIV RNA with viral RNA detected in semen demonstrate low to moderate associations; most correlations range between 0.20 and 0.60.^{9–12} In general, plasma concentrations of HIV tend to be higher than concentrations in semen,^{12,13} with HIV RNA as much as 10-fold higher in plasma than semen.¹¹ Accumulating evidence suggests that the male genital tract constitutes a relatively distinct compartment of HIV replication, with long-lived and frequently replicating cells serving as a sanctuary for HIV to replicate protected from immune responses and adequate levels of some antiretroviral therapies.⁸

Explanations of discrepancies between HIV viral loads in plasma and semen have thus far focused on co-occurring ulcerative and nonulcerative sexually transmitted infections (STIs) as factors that promote HIV shedding in the genital tract

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and therefore potentially increasing infectivity in people living with HIV/AIDS.¹⁴ In one study, HIV concentrations in semen were 8 times greater in men with clinical urethritis and 10 times greater in men with gonorrhea relative to those without clinical urethritis.¹⁵ In addition, successful treatments of STIs demonstrate subsequent reductions of HIV in semen,¹⁶ and treatment of symptomatic STIs can reduce HIV transmission to uninfected sex partners.¹⁷ Thus, co-occurring STIs appear important in promoting infectivity in HIV-infected men. In addition to infectiousness, HIV transmission is a function of sexual transmission risk practices. Studies have not as of yet, however, investigated behavioral cofactors of infectivity in HIV-infected men.

The current study was conducted to identify behavioral correlates of viral infectivity in HIV-positive men. We were particularly interested in patterns of transmission risk behaviors exhibited by men who were more infectious than implicated by their plasma viral load. Given that greater concentrations of virus are typically detected in plasma relative to serum,¹² and the demonstrated association between urethritis and viral load in semen,¹⁷ we hypothesized that men who presented higher viral loads in semen than blood would be more likely to have a recent STI and would exhibit higher rates of HIV transmission risk behaviors than men whose plasma viral load was equal to or less than their semen viral load.

MATERIALS AND METHODS

Clinical specimens and behavioral data were collected early in the year 2000 and our institutional review board for ethical treatment of human research participants approved the study.

Participants

We identified 44 HIV-infected men from a pool of 242 men participating in a community-based survey to serve as semen and blood donors for this study. Men were originally recruited from infectious disease clinics, AIDS service organizations, and chain recruitment (i.e., word of mouth) to participate in a survey-interview study. After the survey, participants were asked whether they would be willing to take part in a subsequent study that would involve providing semen, blood, and urine samples. Among the 187 (78%) men who indicated interest in research involving semen collection, we invited 51 randomly selected men to participate in the current study. One participant declined the invitation to participate and six failed to return for specimen collection.

Behavioral assessments

As part of a larger study and before recruitment for biological specimen collection, participants completed measures of demographic characteristics, health status, and sexual risk behaviors. Therefore, the behavioral assessments were not subject to response biases that can ensue from participating in biological specimen collection.¹⁸

Demographic characteristics. Participants were asked their age, years of education, ethnicity, relationship status, and

whether they identified as homosexual, bisexual, or heterosexual.

Clinical health assessment. To assess current health status, participants reported the year that they first tested HIV positive, whether they had experienced any of 14 symptoms of HIV infection (e.g., persistent respiratory distress, skin rashes, persistent diarrhea, recurring fever, fatigue), had been diagnosed with an AIDS-related condition, and their most recent CD4⁺ cell count. Participants were also interviewed to determine their antiretroviral therapy history and their 3-day adherence to HIV treatments.¹⁹ The number of doses missed was summed across medications and was used to calculate a treatment adherence index.

Sexual transmission risk behavior and sexually transmitted infections. Sexual behaviors were assessed by asking participants to report the number of times they had engaged in vaginal intercourse and the number of times they engaged in anal and oral intercourse as the insertive and receptive partner without and with condoms in the previous 3 months. Participants also recorded the number of sexual partners with whom they had engaged in each behavior. Timeframes and dates were used to help cue memory for sexual events and open response formats were used for sexual behavior measures to reduce response bias and to minimize measurement error. Measures similar to these have been found reliable in self-reported sexual behavior assessments.²⁰

Biological specimen collection and laboratory analysis

Participants provided semen, blood, and urine specimens. Immediately after the collection of blood specimens by a certified phlebotomist, participants masturbated into a sterile container to provide semen samples. Blood and semen specimens were transported within 2 hr of collection to a virology laboratory for analysis. Semen samples ranged from 200 μ l to 1 ml and were aliquoted into 200- μ l volumes and stored at -70°C . Whole blood specimens were centrifuged at $500 \times g$ for 10 min. The plasma was recovered and aliquoted into 200- to 500- μ l samples. Initially plasma viral load was determined by Roche (Branchburg, NJ) Amplicor HIV-1 Monitor and by NucliSens HIV-1 QT (Organon Teknika, Boxtel, The Netherlands) with comparable results (data not shown). Both methods are certified for detection of HIV-1 RNA in plasma. Because of the performance in previous research²¹ and our own preliminary analyses that showed the silica method for extraction of viral RNA from semen superior to Roche Amplicor HIV-1 Monitor, NucliSens HIV-1 QT assays were performed to test viral loads in plasma and semen with a detection limit of 100 copies/ml. Participants were not informed of their viral load test results within this experimental protocol.

During a subsequent appointment, participants provided a urine specimen in a sterile plastic container. Specimens were refrigerated and transported to a microbiology laboratory for processing and analysis by ligase chain reaction (LCR; Abbott Laboratories, Abbott Park, IL) to detect *Chlamydia trachomatis* (chlamydia) and *Neisseria gonorrhoeae* (gonorrhea). Participants were notified of positive results and were referred for treatment.

Statistical analyses

For the purposes of the current study, groups were defined on the basis of differences between plasma and semen viral loads. Using $\log_{10}$ values for both plasma and semen viral loads, we defined men as either (1) having equal or greater viral loads in plasma relative to semen or (2) having greater values of viral load in their semen relative to plasma. Associations between semen viral load and plasma viral load were examined by using Spearman rank order correlations (ρ). Concordance between undetectable virus in plasma and semen was tested by a contingency table χ^2 test and contingency coefficient (CC). Consistent with previous research,¹¹ we correlated viral loads for all participants as well as only the subset of participants with detectable virus in their plasma and semen. Group comparisons for continuous measures of demographic and health status characteristics were conducted by t tests and for nominal data we used contingency table χ^2 tests. Group differences for sexual practices were tested by analyses of covariance. Because HIV disease processes and sexual practices change over the course of time that a person lives with HIV AIDS,¹ we controlled the number of years since the participant had tested HIV positive in these analyses. Distributions of sexual behaviors were highly skewed and were transformed for analysis by using the formula $\log_{10}(x + 1)$,²² with observed values presented in the tables. Significance levels of $p < 0.05$ were used for all analyses.

RESULTS

Among the 242 men who were asked if they would be interested in participating in a study that involved semen collec-

tion, 54 declined. Analyses were conducted to identify potential volunteer biases by comparing three groups: (1) men who declined interest in participating ($n = 54$), (2) men who indicated an interest in participating but were not asked to enroll ($n = 138$), and men who were randomly selected, approached, and enrolled in the study ($n = 50$). Analyses did not indicate any differences in age, years of education, ethnicity, sexual orientation, current relationship status, sexual behaviors, years since testing HIV positive, most recent CD4⁺ cell count, and most recent viral load. We therefore failed to identify potential selection and volunteer biases along key participant characteristics.

Associations between viral load in plasma and semen

The Spearman's ρ correlation between viral load in semen and plasma was not significant, $\rho(44) = 0.07, p > 0.1$ (see Fig. 1). When restricted to participants with detectable virus in semen and plasma, the correlation remained nonsignificant, $\rho(20) = -0.16, p > 0.1$ (see Fig. 2). There was also poor concordance between undetectable viral loads in plasma and semen; 53% of men with undetectable virus in plasma had detectable viral loads in semen and 31% of men with undetectable virus in semen had detectable plasma viral loads, $\chi^2(1, n = 44) = 1.0, p > 0.1$. The contingency coefficient for undetectable viral load in blood and semen was also nonsignificant, $CC = 0.15, p > 0.1$.

Demographic and health status characteristics

For all participants, the median absolute difference between log values of viral load in semen and plasma was 0.7, with greater values in plasma than semen. The greatest difference

FIG. 1. Scatter plot showing the association of log viral load in semen and log viral load in blood plasma for all study participants.

FIG. 2. Scatter plot showing the association of log viral load in semen and log viral load in blood plasma for men with detectable virus in both semen and blood.

between semen and plasma values was 2.7 log copies. A total of 15 (34%) men had greater HIV concentrations in semen than plasma. Among men with greater viral loads in their plasma than semen, a mean difference of 1.9 log copies of HIV was found in plasma relative to semen. For men who had greater

viral loads in their semen than plasma, the mean difference was 3.5 log copies of HIV in semen relative to plasma. Table 1 presents the demographic and health status characteristics of men with equal or greater viral loads in their plasma than semen in comparison with men with greater concentrations

TABLE 1. DEMOGRAPHIC CHARACTERISTICS OF MEN WITH HIGHER VIRAL LOADS IN PLASMA THAN SEMEN COMPARED WITH MEN WITH HIGHER VIRAL LOADS IN SEMEN THAN PLASMA

	Higher or equal HIV concentrations in plasma than semen (n = 29)		Higher HIV concentrations in semen than plasma (n = 15)		t Value	p Value
	Mean	SD	Mean	SD		
Age (years)	39.7	7.0	42.3	8.2	1.2	NS
Years of education	13.2	2.0	12.8	2.1	0.6	NS
Years since tested HIV seropositive	7.2	5.1	9.2	5.4	1.2	NS
Number of current HIV symptoms	5.0	4.3	6.2	2.5	1.0	NS
CD4 ⁺ cell count (cells/mm ³)	307.2	302.2	293.1	125.4	0.7	NS
Log plasma viral load	3.5	2.2	1.6	1.9	2.8	<0.01
Log semen viral load	1.7	2.0	5.2	0.7	6.6	<0.01
Number of missed medication doses in past 2 days	1.0	3.0	2.9	6.1	1.1	NS
	n	%	n	%	χ ²	p Value
Ethnic background						
White	5	17	4	27		
Minorities	24	83	11	73	0.5	NS ^a
Homosexual/bisexual	24	82	10	67	1.4	NS
AIDS diagnosis	18	78	10	77	0.1	NS
Currently receiving antiretrovirals	23	79	12	80	0.1	NS

^aTested with Fisher exact test.

TABLE 2. OBSERVED VIRAL LOAD, SEXUAL BEHAVIORS, AND CURRENT ANTIRETROVIRAL THERAPIES FOR SAMPLE OF HIV-POSITIVE MEN^a

ID	<i>log₁₀ semen viral load^b</i>	<i>log₁₀ plasma viral load^b</i>	<i>Insertive anal intercourse</i>	<i>Vaginal intercourse</i>	<i>Insertive oral intercourse</i>	<i>Total insertive acts</i>	<i>Current antiretrovirals^c</i>
1	LDL	3.08	3	0	0	3	d4T + Viramune + Viracept
2	LDL	4.38	0	0	0	0	Combivir + Rescriptor
3	LDL	4.54	5	0	0	5	Combivir + Viracept
4	LDL	LDL	0	0	0	0	ddl + Fortovase + Norvir
5	LDL	4.67	7	0	1	8	Not currently treated
6	LDL	4.58	0	0	0	0	3TC + ddl + Agenerase
7	LDL	3.15	0	0	0	0	3TC + ddl + Crixivan
8	LDL	LDL	2	0	3	5	ddl + Ziagen + Fortovase + Norvir
9	LDL	LDL	0	0	0	0	Not currently treated
10	LDL	3.15	0	0	0	0	Not currently treated
11	LDL	3.99	0	8	0	8	3TC + d4T + Crixivan
12	LDL	LDL	2	0	2	4	Combivir + Ziagen
13	LDL	LDL	0	0	0	0	Not currently treated
14	LDL	LDL	0	0	0	0	3TC + d4T + Crixivan
15	LDL	LDL	0	0	0	0	Not currently treated
16	LDL	3.67	0	0	0	0	3TC + d4T + Viracept
17	2.15	4.86	0	0	0	0	Combivir + Ziagen + Viracept
18	2.46	5.70	0	0	0	0	Not currently treated
19	2.74	3.30	0	8	0	8	ZDV + ddC
20	3.28	5.18	0	1	0	1	Not currently treated
21	3.59	4.52	0	0	0	0	Ziagen + Rescriptor + Agenerase
22	3.84	3.85	0	0	0	0	Combivir + Crixivan
23	3.86	5.41	0	0	0	0	Combivir + Crixivan
24	3.90	4.04	2	0	5	7	ddl + d4T + Sustiva
25	4.04	5.65	0	0	0	0	Combivir + Ziagen
26	4.15	6.49	0	0	0	0	Not currently treated
27	4.18	LDL	0	0	0	0	Combivir + Viracept

(continued)

TABLE 2. OBSERVED VIRAL LOAD, SEXUAL BEHAVIORS, AND CURRENT ANTIRETROVIRAL THERAPIES FOR SAMPLE OF HIV-POSITIVE MEN^a (CONTINUED)

ID	<i>log₁₀ semen viral load^b</i>	<i>log₁₀ plasma viral load^b</i>	<i>Insertive anal intercourse</i>	<i>Vaginal intercourse</i>	<i>Insertive oral intercourse</i>	<i>Total insertive acts</i>	<i>Current antiretrovirals^c</i>
28	4.41	LDL	0	0	0	0	3TC + ddI + Crixivan
29	4.52	5.38	0	0	0	0	Not currently treated
30	4.56	LDL	0	0	0	0	Combivir + Crixivan + Viracept
31	4.66	LDL	0	0	0	0	ZDV + 3TC
32	4.85	5.23	0	0	0	0	Combivir + d4T + Crixivan
33	5.00	3.20	0	0	0	0	3TC + d4T + Crixivan
34	5.04	LDL	0	75	0	75	Combivir + Crixivan
35	5.04	3.08	31	2	4	37	3TC + d4T + Viracept
36	5.15	2.79	0	12	0	12	ddI + d4T + Viracept
37	5.15	LDL	4	0	0	4	ddI + Fortovase + Norvir
38	5.20	2.15	0	7	0	7	3TC + d4T + Viracept
39	5.20	LDL	0	0	2	2	ddI + Sustiva + Fortovase + Norvir
40	5.26	2.48	0	0	0	0	Not currently treated
41	5.36	6.00	9	0	8	17	d4T + Sustiva + Fortovase + Norvir
42	5.70	LDL	0	2	0	2	ddI + d4T + Agenerase + Fortovase
43	6.24	4.67	45	3	12	60	Not currently treated
44	6.75	5.52	0	0	0	0	ddI + Fortovase + Norvir + hydroxyurea

Abbreviation: LDL, less than lower limit of detection.

^aParticipants with recent STIs are set in boldface.^bViral load (in $\log_{10}$ copies/ml) limit of detection is 100 copies/ml.^c3TC, lamivudine; d4T, stavudine; ddC, zalcitabine; ddI, didanosine; ZDV, zidovudine; Agenerase, amprenavir; Crixivan, indinavir sulfate; Combivir, lamivudine-zidovudine; Fortovase, saquinavir; Norvir, ritonavir; Rescriptor, delavirdine; Sustiva, efavirenz; Viracept, nelfinavir; Viramune, nevirapine; Ziagen, abacavir.

TABLE 3. SEXUAL TRANSMISSION RISK BEHAVIORS AMONG MEN WITH HIGHER VIRAL LOADS IN PLASMA THAN SEMEN COMPARED WITH MEN WITH HIGHER VIRAL LOADS IN SEMEN THAN PLASMA

Sexual behavior	Higher or equal HIV concentrations in plasma than semen (n = 29)		Higher HIV concentrations in semen than plasma (n = 15)		F (1,41) ^a	p Value
	Mean	SD	Mean	SD		
Unprotected anal—receptive	1.0	2.3	0.2	0.4	0.8	NS
Unprotected anal—insertive	0.5	1.2	3.7	10.9	0.5	NS
Total unprotected anal intercourse	1.5	2.9	3.9	10.8	0.1	NS
Unprotected vaginal intercourse	0.1	0.7	0.7	1.4	3.9	0.05
Total unprotected insertive anal and vaginal intercourse acts	2.7	4.0	13.3	24.1	4.7	0.05
Unprotected oral—insertive	0.6	1.8	1.2	3.1	0.2	NS
Number of HIV-negative and unknown HIV status partners	1.9	2.7	1.5	2.1	0.1	NS
Total number of partners	1.9	2.3	2.7	2.7	1.6	NS
Recent diagnosis of a sexually transmitted infection (n, %)	4	13	1	7	0.5	NS
Diagnosis of a current STD (n, %)	1	1	0	0		

^aF ratios for analyses of covariance adjusted for years since testing HIV positive.

of HIV in their semen than plasma. Men with equal or greater virus in their plasma than their semen compared with men with greater virus in their semen than plasma showed no differences in age, ethnicity, sexual orientation, years since testing HIV positive, HIV symptoms experienced, CD4⁺ cell counts, current HIV treatment status, or current HIV treatment adherence.

Sexual practices and sexually transmitted infections

Table 2 presents the individual participant log values for viral load in plasma and semen, sorted in ascending order of viral load values in semen, as well as frequencies of insertive sexual intercourse and current antiretroviral regimens. Of 44 men in the study, 16 had semen viral load lower than the level of detection and 15 had undetectable virus in their plasma; among men with detectable viral loads, 7 had both undetectable viral loads in semen and plasma. We grouped together the 15 (34%) men who had viral loads in semen that were higher than viral loads in plasma. Analyses of sexual transmission risk behaviors showed that men with greater concentrations of HIV in their semen relative to concentrations of HIV in plasma reported significantly greater rates of unprotected vaginal intercourse and total number of unprotected sexual intercourse occasions as the insertive partner than men with equal to or greater concentrations of virus in their plasma than semen. The difference for unprotected insertive anal intercourse approached significance ($p < 0.06$). Differences between groups for receptive intercourse acts and numbers of sex partners were not significant (see Table 3).

As shown in boldface in Table 2, five participants had been diagnosed with a sexually transmitted infection in the previous 3 months (participants 5, 21, 25, 26, and 37) and one participant was diagnosed with chlamydia via urine specimens (participant 20). Results failed to find differences in STI occurrences between men with relatively higher and lower semen viral loads.

DISCUSSION

In contrast to previous research reporting moderate degrees of association between HIV concentrations in plasma and semen, the current study found no such relationship. We also found poor concordance between undetectable levels of HIV RNA in plasma and semen. A factor that may account for these discrepancies is differences in samples under study. Unlike previous investigations of HIV levels detected in semen, the current sample was not solely recruited from infectious disease clinics; one in five of our participants were not currently receiving antiretroviral medications. In addition, our participants who were receiving treatment represented a wide range of antiretroviral regimens, with potential differences among drugs in their penetration of semen.²³ Therefore, our data suggest that degrees of sexual infectivity in a heterogeneous sample of HIV-infected men cannot be estimated from plasma viral loads. We found that 34% of HIV-infected men had greater concentrations of HIV in their semen than their plasma—the inverse of the expected direction of association, and a proportion that is similar to the 38% of men with greater semen than plasma viral loads reported by Tachet *et al.*¹² Therefore, a considerable number of HIV-infected men are more infectious than they may assume on the basis of results of viral load assayed from peripheral blood. Although the threshold for HIV infectivity is not yet established and persons with viral loads below levels of detection are likely infectious, studies show that HIV-positive and HIV-negative persons perceive less risk for contracting HIV when HIV-infected persons have undetectable plasma viral loads.^{3,6,7} Transmission risk perceptions may therefore be particularly hazardous because of the inability to infer sexual infectivity from plasma viral loads.

The lack of association between viral load in plasma and semen in the current study could not be accounted for by HIV disease status, antiretroviral therapy history, or current treatment adherence. Some antiretrovirals do not penetrate semen

as effectively as they do blood, allowing semen to harbor replication-competent virus that can be sexually transmitted.^{13,23,24} We found that 53% of men with undetectable plasma viral loads had measurable virus in their semen. In addition, the majority of HIV transmission risk behavior in our sample occurred among men who had the highest concentration of HIV in their semen. It is noteworthy that differences in sexual activity between men with higher and relatively lower concentrations of HIV in semen were significant only for insertive sexual acts. One factor that may explain these findings was the potential co-occurrence of other STIs. However, we failed to identify current *Gonorrhea*, *Chlamydia*, or clinically reported recent STIs in greater proportions among men with higher viral loads in their semen than plasma. However, our ability to detect associations between semen viral load and STIs was limited by our relatively small sample size. The association of higher rates of insertive intercourse and semen viral loads may therefore be a function of asymptomatic or subclinical urethritis. We are not aware of research that has tested for subclinical urethritis in relation to HIV viral load in semen. We recommend that future research investigating relationships between sexual transmission risk behavior and semen viral loads perform more comprehensive clinical examinations for clinical and subclinical urethritis and conduct more comprehensive testing for STIs on larger samples. We also recommend that HIV-positive men be warned that they cannot infer their infectiousness from their plasma viral load test results and that behavioral risk reduction practices remain the only means for preventing the spread of HIV.

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