Semen factors associated with semen viral load and infection-enhancing activity

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Introduction

We have previously reported that seminal plasma from HIV negative men can markedly enhance HIV infection of permissive cells, and that this activity is positively associated with endogenous concentrations of SEM1(86-107), a peptide derived from a protein produced by the seminal vesicles. *In vitro*, SEM1(86-107) polymerizes to form amyloid fibrils that enhance HIV infection, and endogenous SEM1(86-107) amyloid aggregates can be detected in semen. We hypothesized that in HIV-infected individuals, semen factors that promote HIV infection might also increase the semen HIV viral load.

Methods

We examined the relationships among semen viral load, HIV infection enhancing activity, and inflammatory cytokines in semen samples from 122 HIV-infected individuals. Samples were obtained at least 4 months post seroconversion; 149 specimens were obtained from 103 ART naïve donors, 20 donated pre-and post-ART suppression, and 20 pre-and post-interruption of ART. HIV infection of TZM-bl cells in the presence vs. absence of semen was used to quantitate viral enhancing activity. Inflammatory cytokines and chemokines were measured by Luminex in semen and blood.

Results

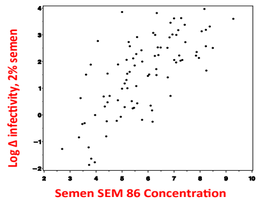
Semenogelin concentrations and infectivity enhancement in HIV+ semen

The degree to which semen enhanced HIV infection varied (from no enhancement to 30-fold) between HIV-infected individuals.

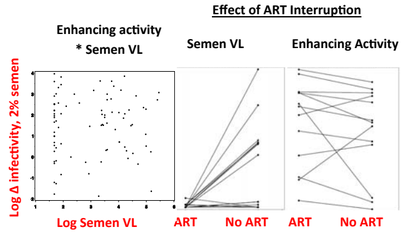
- Higher infectivity enhancement of semen was strongly correlated with the concentration of SEM1(86-107) in HIV-infected men (r=0.70, p<0.0001). In multivariate analyses, semen GMSCF was also associated with infectivity enhancement (p=0.0005). Semen ITAC and IL7 were associated with less enhancement.

We found no evidence that semenogelin concentration or enhancing activity were influenced by ART use in 40 HIV+ subjects donating semen both on and off suppressive ART. Moreover, considering naïve samples, neither factor had a significant association with total semen VL **(HOWEVER…)**

Infectivity enhancing activity of semen from HIV + men is strongly correlated with semenogelin concentration



Infectivity enhancing properties of semen differ between HIV+ individuals, are stable over time, and are not influenced by the semen HIV concentration



Assessing the Determinants of Higher Semen VL and Greater Infectivity Enhancing Activity

A series of multivariate analyses were conducted to examine associations of infectivity enhancement and cytokines with semen VL while **controlling for the blood VL**. The results are summarized in the table at right. Higher semen viral load was strongly associated with semen infectivity enhancing activity (p=0.02), and also with higher levels of semen IL8 (p=0.01) and IL6 (p=0.01). IL6 and IL8 were 25- and 245- fold more concentrated in semen than in blood.

	Induced by HIV? (change w ART)	Concentrated in semen? (semen vs. blood, fold-Δ)	Associated* with: Semen VL?	Infectivity enhancement?
Infectivity enhancement	No	n/a	++	n/a
Semenogelin	No	n/a	0	++
IL8	No	**244.8-fold**	++	0
IL6	No	**24.5**	++	0
GMCSF	No	**1.8**	+	++
MIP1b	No	4.4	+	0
IL2	No	2.6	+	0
MIP1a	No	2.3	+	0
IL21	No	1.3	+	0
IL23	No	1	+	0
IFNg	No	0.9	+	0
IL12p70	No	0.6	+	0
IL17A	**Yes**	0.4	+	0
IL7	No	**430.4**	0	- -
ITAC	No	**164.2**	0	- -
IL5	No	59.1	0	0
Fractalkine	No	46.8	0	0
MIP3a	No	44.4	0	0
TGFb	No	16.4	0	0
IL10	No	6.2	0	0
IL1b	No	5.6	0	0
TNFa	No	3	0	0
IL4	No	2.1	0	0
sCD14	No	0.5	0	0
IL13	No	0	0	0
sCD163	No		0	0

*p<0.05 for association with outcome in **+=univariate** or **(++)multivariate** analyses

Summary/Conclusions

The composition of semen can differ greatly between HIV-infected men. Factors that vary between men, such as infection-enhancing amyloids and certain proinflammatory cytokines, may facilitate HIV transmission in two ways—by promoting local viral replication in the genital tract (increasing semen viral load), and/or by enhancing infection of mucosal target cells.

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