

HIV shedding in semen of men who have sex with men on efficient cART is associated with high HIV-DNA levels in PBMC but not with residual HIV-RNA viremia (ANRS EP49)

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Background

Combined antiretroviral therapy (cART) reduces dramatically the risk of HIV-1 sexual transmission among serodiscordant heterosexual couples. There are, however, several lines of evidence for a dissociation in HIV-1 control between blood and the male genital tract for some men. Most of the data available are cross-sectional, with a small sample size and concern only heterosexual men involved in medically assisted reproduction programs. Few data are available on the efficacy of cART in the male genital tract of HIV-1 infected MSM.

Objective

We aimed at evaluating the frequency of HIV-1 shedding in the genital tract of MSM with sustained viral suppression and no symptoms of sexually-transmitted infections (STI) and identifying factors associated with HIV-1 shedding in the male genital tract in HIV-1 infected MSM.

Patients

The study population comprised:

- HIV-1 infected adults
- declaring themselves as MSM
- on stable cART
- with a plasma HIV-RNA < 50 copies/ml for at least 6 months
- no clinical symptoms of STI
- agreed to a 48-hour period of sexual abstinence prior to sample collection

Methods

Paired samples of semen and blood were collected at baseline and at week 4 for quantitation of blood plasma (bpVL including ultrasensitive assay, LOQ 10 cp/mL) and seminal plasma HIV-RNA (spVL).

Sperm culture, seminal HSV2-DNA PCR, syphilis serology and peripheral blood mononuclear cells (PBMC) – associated HIV-DNA quantitation were performed on baseline samples.

Relationship between spVL and biological variables listed above was assessed using a GEE logistic regression model accounting for repeated sampling in the same individual.

Based on the prevalence of HIV-1 shedding in the genital tract of heterosexual men (\approx 3-5%), a sample size of 150 MSM would allow to find at least one discordance if the prevalence was as low as 3%.

Results

157 HIV-1 infected MSM were enrolled and provided two paired samples of blood and semen 4 weeks apart.

The main characteristics were:

Median age:	44 years (range 27-67)
Median time since HIV-1 diagnosis:	10.4 years (range 0.8-26.3)
Median nadir CD4 cell count:	247/mm ³ (range 3-770)
Median current CD4 cell count:	637/mm ³ (range 152-1721)
History of AIDS defining event:	26 patients (16.6%)
PBMC-HIV-1 DNA (copies/10 ⁶ PBMC):	229 (range 70-2099)
Median time on ART:	6.6 years (range 0.7-21.8)
Median time on stable cART:	2.1 years (range 0.3-12.4)
Median time with bpVL < 50 cp/ml:	3.3 years (range 0.5-13.7)

Patients with a stable partner (exclusive or not): 99 (63%)

% of patients with a stable partner who had casual encounters during the last 3 months: 62/99 (62.6%)

Median number of casual partners (last 3 months): 10 (range 1-160)

HIV-1 seminal shedding among the 157 HIV-1 infected MSM

Day 0	Week 4	N	%
Unsufficient semen volume	No detection	2	1,3
Detection	No detection	5	3,2
Detection	Detection	2	1,3
No detection	Unsufficient semen volume	8	5,1
No detection	Detection	14	8,9
No detection	No detection	126	80,3
TOTAL		157	100,0

Results (continued)

- spVL was detectable in 23/304 semen samples with a median of 145 cp/ml (range 50-1475), yielding a prevalence of 7.6%.
- spVL was detectable on the first sample in 5 patients, on the second sample in 14 patients and on both samples in 2 patients.
- Median spVL was 145 copies/ml (range 50-1475).
- bpVL was undetectable in 74% samples with ultrasensitive assay

Asymptomatic STI identified at baseline

32 patients out of 157 (20.5%) presented with an asymptomatic STI
2/32 had two STIs (syphilis + ureaplasma)

STI	Nb of patients
Syphilis	6
<i>Gardnerella vaginalis</i>	4
<i>Ureaplasma urealyticum</i>	18
<i>Neisseria gonorrhoeae</i>	2
Mycoplasma	1
<i>Chlamydia Trachomatis</i>	3
Herpes Simplex 2	0

Association between biological variables and HIV-1 shedding in semen

Variables	Dissociation (n=23)	No dissociation (n=281)	OR [IC _{95%}]*	P*
History of AIDS defining event, n (%)				
No	21 (8,2%)	235 (91,8%)	1	
Yes	2 (4,2%)	46 (95,8%)	0,5 [0,1 ; 2,1]	0,330
Nadir CD4 (/mm ³), median [IQR]	287 [219 ; 326] VM (n=1)	246 [148 ; 330] VM (n=10)	1,2 [0,8 ; 1,8]	0,265
Current CD4 (/mm ³) n (%) :				
<=554 CD4 /mm ³	4 (4,3%)	94 (95,7%)	1	-
]554 ; 735] CD4/mm ³	14 (13,5%)	90 (86,5%)	0,3 [0,1 ; 0,9]	0,027
>735 CD4 /mm ³	5 (4,9%)	97 (95,1%)	0,8 [0,2 ; 3,1]	0,774
Time spent with bpVL < 50 cp/ml, median [IQR]	2,4 [1,1 ; 5,5]	3,4 [1,8 ; 5,6]	0,9 [0,8 ; 1,1]	0,262
Years on stable cART, n (%) :				
<=1,7 years	8 (7,4%)	100 (92,6%)	1	-
]1,7 ; 2,5] years	13 (13,7%)	82 (86,3%)	2,0 [0,7 ; 5,3]	0,173
> 2,5 years	2 (2,0%)	99 (98,0%)	0,2 [0,1 ; 1,2]	0,090
Years on cART, median [IQR]	5,7 [2,4 ; 10,2]	6,6 [3,3 ; 13,9] VM (n=4)	1,0 [0,9 ; 1,0]	0,248
PBMC-HIV-DNA, n (%)				
<= 318 ^(a) (10 ⁶ PBMC)	9 (4,6%)	187 (95,4%)	1	-
> 318 ^(a) (10 ⁶ PBMC)	13 (13,0%) VM (n=1)	87 (87,0%) VM (n=6)	3,1 [1,2 ; 7,7]	0,015
Chronic Hepatitis B, n (%)				
No	22 (7,9%)	257 (92,1%)	1	
Yes	1 (8,3%)	11 (91,7%) VM (n=13)	1,1 [0,1 ; 7,9]	0,950
Having a STI at baseline, n(%)				
No	17 (7,1%)	222 (92,9%)	1	-
Yes	6 (9,4 %)	58 (90,6%) VM (n=1)	1,4 [0,5 ; 4,0]	0,577
Missing data				
<i>Ureaplasma urealyticum</i> (+), n (%)				
No	14 (6,2%)	212 (93,8%)	1	-
Yes	5 (13,9%) VM (n=4)	31 (86,1%) VM (n=38)	2,4 [0,7 ; 8,3]	0,149
Missing data				

There was no association between spVL and STI, CDC stage, nadir or current CD4, duration of bpVL undetectability, bpVL measured by ultrasensitive assay, adherence to treatment or number of sexual partners (data not shown). **Intracellular PBMC HIV DNA predicted significantly spVL detection (OR (IC95%) 3.1 (1.2-7.7) for HIV DNA>2.5 log₁₀ cp/10⁶PBMC).**

CONCLUSION

Our objective was to evaluate the prevalence of seminal HIV-1 shedding in HIV-1 infected MSM with a sustained undetectable bpVL. This is the first longitudinal study focusing on HIV infected MSM with sustained viral suppression in blood plasma and no symptom of genital infection. We show that HIV RNA can be detected in semen of HIV-1 infected MSM despite sustained successful cART, with a significantly higher prevalence than in heterosexual men (7.6 vs 3.1% p=0.016 (Lambert-Niclot *et al*, AIDS 2012)). The shedding was intermittent and not associated with the presence of an asymptomatic STI. Whether such levels of spVL are infectious remains to be determined. We also show, for the first time, that the size of blood HIV-1 reservoir predicts spVL detection. Although smaller, patients with a PBMC-HIV-DNA < 2.5 log₁₀/10⁶ PBMC were also at risk of intermittent HIV-1 seminal shedding.