HIV-1 DNA Levels in Peripheral Blood Mononuclear Cells and Cannabis Use are Associated With Intermittent HIV Shedding in Semen of Men Who Have Sex With Men on Successful Antiretroviral Regimens

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Background. Few data exist on the efficacy of combined antiretroviral therapy (cART) in semen of human immunodeficiency virus type 1 (HIV-1) infected men who have sex with men (MSM) with sustained control of HIV replication in blood.

Methods. HIV-1 infected MSM on successful cART for >6 months were enrolled. HIV-RNA was quantified in seminal plasma (spVL) and in blood plasma (bpVL) from 2 paired samples collected 4 weeks apart. Relationship between spVL and bpVL (measured by an ultrasensitive assay, LOQ 10 copies/mL), total peripheral blood mononuclear cells (PBMC)-associated HIV-DNA, sexually transmitted infections (STIs), and self-reported socio-behavioral characteristics was assessed using GEE logistic regression.

Results. In total, 157 patients were included. Median time with bpVL <50 copies/mL was 3.3 years. spVL was detectable in 23/304 samples (prevalence 7.6%). Median spVL was 145 cp/mL (100–1475). spVL was detectable on the first, on the second, and on both samples in 5, 14, and 2 men, respectively. In sum, 33 individuals (21%) had STIs (asymptomatic in 24/33). Residual bpVL was undetectable by ultrasensitive assay in 225/300 samples (75%). After multivariable adjustments, PBMC-associated HIV-DNA (OR 2.6[1.2; 6.0], for HIV-DNA > 2.5 $\log_{10}$ cp/10^6 PBMC, $P = .02$), and cannabis use during sexual intercourse (OR 2.8[1.2; 6.7], $P = .02$) were the only factors associated significantly with spVL.

Conclusion. We show that HIV-RNA can be detected intermittently in semen of HIV-1 infected MSM despite successful cART. The size of blood HIV-1 reservoir predicted spVL detection. Our results indicated also that the possible effect of cannabis should be taken into account when developing prevention interventions targeted toward HIV-infected MSM on successful cART.

Keywords. compartmentalization; seminal HIV-RNA; sexual transmission; sexually transmitted infections.

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Human immunodeficiency virus type 1 (HIV-1) is transmitted mainly via the sexual route, semen being one of the principal vectors. The risk of sexual HIV-1 transmission correlates strongly with the burden of HIV-1 RNA in genital fluids [1], the latter in turn being associated with blood plasma HIV-1 RNA [2]. Combined antiretroviral regimens (cART) significantly reduce blood plasma HIV-1 RNA to below the limit of detection of commercial kits and consequently also reduce the level of HIV-1 RNA in seminal plasma in the vast majority of patients initiating potent cART [3, 4]. Indeed, several observational studies have shown that the control of HIV-1 replication in blood plasma translates into a dramatic reduction in the risk of sexual transmission of HIV-1 among serodifferent heterosexual couples [5, 6]. The randomized HPTN052 study demonstrated that cART was able to reduce the risk of HIV-1 sexual transmission by 96% in serodifferent heterosexual couples [7]. Furthermore, the Swiss Federal Commission for HIV/AIDS stated that HIV-positive heterosexual individuals on effective cART who have had an undetectable plasma viral load for at least 6 months and have no sexually transmitted infections (STIs) are sexually noninfectious [8]. This statement has raised the question of the dissociation between the levels of HIV-1 RNA in blood and in seminal plasma. The proportion of HIV-1 infected men with sustained suppressed HIV-1 RNA in blood plasma who have detectable levels of HIV-1 RNA in seminal plasma, ranges from 5% to 30% [4, 9–12]. To date, studies on the dissociation between HIV-1 RNA in blood plasma and in seminal plasma have been limited by small sample sizes and by their cross-sectional design. Moreover, studies with sequential collection of paired samples of blood and semen are scarce and have mainly been performed in HIV-1 infected men seeking medically assisted reproduction techniques, that is, heterosexual men in stable heterosexual partnerships [13, 14]. All have highlighted intermittent shedding of HIV-1, the proportion of dissociation between blood and semen levels being around 3% [13, 14]. However, these results cannot be extrapolated to men who have sex with men (MSM), the population most at risk of acquiring HIV-1 infection. To date, only 2 cross-sectional studies have addressed the proportion of dissociation in HIV-1 RNA between blood and semen in HIV-1 infected MSM [10, 12]. Accordingly, we evaluated the prevalence of HIV-1 shedding in semen in a longitudinal study with a short sampling interval, focusing on MSM with suppressed HIV-1 replication in blood plasma.

PATIENTS AND METHODS

Study Design and Study Participants

HIV-1 infected MSM over 18 years of age on stable (>3 months) successful cART, that is, with blood plasma HIV-1 RNA < 50 copies/mL for at least 6 months, were enrolled in 6 HIV clinical centers in Paris and nearby suburbs. The main objective of the study was to estimate the proportion of individuals with a blood plasma viral load (bpVL) below 50 copies/mL who had a detectable viral load in semen (spVL). The secondary objective was to characterize the biological and behavioral components that might be associated with VL dissociation between blood and semen. Patients were seen at baseline (D0) and at day 28 (D28) for clinical examination, for collection of paired samples of blood and semen, and for completion of self-administered questionnaires. STIs that were detected at D0 visit were captured, and results were sent in real-time to the local referent physician in order to prescribe the appropriate treatment. The Ethics Committee of Bicêtre Hospital approved the study protocol, and all participating patients provided written informed consent. A paired sample of blood and semen was defined as "dissociated" when HIV-1 RNA could be quantified in seminal plasma but not in blood plasma at one and/or the other time point (ie, D0 and/or D28).

Assessments of Semen Samples

Semen samples were obtained by self-masturbation after a 48-hour abstinence period and collected in sterile containers at each participating center and then sent to the Virology Laboratory in Necker hospital within 4 hours of collection. Seminal plasma was recovered and processed for HIV-1 RNA quantification (detection threshold of 100 copies/mL) as described elsewhere [14].

Sperm culture was performed in the usual media at the D0 visit. *Mycoplasma hominis* and *Ureaplasma urealyticum* were cultured with MYCOFAST EvolutioN3 (Elitech, Puteaux, France). Sperm culture was considered positive when the concentration of Ureaplasma *urealyticum* and of *Mycoplasma hominis* were $>10^4$ UCC/mL and $>10^5$ UCC/mL, respectively.

Total DNA was extracted from semen at the D0 visit using a MagNA Pure LC Instrument and the DNA Isolation kit III (Bacteria Fungi; Roche Diagnostic, Meylan, France). *Chlamydia trachomatis* DNA and *Neisseria gonorrhoea* DNA were amplified with Dia-CT/NG-050 (Diagenode, Liege, Belgium). HSV-1 DNA and HSV-2 DNA were amplified from semen samples with HSV-1 R-gene and HSV-2 R-gene (Argène, Verniolle, France).

Assessment of Blood Samples

HIV-1 RNA in plasma was quantified at the D0 and D28 visits using ultrasensitive real-time polymerase chain reaction (PCR; Generic HIV Charge Virale, Biocentric, Bandol, France). HIV-1 RNA was extracted from a 3 mL centrifuged plasma sample (90 minutes at 15 000 rpm) with the QiAamp Viral RNA Mini kit (Qiagen, Courtaboeuf, France) and extracts were tested in 2 PCRs. The detection threshold of this ultrasensitive PCR was 10 copies/mL.

The method for quantifying total cell-associated HIV-1 DNA in whole blood at the D0 visit is described elsewhere (detection threshold of 3 copies/PCR) [15]. Results were reported as HIV-1 DNA copy number/10^6 peripheral blood mononuclear cells (PBMC), taking into account the white blood cell number and the blood formula [16].

Syphilis serology was performed at the D0 visit using both Liaison treponema screen (Diasorin, Antony, France) and Sypal CB (Diagast, Loos, France).

Sociobehavioral Data Collection

The following data were collected using self-administered questionnaires at both the D0 and D28 visits for the previous 3 months and the previous 4 weeks, respectively: sociodemographic characteristics; HIV disease history (duration on cART, adherence); tobacco, alcohol, and drug consumption; sexual behaviors (number and types of partners (steady, or casual), sexual practices, condom use).

Variables

Adherence to cART was assessed with a dichotomous outcome (nonadherent vs highly adherent) using 4 questions about dose-taking during the previous month [17].

The variable "Cannabis use" was assessed using the question "During the last 3 months (at D0) or the last 4 weeks (at D28), have you been under the influence of cannabis during sexual encounters with your steady or regular/casual partners?" (sometimes/often vs rarely/never).

The inconsistent condom use (ICU) variable was built as follows: participants who reported that they did not systematically use condoms during anal intercourse with either steady or casual partners in the previous 3 months (at D0) or in the previous 4 weeks (at D28) were classified as ICU.

Statistical Considerations

With the inclusion of 150 patients, and the collection of 300 samples, the probability of detecting at least 1 dissociation between semen and plasma HIV-1 RNA was >0.99, considering a rate of dissociation of at least 3% and that the planned number of observed discordances would range from 9 to 15. We chose a conservative measure of dissociation by evaluating the proportion of dissociated samples by sample and not by subject. For instance, if shedding occurs occasionally in each individual, the frequency of reporting the proportion of individuals with at least 1 dissociated sample—as has already been performed in previous studies—will increase with an increasing number of samples per patient, precluding fair comparisons with other studies. Variables were summarized as proportions for categorical variables, the median and interquartile range (IQR) for continuous variables. The relationship between having a detectable spVL or not and biological and/or eligible socio-behavioral variables was assessed using GEE logistic regression models, repeated sampling in the same individual being accounted for. We examined different ways of modeling continuous variables, selecting the one for which the univariate Akaike information criterion was the lowest.

RESULTS

Patients' Characteristics at Baseline Visit

One hundred and sixty-nine patients were screened, and 157 were enrolled between July 2011 and April 2012. Their baseline characteristics are summarized in Table 1. Forty-two percent of patients were receiving 2 nucleoside analogue reverse transcriptase inhibitors (NRTI) and 1 non-NRTI, 30% were receiving 2 NRTIs and 1 ritonavir-boosted protease inhibitor, and 10% 2 NRTIs and 1 integrase inhibitor. Self-reported adherence was scored "high" in 41.3% of patients.

Detection of HIV-1 RNA in Seminal Plasma

The following analyses were performed on 304 samples of seminal plasma, because 10 semen samples were missing or in insufficient quantity. spVL was detected in 23/304 seminal plasma samples with a median value of 145 copies/mL (range 100–1450), yielding a prevalence of 7.6%. These 23 samples corresponded to 21 patients: 5 had detectable spVL at D0, 14 at D28, and 2 had detectable spVL at both visits.

Ultra-sensitive Quantification of HIV-1 RNA in Blood Plasma

Data were missing in 4 of the 304 blood plasma samples. HIV-1 RNA was <10 copies/mL in 225/300 blood plasma samples (75%) and between 10 and 50 copies/mL in 70 samples (23.3%). bpVL was >50 copies/mL in the remaining 5 samples (1.7%) corresponding to 4 patients: 1 of the 2 blood samples (D0 or D28) in 3 men and both blood samples in 1 man.

Screening for STIs at Enrolment

Thirty-three patients (21%) had at least 1 STI at enrolment: syphilis (n = 6), *Gardnerella vaginalis* (n = 4), *Ureaplasma urealyticum* (n = 18), *Neisseria gonorrhoea* (n = 2), *Mycoplasma hominis* (n = 1), *Chlamydia trachomatis* (n = 3). Two of the 33 had both syphilis and *Ureaplasma urealyticum,* and 9/33 had clinical symptoms of STI. No semen sample tested positive for herpes simplex virus type 1 (HSV-1) or herpes simplex virus type 2 (HSV-2) DNA.

Factors Associated With Viral Load Dissociation

Table 2 shows GEE logistic regression analysis of data from the 157 men enrolled in the study. The following factors were not significantly associated with HIV-1 shedding in semen ($P \geq .20$): history of AIDS-defining events, nadir and current CD4 cell counts, time spent on cART and on stable cART, duration with bpVL < 50 copies/mL, ultrasensitive bpVL,

Table 1. Participants' Characteristics at Baseline (D0), n = 157 (Evarist-ANRS EP49 Study)

Characteristic	N (%) or Median [IQR]
Age, years	44 [39–50]
Nationality (n = 156)	
French	137 (87.8)
Other	19 (12.2)
Educational level (n = 155)	
Lower than secondary school	34 (21.9)
Secondary school or higher	121 (78.1)
Active employment (n = 123)	
No	24 (19.5)
Yes	99 (80.5)
Time since HIV diagnosis, years	10.3 [5.1–16.5]
History of AIDS defining events	26 (16.6)
Nadir CD4 cell count, cell/mm^3 (n = 151)	247 [150–330]
Current CD4 cell count, cell/mm^3	637 [496–792]
Time on ART, years (n = 155)	6.6 [3.3–13.9]
Time on stable ART, years	2.1 [1.2–3.3]
Time with bpVL < 50 cp/mL (years)	3.3 [1.8–5.6]
Ultrasensitive bpVL (n = 300 samples)[a]	
<10 cp/mL	225 (75.0)
10 ; 50 cp/mL	70 (23.3)
>50 cp/mL	5 (1.7)
HIV DNA in PBMC, copies/10^6 PBMC (n = 151)	229 [88–405]
Adherence to cART (n = 155)	
Nonadherent	91 (58.7)
Highly adherent	64 (41.3)
STI at baseline	
No	124 (79.0)
Yes	33 (21.0)
Sexual life	
Having a steady partner (exclusive or not) (n = 145)	97 (66.9)
Having casual partners (previous 3 mo) (n = 138)	107 (77.5)
Number of casual partners (n = 143)	6 [3–13]
Inconsistent condom use,[b] with any type of partner (n = 141)	
No	38 (27.0)
Yes	72 (51.1)
No partner/no anal intercourse	31 (22.0)
Sex under the influence of (previous 3 mo)	
Alcohol (n = 157)	
Never	94 (59.9)
Rarely	26 (16.6)
Sometimes	26 (16.6)
Often	11 (7.0)
Cannabis (n = 157)	
Never	135 (87.0)
Rarely	4 (2.6)
Sometimes	13 (8.3)
Often	5 (3.2)
Club drugs[c]	
Never	123 (78.3)
Rarely	10 (6.4)
Sometimes	13 (8.3)
Often	11 (7.0)

Table 1 continued.

Abbreviations: ART, antiretroviral therapy; cART, combined antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; PBMC, Peripheral Blood Mononuclear Cells; STI, sexually transmitted infections.

[a] Ultrasensitive bpVL: HIV RNA viral load in blood plasma samples at D0 and D28.

[b] Inconsistent condom use: no systematic condom use with steady or other partners during anal intercourse.

[c] Club drugs included GHB, ecstasy, MDMA, cocaine, crack, poppers.

adherence to cART, having a STI detected at baseline, number of sexual partners and, finally, inconsistent condom use.

In univariate analyses, the only biological factor associated significantly with the detection of HIV-1 RNA in seminal plasma was the level of HIV-1 DNA in PBMC measured at D0 (OR 2.8[1.2;6.5] for HIV-1 DNA $\geq$ 313 copies/10^6 PBMC; $P = .01$). The cutoff of 313 copies/10^6 PBMC was the value of the third tercile. Among the psychosocial factors analyzed, cannabis use during sexual intercourse was the only factor significantly associated with HIV-1 genital shedding (OR 2.9[1.2; 7.3], $P = .02$). No significant association was found between cannabis use and either adherence or sexual practices (number of sexual partners, inconsistent condom use, and hard sexual practices).

In multivariate analysis, HIV-1 DNA levels in PBMC (OR 2.6 [1.2; 6.0], $P = .02$) and cannabis use during sexual intercourse (OR 2.8[1.2; 6.7], $P = .02$) were significantly associated with the risk of detection of HIV-1 RNA in semen. Sensitivity analyses restricted to patients with an asymptomatic STI and analyses restricted to patients with an ultrasensitive bpVL < 50 copies/mL confirmed the model identified (data not shown).

DISCUSSION

In this longitudinal study of infected MSM on cART with sustained control of HIV-1 replication in blood plasma, the prevalence of detected intermittent HIV-1 RNA in seminal plasma was 7.6%. This value was significantly higher than that previously reported in a study enrolling HIV-1 infected heterosexual men seeking medically assisted reproduction programs and using a similar analysis plan (7.6% vs 3.1%, χ^2 test: $P = .016$) [18].

The main strength of our study relies first in its sample size since; to the best of our knowledge, it is the largest study

Table 2. Factors Associated With Intermittent HIV Shedding in Semen of MSM, n = 304 Samples (Evarist-ANRS EP49 Study)

	Semen Samples With HIV Detection (n = 23) N (%) or Median[IQR]	Semen Samples With No HIV Detection (n = 281) N (%) or Median[IQR]	Univariate Analysis		Multivariate Analysis	
			OR [CI 95%]	*P* Value	OR [CI 95%]	*P* Value
History of AIDS defining event (n = 302)						
No	21 (8.3)	233 (91.7)	1			
Yes	2 (4.2)	46 (95.8)	0.5 [.1 ; 2.2]	.36		
Nadir CD4 (cell/mm^3) (n = 293)	287 [219 ; 326]	246 [148 ; 330]	1.0 [1.0 ; 1.0]	.59		
Current CD4[a] (cell/mm^3)						
≤565	4 (3.9)	98 (96.1)	1			
[565 ; 725]	14 (14.3)	84 (85.7)	3.6 [1.2 ; 10.8]	.02		
>725	5 (4.8)	99 (95.2)	1.2 [.3 ; 4.5]	.76		
Time with bpVL <50 cp/mL	2.4 [1.1 ; 5.5]	3.4 [1.8 ; 5.6]	0.9 [.8 ; 1.1]	.24		
Years on cART (n = 300)	5.7 [2.4 ; 10.2]	6.6 [3.3; 13.9]	0.96 [.9 ; 1.0]	.30		
Years on stable cART						
≤1.7	7 (7.0)	93 (93.0)	1			
>1.7 ; ≤2.5	12 (12.8)	82 (87.2)	1.9 [.7 ; 4.7]	.19		
>2.5	4 (3.6)	106 (96.4)	0.5 [.2 ; 1.9]	.33		
Ultrasensitive bpVL[b] (cp/mL) (n = 300)						
<10	18 (8.0)	207 (92.0)	1			
10 ; 50	4 (5.7)	66 (94.3)	0.7 [.2 ; 2.0]	.49		
>50	1 (20)	4 (80)	2.7 [.5 ; 15.5]	.27		
PBMC HIV-DNA[c] (n = 296)						
<313	9 (4.6)	187 (95.4)	1		1	.02
≥313	13 (13.0)	87 (87.0)	2.8 [1.2 ; 6.5]	0.01	2.6 [1.2 ; 6.0]	
Adherence to cART (n = 300)						
Nonadherent	14 (8.0)	161 (92.0)	1			
Highly adherent	9 (7.2)	116 (92.8)	0.9 [.4 ; 2.1]	.81		
Having a STI detected at baseline						
No	22 (8.2)	249 (91.9)	1	.26		
Yes	1 (3.0)	32 (97.0)	0.29 [.0 ; 2.5]			
Number of sexual partners over the last 3 mo steady and/or casual[d] (n = 303)	1 [1 ; 4]	2 [1 ; 7]	1.0 [.9 ; 1.0]	.26		
Inconsistent condom use[e] (n = 249)						
No	5 (7.9)	58 (92.1)				
Yes	8 (6.5)	116 (93.6)	0.8 [.3 ; 2.3]	.65		
No partners/no sexual intercourse	3 (4.8)	59 (95.2)	0.6 [.2 ; 2.4]	.48		
Cannabis use during sexual relationships						
Never/rarely	18 (6.5)	260 (93.5)	1		1	.02
Sometimes/often	5 (19.2)	21 (80.8)	2.9 [1.2 ; 7.3]	.021	2.8 [1.2 ; 6.7]	

Abbreviations: cART, combined antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; MSM, men who have sex with men; OR, odds ratio; PBMC, peripheral blood mononuclear cells; STI, sexually transmitted infections.

[a] Current CD4: CD4 cell count at baseline (D0).

[b] Ultrasensitive bpVL: HIV RNA viral load in blood plasma samples.

[c] PBMC HIV-DNA: HIV DNA in PBMC (copies/10^6 PBMC), value of the third tercile.

[d] Number of sexual steady and/or casual partners for the previous 3 months (at D0) and the previous 4 weeks (at D28).

[e] Inconsistent condom use: no systematic condom use with steady or casual partners during anal intercourse.

focusing on HIV-1 infected MSM with sustained HIV-1 control. Another strength of the study is its longitudinal design. Indeed, to date the only 2 other studies addressing the same issue have been cross-sectional [10, 12]. In the present study, we showed that HIV-1 RNA shedding in semen was intermittent. This fact emphasizes how difficult it is to draw definitive

conclusions based on one single HIV-1 RNA measurement in seminal plasma.

Local viral production in the male genital tract may be enhanced by the concomitant presence of STIs [19]. The detection of HIV-RNA in seminal plasma correlated strongly with the presence of symptomatic STIs in a recent study on HIV-1 infected MSM with sustained bpVL < 50 copies/mL and the prevalence of HIV-RNA detection in semen was higher in that study than in ours (25% vs 7.6%) [10]. We did not find such an association. One explanation might be that the vast majority of patients with STIs enrolled in our study were asymptomatic. Another possible explanation may be the limited power of our study to detect such an association. The absence of information about seminal leukocytosis is a weakness of our study. Our results are in agreement with those reported in a recent cross-sectional study [12]. Overall, the prevalence of STIs (symptomatic or not) reported here and in other studies suggests persistent at-risk sexual behaviors among HIV-1 infected MSM. Human herpesviruses replication, especially cytomegalovirus replication in the male genital tract, may also yield local inflammation, which has been shown to be associated significantly with shedding of HIV-1 RNA in semen [12]. We only focused on HSV-1 and HSV-2 in the current study.

In keeping with Lambert-Niclot et al, we did not find an association between residual viremia and the detection of HIV-1 RNA in seminal plasma [18]. A sensitivity analysis excluding the 5 blood samples with a HIV-1 RNA >50 copies/mL yielded similar results.

The only biological factor significantly associated with the detection of HIV-1 RNA in seminal plasma was the level of HIV-1 DNA in PBMC. This marker has been shown to reflect accurately the size of HIV reservoir, when expressed as HIV-1 DNA copies/10^6 PBMC or copies/10^6 CD4 cells [20]. In the present study, a level of HIV-1 DNA >2.5 $\log_{10}$ copies/10^6 PBMC was associated with a 2.6 times greater risk of detection of HIV-1 RNA in seminal plasma. Such an association was not seen in a recent study on heterosexual HIV-1 infected men seeking medically assisted reproduction techniques [18], but this is most probably due to the lack of power, given the low prevalence rate of HIV-1 RNA detection in the semen of the latter population. The risk of sexual transmission of HIV may also be due to HIV-1 DNA in nonsperm cells [21, 22]. However, data generated from transmitting pairs of MSM suggested that the blood plasma virus in the recipient partner was consistently more closely related to the seminal plasma virus and not to HIV-1 DNA integrated in infected seminal leukocytes in the source partner [23].

The risk of sexual HIV-1 transmission correlates strongly with the burden of HIV-1 RNA in genital fluids [1]. In our study, the median value of HIV-1 RNA in semen was 145 copies/mL (range 100–1450). The question that remains unanswered is whether such levels of HIV-1 RNA are infectious, ie, whether there is a transmission threshold. Seminal HIV-1 RNA might not be the only limiting factor for HIV-1 sexual transmission. Endogenous factors such as amyloid fibrils in semen may sharply increase the infectiousness of HIV by promoting virion-cell attachment and fusion [22]. Also, the risk of sexual transmission of HIV-1 has been found to be 18 times higher through anal intercourse than through vaginal intercourse [24]. Both theoretical and clinical studies have suggested that a viral load of <1000 copies/mL in semen poses a low but real risk of male-to-female transmission [1, 25]. A study on macaques showed that rectal transmission could occur with a simian/human immunodeficiency virus (SHIV) level 5 times lower than that needed for vaginal transmission [26]. A 5-fold reduction in this number (ie, 1000 copies/mL) falls within the range detected in our study in the context of rectal transmission. In addition, Butler et al [27] reported a median spVL of 4300 copies/mL (range 110–69 000) for men transmitting HIV-1 to their MSM partners. Altogether, these results suggest that sexually active HIV-1 infected MSM on cART who continue to shed low levels of HIV-RNA in semen might be infectious to their sexual partners, although the likelihood of transmission is low.

Cannabis and its derivatives have been shown to mediate beneficial effects in a wide range of immune-mediated diseases [28]. One randomized placebo-controlled trial in HIV-1 infected adults revealed no significant effects of frequent or continuous use of cannabinoids on immune cells functions or on bpVL [29–31]. However, other in vitro studies reported that cannabis enhanced HIV-1 replication in a human T-cell line [32] and in humanized SCID mice [33]. In the present study, we show a significant association between its use during sexual intercourse and the detection of HIV-1 RNA in semen. Of note, there were only 26 individuals self-reporting cannabis use during sexual intercourse, of whom only 7 used it often; this precluded the exploration of a dose effect between the level of cannabis use and HIV-1 RNA level in semen. Gianella et al [12] did not find such an association, but assessment of cannabis use differed between their study and ours. Although the mechanisms underlying cannabis influence on HIV-1 replication are still unknown, we cannot exclude the potential effect of cannabis on HIV-1 replication in the genital tract. Perhaps cannabis induces a generalized inflammatory response that induces enhanced viral shedding or serves as a proxy for other predisposing lifestyle factors not readily accounted for in this study.

A resurgence of the HIV-1 epidemic among MSM is occurring in countries where potent cART is widely available [34]. At present, there is insufficient evidence to make a general claim that HIV-1 infected MSM successfully treated with cART are not infectious. Further studies are needed to better understand the origin and cause of intermittent viral shedding in semen of

MSM who are taking effective cART, to understand the effect of cannabis use on HIV-1 genital secretion, and to assess whether this intermittent viral shedding in semen may result in sexual transmission in this context. Repeated HIV testing is needed in MSM who engage in at-risk sexual behavior in order to improve HIV diagnosis during the early phases of infection and allow early cART initiation to limit the expansion of HIV-1 DNA reservoir. The present results also indicate that the possible effect of cannabis on HIV seminal shedding should be taken into account when developing prevention interventions to reduce sexual risk behavior in HIV-1 infected MSM taking successful cART.

Notes

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