Case report

Antiviral effect of maraviroc in semen: a case report

Christophe Pasquier1*, Nathalie Moinard2, Karine Sauné3, Myriam Daudin2, Stéphanie Trancart3, Patrice Massip1, Jacques Izopet1, Louis Bujan2

1Laboratory of Virology, INSERM U1043, IFB, CHU de Toulouse, Université Paul Sabatier – Toulouse 3, Toulouse, France
2Human Fertility Research Group, Université Toulouse III Paul Sabatier (EA 3694) and CECOS Midi-Pyrénées, CHU de Toulouse, Hôpital Paule de Viguier, Toulouse, France
3Laboratory of Pharmacokinetics and Toxicology, CHU de Toulouse, Toulouse, France
4Infectious Diseases Unit, CHU de Toulouse, Hôpital Purpan, Université Paul Sabatier – Toulouse 3, Toulouse, France

*Corresponding author e-mail: pasquier.c@chu-toulouse.fr

We describe the antiviral effect of maraviroc in a patient who had been shedding high levels of HIV-1 in seminal fluid for three years despite an undetectable blood plasma viral load. Adding maraviroc to HAART stopped the seminal shedding. We discuss the mechanisms involved and the effect on sexual transmission.

Introduction

HAART is a potent suppressor of HIV-1 replication, as assessed by blood plasma virus load (BPL). If drug adherence is good, BPL is usually <40 HIV-1 RNA copies/ml within six months of HAART initiation and remains so for years [1]. HAART also acts within the genital tract to make the seminal plasma virus load (SVL) undetectable in most male patients. Nevertheless, about 7–48% of patients have HIV-1 genital shedding despite efficient HAART for more than six months [2–4]. This report describes the antiviral effect of maraviroc in a patient who had been shedding high concentrations of HIV-1 in seminal fluid for three years, despite being on HAART that suppressed HIV-1 to undetectable levels in his blood plasma.

Case report

A 34-year-old HIV-1-infected man and his uninfected wife attended Toulouse University Hospital reproductive unit in 2007 in order to conceive a child using the sperm washing method [5]. The man was investigated for his HIV infection and fertility status was investigated in both partners. The man was asymptomatic with no history of opportunistic infections. Analysis on a COBAS Ampliprep/Taqman 96 analyzer [6] showed his BPL to be 7,283 HIV-1 RNA copies/ml and his SVL to be 1,185,000 HIV-1 RNA copies/ml. His CD4+ T-cell count was 188/mm3 and HCV, HBV and syphilis tests were negative. His seminal parameters, assessed according to the WHO laboratory recommendations, were normal: semen volume 2.7 ml, pH 8.3, total sperm count 100×10⁶ per ejaculate, total round cells 0.3×10⁶ per ejaculate and no polymorphonuclear cells. Since his SVL was above the cutoff set by French regulations for assisted reproductive technology in HIV-infected couples, he began HAART (tenofovir 300 mg once daily plus emtricitabine 200 mg once daily plus lopinavir/ritonavir 400/100 mg twice daily) in July 2007 (Figure 1). His BPL was <40 HIV-1 RNA copies/ml two months later (August 2007), demonstrating effective treatment, and BPL remained at this level throughout follow-up. His SVL was 1,805,263 HIV-1 RNA copies/ml in April 2008, confirmed by testing six samples between April 2008 and September 2009. As his SVL was 244,000 HIV-1 RNA copies/ml in September 2009, we added raltegravir (400 mg twice daily) and replaced lopinavir/ritonavir with darunavir/ritonavir (600/100 mg twice daily). However, six months of this treatment did not reduce his SVL. Raltegravir was replaced by maraviroc (300 mg twice daily) in February 2010. His SVL gradually dropped to below 200 HIV-1 RNA copies/ml within nine months and has remained so ever since. In June 2010 we performed the first intra-uterine insemination with sperm prepared according to our published method [5].

We carried out further tests to attempt to account for this atypical virus response in the semen. The viruses in the blood and seminal compartments were identical throughout follow-up. Tests performed before first starting HAART in 2008 and again in 2010 showed
that his HIV-1 was subtype B with wild type RT and PR genes. HIV-1 tropism in both compartments was R5 by genotyping (detection limit: 20%) and phenotyping using a recombinant virus assay (detection limit for non-R5: 0.5%) [7]. Tropism, genotype and phenotype were R5 in both compartments and remained R5 in 2010.

Residual concentrations of antiretroviral drugs in the blood and semen showed good diffusion of tenofovir (126 and 72 ng/ml) and emtricitabine (279 and 1,694 ng/ml) in the semen, with poor diffusion of the protease inhibitors lopinavir (8,930 and 690 ng/ml), darunavir (3,714 and 398 ng/ml) and ritonavir (986 and <30 ng/ml). Raltegravir concentrations were not assessed. Maraviroc diffused well (177 and 129 ng/ml).

There was no significant change in semen parameters (volume, pH, mobility, total sperm count, total round cell count and vitality) throughout follow-up, in particular, no significant polymorphonuclear cell counts or positive spermocultures were observed in the 12 ejaculates tested. Research for sperm antibodies was negative. Seminal biochemical markers that could be modified by genital inflammation were also normal in May 2009 (citric acid, zinc, free carnitine, glycerophosphocholine, alpha glucosidase, fructose, choline and proteins). Prostate-specific antigen and genital tract echography were normal. The patient was asymptomatic throughout follow-up, with no sexually transmitted infections (STI; HBV, syphilis, HSV-2, C. trachomatis, N. gonorhoeae or Ureaplasma). Lastly, empiric treatment for chlamydia and gonorrhoea infection (azithromycin [500 mg/day] and ciprofloxacin [500 mg twice daily] for 3 and 10 days, respectively) had no effect on SVL. Seminal shedding of cytomegalovirus was negative. His CD4+ T-cell count was 274/mm3 in June 2010.

**Discussion**

HIV-1 becomes undetectable in the semen in 7–48% of patients after six months of treatment, but seems to be delayed compared with BPL undetectability and intermittent shedding does occur [4]. In most patients, SVL is about tenfold less than BPL [8]. The SVL of this patient was atypical in two ways; before treatment his SVL was much higher than his BPL, making him one of the up to 38% of patients who are so-called supershedders [8], and after two months of HAART his BPL became undetectable but his SVL still...
remained very high for a long period. This is in agreement with the finding that pretherapy SVL, but not BPL, is predictive of SVL suppression under HAART, as previously reported [4]. Our extensive clinical and biological searches for factors involved in HIV shedding in semen, such as genital inflammation, STI, polymorphonuclear cells in semen or coinfection with other viruses, were all negative. We found no specific parameters to explain this high seminal shedding.

HAART initiated in 2007 had the expected effect on BPL but no significant effect on SVL. As the patient was HAART-naive, genotyping showed no resistant mutation before initiation, and there was no selection of resistant HIV-1 during follow-up despite the high levels of replication in semen. Virus resistance was, therefore, probably not the cause of the persistently high SVL. The presence of drug-sensitive virus in semen has previously been reported at six months follow-up after HAART initiation in patients with persistent HIV seminal shedding despite BPL undetectability [4], and also in another case report [9]. This very high SVL without resistant virus selection could have been due to treatment inefficacy because of poor drug diffusion in the genital tract, or to persistent release of HIV-1 from activated infected cells. The semen concentrations of protease inhibitors were low, in agreement with previous reports [10]. However, the semen concentrations of tenofovir, emtricitabine and maraviroc were theoretically therapeutic as they were close to those obtained in blood plasma [11,12]. Raltegravir has been found to diffuse well but variably in semen [13]. However, efficient concentrations in semen do not necessarily mean efficient concentrations throughout the genital tract, particularly at sites producing HIV within the genital glands. Furthermore, nucleoside analogues may not be phosphorylated as well as in other compartments [14] and drugs may be the substrates of efflux systems that are very prevalent in the genital tract, so impairing drug entry into cells. The lack of early decrease in SVL that we observed suggests that HAART had low efficiency in this compartment. However, we cannot identify any general mechanism because we only studied the rate of SVL decrease after HAART initiation in one individual. Nevertheless, SVL generally becomes undetectable six months after initiating HAART. One possibility is that it takes longer to reach an undetectable SVL than an undetectable BPL, particularly for patients with a high SVL [4].

Our patient’s SVL became undetectable after three consecutive years on efficient HAART, after a slow, gradual decrease. This could indicate the extinction of genital HIV replication once the genital compartment was no longer being seeded from the blood and lymphoid compartments. Seeding is one of the main sources of HIV in semen [15]. The immune reconstitution of this patient during the 3-year follow-up was poor (+86 CD4+ T-cells/mm³). This may be linked to the patient’s specific immune or inflammatory characteristics that may or may not be involved in the high shedding level and drug response in semen.

Nevertheless, adding maraviroc to the drug regimen appeared to accelerate the decrease in SVL, until it became undetectable. The efficiency of maraviroc in semen is probably linked to its good diffusion in this compartment and the involvement of HIV-permissive cells expressing CCR5 in HIV-1 release in semen. In semen, macrophages and CD4+ T lymphocytes are the best candidate cells for HIV replication [16], but in the present case it was not possible to assess their respective counts. Further studies are now needed to confirm the antiviral effect of maraviroc in the male genital tract and the effect on risk of sexual transmission.

This case confirmed that some HIV-infected patients can shed high concentrations of HIV in their genital fluids despite being on efficient HAART for more than six months. There may be few patients with a similar response profile, but this could dramatically influence models of the spread of HIV epidemics in populations on efficient HAART, and thus raise questions as to the usefulness and efficiency of HAART for preventing sexual transmission of HIV-1 as proposed by the Swiss statement [17]. Such patients are clearly at risk of sexually transmitting HIV-1 [18]. It may therefore be important to assess the effects of various HAART regimens on SVL and to ensure that SVL is undetectable after HAART treatment initiation. In our case, maraviroc seems to have played a key role, but this now should be confirmed by further studies. It might be that for selected patients, three antiretrovirals of at least two different classes and with good seminal penetration are needed to rapidly suppress the SVL to below the limit of detection.

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Disclosure statement

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References


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