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Seminal pharmacokinetics and antiviral efficacy of once-daily maraviroc plus lopinavir/ritonavir in HIV-infected patients.

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29 **Seminal Pharmacokinetics and Antiviral Efficacy of Once-daily Maraviroc plus**
30 **Lopinavir/ritonavir in HIV-positive Patients**

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38 **Running Head:** Once-daily maraviroc seminal PK

39 **Key words:** seminal fluid; genital; HIV RNA; maraviroc; lopinavir/ritonavir; NRTI-sparing; dual
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63 Sexual transmission of HIV-1 is currently the major way of viral spread worldwide: the
64 quantification of HIV-1 RNA has been clearly linked to the risk of transmission.¹ The use of highly
65 active antiretroviral treatment (HAART) besides providing immunovirological benefits has been
66 associated with viral control in the genital compartment of males and females. Nevertheless
67 occasional HIV-1 shedding has been demonstrated despite effective systemic therapy: insufficient
68 penetration of antiretrovirals has been advocated as one of the reasons for HIV-1
69 compartmentalization.² Although dual and mono-therapies have been shown to be effective in the
70 majority of stable HIV-positive patients although limited data exists on their effectiveness in the
71 genital compartment.³ Furthermore maraviroc dosage when administered with boosted protease
72 inhibitors is still debated: 150 mg once-daily showed promising antiviral efficacy when combined
73 with lopinavir/ritonavir and lower than expected results in association with atazanavir/ritonavir and
74 darunavir/ritonavir.^{4,5} Primary aim of this study was to describe the seminal pharmacokinetics of
75 maraviroc (150 mg once-daily) when given in association with lopinavir/ritonavir; secondary
76 objective was to analyze seminal HIV-1 replication in patients receiving this dual regimen.

77 Adult male patients enrolled in the VEMAN protocol⁴ were eligible for this sub-study. Main
78 inclusion criteria were no concomitant systemic nor genital illness, a confirmed viral load below 37
79 copies/mL, to be on protocol between weeks 48 and 96, and no coadministration of potentially
80 interacting drugs. A written informed consent was signed by each participant after approval by the
81 San Raffaele Scientific Institute Ethics Committee, Milano, Italy. Blood plasma and seminal plasma
82 levels were measured by a validated ultra-performance liquid chromatography coupled with triple-
83 quadrupole mass spectrometry method (UPLC-MS-MS) with a limit of detection of 0.125 ng/mL.
84 Plasma HIV RNA was measured through kinetic PCR molecular system (kPCR) (Versant HIV-1
85 RNA kPCR 1.0; Siemens Diagnostics) with a limit of quantification o 37 copies/mL; seminal
86 plasma HIV RNA was measured through a NASBATM-based real-time amplification, the NucliSENS
87 EasyQ[®] HIV-1 v2.0 (with a detection rate of 79% at 500 copies/mL).⁶ Chi square and Mann-Whiney

88 tests were used to test differences between variables while Spearman's rho was used to quantify
89 correlations significance. Data are expressed as medians (interquartile ranges); coefficient of
90 variation was calculated as standard deviation/average.

91 Ten male patients were enrolled [aged 39.6 years (34.3-45.8) and with a body mass index of 23.5
92 mg/Kg² (22.2-29.4)]. All patients had a HIV RNA <37 copies/mL and CD4 cell count was 619/uL
93 (547-683). Plasma and seminal samples were collected respectively 11.6 (10.1-12.4) and 9.2 (8-
94 11.5) hours after maraviroc intake. Maraviroc plasma and seminal concentrations were 223 ng/mL
95 (103.9-312, 55.4%) and 527 ng/mL (234-852, 89.8%): seminal plasma to plasma ratio (ratio_{SP-P})
96 was 291.6% (103.9-405.1, 80.5%) (Figure). Lopinavir plasma and seminal concentrations were
97 7935 ng/mL (6269-8958) and 233 ng/mL (136-803): lopinavir ratio_{SP-P} was 4.3% (2.6-11.7).
98 Ritonavir plasma and seminal concentrations were 275 ng/mL (224-773) and 21 ng/mL (7-31):
99 ritonavir ratio_{SP-P} was 8.3% (IQR 4.6-10.7).

100 The included patients were compared to five patients in the control arm (receiving
101 tenofovir/emtricitabina plus lopinavir/ritonavir): male, with median age, BMI and CD4 cell count of
102 43 years (37.3-44), 22.3 kg/m² (21.5-24.8) and 480/uL (449-531). Lopinavir plasma and seminal
103 concentrations and ratio_{SP-P} were 11521 ng/mL (10111-14018), 517 ng/mL (461-634) and 6.3%
104 (3.3-6.6). Ritonavir plasma and seminal concentrations and ratio_{SP-P} were 436 ng/mL (424-900), 18
105 ng/mL (16-35) and 6.2% (1.3-8.1). While RNA amplification was not effective in two samples,
106 seminal HIV RNA was undetectable in all the other ones (n=13).

107 This is the first report of maraviroc pharmacokinetics in seminal plasma when dosed at 150 mg
108 once-daily with a boosted PI. Maraviroc confirmed to accumulate in seminal plasma and
109 compartmental maraviroc concentrations were found to be adequate, well above the protein-free
110 IC₉₀ (0.5 ng/mL) in all included subjects.

111 Lopinavir and ritonavir exposures in seminal plasma were similar to previous reports. In previous
112 studies maraviroc administered twice-daily (150, 300 or 600 mg)⁷⁻¹⁰ showed median seminal
113 concentrations between 80 and 804 ng/mL, being 89% to 970% of plasma levels with a large inter-
114 patient variability (seminal levels ranging from 15.8 ng/mL to 4920 ng/mL). Interestingly in our
115 patients both plasma and seminal maraviroc exposure resulted to be comparable to the values
116 previously reported for maraviroc at double dosing (150 mg bid) with darunavir/r. This finding
117 further supports the pharmacological suitability of once-daily dosing maraviroc 150 mg with
118 lopinavir/ritonavir. Moreover, pharmacological findings were consistent with virological data: both
119 in patients in the experimental dual regimen arm and in the triple drug arm seminal plasma HIV
120 RNA was undetectable. These data support the seminal virological effectiveness of once-daily
121 maraviroc plus LPV/r association and confirm, in general terms, the result of previous data on PI-
122 based dual regimens in the male genital tract³.

123 In conclusion, once-daily maraviroc at 150 mg administered with with lopinavir/ritonavir showed
124 adequate seminal exposure and full antiviral activity in the male genital tract.

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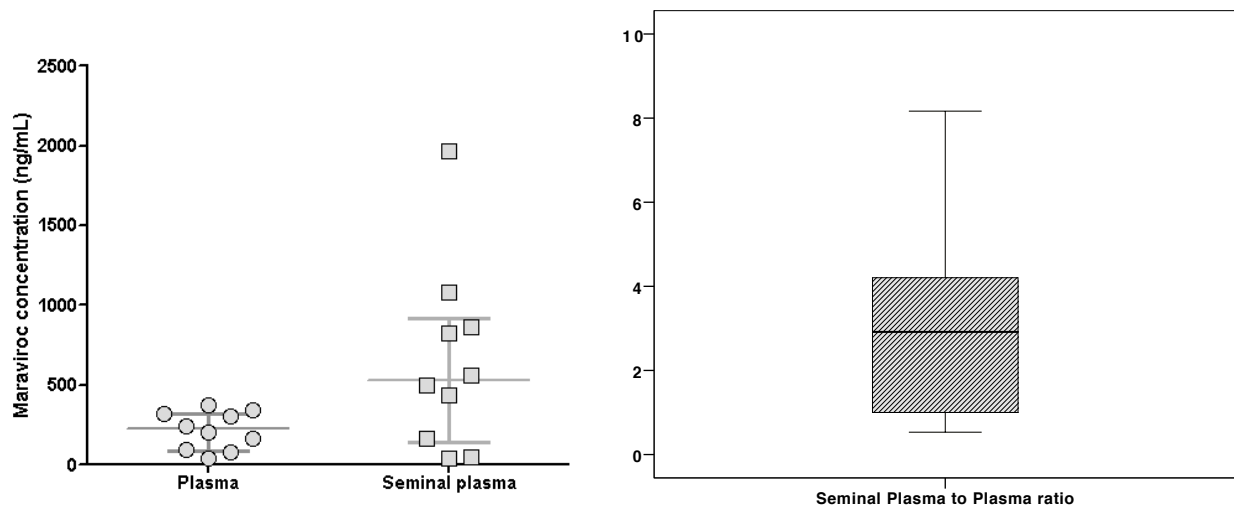
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135 **Figure. Maraviroc seminal pharmacokinetics.** Plasma, and seminal plasma concentrations (left)
 136 (horizontal lines represent median and interquartile range values). Seminal plasma to plasma ratios
 137 (right): horizontal line represents median values; box and whiskers respectively represent
 138 interquartile range and range.

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