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

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Running Head: Once-daily maraviroc seminal PK

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

Adult male patients enrolled in the VEMAN protocol[4] were eligible for this sub-study. Main inclusion criteria were no concomitant systemic nor genital illness, a confirmed viral load below 37 copies/mL, to be on protocol between weeks 48 and 96, and no coadministration of potentially interacting drugs. A written informed consent was signed by each participant after approval by the San Raffaele Scientific Institute Ethics Committee, Milano, Italy. Blood plasma and seminal plasma levels were measured by a validated ultra-performance liquid chromatography coupled with triple-quadrupole mass spectrometry method (UPLC-MS-MS) with a limit of detection of 0.125 ng/mL. Plasma HIV RNA was measured through kinetic PCR molecular system (kPCR) (Versant HIV-1 RNA kPCR 1.0; Siemens Diagnostics) with a limit of quantification o 37 copies/mL; seminal plasma HIV RNA was measured through a NASBA™-based real-time amplification, the NucliSENS EasyQ® HIV-1 v2.0 (with a detection rate of 79% at 500 copies/mL).[6] Chi square and Mann-Whiney

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

Ten male patients were enrolled [aged 39.6 years (34.3-45.8) and with a body mass index of 23.5 mg/Kg^2 (22.2-29.4)]. All patients had a HIV RNA <37 copies/mL and CD4 cell count was 619/uL (547-683). Plasma and seminal samples were collected respectively 11.6 (10.1-12.4) and 9.2 (8-11.5) hours after maraviroc intake. Maraviroc plasma and seminal concentrations were 223 ng/mL (103.9-312, 55.4%) and 527 ng/mL (234-852, 89.8%): seminal plasma to plasma ratio ($ratio_{SP-P}$) was 291.6% (103.9-405.1, 80.5%) (Figure). Lopinavir plasma and seminal concentrations were 7935 ng/mL (6269-8958) and 233 ng/mL (136-803): lopinavir $ratio_{SP-P}$ was 4.3% (2.6-11.7). Ritonavir plasma and seminal concentrations were 275 ng/mL (224-773) and 21 ng/mL (7-31): ritonavir $ratio_{SP-P}$ was 8.3% (IQR 4.6-10.7).

The included patients were compared to five patients in the control arm (receiving tenofovir/emtricitabina plus lopinavir/ritonavir): male, with median age, BMI and CD4 cell count of 43 years (37.3-44), 22.3 kg/m^2 (21.5-24.8) and 480/uL (449-531). Lopinavir plasma and seminal concentrations and $ratio_{SP-P}$ were 11521 ng/mL (10111-14018), 517 ng/mL (461-634) and 6.3% (3.3-6.6). Ritonavir plasma and seminal concentrations and $ratio_{SP-P}$ were 436 ng/mL (424-900), 18 ng/mL (16-35) and 6.2% (1.3-8.1). While RNA amplification was not effective in two samples, seminal HIV RNA was undetectable in all the other ones (n=13).

This is the first report of maraviroc pharmacokinetics in seminal plasma when dosed at 150 mg once-daily with a boosted PI. Maraviroc confirmed to accumulate in seminal plasma and compartmental maraviroc concentrations were found to be adequate, well above the protein-free IC_{90} (0.5 ng/mL) in all included subjects.

Lopinavir and ritonavir exposures in seminal plasma were similar to previous reports. In previous studies maraviroc administered twice-daily (150, 300 or 600 mg)[7-10] showed median seminal concentrations between 80 and 804 ng/mL, being 89% to 970% of plasma levels with a large inter-patient variability (seminal levels ranging from 15.8 ng/mL to 4920 ng/mL). Interestingly in our patients both plasma and seminal maraviroc exposure resulted to be comparable to the values previously reported for maraviroc at double dosing (150 mg bid) with darunavir/r. This finding further supports the pharmacological suitability of once-daily dosing maraviroc 150 mg with lopinavir/ritonavir. Moreover, pharmacological findings were consistent with virological data: both in patients in the experimental dual regimen arm and in the triple drug arm seminal plasma HIV RNA was undetectable. These data support the seminal virological effectiveness of once-daily maraviroc plus LPV/r association and confirm, in general terms, the result of previous data on PI-based dual regimens in the male genital tract[3].

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

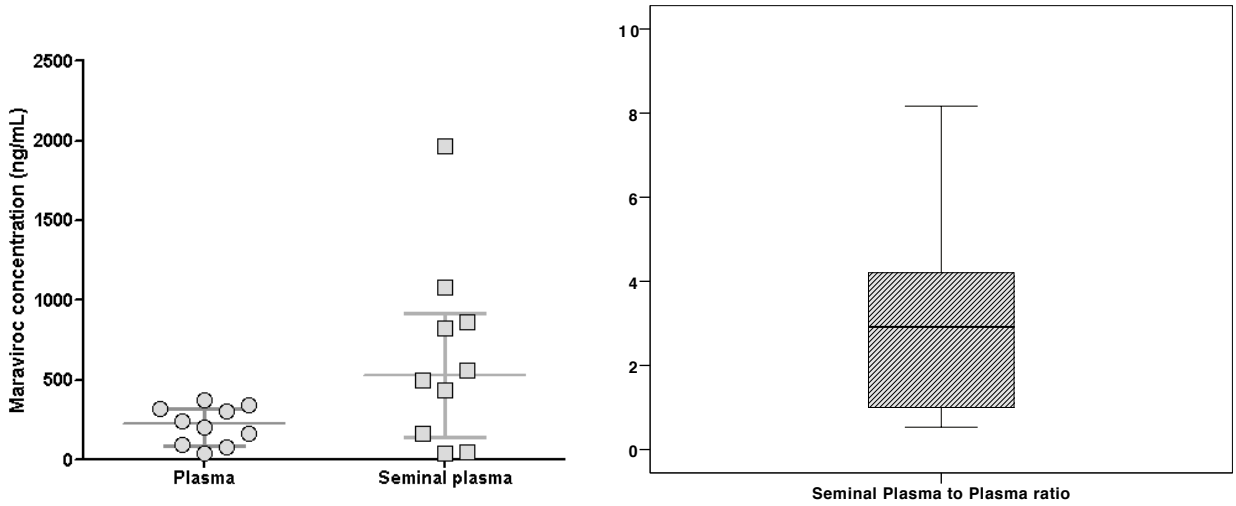

Figure. Maraviroc seminal pharmacokinetics. Plasma, and seminal plasma concentrations (left) (horizontal lines represent median and interquartile range values). Seminal plasma to plasma ratios (right): horizontal line represents median values; box and whiskers respectively represent interquartile range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

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Other authors nothing to declare.

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