Protease inhibitor monotherapy is effective in controlling human immunodeficiency virus 1 shedding in the male genital tract

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Abstract

Cross-sectional study comparing seminal human immunodeficiency virus type 1 (HIV-1) shedding in patients receiving boosted protease inhibitor monotherapy (mtPI/rtv) (n = 66) versus triple therapy (TT) (n = 61). Seminal HIV-1 shedding rates in patients with undetectable plasma HIV-RNA were 16.0% on mtPI/rtv compared with 28.6% on TT (p 0.173). Aviraemic status and time on viral suppression were independently associated with lack of seminal HIV-1 shedding. During TT, non PI/rtv-based regimens were associated with a better control of HIV infection in semen despite similar time on viral suppression. The use of mtPI/rtv in well-controlled patients is not associated with increased seminal HIV excretion compared with TT.

Keywords: Human immunodeficiency virus 1 infection, human immunodeficiency virus 1 treatment, male genital tract, protease inhibitor monotherapy, triple therapy

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Effective triple antiretroviral therapy (TT) is able to control human immunodeficiency virus (HIV) viraemia and significantly decreases transmission to heterosexual partners [1,2]. However, there is evidence of an intermittent seminal HIV shedding in approximately 15% of virologically suppressed males receiving TT [3–8]. Ritonavir-boosted protease inhibitor monotherapy (mtPI/rtv) has been proposed to both facilitate adherence and reduce adverse effects and costs in virologically well-controlled patients [9,10], showing a slightly lower efficacy than TT in controlling viral replication. Nevertheless, little is known about its impact on HIV sanctuaries, such as the male genital tract. In a cross-sectional study, we compare the rate of seminal HIV-1 shedding of patients without previous virological failure on protease inhibitors and ≥6 months of viral suppression on TT who switched to mtPI/rtv (lopinavir/ritonavir, 200/100 mg every 12 h, or darunavir/ritonavir, 800/100 mg once a day) compared with patients on TT for ≥3 months with two nucleos(t)ide reverse transcriptase inhibitors plus a ritonavir-boosted protease inhibitor (PI/rtv; n = 26), a non-nucleoside reverse transcriptase inhibitor (n = 31) or raltegravir (n = 4).

All patients were negative for sexually transmitted infections at enrolment and all provided informed consent. Paired peripheral blood and semen samples were collected and HIV-RNA levels were determined in both blood plasma (BP) and seminal plasma (SP) by real-time PCR (AmpliPrep/COBAS TaqMan HIV-1 Test, Roche Diagnostics, Basel, Switzerland), with limits of detection of 20 and 30 copies/mL, respectively (see Supplementary material, Appendix S1). Linear regression analysis and Spearman's correlation coefficients were used to correlate viral load in blood and semen. For group comparison, the χ^2, Mann–Whitney U or Kruskal–Wallis tests were used. Logistic regression analysis was used to identify the independent predictive variables associated with HIV shedding in semen in the different subsets of patients.

Patients' baseline characteristics are shown in the Supplementary material (Table S1). Longer time on treatment and viral suppression, as well as higher $CD4^+$ T-cell counts were observed on the mtPI/rtv group compared with the TT group. Overall, there was a significant positive correlation between BP and SP viral loads (r = 0.266; p 0.002) and negative correlations between seminal HIV-RNA levels and the time on both

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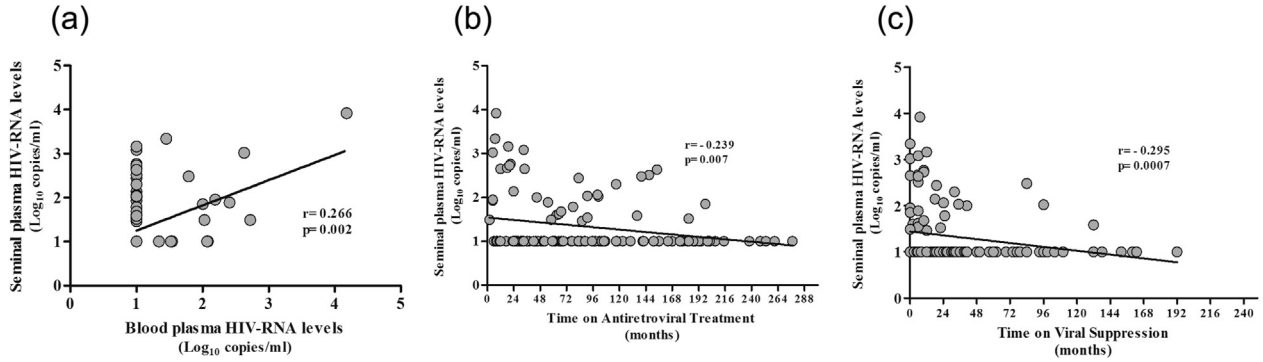
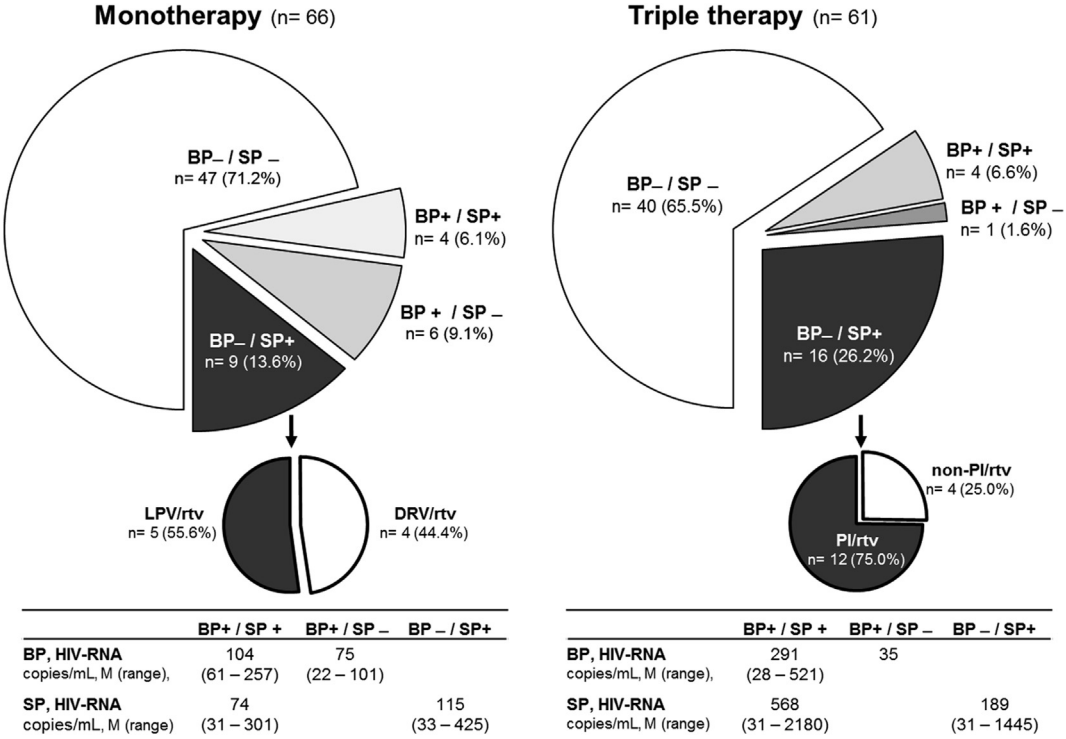


FIG. 1. Correlations between seminal human immunodeficiency virus (HIV) RNA levels and (a) blood plasma, and seminal plasma HIV-RNA levels and (b) seminal plasma HIV-RNA levels and time on antiretroviral therapy, and (c) time on viral suppression.

antiretroviral treatment (r = −0.239, p 0.007) and viral suppression (r = −0.295, p 0.0007) (Fig. 1).

The proportion of patients with undetectable BP viral load and detectable SP HIV-RNA levels (BP−/SP+) was similar for lopinavir/ritonavir and darunavir/ritonavir (19% and 13%, respectively; p 0.719); hence, both groups were analysed together (Fig. 2). Among the 13 patients on mtPI/rtv who showed positive SP HIV-RNA, similar levels of seminal HIV-RNA were found irrespective of the HIV-RNA levels in plasma (p 0.285).

In the setting of TT, the seminal HIV-RNA shedding rate was 28.6% among the 56 patients with undetectable viraemia. The remaining five patients had detectable viraemia and four of them also had positive SP, but without correlation between HIV-RNA levels in both compartments (Fig. 2 and see Supplementary material, Table S2). Among this group, a higher discordance rate (BP−/SP+) was observed on PI/rtv-based treatment than on non-PI/rtv-based regimens (52% versus 12.1%; p < 0.001) despite similar time on treatment (32 versus 37 months; p 0.457), previous time on viral suppression



	BP+ / SP +	BP+ / SP –	BP – / SP+
BP, HIV-RNA copies/mL, M (range),	104 (61 – 257)	75 (22 – 101)	
SP, HIV-RNA copies/mL, M (range)	74 (31 – 301)		115 (33 – 425)

	BP+ / SP +	BP+ / SP –	BP – / SP+
BP, HIV-RNA copies/mL, M (range),	291 (28 – 521)	35	
SP, HIV-RNA copies/mL, M (range)	568 (31 – 2180)		189 (31 – 1445)

FIG. 2. Concordances and discordances of blood and seminal plasma human immunodeficiency virus RNA levels among the two therapeutic strategies.

(6 versus 6 months; p 0.938), and $CD4^+$ T-cell counts (533 versus 608 cells/μL; p 0.373).

As a result of the sample size, differences in HIV seminal shedding between mtPI/rtv and TT did not reach statistical significance within aviraemic patients (16.0% versus 28.6%; p 0.173) or viraemic patients (40.0% versus 80.0%; p 0.282). For those subjects on mtPI/rtv, only the time on viral suppression showed a trend to be associated with HIV shedding in SP (OR 0.98 for each additional month; 95% CI, 0.960–1.0; p 0.090). By contrast, for those patients on TT, the variables independently associated with seminal HIV shedding were an undetectable viraemia (OR 0.076; 95% CI 0.006–0.998; p 0.050) and a non-PI/rtv-based regimen (OR 0.110; 95% CI 0.030–0.420; p 0.001).

To date, only three studies have assessed the seminal viral shedding in patients with undetectable viraemia receiving lopinavir/ritonavir (26 patients) or darunavir/ritonavir (23 patients) monotherapies showing positive SP in 15.4% and 4.3%, respectively [11–14]. However, there are two main differences with our study: the limit of quantification for SP HIV-RNA was established on 200 copies/mL and, in the case of darunavir/ritonavir, the dosing regimen used (600/100 mg twice a day) was higher than the dosing regimen that we used (800/100 mg once daily). Although both factors might contribute to the higher incidence of seminal HIV shedding in our study, we believe that the first one could have more influence as more than 65% of these positive SP samples in our study had HIV-RNA levels <200 copies/mL.

Our results suggest that both monotherapy regimens (lopinavir/ritonavir and darunavir/ritonavir) exert a similar control on HIV replication in the male genital tract, with an incidence of positive SP HIV-RNA even lower than in patients on PI/rtv-based TT, though it could be explained by the shorter time on viral suppression in this TT group (6 months versus 32 months). On the other hand, the lower efficacy of PI/rtv-based TT regimens to control HIV replication in the male genital tract compared with a non-PI/rtv-based TT might be explained, in part, by better drug penetration into the genital compartment by the non-nucleoside reverse transcriptase inhibitors compared with PIs/rtv [15], resulting in a better control of HIV replication in this anatomical compartment. The penetration of the protease inhibitors into the male genital tract is low, largely because of their high degree of plasma protein binding. This, together with the high inter-subject variability in plasma concentrations and transporter activities, makes the protease inhibitor seminal plasma levels vary widely [12,16–18]. It would be worthwhile to evaluate the relationship between pharmacokinetics and viral load in seminal plasma to better understand viral dynamics in the male genital tract and the potential role that low levels of seminal HIV-RNA shedding might have on sexual HIV transmission.

In summary, these data suggest that the use of mtPI/rtv in previously well-controlled patients is not associated with increased seminal HIV excretion when compared with TT.

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Transparencey declaration

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Appendix A. Supplementary material

Additional Supporting Information may be found in the online version of this article at http://dx.doi.org/10.1016/j.cmi.2015.09.028.

References

[1] Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365:493–505.

[2] Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai project study group. N Engl J Med 2000;342:921–9.

[3] Gupta P, Mellors J, Kingsley L, Riddler S, Singh MK, Schreiber S, et al. High viral load in semen of human immunodeficiency virus type 1-infected men at all stages of disease and its reduction by therapy with protease and nonnucleoside reverse transcriptase inhibitors. J Virol 1997;71:6271–5.

[4] Vernazza PL, Gilliam BL, Dyer J, Fiscus SA, Eron JJ, Frank AC, et al. Quantification of HIV in semen: correlation with antiviral treatment and immune status. AIDS 1997;11:987–93.

[5] Zhang H, Dornadula G, Beumont M, Livornese Jr L, Van Uitert B, Henning K, et al. Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy. N Engl J Med 1998;339:1803–9.

[6] Coombs RW, Speck CE, Hughes JP, Lee W, Sampoleo R, Ross SO, et al. Association between culturable human immunodeficiency virus type 1 (HIV-1) in semen and HIV-1 RNA levels in semen and blood: evidence for compartmentalization of HIV-1 between semen and blood. J Infect Dis 1998;177:320–30.

[7] Kalichman SC, Di Berto G, Eaton L. Human immunodeficiency virus viral load in blood plasma and semen: review and implications of empirical findings. Sex Transm Dis 2008;35:55–60.

[8] Lambert-Niclot S, Tubiana R, Beaudoux C, Lefebvre G, Caby F, Bonmarchand M, et al. Detection of HIV-1 RNA in seminal plasma samples from treated patients with undetectable HIV-1 RNA in blood plasma on a 2002–2011 survey. AIDS 2012;26:971–5.

[9] Arribas JR, Doroana M, Turner D, Vandekerckhove L, Streinu-Cercel A. Boosted protease inhibitor monotherapy in HIV-infected adults: outputs from a pan-European expert panel meeting. AIDS Res Ther 2013;10:3.

[10] Arribas J, Girard PM, Paton N, Winston A, Marcelin A, Elbirt D, et al. Efficacy of PI monotherapy versus triple therapy for 2202 patients in 12 randomised trials. 12th International Congress on Drug Therapy in HIV Infection. 2014. Glasgow, United Kingdom.

[11] Bunupuradah T, Bowonwattanuwong C, Jirajariyavej S, Munsakul W, Klinbuayaem V, Sophonphan J, et al. HIV-1 genital shedding in HIV-infected patients randomized to second-line lopinavir/ritonavir monotherapy versus tenofovir/lamivudine/lopinavir/ritonavir. Antivir Ther 2014;19:579–86.

[12] Ghosn J, Chaix ML, Peytavin G, Bresson JL, Galimand J, Girard PM, et al. Absence of HIV-1 shedding in male genital tract after 1 year of first-line lopinavir/ritonavir alone or in combination with zidovudine/lamivudine. J Antimicrob Chemother 2008;61:1344–7.

[13] Nunes EP, Santini de Oliveira M, Mercon M, Zajdenverg R, Faulhaber JC, Pilotto JH, et al. Monotherapy with lopinavir/ritonavir as maintenance after HIV-1 viral suppression: results of a 96-week randomized, controlled, open-label, pilot trial (Kalmo study). HIV Clin Trials 2009;10:368–74.

[14] Lambert-Niclot S, Peytavin G, Duvivier C, Poirot C, Algarte-Genin M, Pakianather S, et al. Low frequency of intermittent HIV-1 semen excretion in patients treated with darunavir-ritonavir at 600/100 milligrams twice a day plus two nucleoside reverse transcriptase inhibitors or monotherapy. Antimicrob Agents Chemother 2010;54:4910–3.

[15] Else LJ, Taylor S, Back DJ, Khoo SH. Pharmacokinetics of antiretroviral drugs in anatomical sanctuary sites: the male and female genital tract. Antivir Ther 2011;16:1149–67.

[16] Ghosn J, Chaix ML, Peytavin G, Rey E, Bresson JL, Goujard C, et al. Penetration of enfuvirtide, tenofovir, efavirenz, and protease inhibitors in the genital tract of HIV-1-infected men. AIDS 2004;18(14):1958–61.

[17] Taylor S, Javasuriva AN, Berry A, Gilleran G, Dufty NE, Else L, et al. Darunavir concentrations exceed the protein-corrected EC_{50} for wild-type HIV in the semen of HIV-1-infected men. AIDS 2010;24(16):2583–7.

[18] Estrela Rde C, Ribeiro FS, Barroso PF, Tuyama M, Gregorio SP, Dias-Neto E, et al. ABCB1 polymorphisms and the concentrations of lopinavir and ritonavir in blood, semen and saliva of HIV-infected men under antiretroviral therapy. Pharmacogenomics 2009;10(2):311–8.