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 the once-daily maraviroc plus lopinavir/ritonavir association and confirm, in general terms, the results of previous data on protease inhibitor-based dual regimens in the male genital tract.  

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

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Transparency declarations
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Change in HIV-1 DNA tropism despite virological success in patients receiving an enfuvirtide-based regimen

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Sir,
In patients receiving combined antiretroviral therapy (cART), without CCR5 antagonists, viral tropism can change even in patients with suppressed viremia.1,2 In this setting, tropism can be determined from cellular HIV-1 DNA.3 However, it remains unclear how potent cART without CCR5 antagonists might influence the evolution of HIV-1 DNA tropism.

The objective of this study was to describe the evolution of HIV–1 DNA tropism in patients receiving a fusion inhibitor-based regimen in different clinical settings.

Patients from two randomized clinical trials with a fusion inhibitor (enfuvirtide) arm were analysed: (i) the Agence Nationale de Recherches sur le SIDA et les hépatites virales (ANRS) 130 APOLLO study that enrolled severely immunocompromised cART-naïve patients,4 and (ii) the INNOVE study that enrolled cART-experienced patients with virological failure.5,6 Patients received enfuvirtide in addition to cART for 6 months in the APOLLO study and 3 months in the INNOVE study. In the APOLLO and INNOVE studies, 100 and 14 patients were included in the enfuvirtide arm, respectively.
HIV-1 DNA tropism was assessed at baseline and at week 24 of cART by V3 loop sequencing using the ANRS protocol (www.hivfrenchresistance.org). HIV-1 tropism was interpreted using the Geno2Pheno algorithm (http://www.geno2pheno.org) with a false positive rate of 10%.

At baseline, among all patients enrolled in both studies, the proportion harbouring X4 viruses in peripheral blood mononuclear cells (PBMCs) was 56/121 (46%) and 10/29 (34%) in the APOLLO and INNOVE studies, respectively. Overall, tropism evolution in HIV-1 DNA was observed in 29 cases (Table 1). HIV-1 DNA tropism change from R5 at baseline to X4 at week 24 in the enfuvirtide arms was observed in 9/48 (19%) patients in the APOLLO study and in 4/13 (31%) patients in the INNOVE study (Table 1). Combining the APOLLO and INNOVE data, a higher frequency of HIV-1 DNA tropism change from R5 at baseline to X4 at week 24 was observed in the enfuvirtide arms than in the control arms: 13/62 (21%) versus 4/77 (5%) (P=0.0077).

Among the 13 patients displaying a tropism change from R5 at baseline to X4 at week 24 in PBMCs in the enfuvirtide arms, 10 were infected with HIV-1 subtype B. Six out of these 13 (46%) patients exhibited baseline false positive rate values between 10% and 20%, but at week 24 all false positive rate values were very low, below 5.3%. Among these 13 samples, the 12/25 rule would have predicted X4 tropism at baseline in 2 samples, were very low, below 5.3%. Among these 13 samples, the 12/25 rule would have predicted X4 tropism at baseline in 2 samples, exhibiting a tropism switch from R5 to X4 in PBMCs, was in the CD4 cell count between baseline and week 24, in patients exhibiting a tropism switch from R5 to X4 in PBMCs. Among those with changes, switches from X4 to R5 or R5 to X4 were reported in similar proportions.

In the present study, no factor associated with an increased risk of switch from R5 to X4 could be evidenced, as previously described for a low CD4 nadir. In addition, in the APOLLO study, the intensification of initial cART with enfuvirtide did not improve immunological reconstitution in spite of a higher rate of virological response. So, one can speculate that the R5 to X4 tropism switch might have a deleterious effect on immune reconstitution.

European guidelines on tropism testing in the clinical management of HIV-1 recommend increasing the false positive rate to up to 20% in case of tropism determination from PBMCs. Thus, the proportion of HIV-1 DNA change due to a misclassification of baseline HIV-1 DNA tropism might have been underestimated in our study when using the 10% false positive rate threshold. Indeed, when taking 20% as the false positive rate threshold, a switch from X4 to R5 in PBMCs at baseline and week 24 was observed in 11% of the patients, compared with 21% with a 10% false positive rate threshold.

Thus, when a CART switch to a CCR5 inhibitor-based regimen is considered in virologically suppressed patients, a higher false positive rate threshold might be relevant to improve tropism prediction in patients on a regimen containing enfuvirtide (or another fusion inhibitor). The molecular mechanisms involved in tropism change whilst taking a fusion inhibitor are as yet unclear and further studies are warranted to better understand these underlying mechanisms.

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Transparency declarations
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