alfa-2b weekly + 800 mg of ribavirin daily + telaprevir (750 mg/8 h) she achieved undetectable HCV-RNA at weeks 4 and 12. Treatment was complicated by severe anaemia, requiring pegylated interferon and ribavirin dose reduction and blood transfusion. HCV-RNA remained <15 IU/L, and she continued on pegylated interferon + ribavirin treatment. HIV-RNA remained undetectable at treatment weeks 4, 8 and 12.

Darunavir and telaprevir PK data are shown in Table 1. There were decreases in all darunavir PK parameters when administered with telaprevir for both patients, except for unbound trough concentration in Patient 2. These decreases, ranging from 58% to 97%, were even higher than those previously described in healthy volunteers.[2,3] However, darunavir/ritonavir doses were different in both cases (800/100 mg once daily in our patients and 600/100 mg twice daily in healthy volunteers).[2] We also observed decreases in unbound darunavir concentrations in both patients (except for the aforementioned increase in unbound C_{trough} in Patient 2), although the free fraction decreased less than total drug (ranging from 46% to 93%). There are scarce data on darunavir PK in HIV/HCV-coinfected patients: in a Spanish cohort, darunavir once-daily concentrations (total and unbound) were higher than those observed in our two patients, even before telaprevir co-administration.[5]

We could not evaluate the impact of darunavir on telaprevir concentrations, as antiretroviral therapy was maintained. However, telaprevir concentrations in our patients were much higher than previously reported in healthy volunteers or HCV-monoinfected patients.[2,3,6] These high telaprevir concentrations in our coinfected patients with advanced fibrosis could partially explain the marked reduction in darunavir levels, although an association between telaprevir exposure and extent of drug interaction with antiretrovirals has not been previously described.

Despite the impact of telaprevir co-administration on darunavir concentrations (total darunavir C_{trough} was below wild-type virus IC_{50} in one patient), HIV-RNA remained undetectable during the 12 weeks of telaprevir therapy. Prolonged HIV suppression prior to starting anti-HCV therapy, preserved antiviral potency of the darunavir-based regimen and interferon anti-HIV effect[7] could have played a role in keeping HIV-RNA undetectable.

Having only two patients, we must take into account all the potential confounding factors and the inter- and intra-individual variability, which hamper generalization of our results. However, our results are concordant between both patients. Besides, as PK parameters can be modified with hepatic impairment, it is very important to have data on interaction between telaprevir and darunavir/ritonavir in HIV/HCV-coinfected patients with hepatic cirrhosis.

In summary, decreases in darunavir total and unbound concentrations were seen in two HIV/HCV-coinfected patients when co-administered with telaprevir. Data from larger trials with once-daily and twice-daily darunavir are necessary in order to find the most appropriate darunavir dose in coinfected patients receiving telaprevir.

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Viral rebound after switch to maraviroc/raltegravir dual therapy in highly experienced and virologically suppressed patients with HIV-1 infection

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Sir,

Strategies of treatment simplification have been explored in order to improve adherence and long-term toxicities,[1] but limited data are available in treatment-experienced subjects.[2] Maraviroc and raltegravir appeared well tolerated, with low metabolic toxicity.[3,4] The aim of this study was to explore the efficacy of a dual simplification regimen including maraviroc and raltegravir in highly experienced patients.

The study included 26 HIV-1-infected highly experienced patients followed at San Raffaele Scientific Institute who were successfully rescued with a complex regimen including maraviroc and raltegravir; their treatment was simplified to dual therapy consisting of maraviroc (300 mg twice daily) and raltegravir (400 mg twice daily) and they were followed prospectively for 24 weeks with monthly visits. Before simplification, patients underwent a co-receptor tropism test on HIV DNA using the geno2pheno algorithm with a false positive rate (FPR) cut-off of 20%, in accordance with European guidelines; at baseline all patients had R5 tropic virus and their antiretroviral regimen was simplified.

In the case of viral rebound (a single value of HIV RNA >50 copies/mL), treatment was immediately re-intensified to the previous full regimen. At viral rebound, resistance tests for viral tropism, reverse transcriptase, protease and integrase were performed. Therapeutic drug monitoring (TDM) was performed using validated methods[5,6] at simplification (baseline), at week 8, at week 24 and at virological failure.

Results are described as median (IQR) or frequency (%). Intention-to-treat analysis was performed. Changes since baseline were evaluated by the Wilcoxon signed rank test and comparisons between groups were performed using the Mann–Whitney *U*-test.

The baseline characteristics of the patients were as follows: 24 (92%) males; 6 (23%) co-infected with hepatitis C virus; 11 (42%) in CDC stage C; age 48 (46–54) years; duration of HIV infection 20.1 (17.4–24.1) years; duration of antiretroviral therapy (ART) 16.3 (15.1–19.8) years; CD4+ cell count 654 (507–755) cells/μL; and FPR 50% (43%–69%). All patients had been on optimal viral suppression [10 (38%) with <1 copy/mL] for 46 (41–49) months; for 16 and 10 patients, treatment was simplified from regimens including maraviroc, raltegravir and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (88% etravirine) or maraviroc, raltegravir and protease inhibitors (PIs) (80% darunavir/ritonavir), respectively.

By week 24, nine patients (35%) had viral rebound [HIV RNA at virological failure: 2309 (1088–7719) copies/mL]: five patients (56%) had previously been treated with NNRTIs and four (44%) with PIs. All of them restarted their original therapy: 7/9 (78%) achieved an undetectable viral load within 12 weeks; failed patients changed antiretroviral therapy and currently viruses are undetectable in them.

Regimen, genotypes and FPR at simplification and at failure are reported in Table 1.

The CD4+ cell count did not decrease significantly during follow-up ($P=0.351$): the count at week 24 was 647 (508–798) cells/mm^3 and the median change was −27 (−84 to 21) cells/mm^3.

At baseline, maraviroc concentrations were similar between patients who had virological rebound and those who did not fail [122 (75–148) ng/mL versus 93 (71–108) ng/mL; $P=0.210$]. At week 24 the maraviroc concentration was significantly lower than at baseline [−26 (−76 to −9) ng/mL; $P=0.001$], but was more marked in patients with virological failure [change at week 24: −44 (−85 to 26) ng/mL; $P=0.063$]. At virological failure, seven out of nine (78%) patients had levels below the minimum effective concentration.

Raltegravir concentrations at baseline did not differ between patients with and without virological rebound [110 (50–511) ng/mL versus 217 (62–345) ng/mL; $P=0.661$]. The concentrations were stable during 24 weeks of follow-up [85 (−139 to 403) ng/mL; $P=0.431$] and similar between patients with and without virological rebound [129 (−252 and 398) ng/mL versus 25 (−125 and 569) ng/mL; $P=0.958$]. Figures represent changes during 24 weeks. TDM data are reported in Figure S1 (available as Supplementary data at *JAC* Online).

Dual therapies may reduce exposure to drug toxicity and are therefore appealing in patients with long-term treatment experience; we chose the combination of raltegravir and maraviroc because of their efficacy and good tolerability.[7] Nevertheless, this simplification strategy led to an unexpectedly high rate of virological rebound over 24 weeks. In a recently reported study (the ROCnRAL study),[8] patients with lipoatrophy were switched to raltegravir and maraviroc: this trial was prematurely discontinued because of a high rate of virological failure (16% in 48 weeks).

Switching of maraviroc from previous adjusted dosing with PI/ritonavir and NNRTI to standard dosing with raltegravir led to an expected decrease in maraviroc plasma exposure, especially in patients switching from PI-associated dosing. However, in patients with virological failure this decrease was significantly more marked compared with other subjects, leading to suboptimal exposure in 78% and suggesting a possible additional role of adherence or drug–drug interaction. Data from healthy subjects showed that co-administration of raltegravir and maraviroc led to a decrease in C_{min} of the latter; although considered not generally relevant, the magnitude of the interaction could be more pronounced in some patients.[9] In the ROCnRAL trial, however, the pharmacokinetic substudy did not find evidence of significant maraviroc and raltegravir interactions.[10]

The removal of an antiretroviral drug with a high genetic barrier may be a further explanation for the observed results relating to the virological robustness of the regimen.

Despite the small sample size, our findings suggest that the simplification to a dual regimen with maraviroc and raltegravir after successful rescue in patients infected with R5 HIV may be associated with short-term viral rebound.

Ethics

Patients were treated with antiretroviral drugs containing maraviroc and raltegravir; Ethics Committee approval was not required because simplification is part of routine care.

Table 1. Previous therapy and historical mutations of 26 experienced HIV-1-infected patients treated with a regimen containing maraviroc and raltegravir

	Drug removed at simplification	FPR at baseline (%)	Historical mutations	FPR at failure (%)	Mutations at failure
1	ETR	42.8	NNRTI: K103N PI: L24I, L33F, M46L	1.7	NNRTI: K103N PI: L10IL INI: G140GS, Q148H
2	ETR	36.8	NNRTI: Y88L PI: V32I, L33F, I47A, I50V, F53L	73.9	NNRTI: none PI: none INI: N155H
3	ETR	31.6	PI: M46I, I47V, I54V, I84V, L90M	31.7	NNRTI: none PI: none INI: Y143C
4	ETR	33.2	NNRTI: none PI: I47V, I54V, I84V, L90M	33.2	NNRTI: L100I, K103N, E138EK PI: none INI: N155H
5	ETR	64	NNRTI: K103N PI: M46I, I47V, I54V, I84V, L90M	1.7	NNRTI: none PI: none INI: N155H
6	DRV/r	73.9	NNRTI: none PI: M46L, G48M, I54V, V82S, I84V	16.9	NNRTI: not amplifiable PI: not amplifiable
7	DRV/r	76	NNRTI: none PI: M46L, I54V, V82A	1.7	NNRTI: none PI: none
8	DRV/r	41.4	NNRTI: K103S PI: M32I, L33F, M46I, I74V, I54L, V82A, L90M	31.7	NNRTI: not amplifiable PI: not amplifiable
9	ATV	45.4	NNRTI: none PI: V32I, M46I, I54L, I84V, L90M	23.6	NNRTI: none PI: I84V, L90M
10	ETR	53.5	NNRTI: V179F PI: L33F, M46I, I54V, V82T, I84V, L90M		
11	ETR	25.6	NNRTI: none PI: M46MI, I50IV, I54IV, V82VAIT, L90M		
12	ETR	44.9	NNRTI: none PI: V32I, L33F, M46I, I47V, I84V, L90M		
13	ETR	47	NNRTI: A98G PI: V32I, M46I, N88S		
14	NVP	30.1	NNRTI: none PI: I50V, I54I, L90M		
15	EFV	48.6	NNRTI: none PI: L33F, I84V, L90M		
16	ETR	50.5	NNRTI: K103N, V108I PI: M46I, I54V, V82T, I84V, L90M		
17	ETR	52.1	NNRTI: none PI: V32I, M46I, I74V, V82A, L90M		
18	ETR	96.4	NNRTI: none PI: V32I, L33F, M46I, I47V, I84V, L90M		
19	ETR	73.1	NNRTI: K103N, Y181C PI: L24I, V32VI, L33LF, M46L, I54LV, V82AV, I84V		
20	ETR	62.5	NNRTI: Y188LH PI: V32I, L33F, M46I, V82A, N88S		
21	ETR	46	NNRTI: Y188L PI: M46L, I54V, I84V, L90M		
22	DRV/r	73.9	NNRTI: K101AEKT PI: none		
23	DRV/r	60.2	NNRTI: K103N PI: M46I, I54V, V82T, L90M		

Continued

Table 1. *Continued*

	Drug removed at simplification	FPR at baseline (%)	Historical mutations	FPR at failure (%)	Mutations at failure
24	DRV/r	42.6	NNRTI: I135T, G245T PI: I84V, V82S, L90M		
25	DRV/r	79.5	NNRTI: I135T PI: V82A, I84V, L90M		
26	LPV/r	67	NNRTI: Y181C PI: none		

ETR, etravirine; DRV/r, darunavir/ritonavir; ATV, atazanavir; NVP, nevirapine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; INI, integrase inhibitor.
Patients 1–9 had viral rebound.

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Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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