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Durability of Boosted Atazanavir (ATV) or Darunavir (DRV) Plus Maraviroc (MVC) Dual rescue Therapy in Poorly Adherent Subjects in View of Long-Acting Drugs

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Abstract

In poorly adherent HIV-infected subjects strategic approaches may avoid resistance to long-acting compounds. This study means to assess the safety of a strategy which was being carried out in our Division in several non-adherent subjects with general satisfaction.

All subjects who had been switched to boosted protease inhibitors plus maraviroc for treatment failure between June 2014, and April 2015, were retrospectively evaluated. Eighteen were taking darunavir/ritonavir and 26 atazanavir/ritonavir plus maraviroc 300 mg once daily. All had a follow-up of 104 weeks and 27 exceeded 156 weeks. One patient, who was INSTI-experienced and still had >500 HIV-1 RNA copies/mL at week 60, switched to dolutegravir plus darunavir/ritonavir and rapidly failed, selecting for INSTI cross resistance-associated mutations (97A, 140S and 148H). At week 96 and 140, 81.8% and 85.2% had <50 HIV-1 RNA copies/mL, respectively. No one else selected resistance mutations nor switched co-receptor tropism. All remain eligible for long-acting therapy.

Keywords: Maraviroc; Atazanavir; Darunavir; Adherence; Resistance; Strategic; Durability

Introduction

HIV-infected subjects who are poorly adherent to therapy pose several problems for the physicians and for the whole community [1]. They must be closely followed and must undergo many exams, in particular genotypic resistance tests. They often require complex and expensive regimens, they may transmit drug resistance strains to others, and disease progression is more likely to occur [2].

A long-acting intramuscular association of cabotegravir plus rilpivirine is currently being studied in two phase III trials on treatment-naïve patients and on switch from stable therapy [3,4]. Nanoformulation allows drugs to maintain stable plasma levels over time [5,6], overcoming the problem of daily adherence but not that of adherence to a monthly schedule. This paper presents an update of the preliminary data published elsewhere [7], concerning the concept of a 'disposable' regimen, in which the high risk of drug failure may not hamper the future eligibility of patients for long-acting regimens. The aim of this study was therefore assess a way to prevent non-adherent subjects from accumulating resistance mutations that may exclude them from benefiting from future options.

Material and Methods

In April 2016 we decided to retrospectively evaluate poorly adherent patients, with active HIV-1 replication despite attempts of adherence correction through directly observed therapy, admission in ward to better control the response to therapy, or referral to a psychiatrist or a psychologist. These patients had been switched to once daily boosted atazanavir (ATV/r, 300/100 mg) or darunavir (DRV/r, 800/100 mg) plus maraviroc (MVC, 300 mg or adjusted for the eGFR) between June, 2014, and April, 2015. A second analysis of the same population was conducted in March, 2017. Before switching, the patients had signed an informed consent with privacy disclosure approval, as this is a non-conventional (although not off-label) antiretroviral regimen, and they underwent a genotypic tropism test, interpreted according to the geno2pheno algorithm, version 3.4. Detailed methods have been described in our previous publication [7].

The statistical analysis was limited to means ± standard deviation (SD), the two-tailed Fisher exact test, for <50 copies HIV-1 RNA/mL and for 'no virus detected' (NVD=0 copies) at week 96 between the ATV/r and the DRV/r group and the paired t test for the CD4+ T-cell increase.

The subpopulation who reached at least 96 weeks of follow-up was analysed in order to compare the results with its baseline and not as the progressive narrowing of the whole group.

The glomerular filtration rate (e-GFR) was estimated at baseline and at follow-up according to the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation [8]. For the toxicity analysis the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03, June 14, 2010) was considered [9]. Adverse clinical events were reported to the local Ethics Committees and authorities as required by the law.

Results

Baseline data and demographic data of the entire cohort appear in our previous article (Table 1) [7].

	MVC+ATV/r (n=26)	MVC+DRV/r(c) (n=18)
Median age (range)	48.6 (21-59)	47.9 (32-56)
Female sex , n (%)	6 (23.1%)	4 (22.2%)
Risk factors, n (%): past/active intravenous drug user: male homosexual: heterosexual	9 : 10 : 7 (34.6 : 38.5 : 26.9)	6 : 6 : 6 (33.3 : 33.3 : 33.3)
CDC stage C, n (%)	4 (15.4%)	3 (16.7%)
Switch from a bPI- : NNRTI- : or INSTI-based regimen, %	53.8 : 30.8 : 15.4	61.1 : 22.2 : 16.7
Median number of previous regimens (range)	3.3 (2-5)	3.6 (2-6)
HCV coinfection	23.1	27.8
CD4+ T-cells/mm3, median (range)	249 (83-371)	226 (74-349)
HIV-1 RNA, copies/mL, median (range)	877 (217-3256)	1023 (412-2998)
Baseline major resistance-associated mutations(RAMs) to NRTIs : NNRTIs : PIs : INSTIs	28 : 3 : 13 : 0	23 : 3 : 9 : 0
Subjects with known co-morbidities, %	30.8	30.0

(c)=Cobicistant, ATV/r=Atazanavir/Ritonavir, bPI=Boosted Protease Inhibitor, CDC=Centers for disease control and prevention, DRV/r=Darunavir/Ritonavir, HIV=Human immunodeficiency virus, INSTI=Integrase stand transfer inhibitor, MVC=Maraviroc, NNRTI=Non-nucleoside reverse transcriptase inhibitor, RAM=Resistance-associated mutation, RNA=Ribonucleic acid.

Table 1: Baseline characteristics of the population, divided for the two bPIs (Permissions obtained from Medicine (Baltimore), Capetti AF, et al. 2017, e5728 [7]).

At present 43/44 patients have reached at least 104 weeks of follow-up (one has changed therapy and subsequently failed) and 27 have reached at least 156 weeks of observation (median follow-up of the entire cohort=156.5; interquartile range, IQR=102.5-161). In the attempt to correct their adherence six patients had restarted a regimen while admitted in ward for other reasons, and dismissal had been delayed for a median of four days to control viral decay. Two had been specifically admitted to control adherence in a highly risky situation (wasting syndrome) and four were tentatively managed with two-weeks' DOT. Fifteen had been referred to a psychiatrist and seventeen to a psychologist. None of the approaches had durable effect (more than three months).

At week 104, at the intention-to-treat, missing equal to failure (ITT, M=F) analysis, 22 subjects (50%) had NVD, 36 (81.8%) had <50 HIV-1 RNA copies/mL and 40 (93.2%) had <200 copies/mL. The three subjects who maintained HIV-1 RNA levels above 200 copies/mL (278, 366 and 485 copies/mL) accumulated only synonymous and non-synonymous polymorphic mutations and the false positive rate slightly decreased.

Of the subgroup with 156 weeks' follow-up, 12 (44.4%) had NVD, while 23 (85.2%) and 26 (96.3%) had <50 and <200 HIV-1 RNA copies/mL, respectively. One subject had 367 copies/mL but for now no major RAMs has been selected and tropism remains R5. The CD4 count increased significantly at week 96 and at week 140 as compared to the switch values and also to the immunologic status 24 weeks before the switch. The detailed virologic and immunologic evolution of the cohort is described in Figures 1A-1D.

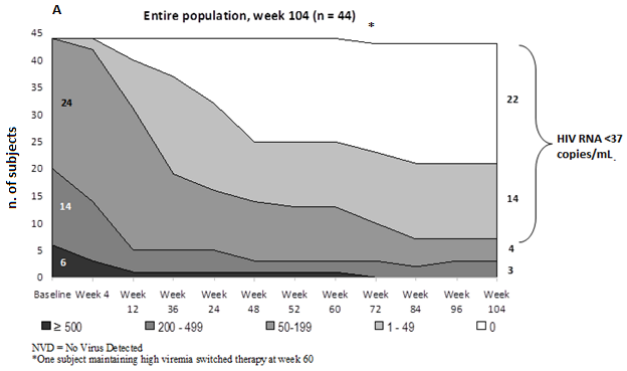

Figure 1A: HIV-1 RNA decay by ranges of values.

NVD=No Virus Detected; *One subject maintaining high viremia switched therapy at week 60.

The Odds ratio for reaching <50 copies HIV-1 RNA/mL at week 96 between the ATV/r and DRV/r groups is 0.89 and the two-tailed Fisher exact test is non-significant (p=1).

The only subject maintaining a relatively high viral load at week 60 (1545 HIV-1 RNA copies/mL) was switched by his physician from MVC to dolutegravir.

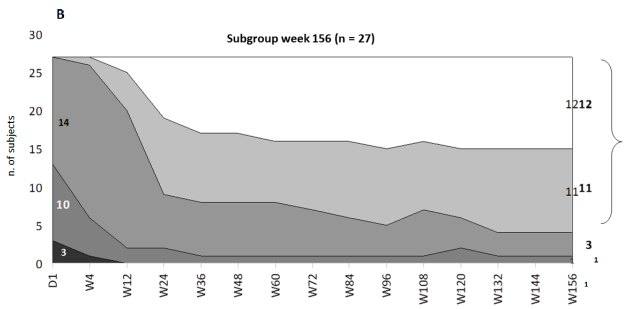

Figure 1B: HIV-1 RNA decay by ranges of values.

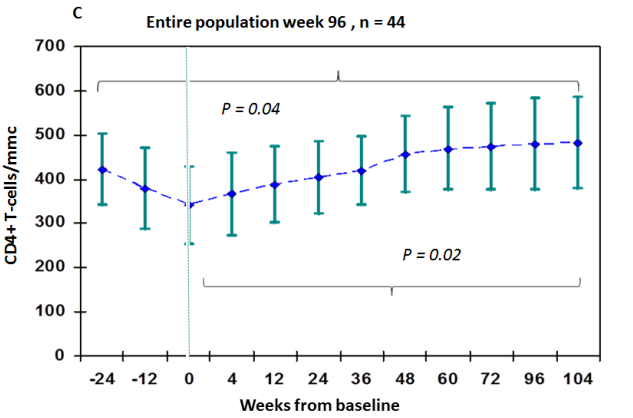

Figure 1C: C4+ T-lymphocyte increase (mean ± SD).

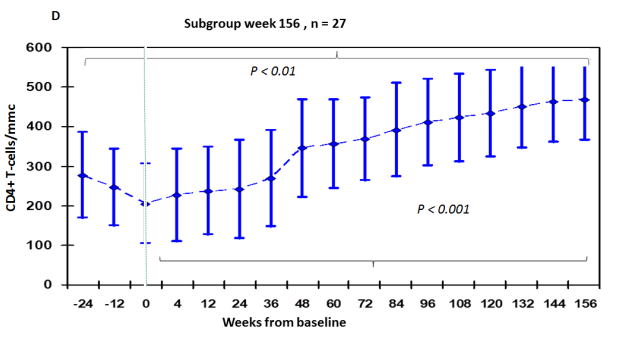

Figure 1D: C4+ T-lymphocyte increase (mean ± SD).

His previous regimen had been tenofovir/emtricitabine plus raltegravir and he had developed several minor INSTI mutations (at positions 72, 123 and 124). After three months of the new switch HIV-1 RNA did not decrease and major integrase strand inhibitor (INSTI) resistance-associated mutations (RAMs) appeared, related to complete cross-resistance, without evolution in the protease gene. The subsequent switch to DRV/r plus MVC plus tenofovir/emtricitabine, on a basis of an archived M184V mutation, led to rapid HIV-1 RNA decay with 107 copes/mL at week 96. Resistance mutation profiles are illustrated in Table 2.

From a pharmaco-economic point of view, the cost of once-daily MVC is comparable to that of a fixed dose combination of nucleoside/nucleotide analogues (€ 670/month *vs.* 678 for tenofovir alafenamide/emtricitabine and 568 for abacavir/lamivudine). The cost of the attempts to obtain adherence had been: € 41600 (days spent in ward) plus € 10560 (105 accesses to psychiatric clinics and about 90 sessions of psychotherapy) 56 working days lost for DOT. Furthermore, the reduced need for frequent HIV RNA testing and genotypic resistance testing resulting from improved viral suppression generated relevant savings (about 760 € per patient for the period from week 48 to week 96 as compared to the previous 48 weeks).

Discussion

This is the first study of the strategic use of a 'disposable' regimen for poorly adherent subjects to prevent the accumulation of RAMs in view of future options that may resolve the problem of adherence. Indeed, poorly adherent subjects who will not be eligible to benefit from long-acting therapies will select multi-drug resistant strains that will likely shorten their life expectancy [2] and continue to pose a threat to the entire society.

The way the tropism test and the 'last option' had been presented to the patients may have had emotional impact, improving motivation towards adherence and providing such an unexpectedly favorable outcome, which exceeds those observed in switch trials of dual regimens of boosted protease inhibitors (bPI) plus MVC [10-12].

Indeed, in the GUSTA study [10] the 8 subjects who failed the dual combination of DRV/r and MVC at week 48, mainly due to adherence issues, did not develop resistance to either drug. The results in general are similar to our study but in our population viral replication was ongoing at baseline.

Another possible option has emerged during the observation period, but the analysis in a poorly adherent population has not been performed yet. The MOBIDIP Study, conducted in Africa in subjects harbouring the M184V mutation, compared bPI monotherapy versus dual lamivudine(3TC)/bPI regimens, showing superior efficacy of the dual regimen at 96 weeks [13]. However, in the 3TC/bPI group 83% of the subjects had HIV-1 RNA <50 copies/mL at baseline.

Evident biases of our study are the small patient population and the absence of a randomized control arm, although the durable suppression of HIV-1 replication was absolutely unexpected given the history of drug failures of this population [7].

The rapid failure on DTG/DRV/r does not seem to reflect an instrinsic inferior potency of the association, as showed in other studies [14], but rather a predictable dramatic consequence of poor adherence (in this case constantly 75 to 80%).

	Baseline	Week 4	Week 12	Week 24	Week 36	Week 48	Week 52	Week 60*	Week 72	Week 84	Week 96	Week 108	Week 120	Week 134	Week 144	Week 156
Global population	N=44	N=44	N=44	N=44	N=44	N=44	N=44	N=43	N = 43	N=43	N=43	N=27	N=27	N=27	N=27	N=27
Population with HIV-1 RNA >200 copies/mL	N=20	N=14	N=5	N=5	N=5	N=3	N=3	N=3	N=3	N=2	N=3	N=1	N=2	N=1	N=1	N=1
RT gene mutations (n)	41L (3) 65R (4) 70R (3) 103N (5) 108V (1) 184V (39)			Pt1. 167K>R Pt2. 178>L/V Pt3-5 NE		Pt1. 207Q>A Pt2-3 NE					Pt2. 47I ATT>ATC Pt1,3 NE		NE		NE	NE
Protease gene mutations (n)	20R (8)			Pt1. 7Q>P; 18Q>T; 56K AAA >AAG Pt2. 31T ACA>ACU; 66V, GUA>GUC Pt3. 12T>A; 17G GGG>GGA; 44P CCA>CCC Pt4,5 NE		Pt2. 99F TTT>TTC Pt1,3 NE		NE		NE	NE		NE		NE	NE
Tropism (FPR, %; range)	64% (36%-79 %)					77,5% 53,5% 41%		76,6%			73,2% 53,8% 40,1%		53,2%, 42%		54,2%	54,2%
INSTI-associated mutations								72 123 124*		97A 140S 148H*						

RT=reverse transcriptase; FPR=False Positive Rate; INSTI=Integrase Strand Transer Inhibitor; NE=no evolution
*Week 60 genotype is available only for the patient who switched to boosted darunavir plus dolutegravir

Table 2: Genotypic evolution of the population maintaining HIV-1 RNA>200 copies/mL.

Conclusion

The association of bPIs plus MVC yielded unexpectedly high suppression of viral replication with only minor genotypic evolution in 6 subjects, allowing the whole cohort to remain eligible to long-acting cabotegravir and rilpivirine.

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