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Switch to dolutegravir and unboosted atazanavir in HIV-1 infected patients with undetectable viral load and long exposure to antiretroviral therapy

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SUMMARY

We evaluated efficacy and safety of a two-drug regimen including dolutegravir (DTG) and unboosted atazanavir (uATV) in 151 HIV-1 infected patients with HIV-RNA >50 copies/ml.

During a median follow-up of 62 (42-97) weeks, 2 VFs (1%) and 13 treatment discontinuations (9%) occurred; the 48-week probability of VF was 0.8% (95% CI=0.2%-5.6%) .

Switch to DTG+uATV may represent a boosting and RTIs sparing option in subjects with long exposure to ART and risk of cardiovascular disease.

Keywords: HIV; two-drug regimen; dolutegravir; unboosted atazanavir; switch

In HIV-1 infected subjects on virological suppression, two-drug regimens based on dolutegravir (DTG) plus one transcriptase reverse inhibitor (RTI) have shown encouraging efficacy and safety results [1-6]. Up to date, limited data are available on two-drug regimens based on DTG plus boosted darunavir or atazanavir (ATV) [7-9].

A randomized study in healthy adult subjects documented that the co-administration of DTG 30 mg QD with unboosted ATV (uATV) resulted in increased plasma DTG AUC, C_{max}, and $C_{through}$ by 91%, 50% and 180%, respectively, without substantial modification of ATV levels [10]. Previous studies have evidenced the efficacy of antiretroviral regimens including uATV [11-14] and several guidelines [15-17] suggest that a switch from ATV/r or ATV/c to uATV may be planned in order to reduce side effects such as hyperbilirubinemia, hypercholesterolemia and hypertriglyceridemia.

The increased exposure to DTG, when given in association with unboosted ATV, the high genetic barrier of DTG plus uATV, as well as the favorable impact of both ATV [18] and hyperbilirubinemia [19-20] in reducing cardiovascular risk, prompted us to evaluate the efficacy and safety of a two-drug regimen including **D**olutegr**A**vir plus **U**nboosted atazanavir (DAU study).

Multicenter, retrospective study including adult, HIV-1 infected patients, with a negative HBV surface antigen, who switched to DTG plus uATV two-drug regimen from 1st December 2014 to 30th January 2018 while with HIV-RNA<50 copies/mL. Any dosage of DTG and uATV was considered. The study protocol was approved by the Ethic Committees of the participating centers; all patients provided written informed consent.

Virological failure (VF) was defined by the occurrence of two consecutive values of HIV-RNA ≥50 copies/mL.

Treatment failure (TF) was defined by the occurrence of VF or discontinuation of at least one drug for any reason.

Adherence was routinely assessed from patient's self-report during follow-up visits by the referring physicians.

Patients' follow-up accrued from the start of the two-drug regimen (baseline) to VF or discontinuation or last available visit, whichever occurred first.

Results were described as median (quartiles) of frequency (%), as appropriate.

The Kaplan Meier method was applied to estimate time to VF and TF, with the corresponding 95% confidence intervals (95% CI). Univariate mixed linear models with random intercepts and random slopes were calculated to estimate changes in laboratory parameters over time.
All the statistical tests were two-sided at 5% level, and performed using SAS Software (release 9.4; SAS Institute).

A total of 151 patients were included in the study; baseline characteristics are reported in Table 1. At the time of switch, 40 (26.6%), 24 (15.9%), 24 (15.9%) were already receiving DTG, ATV/r or uATV, respectively, and the most frequent RTIs included in the regimen were: lamivudine (65%), emtricitabine (38%), tenofovir (42%), abacavir (22%).

The large majority of subjects (72.6%) switched to DTG 50 mg QD and uATV 400 mg QD. During a median follow-up of 62 (42-97) weeks, 2 VFs were observed: the first VF occurred at week 25 (77 and 51 HIV-RNA copies/mL) in a patient who subsequently re-achieved HIV-RNA ≤50copies/mL without regimen modification; the genotypic resistance test performed at VF showed the presence of one NNRTI polymorphic accessory mutation (the E138A); no primary resistance-associated mutations for NRTI, NNRTI, PI or INSTI were detected. The second VF occurred at week 60 (127 and 749 HIV-RNA copies/mL) in a patient with a laryngeal carcinoma, who stopped ART due to difficulties swallowing pills and died shortly after; due to the severe clinical conditions of this patient, the genotypic resistance test was not performed at VF. The estimated VF probabilities were 0.8% (95% CI: 0.2%-5.6%), 0.8% (95% CI: 0.2%-5.6%) and 2.1% (95% CI: 0.5%-8.3%) at 24, 48 and 96 weeks, respectively. Thirteen (8.6%) TFs occurred after 16 (8-48) weeks and included: 1 VF, 2 discontinuations for physician decision (1 for non-consecutive viral blips, 1 for persistent low ATV concentration despite undetectable viral load) and 10 for adverse events: 2 deaths (1 sepsis and severe pneumonia and 1 laryngeal carcinoma), 1 insomnia and dizziness, 1 gastro intestinal disorders, 1 hypercholesterolemia , 5 hyperbilirubinemia (2 grade 3 and 3 grade 4, ranging from 3.70 to 7.06 mg/dL).

Seven patients discontinued both DTG and uATV, 3 patients stopped only ATV, 2 patients stopped only DTG and 1 patient maintained the ongoing dual regimen (DTG 50 mg QD plus uATV 400 mg QD) and spontaneously achieved virological suppression. Overall, the estimated probabilities of TF were 5.5% (95% CI: 2.8%-10.7%), 7.1% (95% CI: 3.9%-12.8%), and 12.3% (95% CI: 6.6%-22.4%) at 24, 48 and 96 weeks since BL, respectively. CD4+ cell count didn't change over time (slope= +1.5 cells/μL/month, p=0.226), as well as CD8+ cell count (slope=-2.9 cells/μL/month, p=0.236) and CD4+/CD8+ ratio (slope= -0.027

per month, p=0.408). A mild increase in creatinine (slope= 0.009 mg/dL/month, p<0.0001) and a decrease in and eGFR (slope= -0.65 ml/min/1.73m2/month, p<0.0001) were observed. A significant decrease in total cholesterol (slope= -0.65 mg/dL/month, p=0.018), triglycerides (slope= -1.64 mg/dL/month, p=0.020), fasting glucose (slope= -0.55 mg/dL/month, p=0.0002) were also observed. No significant variation were found with regard to total bilirubin (slope= -0.002 mg/dL/month, p=0.844).

Our study showed that, among HIV-1 infected subjects on virological suppression and treated with a DTG+uATV two-drug regimen, only 2 confirmed virological failure occurred. Virological efficacy is similar to that reported for other two-drug DTG-based maintenance regimens, showing high rates of virological suppression mainly at 24, 48 weeks [1-9].

It is plausible that the exposure to high DTG concentrations by ATV boosting [10], the high antiviral activity and high genetic barrier of the DTG+uATV regimen may have contributed to this success, suggesting that this regimen may be considered when the simplification to other, simpler, two-drug RTI-based regimens, could be risky because of previous virological failure or accumulation of RTI associated resistance mutations [21-22]. The antiviral activity and the higher genetic barrier of DTG may also explain the differences in efficacy that have been observed in our study in comparison to other studies with raltegravir/uATV. Based on the hypothesis that ATV could boost raltegravir by inhibiting UGT1, two previous studies evaluated the efficacy of two-drug regimens with raltegravir + ATV in treatment-experienced HIV-1 infected patients, on virological suppression (HIV-RNA<50 copies/mL), and showed high rates of virological failures [23-24].

A low number of treatment discontinuations (9%) and few drug-related discontinuations (3%) occurred, mainly attributable to atazanavir (hyperbilirubinemias); interestingly and differently from other reports [25], only one subject discontinued for neuropsychiatric side effects. Taken together, these findings outline the possible added value of a boosting and RTIS sparing antiretroviral option in this demanding population.

The main study limitations are the retrospective design and the absence of a control group; the major strengths rely on the novelty of the evaluation of the DTG+uATV two-drug regimen, on the study population characterized by an older age, a long exposure to ART and a significant risk of cardiovascular disease.

In this context the switch to a two-drug regimen with DTG+uATV may be a reasonable therapeutic option in HIV-1 allowing to spare both boosting and RTIs.

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S.R., R.G., S.B., G.M., M.E.Q.R., N.L., S.C., A.C., S.D.G., M.M. and A.R. contributed to the development of the study design and provided the data in the eCRF.

L.G. and A.P. performed the statistical analyses and wrote the first draft of the manuscript.
All the authors evaluated the study results, reviewed and edited the manuscript and gave the final approval for the final version of the manuscript submitted for publication.

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Conflicts of interest

L.G., A.P., R.G., S.B., G.M., M.E.Q.R., N.L., S.C., A.C., S.D.G., M.M. have none to declare.

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Table 1. DAU Study: Characteristics of the 151 patients on virological suppression who switched to DTG+uATV regimen

Characteristic	Median (IQR) or frequency (%), (n=151)
Age *(years)*	52.9 (47.0 – 59.0)
Male gender	113 (74.8%)
White race	138 (91.4%)
Positive HCV serology	33 (22.0%)
Years since HIV diagnosis	16.8 (9.9 – 23.9)
C3 CDC stage	19 (12.7%)
Nadir CD4+ *(cells/μL)*	197 (99 – 296)
Pre-ART viral load (log_{10}*copies/mL*)	5.06 (4.70 – 5.44)
Exposure to ART (*years*)	14.6 (8.9 – 19.1)
Years with HIV-RNA <50 copies/mL	3.7 (2.0 – 6.2)
Reason for switch to DTG+uATV regimen	
Toxicity, overall	85 (56.3%)
Concern of cardiovascular disease	39 (25.8%)
Simplification	41 (27.2%)
Drug-drug interaction	8 (5.3%)
Other causes	17 (11.3%)
ART regimen at the time of switch	
NNRTI-based	12 (7.9%)
PI-based	65 (43.0%)
INSTI-based	74 (49.1%)
Anchor drugs at the time of switch	
NNRTI	12 (7.9%)
Rilpivirine	8 (5.3%)
Nevirapine	2 (1.3%)
Efavirenz	2 (1.3%)
PI	65 (43.0%)
Atazanavir/ritonavir	24 (15.9%)
Atazanavir	24 (15.9%)
Darunavir/ritonavir	8 (5.3%)
Lopinavir/ritonavir	7 (4.6%)
Fosamprenavir/ritonavir	2 (1.3%)
INSTI	74 (49.1%)
Dolutegravir	40 (26.6%)
Raltegravir	32 (21.2%)

Characteristic	Median (IQR) or frequency (%), (n=151)
Elvitegravir	2 (1.3%)
CD4+ *(cells/μL)*	701 (530 - 909)
CD8+ *(cells/μL)*	847 (578 - 1159)
CD4/CD8 ratio	0.82 (0.5 - 1.1)
Total cholesterol *(mg/dL)*	189 (156.5 - 222.5)
HDL cholesterol *(mg/dL)*	47 (40 - 60)
LDL cholesterol *(mg/dL)*	106.5 (86 - 136.5)
Triglycerides *(mg/dL)*	129 (85 - 188)
Creatinine *(mg/dL)*	0.97 (0.8 - 1.08)
eGFR *(ml/min/1.73m^2)*	88 (71 - 102)
Fasting glucose *(mg/dL)*	92 (84 - 99)

Abbreviations: ART, antiretroviral therapy; DTG, dolutegravir; uATV, unboosted atazanavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, Integrase strand inhibitor.