Cerebrospinal fluid markers in long-term atazanavir/ritonavir monotherapy

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Background

Central nervous system (CNS) viral escape is a concern in ritonavir boosted protease inhibitors monotherapy[1]. Aim was to assess viral escape and immuneactivation marker levels in the cerebrospinal fluid (CSF) of patients on successful long-term atazanavir/ritonavir (ATV/r) monotherapy.

Methods

MODAt (NCT01511809)[2] is a multicentric, randomized, open-label, non-inferiority trial. Patients on ATV/r 300/100mg+2 N(t)RTIs since ≥48 weeks, virologically suppressed since ≥24 weeks, were randomized to ATV/r monotherapy (Arm A) or to maintain ATV/r +2N(t)RTIs (Arm B).

Table 1. Patients characteristics at baseline

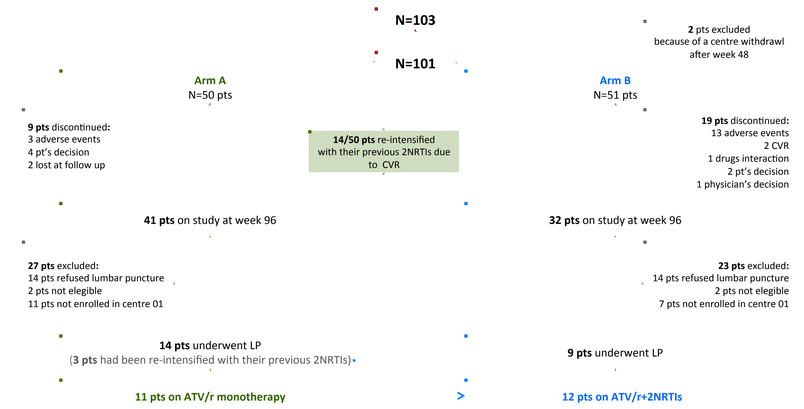
	ATV/r monotherapy N=11	ATV/r + 2N(t)RTIs N=12	p	All N=23
Age	42 (37-50)	43 (41-47)	0.926	43 (38-47)
Male gender (nr, %)	11 (100%)	11 (92%)	0.999	22 (95%)
Years from HIV diagnosis	6 (4-8)	4.5 (3-6.5)	0.352	5 (4-7)
Nadir CD4+ (cells/µL)	282 (228-363)	347 (315-419)	0.103	334 (268-366)
Pre ART HIV-RNA (log10 c/mL)	4.76 (4.05-5.60)	4.88 (4.58-5.32)	0.735	4.86 (4.49-5.43)
Current CD4+ (cells/µL)	641 (464-812)	586 (485-673)	0.644	599 (467-699)
AIDS	0	0	-	0
HCV infection (nr, %)	1 (9%)	3 (25%)	0.590	4 (17%)
Duration of current ART (months)	26.3 (19.5-70.5)	25 (17.9-45)	0.518	25.2 (19.5-54.0)
Duration of HIV-RNA <50 c/mL (months)	20.7 (13.7-65.5)	19.3 (12.1-39.6)	0.518	19.5 (13.7-48.7)

Median (interquartile range IQR) are reported. P values were calculated with Wilcoxon rank sum or Fisher exact test, as appropriate

This was a monocentric sub-study. Fifty-one/103 (49%) screened patients were eligible to this substudy (enrolled in centre 01, HIV-RNA viral load <50 c/mL at ≥96 study weeks, no contraindication to lumbar puncture (LP) or magnetic resonance imaging [MRI]), including 14 patients randomized to ATV-r monotherapy, who, according to protocol, re-intensified with their previous 2 NRTI for confirmed viral rebound (two consecutive plasma HIV-RNA>50 copies/mL) and re-suppressed viremia within 12 weeks. Twenty-three/51 (45%) eligible patients consented to LP, including 3 patients, initially randomized in Arm A, with re-intensification at week 8, 24 and 48, respectively, that were considered in Arm B for analysis. (Figure 1) Paired CSF and plasma samples were collected, after MRI evaluation, to assess HIV-RNA and immuneactivation markers (soluble CD14 [sCD14] and CD163 [sCD163], interleukin 6 [IL6], CCL2, CXCL10) by ELISA. Baseline demographic and clinical data are shown in Table 1**.** Results are expressed as median (interquartile range, IQR) or frequency (%).

Variables were compared by Wilcoxon rank sum or Fisher exact test, as appropriate; Spearman correlation coefficients were calculated to test linear relationships between biomarkers.

Figure 1. MODAt study (NCT01511809) flow chart



Abbreviations: Pt(s)=patient(s), CVR= confirmed viral rebound, LP= lumbar puncture
Three pts with early re-intensification underwent LP and were considered in Arm B in this substudy (blue arrow)

Results

We evaluated 23 patients: Arm A=11, Arm B=12. (Table 2)

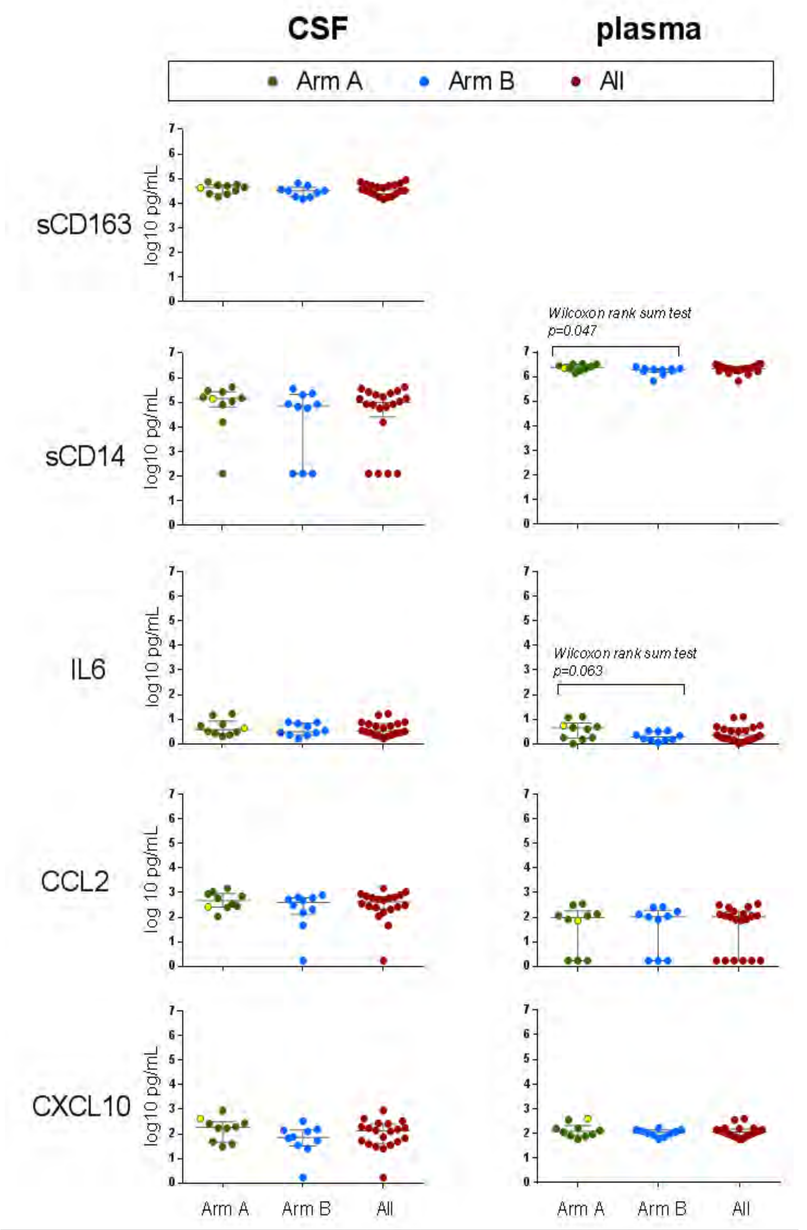
Table 2. Patients characteristics at the time of lumbar puncture

	ATV/r monotherapy N=11	ATV/r + 2N(t)RTIs N=12	p	All N=23
Study week	123 (109-138)	124 (115-133)	0.758	123 (110-134)
Neurological symptoms	0	0	-	0
MRI abnormalities	4 (36%)	4 (33%)	0.998	8 (38%)
CSF HIV-RNA >50 c/mL	1 (9%, 114 c/mL)	0	-	1 (4.3%)
Plasma HIV-RNA <50 c/mL	11 (100%)	12 (100%)	-	23 (100%)
CD4+ (cells/µL)	691 (544-836)	680 (580-813)	0.975	691 (544-836)
CSF mononuclear cells (cells/µL)	2 (1-4)	1 (1-2)	0.056	1.5 (1-3)
CSF Glucose (mg/dL)	63 (62-68)	61 (59-64)	0.156	63 (60-64)
CSF Protein (mg/dL)	36 (27-49)	34 (30-39)	0.669	35 (30-45)

Median (interquartile range IQR) are reported. P values were calculated by Wilcoxon rank sum or Fisher exact test, as appropriate

HIV-RNA was detected in CSF of no patients on triple therapy and of one on monotherapy (study week 120, nadir CD4+ of 311 cells/µL, two HIV-RNA blips of 94 and 99 c/mL during the study). In this latter patient treatment was re-intensified with 2NRTI backbone with suppression of CSF HIV-RNA replication at a 12 weeks follow up. CSF cell number (normal range ≤1 cell/µL) was slightly higher in the monotherapy arm (Table 2). CSF biomarker levels did not differ between the two arms (Figure 1). Overall (Figure 2), CSF sCD14 was significantly correlated with plasma sCD14 (r=0.50, p=0.016) and CSF IL6 with plasma IL6 (r=0.70, p<0.001).

Figure 2. CSF and plasma biomarkers



Green dots: ATV/r monotherapy (arm A), blue dots ATV/r+2N(t)RTIs (arm B), red dots: all patients, yellow dots: patient with detectable CSF HIV-RNA. Median and IQR values are shown

Conclusions

Asymptomatic CSF viral escape was uncommon in a small number of patients receiving long-term, successful ATV/r monotherapy and was effectively controlled by re-intensification with 2N(t)RTI.

Immune activation was not substantially different between patients on ATV/r monotherapy compared to triple therapy.

References. 1. Vernazza, P., et al. (2007) "**The role of compartment penetration in PI-monotherapy: the Atazanavir-Ritonavir Monomaintenance (ATARITMO) Trial.**" AIDS **21**(10): 1309-1315. 2.Castagna, A., et al.(2014) "**Simplification to atazanavir/ritonavir monotherapy for HIV-1 treated individuals on virological suppression: 48-week efficacy and safety results.**" AIDS **28**(15): 2269-2279