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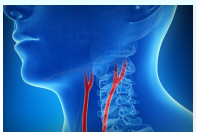

The Carinsti Group

Carotid wall thickness evolution after two years of first-line therapy with dolutegravir/abacavir/lamivudine or elvitegravir/cobicistat/tenofovir/emtricitabine

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Background

The effect of integrase inhibitor (INSTI)-based regimens on the carotid wall thickness has not been widely investigated. Apart from the ACTG A5260s [1], comparing raltegravir, darunavir and atazanavir, and a substudy of the NEAT022 [2] on the switch from protease inhibitors to dolutegravir, nothing has been presented to date on the international arena.

Methods

All subjects initiating a first-line regimen with dolutegravir/abacavir/lamivudine (D/A/L,Triumeq™) or elvitegravir/cobicistat/emtricitabine (E/C/F/T, Stribild™) between January 1, 2015 and January 1, 2016 have been retrospectively investigated, acquiring from the patients' record forms demographic and clinical data. Those who had undergone carotid Doppler ultrasound at baseline and within 96 – 120 weeks were analyzed through the two-tailed paired Student's t-test for intra-patient variations and through the unpaired t-test for comparison between the two groups. Inflammatory and atherogenic biomarkers were also analysed.

Results

Of 84 subjects taking D/A/L and 69 taking E/C/F/T, 22 and 20 had carotid ultrasound performed in window. The two populations differed for higher proportions in the E/C/F/T group of history of drug addiction, CDC stage C, more comorbidities, more cardiovascular agents and statin intake, but lower baseline serum glucose. The intima –media thickening at two years was comparable between the two groups, more evident at the internal carotid artery (ICA) and much lower than described in the ACTG A5260s. The D/A/L arm had sharper HIV-1 suppression (88.1% vs 56.6% with no virus detected at week 96, 92.9% and 95.7%, respectively having achieved <50 copies/mL), better reduction of inflammation, in terms of hs-RCP, while the E/C/F/T arm had better impact on Apo-A1, probably related to the activity of tenofovir. The main results are displayed in Tab.1.

Conclusions

Both INSTI-based regimens showed optimal viral suppression, good tolerability and a favourable impact on carotid intima media thickness, which evolved within the physiological age-adjusted rate [3]. D/A/L was associated with higher rate of virologic suppression to 'no virus detected' level. Overall, several baseline laboratory metabolic abnormalities returned in the range after treatment initiation.

Introduction

Until the commercial availability of dolutegravir (DTG), the choice of an antiretroviral class displaying a high genetic barrier to resistance, such as protease inhibitors, meant running the risk of increasing carotid wall thickness more rapidly compared to normal ageing. Therefore, the attractiveness of less drug regimens was hampered by their metabolic impact, in particular by the concern of worsening atherosclerosis.
Looking for scientific evidence on the impact of elvitegravir or dolutegravir on the arterial walls, we only found an *in vitro* study demonstrating that maraviroc (MVC) and DTG exert an anti-inflammatory effect on adult endothelial cells [4].
Therefore, we decided to investigate the rate of carotid ageing on naïve subjects initiating two different integrase strand inhibitors (INSTI)-based single tablet regimens.

Methods

All HIV-1 infected naïve subjects starting treatment with dolutegravir/abacavir/lamivudine (Triumeq™) or with elvitegravir/cobicistat/tenofovir diisoproxil/emtricitabine (Stribild™) January 1, 2015 and January 1, 2016 were retrospectively included in an observational cohort. The list of subjects was obtained by the Pharmacy Unit and the relative case record forms were investigated. Only those subjects who had undergone carotid Doppler ultrasound at baseline and within 96 – 120 weeks were analyzed through the two-tailed paired Student's t-test for intra-patient variations and through the unpaired t-test for comparison between the two groups. Virologic and immunologic data, blood glucose, creatinine, liver funcion tests, total and fractionated cholesterol, triglycerides, homocystein, hsCRP, apolipoproteins, insulin, C-peptide and glycosilated hemoglobin were also analysed.
Carotid ultrasound was performed with high-resolution B-mode with linear array transducer. The intima-media thickness (IMT) was measures at three different points in the common carotid wall 10-15 mm below the bifurcation in a range of 10 mm. All three measurements have been included in the analysis.

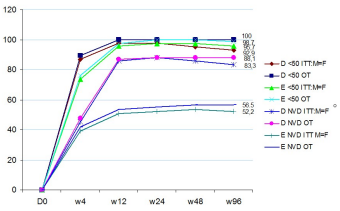
Population

Parameters	Triumeq™ n = 84	Stribild™ n = 69	P
EAge, median (range)	38.3 (20 – 62)	48 (27 – 71)	< 0.0001
Sex, F, n(%)	15 (18)	27 (39)	0.0003
Risk, % Het : MSM : TD : Other	30.9 : 47.6 : 14.3 : 7.2	36.2 : 21.8 : 42 : 0	0.006
Ethniacity n (%) Caucasian : Africana: Asian: Hispanic : Other	71.4 : 5.9 : 3.6 : 16.7 : 2.4	85.5 : 7.2 : 5.8 : 1.5	0.04
Days from HIV disgnosis to treatment start, median (range)	56 (7 – 536)	9 (3 – 28)	< 0.0001
Stadio CDC C, n (%)	9 (10.7)	17 (24.6)	0.01
HCV, n (%)	9 (10.7)	24 (34.8)	0.001
HBV, n (%)	0	8 (11.6)	0.003
Comorbidities, n (%), details	19 (22.6) psyc 7, osteop.2, diabetes1, CV 1, neuro 1, COPD 1, LES 1, kidney transplant 1	26 (37.7) CV 18, dyslipidemia 9, nephrolitiasis 1, GE RD1, spastic colon1	NS
Comedications, n paztentis(%), details	84 (100) colecalcipherol 81, psychotropics 22, immunosupp 2, Antibiotic prophylaxis 4	69 (100) colecalcipherol 63, CV 15, statins 19, antibiotic prophylaxis 17, PPI 4	NS
Study treatment discontinuation, n (%), detail	6 (7.1) pt7doctor choice2, tox GI 1, rash 1, semplif DTG/3TC 1, lost 1	3 (4.3) tGI ox 2, failure 1 with INSTI RAMS E92Q Q148K	NS
Zenith HIV RNA, median [IQR]	164.925 [93.671 – 305.920]	134.527 [87.386 – 278.641]	NS
Nadir CD4, median [IQR]	202 [127 - 312]	187 [113 – 298]	NS
Baseline serum glucose, median [IQR]	101.2 [86 – 129]	92.5 [85 – 105]	0.007
Baseline serum creatinine, median [IQR]	0.95 [0.89 – 1.1]	0.8 [0.6 - 1]	NS
Baseline MDRD, median [IQR]	94.3 [72.7 – 112.5]	109.7 [69.9 – 131.2]	NS
Baseline AST, median [IQR]	33.3 [8 – 51]	39.4 [11 – 54]	NS
Baseline AST, median [IQR]	31.8 [16 – 58]	51.5 [23 – 89]	0.002
Baseline total cholesterol, median [IQR]	205.5 [183 - 236]	202.5 [181 - 229]	NS
Baseline HDL cholesterol, median[IQR]	37.4 [29 - 45]	35.4[26 - 43]	NS
BaselineLDL cholesterol, median[IQR]	131.6 [102 - 159]	129.6 [92 - 160]	NS
Baseline triglycerides, median[IQR]	129.7 [91 - 162]	105 [67 - 148]	NS

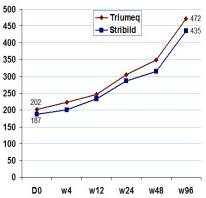
Subpopulation with carotid ultrasound

Parameters	Triumeq™ , n = 22	Stribild™ , n = 20	P
Age, median (range)	41.4 (36 – 51)	44 (33 – 50)	NS
Sex, F, n(%)	8 (36.4)	9 (45)	NS
Risk, % Het : MSM : TD : Other	31.8 : 40.9 : 27.3	35 : 25 : 40	0.043
Ethnicity, n (%) Caucasian : African : Asian: Hispanic : Other	100 : 0 : 0 : 0 : 0	95 : 0 : 0 : 5 : 0	NS
Days from HIV diagnosis to treatment start, median (range)	26 (7 – 124)	8 (3 – 23)	0.006
CDC stage C, n (%)	3 (13.6)	4 (25)	0.02
HCV, n (%)	3 (13.6)	4 (25)	0.02
HBV, n (%)	0	0	NS
Comorbidities, n (%), detail	5 (22.7) osteop.2, diabetes 1, CV 1, COPD 1	7 (35) CV 5, dyslipidemia 7, GERD 1, spastic colon 1	0.033
Comedications, n patients (%), detail	22 (100) colecalcipherol 22, psychotropics 4	20 (100) colecalcipherol 20, statins 12, CV 6, antibiotic prophylaxis 6, PPI 4	0.006
Zenith HIV RNA, median [IQR]	115.468 [95.403 – 204.579]	109.067 [91.554 – 227.832]	NS
Nadir CD4, median [IQR]	217 [159 - 288]	203 [137 – 271]	NS
Baseline serum glucose, median [IQR]	101 [94 – 118]	94 [88 – 100]	0.008
Baseline serum creatinin, median [IQR]	0.95 [0.89 – 1.1]	0.8 [0.6 - 1]	NS
Baseline MDRD, median [IQR]	97 [77.3 – 106.9]	103 [74.5 – 111.3]	NS
Baseline AST, median [IQR]	32 [13 – 47]	36.4 [15 – 49]	NS
Baseline ALT, median [IQR]	33 [19 – 51]	37.8 [25 – 55]	NS
Baseline total cholesterol, median [IQR]	201 [188 - 221]	200 [192 - 219]	NS
Baseline HDL cholesterol, median [IQR]	37 [31 - 42]	38 [32 - 43]	NS
Baseline LDL cholesterol, median [IQR]	126 [107 - 132]	125 [99 - 130]	NS
Baseline triglycerides, median [IQR]	121 [96 - 141]	108 [85 - 137]	NS
Baseline CC IMT, median [IQR]	0.625 [0.515 - 0.730]	0.5 [0.475 - 0.655]	NS
Baseline homocistein, median [IQR]	7.15 [5.9 - 9.05]	6.1 [4.82 - 7.9]	0.0478
Baseline C-RP, median [IQR]	1.7 [0.9 - 2.3]	1.7 [1.1 - 2.4]	1
Baseline APO-A1, median [IQR]	1.47 [1.23 - 1.52]	1.2 [1.08 - 1.4]	0.0402
Baseline APO-B, median [IQR]	1.3 [1.15 - 1.44]	1.41 [1.29 - 1.53]	NS
Baseline APO-B/APO.A1, median [IQR]	0.85 [0.73 - 0.96]	1.18 [1.11 - 1.49]	0.025
Baseline C-peptide, median [IQR]	2.85 [2.43 - 3.29]	3 [2.88 - 3.16]	NS
Baseline insulin, median [IQR]	12 [10.6 - 13.9]	16.1 [13.7 - 17.8]	0.049
Baseline glycosilated Hb, median [IQR]	33 [29 - 38]	32 [27 - 37]	NS
Baseline HOMA score, median [IQR]	2.96 [2.33 - 3.29]	4.11 [3.46 - 4.61]	NS

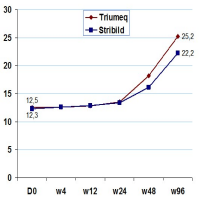
Proportion of subjects suppressing HIV RNA to <50 copies/mL and to 'no virus detected' (NVD)



CD4 /mmc



CD4 %



Entire population – D = dolutegravir, E = elvitegravir, ITT: M=F = intention-to-treat: Missing/Failure, OT = on treatment

Lab Triumeq™ entire population

Timelines	Glucose	Creatinine	MDRD	AST	ALT	TC	HDL	LDL	Tryglicerides	TG/HDL	LDL/HDL
Baseline	101.2±22.7	0.95±0.09	94.3±38.46	33.3±32.9	31.8±30.2	205.5±39.01	37.4±13.96	131.6±37.65	129.7±50.84	3,47	3,52
w24	97.3±19.1	0.90±0.55	91±35.27	32.4±35.5	29.4±27.9	203.1±33.97	38.2±14.18	127.2±34.44	123.3±48.16	3,22	3,33
w48	96.5±14.87	0.99±13.99	89.5±36.61	31.3±30.1	28.7±23.9	200.2±14.79	39.3±12.88	125.1±38.52	135.7±46.21	3,45	3,18
w96	91.8±11.08	0.98±15.4	90±32.64	31.1±24.1	27.9±23.8	198.6±11.01	38.5±13.06	126.9±33.19	126.5±45.58	3,28	3,3

Lab Stribild™ entire population

		Glucose	Creatinine	MDRD	AST	ALT	TC	HDL	LDL	Tryglicerides	TG/HDL	LDL/HDL
Baseline	ES	92.5±13.59	0.8±0.16	109.7±53.6	39.4±38.9	51.5±35.2	202.5±36.07	35.4±15.8	129.6±49.8	105±67.5	3,06	3,66
w24		92±13.20	0.83±0.16	105.1±57.1	36.1±37.2	44.8±33.9	188.5±34.81	39.7±16.81	90.5±51.16	132±68.12	3,32	2,28
w48		93.5±17.02	0.83±0.19	104.7±53.49	30.7±32.3	28.5±32.70	186±32.75	40.5±12.66	88.1±26.13	84.5±54.17	2,17	2,01
w96		96.4±17.05	0.85±0.21	101.4±17.05	30.2±22.7	26.8±26.6	187.3±33.88	40.2±16.51	90.1±47.38	86.6±53.59	2,14	2,15
Δ Triumeq		-9,6	0,03	-4	-2,2	-3,9	7	1,1	5,3	3,2	0,19	0,22
Paired T-test for Δ Triumeq		**<0.0001**	**<0.0001**	0,106	0,083	0,072		**0,034**	0,279	0,405	0,729	0,087	0,093
Δ Stribild		3,9	0,06	-8,3	-9,2	-24,7	15	5,8	39,5	28,4	0,92	1,51
Paired T-test for Δ Stribild		**<0.0001**	**<0.0001**	**0,017**	**0,023**	**<0.0001**		**0,001**	**0,0186**	**<0.0001**	**0,0092**	**0,031**	**0,013**
Δ Triumeq - Stribil		13,5	0,02	4,3	-7	-19,8	8	4,7	34,2	25,2	0,73	1,29
Unpaired T-test for Δ Triumeq - Stribild		**<0.0001**	0,531	0,352	0,087	**<0.0001**		**0,04**	**0,0391**	**<0.0001**	**0,0003**	**0,044**	**0,028**

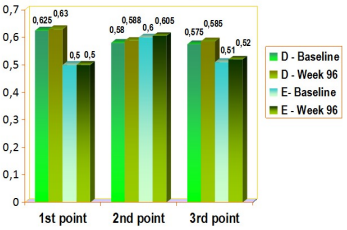
Carotid subgroup Triumeq™

Tot 22	IMT CC	IMT bulbo	IMT CI	Omocisteina PCR	Apo-A1	Apo-B	Apo-A1/Apo-B	Peptide C	Insulina	Hb glicata	Glicemia basale	HOMA score
Baseline	0.625±0.17	0.59±0.16	0.675±0.16	7.15±2.95	1.7±1.36	1.47±0.12	1.3±0.34	0,88	2.85±1.28	12±9.28	33±5.93	100.5±3.81	2,96
w 96	0.63±0.17	0.588±0.15	0.685±0.15	7.05±2.36	1.4±1.03	1.52±0.09	1.23±0.34	0,81	2.60±1.07	11.15±7.01	32.5±5.34	92.5±3.19	2,5
Δ	0,005	0,008	0,010	-0,1	-0,3	0,05	-0,07	-0,7	-0,15	-0,85	-0,5	-8	-0,46

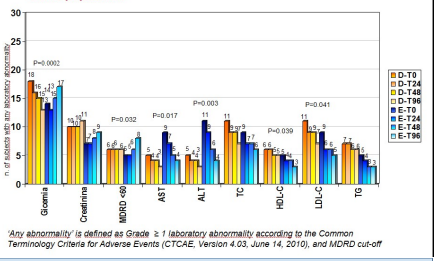
Carotid subgroup Stribild™

Tot 20	IMT CC	IMT bulbo	IMT CI	Omocisteina PCR	Apo-A1	Apo-B	Apo-A1/Apo-B	Peptide C	Insulina	Hb glicata	Glicemia basale	HOMA score
Baseline	0.5±0.13	0.6±0.16	0.51±0.16	6,1±4,08	1,7±1,28	1,2±0,29	1,41±0,44	1,17	3±0,31	16.1±4.84	32±6.74	104.1±4.11	4,11
w 96	0.5±0.16	0.605±0.16	0.52±0.15	6,7±2,23	2,1±0,94	1,29±0,42	1,38±0,43	1,07	3,3±0,13	15.6±4.15	32.8±8.18	103.5±3.27	4,07
Δ	0	0,005	0,010	0,6	0,4	0,09	-0,03	-0,10	0,3	-0,5	0,8	-0,5	-0,04
Paired T-test for Δ Triumeq	0,473	0,429	0,381	0,8	**<0.0001**		0,176	0,066	**<0.0001**		0,106	0,081	0,472	0,094	0,075
Paired T-test for Δ Stribild	1	0,475	0,384	0,117	**<0.0001**		**0,017**	0,245	**<0.0001**		0,077	0,126	0,297	0,876	0,732
Unpaired T-test for D Triumeq - Stribild	Δ = 0.005	0,003	0	-0,7	-0,7	-0,04	-0,04	0,03	-0,45	-0,35	-1,3	-7,5	-0,42
	P =0.462	0,639	1	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**		**0,018**	0,058	0,294	0,186	0,126	0,103

Evolution of carotid IMT by week 96



Subjects displaying any laboratory abnormality over time – entire population



'Any abnormality' is defined as Grade ≥ 1 laboratory abnormality according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03, June 14, 2010), and MDRD cut-off

Conclusion

Both INSTI-based regimens showed optimal viral suppression, good tolerability and a favourable impact on carotid intima media thickness, which evolved within the physiological age-adjusted rate [3]. Many initial laboratory alterations tended to normalize over time in both regimens, except for creatinine and MDRD and for an increase in serum glucose in the Stribild™ group. Triumeq™ was associated with more frequent HIV RNA suppression to complete and stable non detectability. Treatment discontinuations occurred in two (2,4%) patients on Triumeq™ and in two (2,9%) patients on Stribild™.

References

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