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Evaluation of total HIV-DNA changes in HIV-1 infected patients who continue a 2-drug regimen with dolutegravir plus one reverse transcriptase inhibitor or switch to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide enrolled in the Be-OnE Study

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Purpose

To investigate changes in HIV-DNA through 48 weeks (W48) in virologically suppressed HIV-1 infected patients randomized to continue a 2-drug regimen (2DR) with dolutegravir (DTG) plus one reverse-transcriptase-inhibitor (RTI) or to switch to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF).

Methods

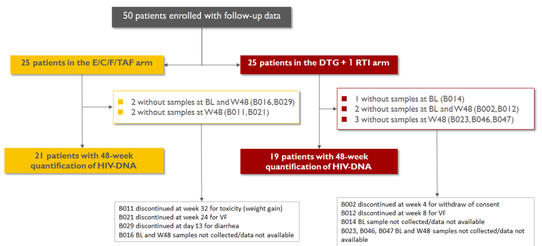
This is a randomized, single-center, open-label, 96-week superiority study (NCT03493568; Be-OnE Study). Patients with HIV-RNA <50 copies/mL for ≥6 months while receiving DTG plus one RTI for at least 3 months were randomized 1:1 to continue the ongoing treatment or to switch to E/C/F/TAF. Those with documented resistance to NRTIs or Integrase inhibitors were excluded.

One of the secondary end points of the study was to evaluate changes in HIV-DNA through W48. To achieve this purpose, total HIV-DNA was measured with a standardized in-house ddPCR-assay and normalized for 10^6 CD4+ T-cells. Spearman correlation coefficients (r_s) were calculated to assess linear relationship between HIV-DNA (log_{10} transformed) and several immunological parameters (including D-Dimer, C-reactive protein [CRP], %CD8+CD38+HLA-DR+, %CD4+CD38+HLA-DR+, CD4+ T-cells, CD8+ T-cells, CD4/CD8) both at baseline and at W48. Results were described by median (IQR) and n (%). Differences in HIV-DNA levels were evaluated by using Wilcoxon rank-sum test among patients within the same arm or the Mann-Whitney test between the two arms.

Results

HIV-DNA measurements at baseline and at W48 were available for 40/50 patients.

Be-OnE Study (NCT03493568) – Patients disposition



Virologic failure was defined as a confirmed rebound in plasma HIV-RNA levels ≥ 50 copies/mL.

Table 1 - Main characteristics of patients enrolled in the Be-OnE Study and assessed for ddPCR HIV-DNA

Variables	Overall (n=40)	E/C/F/TAF (n=21)	DTG +1 RTI (n=19)
Age *(years)*	51.4 (48.2 - 56.0)	54.1 (51.3 - 57.5)	48.9 (43.1 - 54.6)
Male gender	36 (90%)	20 (95%)	16 (84%)
HCV Ab positive	2 (5%)	1 (5%)	1 (5%)
CDC classification			
C2	2 (5%)	1 (5%)	1 (5%)
C3	5 (13%)	3 (14%)	2 (11%)
Years since first HIV diagnosis	11.4 (6.3 - 20.1)	15.1 (7.4 - 21.0)	7.7 (6.1 - 13.2)
Years since ART start	7.3 (4.9 - 17.3)	10.9 (5.3 - 16.8)	6.8 (4.5 - 17.9)
RTI in baseline ART			
3TC	35 (88%)	18 (86%)	17 (89%)
RPV	5 (13%)	3 (14%)	2 (11%)
Residual viremia	7 (18%)	5 (24%)	2 (11%)
Years since HIV-RNA <50 copies/mL	6.0 (4.1 - 9.8)	5.9 (3.8 - 9.4)	6.1 (4.2 - 10.0)
Months on 2DR	10.5 (7.3 - 18.0)	10.7 (7.7-17.1)	9.9 (5.9 - 20.7)
Nadir CD4+ count (cells/µL)	295 (213 - 397)	325 (260 - 399)	265 (204 - 389)
CD4+ (cells/µL)	724 (611 - 870)	792 (623 - 962)	704 (557 - 860)
%CD4+	35.7 (28.8 - 39.6)	38.0 (31.8 - 39.8)	31.9 (28.0 - 39.1)
CD8+ (cells/µL)	854 (684 - 1096)	858 (629 - 1100)	826 (778 - 1092)
%CD8+	39.4 (32.7 - 47.2)	38.9 (29.3 - 46.3)	41.9 (34.9 - 49.3)
CD4+/CD8+ ratio	0.85 (0.66 - 1.24)	0.89 (0.71 - 1.38)	0.80 (0.58 - 1.10)
%CD4+CD38+HLA-DR+	1.1 (0.7 - 1.3)	1.1 (0.2 - 1.5)	1.00 (0.70 - 1.20)
%CD8+CD38+HLA-DR+	1.3 (0.8 - 2.1)	1.5 (0.4 - 2.1)	1.30 (0.80 - 2.10)
CRP	1.2 (0.5 - 3.4)	2.2 (0.5 - 3.7)	0.9 (0.5 - 2.5)
D-dimer	0.27 (0.27 - 0.32)	0.27 (0.27 - 0.36)	0.27 (0.27 - 0.30)
Undetectable IL-6 (≤1.83 pg/mL)	29 (74%)	14 (70%)	15 (79%)

Results described by median (IQR) or n (%), as appropriate. Abbreviations. CRP: C-reactive protein; RPV: rilpivirine; RTI; reverse transcriptase inhibitor. 3TC: lamivudine.

Results

Overall, HIV-DNA was 2247 (767-4268) and 1587 (556-3543) copies/10^6 CD4+ T-cells at baseline and at W48, respectively, without any significant difference between arms (Table 2).
At W48, a modest decrease in HIV-DNA from baseline was observed in both arms: -226 (-1189; 890) copies/10^6 CD4+ T-cells (p=0.465) in the DTG+1RTI-arm and -137 (-983; 133) copies/10^6 CD4+ T-cells (p=0.334) in the E/C/F/TAF-arm, without significant differences between the two arms (p=0.968).

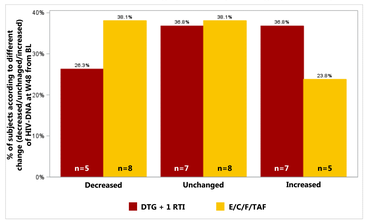
Table 2 - ddPCR HIV-DNA characteristics of patients enrolled in the Be-OnE Study

	HIV-DNA at BL *(copies/10^6 CD4+ T-cells)*	p-value*	HIV-DNA at W48 *(copies/10^6 CD4+ T-cells)*	p-value*	Change in HIV-DNA at W48 from BL *(copies/10^6 CD4+ T-cells)*	p-value*
Overall (n=40)	2247 (767 - 4268)		1587 (556 - 3543)	-	-162 (-1086; 611) p=0.264§	-
DTG+1RTI (n=19)	3077 (781 - 6030)	0.448	1922 (982 - 3804)	0.330	-226 (-1189; 890) p=0.465§	0.968
E/C/F/TAF (n=21)	1971 (632 - 3270)		1053 (458 - 3105)		-137 (-983; 133) p=0.334§	
With RV through 48 weeks of follow-up (n=16)	2168 (579 - 4922)	0.999	966 (478 - 6254)	0.793	-162 (-1202; 238) p=0.404§	0.999
With no RV through 48 weeks of follow-up (n=24)	2247 (898 - 4268)		1830 (1033 - 3138)		-177 (-1086; 849) p=0.403§	
DTG+1RTI with RV through 48 weeks of follow-up (n=5)	3225 (3077 - 6030)	0.547	5782 (883 - 6726)	0.488	414 (-2194; 3501) p=0.999§	0.611
DTG+1RTI with no RV through 48 weeks of follow-up (n=14)	2571 (781 - 4360)		1680 (1084 - 3171)		-229 (-983; 331) p=0.268§	
E/C/F/TAF with RV through 48 weeks of follow-up (n=11)	1190 (525 - 3813)	0.805	944 (458 - 3875)	0.751	-187 (-983; -67) p=0.067§	0.699
E/C/F/TAF with no RV through 48 weeks of follow-up (n=10)	2205 (1176 - 3270)		2246 (421 - 3105)		3 (-1534; 1220) p=0.999§	
With RV through 48 weeks of follow-up among treated with DTG+1RTI (n=5)	3225 (3077 - 6030)	0.428	5782 (883 - 6726)	0.497	414 (-2194; 3501) p=0.999§	0.821
With RV through 48 weeks of follow-up and E/C/F/TAF (n=11)	1190 (525 - 3813)		944 (458 - 3875)		-187 (-983; -67) p=0.067§	
With no RV through 48 weeks of follow-up and DTG+1RTI (n=14)	2571 (781 - 4360)	0.838	1680 (1084 - 3171)	0.977	-229 (-983; 331) p=0.268§	0.619
With no RV through 48 weeks of follow-up and E/C/F/TAF (n=10)	2205 (1176 - 3270)		2246 (421 - 3105)		3 (-1534; 1220) p=0.999§	

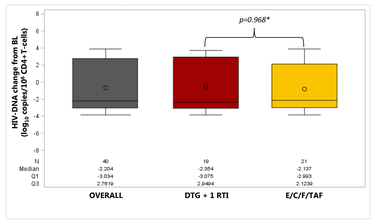
Results described by median (interquartile range, IQR) or n (%), as appropriate. Total HIV-DNA was quantified by Droplet Digital PCR (ddPCR). Viral load was assessed by standard Abbott Real time PCR; residual viremia (RV) was defined as any detectable HIV-RNA <50 copies/mL through week-48. Abbreviations. BL: baseline; DTG: dolutegravir; E/C/F/TAF: elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide; RV: residual viremia; No RV = target not detected; RTI: reverse transcriptase inhibitor; W48: week 48. *Mann-Whitney test; §Wilcoxon signed-rank test.

HIV-DNA slightly increased from baseline to W48 in some patients of both arms (DTG + 1 RTI: 7/19; E/C/F/TAF: 5/21, p=0.495). Interestingly, in the DTG + 1 RTI arm a >4-fold increase in HIV-DNA (15 to 429 and 320 to 1210 copies/10^6 CD4+ T-cells, respectively) was observed in two individuals.

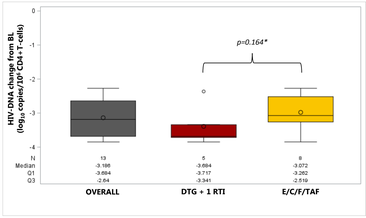
Patients stratified for HIV-DNA change (decreased/unchanged/increased) at W48



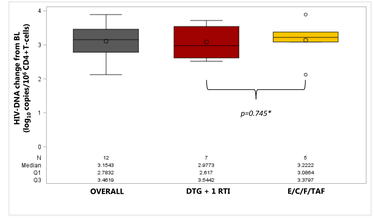
Change of HIV-DNA change from BL to W48, overall and stratified for treatment



Delta decrease of HIV-DNA from BL to W48, overall and stratified for treatment



Delta increase of HIV-DNA from BL to W48, overall and stratified for treatment

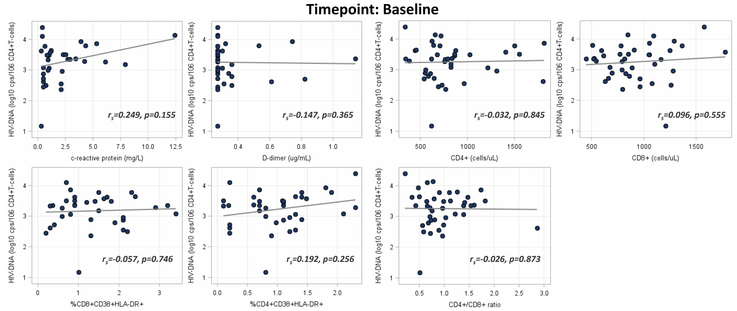


The following formula was used to estimate the extent of changes in HIV-DNA from BL to W48: (HIV-DNA at W48/HIV-DNA at BL)-1. HIV-DNA was considered decreased for reductions greater than -0.4, unchanged for variation between -0.4 and + 0.4, increased for increases greater than +0.4. Patients were grouped according to this stratification in HIV-DNA change.
*By Wilcoxon rank-sum test.

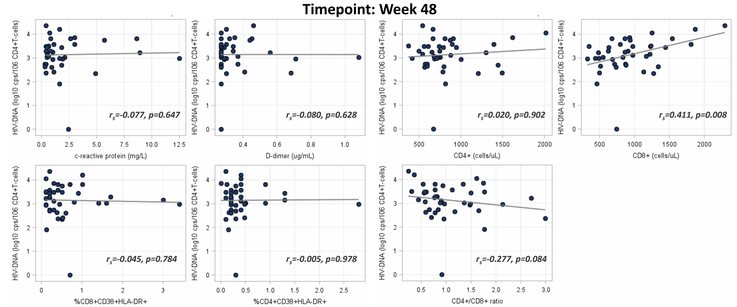
Results

No significant correlations were found between HIV-DNA levels and the immunological parameters, neither at baseline nor at W48, with the only exception of HIV-DNA levels at CD8+ T-cells at W48.

Timepoint: Baseline



Timepoint: Week 48



r_s: Spearman correlation coefficient.

Conclusions

Changes in HIV-DNA from baseline to W48 in virologically suppressed individuals who switch from a 2DR with DTG + 1 RTI to E/C/F/TAF did not significantly differ from changes in those who continue with the ongoing 2DR.

Acknowledgments

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