Switching from Kivexa [ABC/3TC]+Kaletra [LPV/r] to Truvada [TDF/FTC]+Kaletra [LPV/r] Reduces High Cholesterol: Results of a 12 Week Randomized, Controlled Study (ROCKET II)

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Background

- Dyslipidaemia contributes to cardiovascular risk in HIV patients
- Comparative studies suggest tenofovir DF based regimens have a favourable lipid profile relative to abacavir based regimens
- We sought to investigate if such changes are seen in hypercholesterolaemic patients when switched from ABC/3TC + LPV/r to TDF/FTC + LPV/r

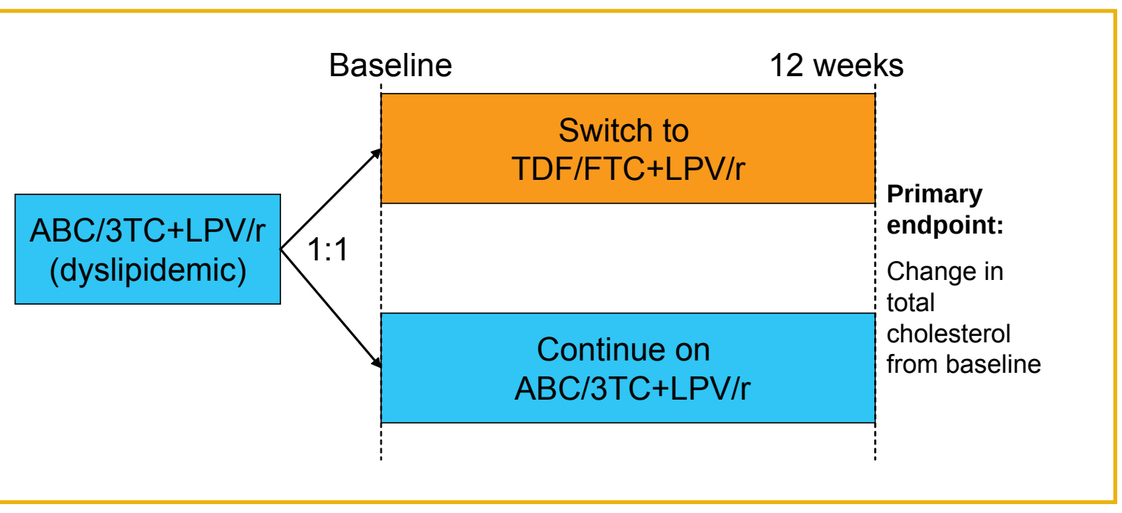
Objectives

- Primary Objective
  - Determine whether switching from ABC/3TC to TDF/FTC while maintaining LPV/r leads to a reduction in fasting total cholesterol (TC) after 12 weeks
- Secondary Objectives
  - Evaluation of fasting metabolic parameters (LDL directly measured, HDL, triglycerides, cholesterol ratios)
  - Evaluation of changes in the 10-year risk for coronary heart disease (CHD) outcomes as measured by Framingham Risk Score
  - Evaluation of efficacy and safety

Methods

- Virologically stable subjects on ABC/3TC+LPV/r for ≥ 6 months, with HIV RNA <50 copies/ml for ≥ 3 months and screening total cholesterol ≥ 5.2 mmol/L were randomized (1:1) to continue ABC/3TC+LPV/r or switch to TDF/FTC+LPV/r
- Analyses assessed changes in fasting metabolic parameters and 10 year-risk for CHD (Framingham equation). Numbers and percentages of subjects with CHD risk in the categories of < 10%, 10% to 20%, and > 20% were summarized at Baseline and Week 12
- All laboratory evaluations were done in a central lab
- This open-label, 2-arm controlled study was conducted in accordance with GCP

Figure 1. Study Design



Results

Baseline Characteristics

- 85 adult subjects were randomized in 29 sites in Spain, Italy, Germany and Austria

Table 1. Baseline Characteristics*

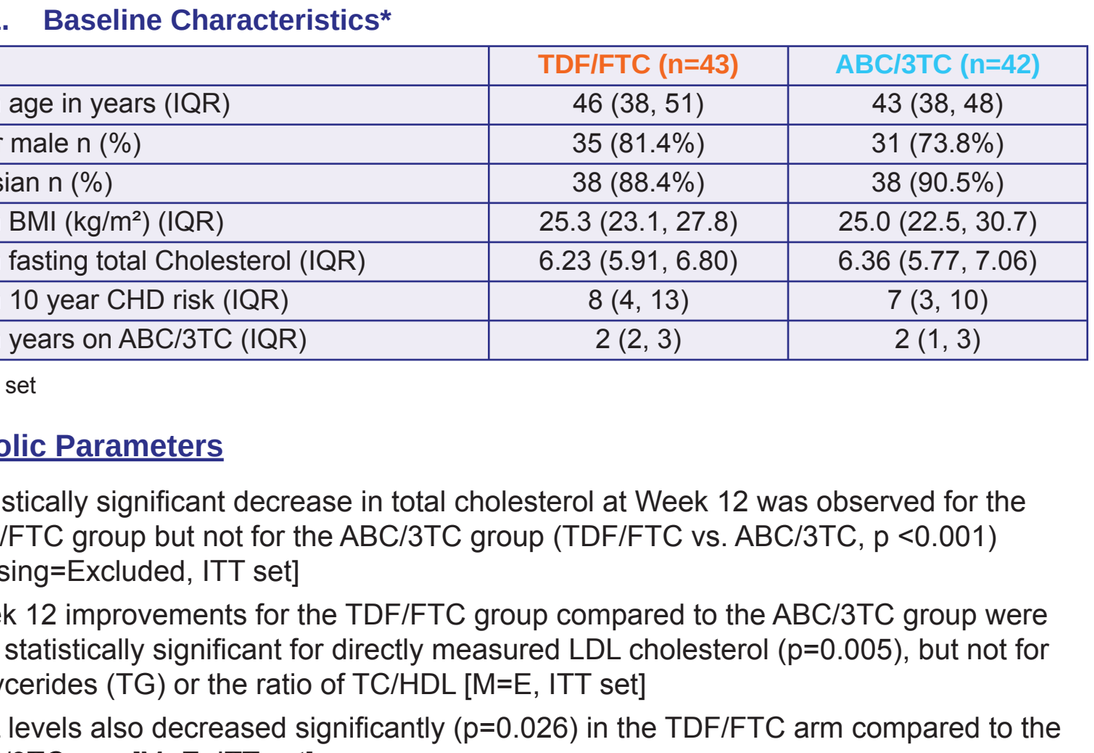
	TDF/FTC (n=43)	ABC/3TC (n=42)
Median age in years (IQR)	46 (38, 51)	43 (38, 48)
Gender male n (%)	35 (81.4%)	31 (73.8%)
Caucasian n (%)	38 (88.4%)	38 (90.5%)
Median BMI (kg/m²) (IQR)	25.3 (23.1, 27.8)	25.0 (22.5, 30.7)
Median fasting total Cholesterol (IQR)	6.23 (5.91, 6.80)	6.36 (5.77, 7.06)
Median 10 year CHD risk (IQR)	8 (4, 13)	7 (3, 10)
Median years on ABC/3TC (IQR)	2 (2, 3)	2 (1, 3)

* Treated set

Metabolic Parameters

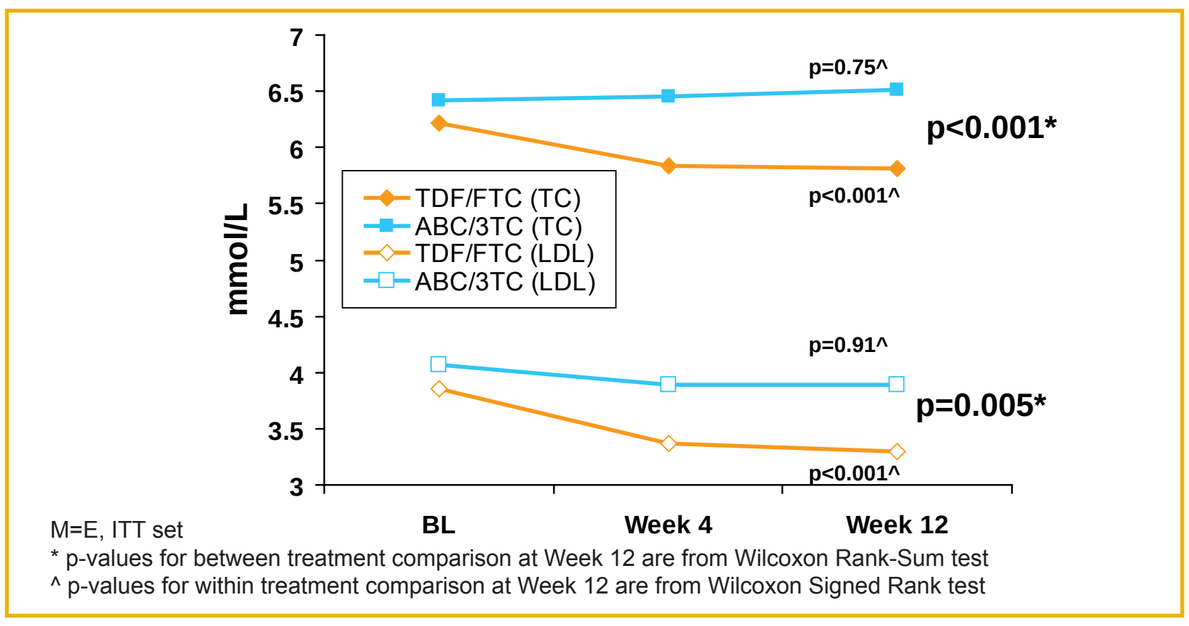
- Statistically significant decrease in total cholesterol at Week 12 was observed for the TDF/FTC group but not for the ABC/3TC group (TDF/FTC vs. ABC/3TC, p <0.001) [Missing=Excluded, ITT set]
- Week 12 improvements for the TDF/FTC group compared to the ABC/3TC group were also statistically significant for directly measured LDL cholesterol (p=0.005), but not for triglycerides (TG) or the ratio of TC/HDL [M=E, ITT set]
- HDL levels also decreased significantly (p=0.026) in the TDF/FTC arm compared to the ABC/3TC arm [M=E, ITT set]
- Results from analyses of last observed carried forward (LOCF) on ITT set and M=E on Treated set were consistent with the above

Figure 2. Lipid Profile of Median Change from BL at Week 12



Results (cont'd)

Figure 3. Median of Total Cholesterol and LDL (Directly Measured)



M=E, ITT set
* p-values for between treatment comparison at Week 12 are from Wilcoxon Rank-Sum test
^ p-values for within treatment comparison at Week 12 are from Wilcoxon Signed Rank test

10 Year CHD Risk

Table 2. Median 10 Year CHD Risk

10 Year CHD Risk (%)	TDF/FTC	ABC/3TC
Baseline median (IQR)	8 (4, 13)	7 (3, 10)
Week 12 median (IQR)	7 (4, 10)	6.5 (4, 10)

M=E, Treated set

- The median changes from Baseline were small but significantly in favour of TDF/FTC (TDF/FTC vs. ABC/3TC p=0.027)
- Categorising patients by the risk scores at Baseline and Week 12 showed a one-category downward shift in risk categories for five (13%) patients receiving TDF/FTC and two (5%) patients receiving ABC/3TC. One (3%) patient receiving TDF/FTC and two (5%) patients receiving ABC/3TC experienced a one-category upward shift in risk

Table 3. Shift Table 10 Year CHD Risk, BL to Week 12

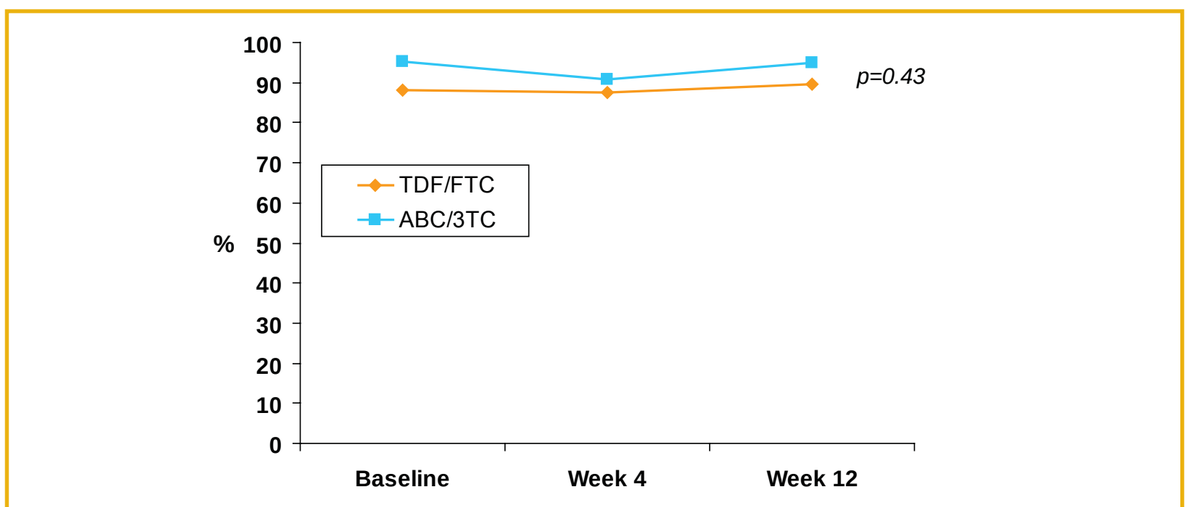
Change in Risk category	TDF/FTC (n=38) [n,%]	ABC/3TC (n=40) [n,%]
<10% unchanged	20 (53%)	24 (60%)
<10% ↗ 10-20%	1 (3%)	2 (5%)
10-20% ↘ <10%	4 (10.5%)	2 (5%)
10-20% unchanged	12 (32%)	11 (27.5%)
>20% ↘ 10-20%	1 (3%)	0
>20% unchanged	0	1 (2.5%)

M=E, Treated set

Efficacy and Safety

- Virological suppression was maintained in both groups (no difference in CD4 cell count or percentage of patients with HIV-RNA < 50 copies/mL)
- None of the patients experienced virological failure (2 consecutive post Baseline HIV RNA values ≥ 400 copies/mL)
- No new safety issues were identified, there were no clinically relevant changes from baseline for hematology and (nonlipid) chemistry parameters (including renal parameters) in either group

Figure 4. Patients with HIV-RNA< 50 copies/ml [%]



M=E, ITT set; p-value is from Fisher Exact Text
(some patients had isolated blips (HIV-RNA ≥50 copies/ml) at baseline and during the study)

Table 4. Median CD4 Cell Count

	Baseline		Week 12		TDF/FTC vs. ABC/3TC
	TDF/FTC	ABC/3TC	TDF/FTC	ABC/3TC	
Median CD4 count (cells/mm³) (IQR)	507 (386, 633)	525 (385, 718)	488 (366, 749)	555 (432, 755)	p=0.53

M=E, ITT set; p-value is is from Wilcoxon Rank Sum test

Conclusions

- **Switching from ABC/3TC (Kivexa) to TDF/FTC (Truvada) in patients with raised cholesterol**
  - **significantly and quickly reduces lipid parameters**
  - **reduces 10 year estimated CHD risk**
  - **maintains virologic control**

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