

Switching HIV-infected, suppressed patients from ABC/3TC to FTC/TDF improves lipids – the SETTLE study

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Background

- HAART is associated with lipid abnormalities and insulin resistance. Agents with fewer metabolic side effects may decrease the risk for potential cardiovascular disease in the treated HIV population.
- Two prospectively controlled switch studies that have shown improvements in lipids with tenofovir fixed-dose combination (TDF) over abacavir (ABC) are RAVE [UK]¹ and BICOMBO [Spain].²
- To date no investigations have demonstrated metabolic benefits when patients are switched from ABC to TDF.

Objectives

Switching Epzicom® To Truvada® for Lipid Evaluation (SETTLE) was a prospective, single-arm, open-label, 48-week trial examining the impact on fasting lipids of switching from abacavir (ABC)/lamivudine (3TC) fixed-dose combination tablets (Epzicom®) to emtricitabine (FTC)/tenofovir DF (TDF) fixed-dose combination tablets (Truvada®) in patients receiving triple agent HAART therapy. The third agent of the HAART regimen could be either a PI or NNRTI which remained unchanged.

Major Inclusion Criteria

- HIV-1 infected, treatment-experienced patients receiving ABC/3TC containing PI- or NNRTI-based HAART for ≥ 12 weeks.
- Patients must have HIV-1 RNA < 400 c/mL and no documented resistance to TDF/FTC.
- Receiving HAART containing ABC/3TC (EPZ) given once daily for ≥ 12 weeks – patients receiving ABC/3TC given BID may be included.
- Adequate renal function defined as the calculated creatinine clearance ≥ 50 mL/min according to the Cockcroft-Gault formula.
- No active opportunistic infection (OI) consistent with CDC definition within 30 days of screening.
- Only patients receiving lipid lowering agents at a stable dose prior to study entry.

Methods

- Subjects consented, enrolled, and followed prospectively for 48 weeks.
- Fasting lipids, CD4 cell count, and HIV-1 RNA evaluated at weeks 0, 4, 12, 24, 36, and 48.
- Primary Endpoint – Change from baseline in fasting total cholesterol at weeks 24 and 48.
- Secondary Endpoints:
 - Proportion of patients with plasma HIV-1 RNA < 400 copies/mL.
 - Change from baseline in CD4+ cell count at each study visit.
 - Change from baseline in clinical laboratory parameters including fasted triglycerides, direct HDL cholesterol, and LDL cholesterol.
- Statistical analysis: descriptive statistics to summarize patient demographics, baseline characteristics; repeated measures GLM and McNemar test for paired proportions to examine changes from baseline.

Results

Baseline Characteristics

n = 24			
Gender–n(%)		Weight (lbs)	
Male	22 (92)	median	183
Female	2 (8)	range	110-251
Race/Ethnicity–n(%)		BMI	
African American	15 (63)	median	26
Caucasian	5 (21)	range	18-34
Hispanic	4 (17)	CD4+ (cells/mm³)	
Age (yrs)		median	480
median	42	range	148-1168
range	23-58	Concurrent HAART agents–n(%)	
Height (inches)		Fosamprenavir, fosamprenavir/r	19 (79)
median	70	Lopinavir/r	3 (13)
range	65-78	Atazanavir/r	1 (4)
		Nevirapine	1 (4)

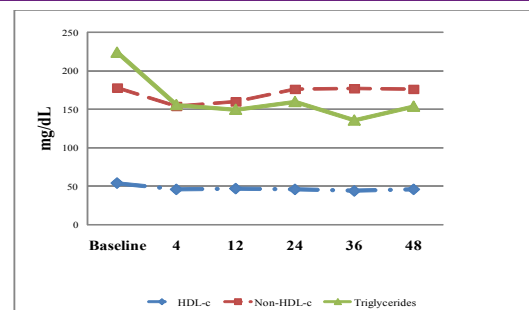
No subjects received lipid lowering agents during the study.

Total Cholesterol Reduction

	Baseline (n=24)	Week 4 (n=24)	Week 12 (n=24)	Week 24 (n=24)	Week 36 (n=23)	Week 48 (n=21)
Total cholesterol (mg/dL)*						
median	230	205	206	224	216	220
range	146-317	103-251	144-271	142-368	122-293	140-322
% reduction (mean)						
median	—	-9%	-4%	-4%	-6%	-1%
range	—	-29 to 11%	-21 to 22%	-21 to 25%	-26 to 26%	-40 to 58%

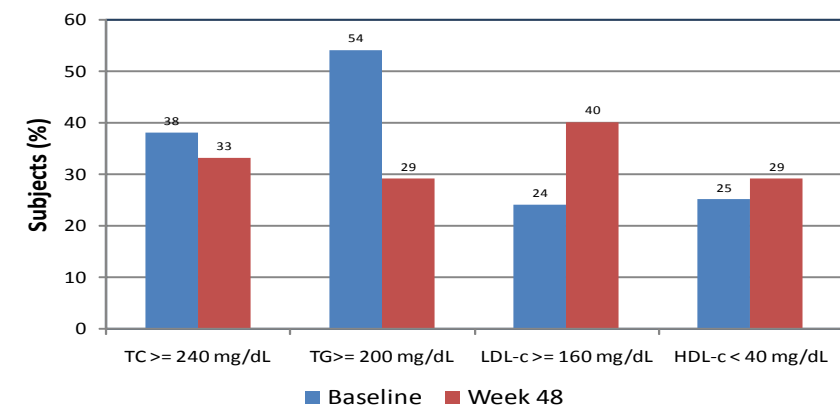
*reductions statistically significant through week 12 (p = 0.007)

HDL-c, non-HDL-c and triglycerides (median)



Results (continued)

Subjects with lipids exceeding NCEP recommended lipid levels – per protocol



p > 0.05

Total Cholesterol: HDL-c ratio

	Baseline (n=24)	Week 4 (n=24)	Week 12 (n=24)	Week 24 (n=24)	Week 36 (n=23)	Week 48 (n=21)
median	4.57	4.38	4.38	4.89	4.94	4.77
range	3.04-6.22	2.94-5.92	2.75-7.33	2.44-8.18	2.97-8.33	2.97-8.21

p > 0.05

CD4+, viral load

	Baseline	Week 4	Week 12	Week 24	Week 36	Week 48
CD4+ (cells/mm³)						
median	480	424	455	470	514	543
range	148-1168	138-1293	188-1379	195-1103	115-937	312-1151
HIV-1 RNA < 400 c/mL [n(%)]						
M = F	22 (92)	21 (89)	20 (83)	20 (83)	19 (79)*	20 (83)†
M = E	22 (92)	21 (89)	20 (83)	20 (83)	19 (83)	20(100)

*2 subjects lost to follow-up (LTFU), 3 subjects viral load > 400 c/mL

†4 subjects LTFU

Conclusions

- Switching to FTC/TDF demonstrated a trend toward total cholesterol (TC) reductions – statistically significant reductions evident through week 12.
- Proportion of subjects meeting NCEP guidelines for TC, and triglycerides remained improved through week 48, thus switching to FTC/TDF therapy may play a role in minimizing metabolic side effects related to HAART.
- Inability to show significance is likely due to small sample size, however, larger, prospective, randomized studies [SWIFT³ study (US), ROCKET-1⁴ (UK) and ROCKET-2 (Spain, Italy, Germany, Austria)] are ongoing to assess the impact of switching from Epzicom® to Truvada®, including fasting lipid changes.

References

- 1 Moyle G, Sabin C, Cartledge J, et al. A randomized, open-label comparative trial of abacavir or tenofovir DF as replacement for a thymidine analogue in persons with lipodystrophy and suppressed HIV RNA on HAART: the RAVE study. Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections; February 22-25, 2005. Boston, Massachusetts. Abstract 44.
- 2 Martinez E, Arranz JA, Podzamczar D, et al. Efficacy and safety of NRTIs switch to tenofovir plus emtricitabine (Truvada) vs. abacavir plus lamivudine (Kivexa) in patients with virologic suppression receiving a lamivudine containing HAART: the BICOMBO study. 4th IAS Conference on HIV Pathogenesis, Treatment, and Prevention. July 22-25, 2007. Sydney. Abstract WESS102.
- 3 SWIFT, Safety and Efficacy Study of Switching From Epzicom to Truvada A prospective, randomized, open-label phase IV study to evaluate the rationale of switching from fixed dose abacavir (ABD)/lamivudine (3TC) to fixed dose tenofovir (TDF)/emtricitabine (FTC) in virologically suppressed, HIV 1 infected patients maintained on a ritonavir boosted protease inhibitor containing antiretroviral regimen. ClinicalTrials.gov Identifier: NCT00724711.
- 4 ROCKET -1 & -2, Randomized Open Label Switch for Cholesterol Elevation on Kivexa Evaluation Trial. A Phase 4, Open Label, Randomized, Controlled Study to Assess the Effect on Lipid Profile of Switching From a Stable HAART Regimen of Fixed Dose Abacavir/Lamivudine (Kivexa) Plus Efavirenz, to Once Daily Atripla in Adult HIV-1 Infected Subjects With Raised Cholesterol. ClinicalTrials.gov identifier: NCT0061581.