Similarity in Efficacy and Safety of Abacavir/Lamivudine (ABC/3TC) Compared to Tenofovir/Emtricitabine (TDF/FTC) in Combination with QD Lopinavir/Ritonavir (LPV/r) Over 96 Weeks in the HEAT Study

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Introduction

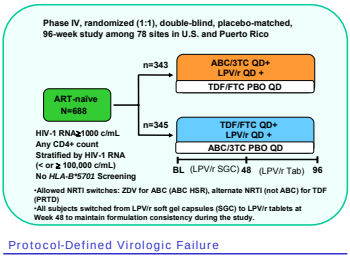
- Limited direct comparative data exist between the recommended dual NRTI fixed dose combinations, ABC/3TC and TDF/FTC.
- The HEAT study is the first completed head-to-head trial to evaluate the efficacy and safety of these dual NRTI backbones with a boosted PI as part of recommended first-line treatments in HIV-1 infected subjects.

Objectives

- To establish that ABC/3TC is virologically noninferior to TDF/FTC when administered in combination with LPV/r over 48 weeks.
- To compare the safety and tolerability of ABC/3TC versus TDF/FTC over 96 weeks.

Methods

Figure 1. HEAT Study Design



•Allowed NRTI switches: ZDV for ABC (ABC HSR), alternate NRTI (not ABC) for TDF (PRTD)
•All subjects switched from LPV/r soft gel capsules (SGC) to LPV/r tablets at Week 48 to maintain formulation consistency during the study.

Protocol-Defined Virologic Failure

- Failure to achieve HIV-1 RNA <200 c/mL or confirmed rebound to ≥ 200 c/mL after confirmed reduction to <50 c/mL by Week 24.
- Confirmed HIV-1 RNA ≥ 200 c/mL after Week 24.

Statistical Analysis

- Non-inferiority of ABC/3TC compared to TDF/FTC was established if the lower bound of the two-sided 95% CI on the difference in proportions achieving an HIV-1 RNA <50 c/mL at Week 48 was -0.12 or greater [ITT-E, missing=failure, switch included].
- Virologic response rates were compared between arms by the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA (< or ≥100,000 c/mL).
- Efficacy and Safety analyses were based on the ITT(E) population.

Results

Table 1. Baseline Demographics and Characteristics

	ABC/3TC N = 343	TDF/FTC N = 345
Mean Age, yrs (range)	38 (18-74)	39 (18-69)
Sex: Female, n (%)	56 (16%)	69 (20%)
Race, n (%)		
White	176 (51%)	173 (50%)
African-American	122 (36%)	124 (36%)
Other	45 (13%)	48 (14%)
Hispanic/Latino Ethnicity, n (%)	73 (21%)	62 (18%)
Plasma HIV-1 RNA (log_{10} c/mL), median	4.90	4.84
≥100,000 c/mL, n (%)	155 (45%)	140 (41%)
CD4+ count (cells/mm^3), median	214	193
<50 cells/mm^3, n (%)	61 (18%)	70 (20%)
50-<200 cells/mm^3, n (%)	99 (29%)	110 (32%)
≥ 200 cells/mm^3, n (%)	183 (53%)	165 (48%)
CDC Class C, n(%)	55 (16%)	57 (17%)
Hepatitis B Positive, n (%)	19 (6%)	9 (3%)
Hepatitis C Positive, n (%)	27 (8%)	24 (7%)
HSV-2 Ig Positive (through Week 96) n(%)	61% (159/260)	63% (156/246)

Table 2. Subject Disposition, ITT(E)

n (%)		ABC/3TC N = 343	TDF/FTC N = 345
Completed 96 weeks		234 (68%)	221 (64%)
Prematurely withdrawn		109 (32%)	124 (36%)
	Adverse Events	20 (6%)	21 (6%)
	Virologic Failure	8 (2%)	6 (2%)
	Non-compliance	10 (3%)	11 (3%)
	Lost to Follow-Up	45 (13%)	52 (15%)
	Protocol Violation	2 (<1%)	0
	Subject Decision	13 (4%)	23 (7%)
	Disease Progression	0	1 (<1%)
	Other	11 (3%)	10 (3%)

Other included pregnancy (2), site closure (2), protocol non-compliance (3), relocation (1) and incarceration (3) in the ABC/3TC arm and site closure (3), death (2), incarceration (2) and relocation (3) in the TDF/FTC arm.

Protocol-Allowable Toxicity Switches

- NRTI switches included suspected ABC HSR [14 (4%) ABC/3TC; 3 (1%) TDF/FTC] and Proximal Renal Tubule Dysfunction (PRTD) [0 ABC/3TC; 5 (1%) TDF/FTC].
  - PRTD definition: serum creatinine rise of ≥0.5 mg/dL from BL and serum phosphate <2 mg/dL or either of the former plus any 2 of the following: proteinuria ≥100 mg/dL, glycosuria ≥250 g/dL, low serum potassium <3 meQ/L, or low serum bicarbonate <19 meQ/L.
- For PI-induced GI intolerability, LPV/r was permitted to be dosed twice daily. For treatment-limiting PI toxicity, LPV/r could be switched to FPV.

Figure 2. HIV-1 RNA <50 and <400 c/mL Through Week 96, ITT-E (M=F)

*95% CI of treatment difference (ABC/3TC – TDF/FTC):
HIV-1 RNA <50 c/ml: [-5.41, 9.32] ; HIV-1 RNA <400 c/ml: [-4.58,9.93]

Figure 3. HIV-1 RNA <50 c/mL at Week 96 Results, ITT (E)*

* Efficacy results were stratified by BL VL (< or ≥ 100K)

- These results corroborate the virologic non-inferiority of ABC/3TC to TDF/FTC that was demonstrated at 48 Weeks.
- Consistent results were observed regardless of analysis method used including when switches were counted as failures (MD=F analysis).
- Protocol defined virologic failure was experienced by 14% of subjects in each treatment arm (ABC3TC: 49/343; TDF/FTC: 48/345) through 96 weeks.

Table 3. Efficacy Results by Baseline HIV-1 RNA

Proportion of subjects with HIV-1 RNA <50 c/mL at Week 96, ITT(E), M=F, m/n (%)	ABC/3TC N = 343	TDF/FTC N = 345
Baseline HIV-1 RNA <100,000 c/mL	118/188 (63)	119/205 (58)
Baseline HIV-1 RNA ≥100,000 c/mL	87/155 (56)	81/140 (58)
BL HIV-1 RNA 100,000 - <250,000 c/mL	40/68 (59)	45/75 (60)
BL HIV-1 RNA 250,000 - <500,000 c/mL	22/37 (59)	19/33 (58)
BL HIV-1 RNA ≥500,000 c/mL	25/50 (50)	17/32 (53)

Figure 4. Median CD4+ Change from Baseline

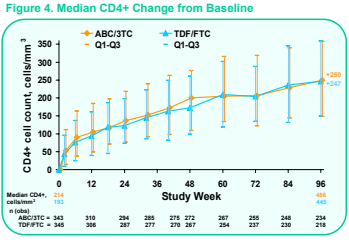


Table 4. Inflammatory Biomarker Analysis Results

Geometric Mean (GM) (95% CI)	ABC/3TC N = 343	TDF/FTC N = 345	Ratio: ABC/3TC vs TDF/FTC
Baseline Interleukin-6 (IL-6), pg/mL	n=243	n=249	-
	1.91 (1.74, 2.09)	1.97 (1.79, 2.17)	
Week 48 fold change from BL, GM ratio Week 48 vs BL (95% CI)	n= 220 0.74 (0.66, 0.82)	n=220 0.77 (0.68, 0.87)	0.96 (0.82, 1.12)
Week 96 fold change from BL, GM ratio Week 96 vs BL (95% CI)	n= 192 0.81 (0.72, 0.92)	n=197 0.75 (0.67, 0.84)	1.08 (0.92, 1.28)
Baseline high sensitivity C-reactive protein (hs CRP), mg/L	n=256 1.88 (1.64, 2.16)	n=252 1.72 (1.50, 1.98)	-
Week 48 fold change from BL, GM ratio Week 48 vs BL (95% CI)	n= 235 0.88 (0.75, 1.03)	n=224 0.80 (0.68, 0.94)	1.10 (0.88, 1.37)
Week 96 fold change from BL, GM ratio Week 96 vs BL (95% CI)	n= 205 0.95 (0.80, 1.13)	n=199 0.83 (0.70, 0.98)	1.15 (0.90, 1.46)

- Both inflammatory biomarkers analyzed (IL-6 and hs-CRP) showed decreases at Weeks 48 and 96 in both treatment arms (ratios <1).
- No significant differences between the treatment arms were noted at any timepoints for either analyte.

Table 5. Treatment-Related Adverse Events (AE)

	ABC/3TC N = 343	TDF/FTC N = 345
Treatment-Related Grade 2-4 AEs (>3%)		
Any Event (all subjects)	171 [50%]	157 [46%]
Diarrhea	66 (19%)	66 (19%)
Nausea	26 (8%)	20 (6%)
Blood triglycerides increased	19 (6%)	20 (6%)
Blood cholesterol increased	24 (7%)	13 (4%)
Glomerular filtration rate decreased	16 (5%)	16 (5%)
Hypophosphatemia	15 (4%)	5 (1%)
Suspected ABC HSR (all grades)	14 (4%)	3 (1%)
Treatment-Related Serious AEs (≥2 subjects)		
Any Event (all subjects)	17 [5%]	19 [3%]
Suspected ABC HSR	14 (4%)	3 (1%)
Immune reconstitution syndrome	2 (<1%)	0
Anemia	1 (<1%)	1 (<1%)
Renal failure	0	2 (<1%)

Retrospective *HLA-B*5701* testing was performed on available samples. Of 14 reported cases in the ABC/3TC arm, 7 were positive, 5 were negative and 2 had unknown *HLA-B*5701* status. Of 3 reported cases in the TDF/FTC arm, 1 was negative and 2 had unknown *HLA-B*5701* status.

Table 6. Median Fasting Lipid Changes at Week 96

Median (mg/dL)	n BL, Wk 96	ABC/3TC N = 343 BL	Wk 96	Median Δ BL	n BL, Wk 96	TDF/FTC N = 345 BL	Wk 96	Median Δ BL
Total Cholesterol	279, 205	158	202	+36	286, 188	159	186	+28
Triglycerides	279, 205	122	187	+54	286, 188	134	180	+42
LDL cholesterol	261, 186	93	107	+9	270, 172	92	94	+8
HDL cholesterol	278, 204	36	47	+10	286, 189	35	47	+12
TC:HDL Ratio	278, 204	4.4	4.1	-0.3	286, 187	4.5	4.0	-0.4

Table 7. Renal Function Changes at Week 96

Median	n BL, Wk 96	ABC/3TC N = 343 BL	Wk 96	Median Δ BL	n BL, Wk 96	TDF/FTC N = 345 BL	Wk 96	Median Δ BL
MDRD (mL/min/1.73^2)	343, 236	88	93	0	345, 219	87	88	0
CrCl (mL/min)	343, 236	104	110	+7	345, 219	100	106	+5
Protein:Cr Ratio	327, 207	0.09	0.07	-0.02	329, 184	0.09	0.10	+0.01
Serum phosphate (mg/dL)	343, 236	3.60	3.00	-0.5	344, 219	3.70	3.00	-0.5
Urine glucose (mg/dL)	294, 230	7.0	7.0	0	292, 211	7.0	7.0	0

Discussion

- ABC/3TC remained virologically comparable to TDF/FTC through 96 weeks when each was combined with LPV/r.
  - 60% vs. 58% of subjects (ABC/3TC vs. TDF/FTC) achieved an HIV-1 RNA <50 c/mL at Week 96 (ITT-E, M=F, switch included).
  - 64% vs. 61% of subjects (ABC/3TC vs. TDF/FTC) achieved an HIV-1 RNA <400 c/mL at Week 96 (ITT-E, M=F, switch included).
- Consistent results were noted in antiviral response rates (HIV-1 RNA <50 c/mL) by increasing baseline viral load strata.
- Median CD4+ cell responses were similar at Week 96 (466 cells/mm^3 for ABC/3TC and 445 cells/mm^3 for TDF/FTC).
- A conservative protocol definition of virologic failure resulted in a somewhat elevated virologic failure rate in both arms.
- Similar tolerability was noted for both regimens with no new safety findings observed.
  - Rate of ABC HSR was 4% with ABC/3TC and 1% with TDF/FTC. Prospective *HLA-B*5701* screening was not performed in this study.
  - PRTD occurred in 0% with ABC/3TC and 1% with TDF/FTC.
  - Lipid elevations were observed in both arms; TC:HDL ratio remained <5 for each.
- Decreases were seen in both interleukin-6 and highly sensitivity CRP; while these changes may be attributable to antiviral suppression, no differences were seen between the treatment arms.

Conclusions

- ABC/3TC is comparable to TDF/FTC in virologic efficacy and safety when combined with LPV/r through 96 weeks.
- Both treatment regimens were well tolerated with few discontinuations due to adverse events in either arm.

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