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Efficacy and Safety of Abacavir/Lamivudine Compared to Tenofovir/Emtricitabine in Combination with Once-Daily Lopinavir/Ritonavir through 48 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 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.

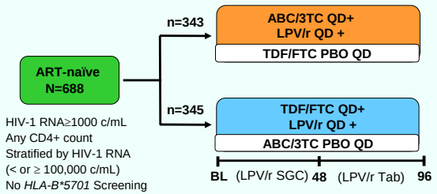
Objectives

- 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

Phase IV, randomized (1:1), double-blind, placebo-matched, 96-week study among 78 sites in U.S. and Puerto Rico



Allowed NRTI switches: ZDV for ABC (ABC HSR), alternate NRTI (not ABC) for TDF (PRTD)

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 would be 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].
- For stratified analyses by baseline HIV-1 RNA (< or ≥100,000 c/mL), the Cochran-Mantel-Haenszel method was used to compare virologic response between treatment groups.

Acknowledgements

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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)
Female sex		16%	20%
Race	White	52%	50%
	African-American	36%	36%
	Other	13%	14%
Hispanic/Latino Ethnicity		21%	19%
Non-Hispanic/Latino Ethnicity		79%	81%
Median Plasma HIV-1 RNA, log_{10} c/mL		4.90	4.84
HIV-1 RNA ≥100,000 c/mL		45%	41%
Median CD4+ count (cells/mm³)		214	193
<50 cells/mm³		18%	20%
50-<200 cells/mm³		29%	32%
≥ 200 cells/mm³		53%	48%
CDC Class C		16%	17%
Hepatitis B Positive		6%	3%
Hepatitis C Positive		8%	7%
HSV-2 Ig Positive (through Week 48)		62% (113/183)	64% (106/165)

Table 2. Subject Disposition

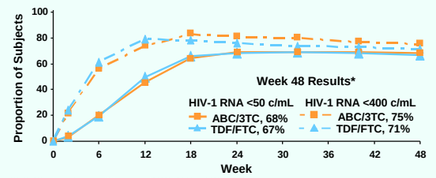
	ABC/3TC n = 343	TDF/FTC n = 345
Completed 48 weeks	275 (80%)	262 (76%)
Prematurely withdrawn	68 (20%)	83 (24%)
Adverse Events	13 (4%)	20 (6%)
Virologic Failure	4 (1%)	4 (1%)
Non-compliance	7 (2%)	9 (3%)
Lost to Follow-Up	27 (8%)	30 (9%)
Protocol Violation	2 (1%)	0
Subject Decision	9 (3%)	14 (4%)
Other	6 (2%)	6 (2%)

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

Protocol-Allowable Toxicity Switches

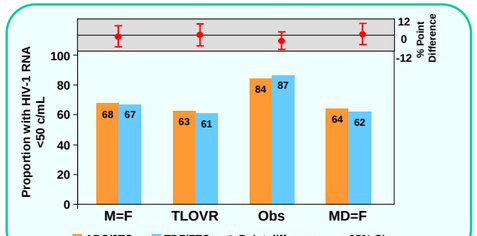
- NRTI switches included suspected ABC HSR [14 (4%) ABC/3TC; 3 (1%) TDF/FTC] and Proximal Renal Tubule Dysfunction (PRTD) [0 ABC/3TC; 3 (1%) TDF/FTC].
  - PRTD definition: serum creatinine rise of ≥0.5 mg/dL from BL and serum phosphate < 2mg/dL or either of the former plus any 2 of the following: proteinuria ≥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.
- All subjects switched from LPV/r soft gel capsules (SGC) to LPV/r tablets at Week 48 to maintain formulation consistency during the study.

Figure 2. HIV-1 RNA <50 and <400 c/mL through Wk 48, ITT-E (M=F)



*95% CI of treatment difference (ABC/3TC – TDF/FTC):
HIV-1 RNA <50 c/ml: [-6.63, 7.40] ; HIV-1 RNA <400 c/ml: [-2.71,10.56]

Figure 3. Primary Efficacy Endpoint (HIV-1 RNA <50 c/mL)



- The lower bound of the 95% CI was greater than -0.12, thus establishing non-inferiority of ABC/3TC to TDF/FTC, (ITT-E, M=F, 95% CI (ABC/3TC-TDF/FTC) [-6.63,7.40]).
- Consistent results were observed regardless of analysis method used including when switches were counted as failures (MD=F analysis).
- In stratified analyses (ABC/3TC vs. TDF/FTC), 71% vs. 69% of subjects in the <100K viral strata achieved an HIV-1 RNA <50 c/mL; 63% vs. 65% of subjects in the ≥100K viral strata achieved this same endpoint at Week 48 (ITT-E, M=F).

Figure 4. Median CD4+ Change from Baseline

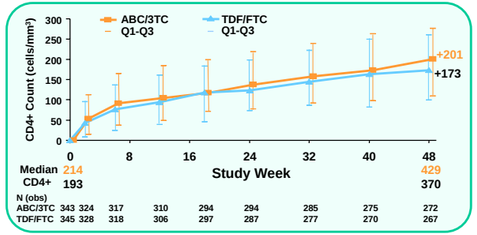


Table 3. Resistance Through 48 Weeks

	ABC/3TC n = 343	TDF/FTC n = 345
Confirmed virologic failure (CVF) per protocol	40 (12%)	39 (11%)
Matched GT data at both BL and VF	35	32
Subjects with Treatment-emergent mutations	12 (34%)	17 (53%)
NRTI Associated Mutations	7 (20%)	14 (44%)
M184V or mixtures	7	14
K70K/R	1	0
NNRTI Associated Mutations	1 (3%)	0
Y181Y/C	1	0
PI Associated Mutations*	6 (17%)	6 (19%)

*No primary PI associated mutations detected. Secondary PI associated mutations seen were as follows: M36M/I, V77V/I, A71A/T, I62I/V, L10L/V, V11V/I, G16E, I13I/V, L10L/F.

- Rate of virologic failure was similar in both groups.
- The slightly higher rate of protocol-defined virologic failure may be attributed to the use of a more stringent criteria to determine success (HIV-1 RNA <200 c/mL).

Safety

Table 4. Treatment-Related Adverse Events (AE)

	ABC/3TC n = 343	TDF/FTC n = 345
Treatment-Related Grade 2-4 AEs (>3%)		
Any Event (all subjects)	154 [45%]	152 [44%]
Diarrhea	61 (18%)	64 (19%)
Nausea	25 (7%)	20 (6%)
Hypertriglyceridemia	20 (6%)	17 (5%)
Hypercholesterolemia	22 (6%)	12 (3%)
Glomerular filtration rate decreased	17 (5%)	16 (5%)
Vomiting	11 (3%)	11 (3%)
Suspected ABC HSR	14 (4%)	3 (1%)
Treatment-Related Serious AEs (≥2 subjects)		
Any Event (all subjects)	18 [5%]	10 [3%]
Suspected ABC HSR	14 (4%)	3 (1%)
Immune reconstitution syndrome	2 (<1%)	0
Anemia	1 (<1%)	1 (<1%)
Renal failure	0	2 (<1%)

Table 5. Median Fasting Lipid Changes at Week 48

Median (mg/dL)	n BL, Wk 48	ABC/3TC n = 343 BL	Wk 48	Change from BL	n BL, Wk 48	TDF/FTC n = 345 BL	Wk 48	Change from BL
Total Cholesterol	278, 243	159	202	+32	286, 229	159	184	+23
Triglycerides	278, 243	122	215	+64	286, 229	134	189	+38
LDL cholesterol	260, 213	93	105	+8	270, 210	92	97	-1
HDL cholesterol	277, 243	36	48	+13	286, 231	35	47	+11
TC:HDL Ratio	277, 243	4.4	4.2	-0.26	286, 229	4.5	4	-0.56

Table 6. Renal Function Changes at Week 48

Median		n BL, Wk 48	ABC/3TC n = 343 BL	Wk 48	Change from BL	n BL, Wk 48	TDF/FTC n = 345 BL	Wk 48	Change from BL
MDRD (mL/min/1.73²)		343, 276	88	93	+7	345, 268	87	90	0
	Black	122, 90	92	100	+9	124, 87	94	95	0
	Non-Black	221, 186	86	89	+3	221, 181	84	88	0
CrCl (mL/min)		342, 275	105	113	+9	343, 268	100	106	+6
Protein:Cr Ratio		326, 243	0.9	0.07	-0.01	328, 228	0.09	0.09	0
Serum phosphate (mg/dL)		342, 275	3.60	3.20	-0.3	343, 268	3.70	3.20	-0.4
Urine glucose (mg/dL)	Median	293, 270	7.0	7.0	0	291, 260	7.0	7.0	0
	Mean	293, 270	34.7	34.8	-2.4	291, 260	26.2	58.4	+26

Discussion

- ABC/3TC was virologically non-inferior to TDF/FTC through 48 weeks when each was combined with LPV/r.
  - 68% vs. 67% of subjects (ABC/3TC vs. TDF/FTC) achieved an HIV-1 RNA <50 c/mL at Week 48 (ITT-E, M=F, switch included).
  - 75% vs. 71% of subjects (ABC/3TC vs. TDF/FTC) achieved an HIV-1 RNA <400 c/mL at Week 48 (ITT-E, M=F, switch included).
- Efficacy results were consistent and robust to multiple analyses including when switches were counted as failures.
- Median CD4+ cell responses differed between arms at Week 48 (429 cells/mm³ for ABC/3TC and 370 cells/mm³ for TDF/FTC).
- A conservative definition of virologic failure resulted in a somewhat elevated failure rate in both arms. Twice as many subjects receiving TDF/FTC failed therapy with an M184V or mixture which was a finding not previously reported.
- No new safety findings were observed for either NRTI backbone.
  - Rate of ABC HSR was 4% with ABC/3TC and 1% with TDF/FTC. (*HLA-B*5701* screening was not performed in this study)
  - PRTD occurred in 0% with ABC/3TC and 1% with TDF/FTC.
  - Lipids elevations were observed in both arms, however TC:HDL ratio remained below 5 for each.
- A blinded analysis of the data was performed at Week 48 to protect the integrity of this 96 week study.

Conclusions

- ABC/3TC is comparable to TDF/FTC in virologic efficacy when combined with LPV/r through 48 weeks.
- Both treatment regimens were well tolerated with few discontinuations due to adverse events in either arm.