Characterization of Virologic Failure Over 96 Weeks by Drug Resistance and Antiviral Response in ART Naïve Patients Receiving Abacavir/Lamivudine (ABC/3TC) or Tenofovir/Emtricitabine (TDF/FTC) Each with Lopinavir/Ritonavir QD in the HEAT Study

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Background

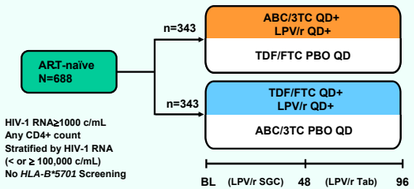
- The HEAT study is the first head-to-head study to evaluate the efficacy and safety of the dual NRTI backbones Epzicom and Truvada each in combination with Kaletra in ART- naïve patients
- At week 48 non-inferiority of Epzicom to Truvada was established and at week 96 Epzicom remained virologically comparable to Truvada (Smith, 2008)

Objectives

- To compare the proportion of subjects with protocol-defined virologic failure receiving Epzicom QD versus Truvada QD when each was given in combination with Kaletra QD over 96 weeks in ART-naïve HIV-1 infected subjects
- To characterize resistance patterns that arise in subjects experiencing virologic failure while on study

Methods

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)
- 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

Virus Characterization

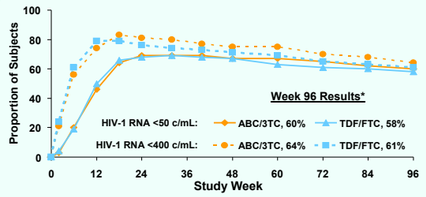
- Viral samples taken at baseline and time of virologic failure were tested at Monogram BioSciences, Inc. (MBI) using PhenoSense GT™
- Drug resistance genotypic profiles were generated using IAS Resistance Guidelines (Fall 2007)
- Phenotypic profiles for drug susceptibility were generated using the MBI clinical (where possible) and biological cut offs

Statistical Analysis

- Virology analyses are based on the ITT (E) population
- Descriptive statistics of genotypic and phenotypic findings by treatment group were summarized
- Association of each baseline variable with virologic failure was studied using univariate logistic regression models. In the analysis categorical variables were given a value of 1 or 0 (e.g. Male vs Female==> Male = 1, Female = 0)
- Final logistic regression model included significant baseline variables (p<0.05) from the univariate analyses and retained only significant variables (p<0.05) selected by the stepwise selection method

Results

Figure 1. Efficacy Results through Week 96



*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]

Table 1. Virologic Failure Through Week 96 (ITT—E)

Virologic Failure	ABC/3TC N=343	TDF/FTC N=345
Protocol-defined	49 (14%)	48 (14%)
Confirmed Rebound to ≥200 c/mL	28 (8%)	24 (7%)
Failure to Achieve Confirmed <200 c/mL by Week 24	21 (6%)	24 (7%)

- Baseline characteristics for subjects with virologic failure match those of the full study with two exceptions, race and baseline plasma HIV-1 RNA
- 36% of subjects in the full study were African American but 56% of subjects experiencing virologic failure were African American [ABC/3TC: 22 (45%); TDF/FTC: 30 (63%)]

Figure 2. Virologic Failure by Baseline HIV-1 RNA strata

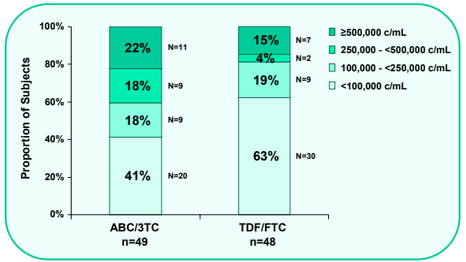
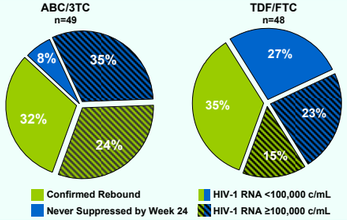


Figure 3. Virologic Failure by Baseline HIV-1 RNA Strata and Failure Criterion



- There was a greater proportion of subjects in the TDF/FTC treatment group with baseline plasma HIV-1 RNA <100,000 and never suppressing to <200 c/mL by Week 24 as compared to ABC/3TC

Table 2. Summary of Treatment Emergent Resistance in Subjects with Protocol-defined Virologic Failure

	ABC/3TC N=49	TDF/FTC N=48
Subjects with Geno data at BL and VF	45	41
No treatment-emergent mutations	27 (60%)	19 (46%)
Treatment-emergent mutations	18 (40%)	22 (54%)
NRTI-associated mutations	11 (24%)	17 (41%)
K70K/R	1	0
K70R	1	0
K65K/R	0	1
D67N	1	0
K219E	1	0
M41L	1	0
M184V	4	9
M184M/V	7	2
M184M/I[1]	0	3
M184A/V[1]	0	1
M184I[1]	0	1
M184M/I/V[1]	0	1
NNRTI-associated mutations[2]	4 (9%)	3 (7%)
PI associated mutations[3]	11 (24%)	7 (17%)
Major PI-associated mutations	1	0
Minor PI-associated mutations	11	7

1. Mutations detected during the first 48 weeks of treatment.
2. NNRTI-associated mutations detected were V90V/I (ABC/3TC:2; TDF/FTC:3), L100I, and Y181Y/C
3. Major PI-associated mutations detected in a single patient and were as follows: G48V, I54M, V82A, I84V, I47V, L33F, V32I, and M46I. Minor PI-associated mutations were L10L/V/I/F, V11V/I, I13I/V, G16E, M36M/I/L, I62I/V, L63L/P, A71A/T, V77V/I, N83D, I85V, I93I/L.

Table 3. Phenotypic Correlations to Treatment-emergent Mutations or Mixtures at Codon 184

	Reduced Susceptibility			
	Lamivudine		Emtricitabine	
Mutation	ABC/3TC n=11	TDF/FTC n=17	ABC/3TC n=11	TDF/FTC n=17
M184V	4/4	9/9	4/4	9/9
M184M/V	3/7	0/2	3/7	0/2
M184M/I		1/3		1/3
M184A/V		1/1		1/1
M184I		1/1		1/1
M184M/I/V		1/1		1/1

- A phenotypic correlation of lamivudine and emtricitabine susceptibility to resistance mutations or mixtures of mutations at codon 184 were seen in 7/11 subjects receiving ABC/3TC and 13/17 subjects receiving TDF/FTC.

Figure 4. Subject Profile

Subject randomized to the ABC/3TC + LPV/r treatment group. Baseline HIV-1 RNA was 949,000 c/mL and baseline CD4 was 19 which increased to 258 at wk 48 but fell to 163 at W/D. Virologic failure was due to viral rebound at week 60. Prior to Virologic failure subject had documented re-exposure to HIV from a partner who was heavily ART experienced.

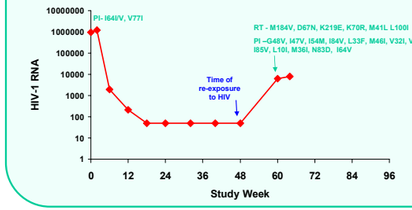


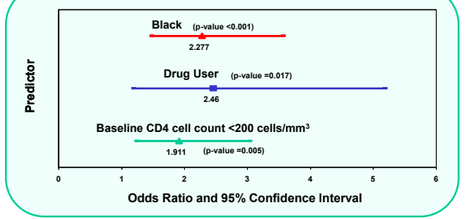
Table 4. Baseline Covariates Studied as Potential Predictors of Virologic Failure (Univariate Logistic Regression Model)

Treatment group*	Diabetes*	CDC Class A*
Gender*	Homosexual Contact*	CDC Class B*
White*	Heterosexual Contact*	CDC Class C*
Black*	Injectable Drug Use*	HIV-1 RNA (log_{10} c/mL)
American Hispanic*	Transfusion*	CD4+count (cells/mm³)
Weight	Other HIV Risk Factors*	Baseline HIV-1 RNA Strata*
Hypertension*	Hepatitis C positive*	CD4+ count <50 cells/mm³)*
Hypercholesterolaemia*	Hepatitis B Positive*	CD4+ count <200 cells/mm³)*
Drug User*		

*Categorical variables — P-value <0.05 in red

- Covariates with p-value <0.05 were put into a multivariate logistic regression model for prediction of virologic failure

Figure 5. Predictor of Virologic Failure by Logistic Regression Model



Discussion

- Overall virologic failure rates were similar across both treatment arms. Among subjects with baseline HIV-1 RNA <100,000 c/mL, more TDF/FTC subjects experienced virologic failure (ABC/3TC: 41%; TDF/FTC: 63%). Among subjects with baseline HIV-1RNA >100,000 c/mL more subjects receiving ABC/3TC experienced virologic failure (ABC/3TC: 59%; TDF/FTC: 37%)
- Among subjects experiencing virologic failure with treatment emergent mutations, mutations at codon 184 were more common among subjects receiving TDF/FTC than subjects receiving ABC/3TC. Phenotypic analyses confirmed the importance of the genotypic findings.
- One subject receiving ABC/3TC + LPV/r developed PI and NRTI-associated mutations. Additional analyses (not shown) suggest that this may represent a case of HIV superinfection with a multi-drug resistant viral strain.
- African American subjects were more likely to experience virologic failure; these observations were corroborated by univariate and multivariate analyses predicting virologic failure.

Conclusions

- The number of subjects with protocol-defined virologic failure was similar between the two treatment groups [ABC/3TC: 14% vs TDF/FTC: 14%].
- The TDF/FTC treatment group had 63% of subjects experiencing virologic failure in the baseline HIV-1 RNA strata of <100,000 c/mL, while in the ABC/3TC treatment group had 59% of subjects experiencing virologic failure in the baseline HIV-1 RNA strata of ≥100,000 c/mL.
- Subjects with virologic failure receiving ABC/3TC had fewer mutations or mixtures of mutations at codon 184 as compared to subjects receiving TDF/FTC.
- Treatment-emergent PI-associated mutations were rare.

Acknowledgements

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References

Smith, K; Fine, D; Patel, P; et al. 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. 18th International AIDS Conference, Mexico City, Mexico, Aug.3-8, 2008