Poster Number

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Improvements in lipoatrophy (LA) are observed after 24 weeks when stavudine (d4T) is replaced by either abacavir (ABC) or zidovudine (ZDV)

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Introduction

Due to the widespread use of potent highly active antiretroviral therapies (HAART), HIV-1 infected subjects are living longer, more productive lives. As a result, long-term side effects of HAART have emerged and should be considered when discussing treatment options with patients. One of the most troublesome of these side effects is lipodystrophy.

Although definitions of lipodystrophy differ, this term typically encompasses both fat accumulation and fat wasting or lipoatrophy. It is generally accepted that lipoatrophy refers to the syndrome of loss of subcutaneous tissue from facial pads, extremities and buttocks resulting in a cachectic appearance, prominent zygomata and sunken eyeballs.

HIV lipodystrophy remains controversial as the number of known variables further complicating this condition continues to increase and the lack of consensus regarding standard definitions and proposed treatments persists. Current information is emerging that suggests there may be a number of other factors associated with lipodystrophy such as insulin resistance, serum leptin levels and serum concentrations of tumor necrosis factor (TNF) [1]. To date, however, ART remains the primary implication. PI use is typically linked to fat accumulation, while NRTIs are more frequently associated with lipoatrophy. Like other ART-related metabolic disorders, the latter may also be linked to mitochondrial toxicity.

Due to the multifaceted nature of lipodystrophy, diverse treatment strategies have evolved including switch therapies. Several randomized trials and cohort studies have shown greater lipoatrophy and hyperlactatemia risks associated with d4T as compared to other NRTIs [2]. ESS40010 (TARHEEL) was designed to assess the reversibility of lipoatrophy and hyperlactatemia following the substitution of stavudine (d4T) with either abacavir (ABC) or zidovudine (ZDV as Combivir®, [COM]) in symptomatic subjects. Results presented below concentrate primarily on the lipoatrophy objective of this study.

Methods

- This phase IV, open-label, multicenter 48-week switch study was designed to assess the regression of lipoatrophy and hyperlactatemia in HIV-1 subjects previously treated with d4T after ABC or ZDV (as COM) was substituted for d4T or d4T and one other agent.
- ZDV-naïve subjects substituted COM for d4T and ZDV experienced or intolerant subjects substituted ABC for d4T.
- All subjects must have been taking a d4T-containing regimen consistently for 6 months preceding study entry with undetectable HIV-1 RNA (< 400 copies/mL on two consecutive measurements) prior to study entry in addition to one of the following:
  1. physical findings of lipoatrophy (via physical exam or self report) ± elevated lactate
  2. symptoms compatible with hyperlactatemia and lactate levels > 2.2 mmol/L
  3. lactate levels > 3.2 mmol/L
- Physical signs of lipoatrophy were determined by change in percent of body fat distribution using full-body dual-energy x-ray absorptiometry (DEXA), single abdominal computerized axial tomography (CT) scan, anthropometric measurements and patient self-reports of lipoatrophy using a Body Image Questionnaire developed by GSK.
- Hyperlactatemia changes were determined by changes in both lactate laboratory parameters and patient self-reports of symptoms compatible with hyperlactatemia using a symptoms questionnaire.
- Subjects with confirmed entry lactates > 2.2 mmol/L could have discontinued ART until lactate levels were < 2.2 mmol/L or until subjects were asymptomatic, at the discretion of the investigator. ART was then resumed substituting either ABC or COM for d4T and restarting all other ART that the subject was taking at the time of screening.
- HIV-1 RNA was measured by the Roche AMPLICOR PCR Ultrasensitive 1.0 assay.
- To further evaluate mitochondrial toxicity, liver, muscle and fat biopsies as well as serum samples were collected at baseline and will be collected at Week 48 or early termination from a subset of subjects (N = 16).
- Frozen skeletal muscle specimens were thawed and homogenates prepared using cholate as the detergent. The mitochondrial electron transport chain assays were performed using CLIA validated methods.

Statistical Methodology

- This analysis represents complete 24-week data. For this interim analysis, the Intent-to-Treat (ITT) population was used (all enrolled subjects with at least one post-baseline measurement) and all data observed at the time of cutoff were summarized (observed analysis). There was no imputation for missing assessments.
- The odds of having elevated lactate (EL) levels versus non-elevated lactates (NL) at baseline for females was compared to the same odds for males. A similar odds ratio was calculated for African-Americans compared to all others. Associated 95% confidence intervals were computed. SAS®, Procedure FREQ with the CMH option was used to generate estimates and associated confidence intervals.

Results

Enrollment is complete with a total of 118 subjects enrolled. Of these 118 subjects, 102 were enrolled with normal lactate levels at baseline; the other 16 had screening lactates ≥ 2.2 mmol/L and therefore met our hyperlactatemia criteria.

ZDV-naïve subjects substituted COM for d4T and ZDV experienced or intolerant subjects substituted ABC for d4T; 86/118 subjects replaced d4T with ABC while 32/118 replaced d4T with COM. Twenty subjects withdrew prior to Week 24 for the following reasons: adverse event (4), consent withdrawn (5), lost to follow-up (2), protocol violation (3), virologic failure (1) and hypersensitivity reaction to ABC (5).

Baseline demographics and characteristics for these subjects, stratified by entry lactate levels, are shown in Table 1.

Table 1 • Demographics and baseline characteristics

Normal lactate subjects (NL, n = 102) Elevated lactate subjects (EL, n = 16) Relative risk (RR) and 95% confidence intervals (CI)			
Characteristic	NL	EL	OR
Age, years			
Median (range)	43 (28-59)	43 (30-59)	
Gender, No. (%)			
Male	87 (85)	11 (69)	–
Female	15 (15)	5 (31)	2.64[1] (0.801-8.67)
Race, No. (%)			
White	69 (68)	8 (50)	–
Black	12 (12)	6 (38)	4.50[2] (1.39-14.61)
Asian	2 (2)	1 (6)	–
Hispanic	15 (15)	1 (6)	–
Other	4 (4)	0 (0)	–

Normal lactate subjects (NL, n = 102) Elevated lactate subjects (EL, n = 16)		
Characteristic	**NL median (range)**	**EL median (range)**
Screening plasma HIV-1 RNA (log_{10} copies/mL)	N/A	1.69 (1.69-2.28)
Day 1 plasma HIV-1 RNA (log_{10} copies/mL)	1.69 (1.69-3.45)	3.47 (1.69-5.28)[3]
Screening plasma lactate level (mmol/L)	N/A	2.90 (2.2-5.0)
Day 1 plasma lactate level (mmol/L)	1.4 (0.6-4.1)	2.05 (1.1-3.3)[3]
Symptoms of hyperlactatemia (%)		
No	56 (55)	10 (63)
Yes	45 (45)	6 (38)
Time (days) off ART	N/A	31 (1-77)
Time (months) on d4T, No. (%)		
<6 mo	2 (2)	0 (0)
6 mo–1 year	5 (5)	1 (6)
1–2 years	10 (10)	2 (13)
>2 years	85 (83)	13 (81)
d4T replaced, No. (%)		
abacavir	74 (73)	12 (75)
Combivir®	28 (27)	4 (25)

[1] Odds of having hyperlactatemia versus having normal lactate levels for females compared to the same odds for males.
[2] Odds of having hyperlactatemia versus having normal lactate levels for blacks compared to the same odds for other ethnic groups.
[3] Change from screening is a result of ART discontinuation (10 of 16 subjects discontinued).

Figure 1 presents the median change in DEXA data (arm, leg and trunk) from baseline through Week 24. At Week 24, an analysis including results from both normal lactate subjects and elevated lactate subjects, showed a median increase in regional fat for arms, legs and trunk of 25%, 6% and 9%, respectively.

Figure 2 presents the comparison of baseline self-reported lipodystrophy symptoms at Weeks 12 and 24 using the Body Image Questionnaire. Baseline results were a comparison to 2 months earlier; Week 12 and Week 24 results were a comparison to baseline. Note the increase from baseline to Week 24 in the "gained some/a lot" categories across all body regions. At Week 24, the percentage of subjects reporting positive body changes for face, legs, arms and buttocks were 27%, 21%, 21% and 11%, respectively.

Figure 1 • Median change in DEXA data (arm, leg and trunk) from baseline (N = 118)

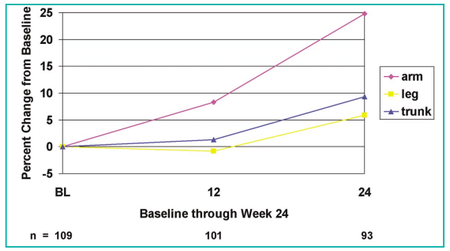

Figure 2 • Comparison of baseline self-reported lipodystrophy symptoms to Week 24 (using the Body Image Questionnaire) (N = 118)

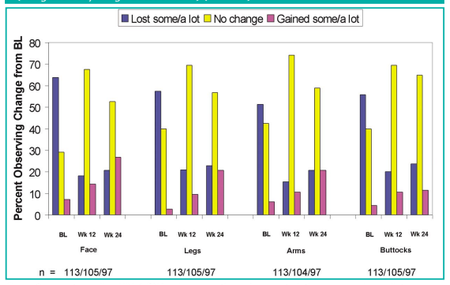

Figure 3 presents median HIV-1 RNA values over time. As expected, there was an immediate increase in median HIV-1 RNA for the elevated lactate subjects who discontinued therapy followed by a rapid return to undetectable levels once ART was resumed. The baseline median HIV-1 RNA value for normal lactate subjects was 1.69 log_{10} copies/mL and this was sustained through Week 24. At Week 24, 95% of all subjects maintained HIV-1 RNA < 400 c/mL (ITT, observed rates).

Figure 3 • Summary of median HIV-1 RNA over time

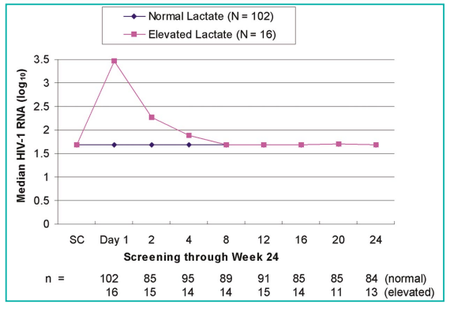

Figure 4 presents median lactate levels over time. A gradual decrease in lactate levels was observed in both groups. The initial decrease observed between screening and baseline in the elevated lactate population was most likely attributable to treatment interruptions (n = 10). However, these levels continued to decrease and subsequently remained below the upper limit of normal following the reintroduction of ART without d4T. For subjects with high lactates, the median lactate levels at screening, at ART re-initiation and Week 24 were 2.9, 2.1 and 1.6 mmol/L, respectively. For the normal lactate subjects, the median lactate level at Week 24 remained ~1.3 mmol/L.

Figure 4 • Summary of median lactate levels over time

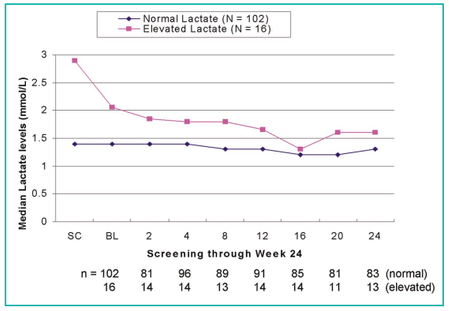

Table 2 shows the median change from baseline in the specified laboratory parameters most frequently associated with symptomatic hyperlactatemia or lipoatrophy.

Table 2 • Median change from Day 1 in associated laboratory markers (N = 118)

	AST (U/L)	ALT (U/L)	Anion gap (mEq/L)	Bicarbonate (mEq/L)	Cholesterol (mg/dL)	Triglycerides (mg/dL)
Screening	40.0	51.0	19.0	23.4		
Day1	29.5	32.5	17.0	23.4	206.5	244.5
Week 2	-2.0	-0.5	0.0	0.25	-24.0	-29.0
Week 4	-3.0	-3.0	-1.0	0.45	13.0	-29.0
Week 8	-3.0	-4.0	-1.0	-0.05	-1.0	-9.5
Week 12	-3.0	-4.0	0.0	-0.2	-2.5	7.0
Week 16	-4.0	-4.0	-1.0	-0.25	-4.0	16.0
Week 20	-5.0	-4.0	-0.5	-0.4	40.0	34.0
Week 24	-3.0	-3.0	0.5	-0.7	-2.5	-12.0

As seen in Table 3, data from the mitochondrial electron transport chain (ETC) assays indicated that the mean levels of all mitochondrially encoded ETC complexes were lower for the 16 TARHEEL subjects compared to the mean value for the controls (n = 49). Mitochondrial respiratory chain dysfunction was noted in 7/16 subjects at baseline with assay values at or below the control value range, with the most consistent being a decrease in complexes I, II and III. Decreased citrate synthase was also observed, reflecting a quantitative mitochondrial functional loss.

Table 3 • Mitochondrial functional assays

	NADH Cytochrome C reductase[1]	NADH Ferricyanide reductase	Succinate Cytochrome C reductase[2]	Succinate dehydrogenase	Decylubiquinone Cytochrome C reductase[2]	Cytochrome C Oxidase	Citrate Synthase
Patient mean value (n = 16)	0.708	24.53	1.12	0.55	11.2	92.6	11.7
STD	0.58	10.1	0.80	0.34	6.78	15.6	6.00
Range	0-2.5	9.5-40	0.04-2.8	0-1.2	0.4-23.5	62.9-123	2-23.3
Normal control mean value (n = 49)	1.2	29.9	2.1	0.8	15.2	148.9	18.6
STD	1.1	12.9	1.2	0.4	6.8	67.2	4.7
Range	0.2-4.7	11.5-60.1	0.4-4.9	0.1-2.0	6.8-35.2	57.3-373	9.4-30

[1]rotenone-sensitive [2]antimycin A-sensitive

Discussion

- Peripheral fat wasting is a multifaceted condition that has prompted the need for diverse and innovative treatment strategies.
- Week 24 DEXA results in this study are encouraging as they suggest the switch from d4T to either ABC or COM was effective in achieving improvements in peripheral fat across all specified body regions. The median increases from baseline achieved at Week 24 for arms, legs and trunk were 25%, 6% and 9%, respectively.
- Similarly, the subjects' self-reported comparison of symptoms from baseline also indicated that some lipoatrophy regression was achieved and that the therapy substitution was favorable. At Week 24, the percentage of subjects reporting positive body changes for face, legs, arms and buttocks were 27%, 21%, 21% and 11%, respectively. These findings complement the DEXA results described above.
- Median HIV-RNA values remained constant throughout the study with the exception of the planned treatment interruption period (median 32 days) for 10 out of 16 subjects with symptomatic hyperlactatemia.
- Lactate levels improved in both normal lactate and elevated lactate subjects. For the elevated lactate subjects who interrupted therapy (n = 10), improvements occurred after the discontinuation of d4T and continued subsequent to the re-initiation of therapy with either ABC or ZDV. The decrease was accompanied by improvement in metabolic parameters typically associated with hyperlactatemia.
- Laboratory parameters most frequently associated with symptomatic hyperlactatemia or lipoatrophy improved following the discontinuation of d4T and initiation of therapy with either ABC or ZDV.
- The mitochondrial studies provided biochemical evidence of mitochondrial electron transport chain dysfunction in 7 out of 16 patient samples. In addition, loss of mitochondria was noted in selected specimens. While a defect at complex III provides a common mechanism for the decrease in the combined activities of rotenone-sensitive NADH cytochrome c reductase and antimycin A-sensitive succinate cytochrome c reductase, there was evidence of losses of activity of complex II, which does not have any subunits coded by mitochondrial DNA.
- The results presented above indicate that therapy substitution of ABC or ZDV (as COM) for d4T, as carried out in this study, may be a useful treatment strategy for some subjects with lipoatrophy.
- The above support the continued need for well-designed clinical trials that further investigate the etiology and pathogenesis of lipodystrophy and hyperlactatemia.

Conclusions

- Subjects with lipoatrophy showed progressive gains in body fat through Week 24 while maintaining virologic control when d4T was replaced with either ABC or ZDV (as COM).
- Subjects with hyperlactatemia also showed favorable decreases in lactate levels by Week 4, sustained through Week 24, when d4T was replaced with either ABC or ZDV (as COM).

References

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2. White, AJ. *Sex Trans Inf* 2001; 77:158-173.

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