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Uridine supplementation in the treatment of HIV lipoatrophy: Results of ACTG 5229

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Abstract

BACKGROUND—Lipoatrophy is prevalent on thymidine NRTIs (tNRTI). A pilot trial showed that uridine (NucleomaxX®) increased limb fat.

METHODS—A5229 was a multicenter trial in which HIV-infected individuals with lipoatrophy on tNRTI-regimens were randomized to NucleomaxX or placebo. Primary endpoint was change in limb fat from baseline to week-48. The study was powered to detect 400-gram difference between arms at week-48. A stratified Wilcoxon rank-sum test was used to assess between-arm differences.

RESULTS—The 165 subjects were 91% male, 62% white; median age 49 years, CD4 506 cells/mm^3, and limb fat 3037 grams; 81% had HIV-1 RNA ≤50 copies/mL; 76% were on AZT. Baseline characteristics were similar between groups. Only 59% completed 48-weeks of treatment, however only 3 subjects (1 on uridine) discontinued due to toxicity (diarrhea). In intent-

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Description of the role of authors:
Grace A McComsey: designed the study, wrote the protocol, enrolled patients, supervised the conduct of the study at the sites, wrote the manuscript which was edited by the coauthors
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Potential conflicts: Grace A McComsey has served as a scientific advisor for Bristol Myers Squibb, GlaxoSmithKline, Abbott, and Gilead Sciences, has received research grants from Bristol Myers Squibb, GlaxoSmithKline, Abbott, Merck, and Gilead Sciences, and is currently serving as the DSMB Chair for a Pfizer-sponsored study. UA Walker has applied for patents regarding to use of uridine or its precursors in lipodystrophy, serves as a consultant for the company that produces NucleomaxX®, and has received research grants from GlaxoSmithKline and Gilead Sciences. Judith Currier has received research grants from Merck and Company, Theratechnologies, Schering Plough and Tibotec. Judith Aberg has served as a scientific advisor to Abbott Laboratories, Boehringer Ingelheim Pharmaceutical, Inc, Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Theratechnologies Inc, Tibotec Therapeutics, and ViiV Healthcare. She has received research support from Gilead Sciences, Inc, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Schering-Plough Corp, Theratechnologies Inc, Tibotec Therapeutics, Virco Lab, Inc, and Wyeth. She has received honoraria from Abbott Laboratories, Bristol-Myers Squibb, and Gilead Sciences, Inc.

to-treat, there was no difference for changes in limb fat between treatments at week-24 or week-48. On as-treated analysis, uridine resulted in an increase in %limb fat vs. placebo (3.4% vs. −0.8%, p=0.01) at week-24 but not at week-48 (1.8% vs.3.8%, p=0.93). Similar results were seen when limiting the analysis to subjects with ≥80% adherence. The results were not related to severity of lipoatrophy or type of tNRTI. No changes were found in facial-anthropometrics, fasting lipids, trunk-fat, CD4, or HIV-RNA.

CONCLUSIONS—We found a modest transient improvement in limb fat after 24 weeks of uridine. The lack of sustained efficacy at week-48 was not due to changes in adherence or reduction in sample size. Uridine was safe and did not impair virologic control.

Introduction

Lipoatrophy of the face, arms, buttocks, and/or legs is a distressing and stigmatizing long term effect of antiretroviral therapy (ART). The pathogenesis of lipoatrophy is not fully understood, but several lines of evidence point towards an important role of nucleoside reverse transcriptase inhibitors (NRTI) in general, and the mitochondrial toxicity of thymidine NRTIs in particular (1–3). Some NRTIs, in particular thymidine NRTIs (tNRTIs, AZT and d4T) impair DNA polymerase-gamma or thymidine-kinase 2 and therefore interfere with the replication of mitochondrial DNA (mtDNA), leading to depletion in mtDNA, increased adipocyte apoptosis and ultrastructural abnormalities of adipocyte mitochondria (1–3). Lipoatrophy can be partially reversed by substituting tNRTIs with abacavir or tenofovir or by switching to NRTI-sparing regimens (4–6). Unfortunately, the reversal of lipoatrophy in these switch studies has been slow and only partial. Thus, it remains important to find a medical treatment for lipoatrophy that would prevent further development and improve the recovery of peripheral fat.

The supplementation of uridine is a new promising strategy in the treatment of lipoatrophy (7). In cultured adipocytes, uridine supplementation prevented and treated stavudine-related mtDNA-depletion, mitochondrial dysfunction, and consequent adipocyte apoptosis (8). A small placebo-controlled study (n=20) found that 3-months of NucleomaxX improved limb fat, but also increased visceral abdominal fat and decreased HDL-cholesterol (9). Another small single arm open-labeled study found improvement of subjective lipoatrophy scores but no changes in fat or peripheral blood mononuclear cells mtDNA levels in 16 lipoatrophic subjects who were treated with the uridine supplement for 4 months (10).

Doses of oral uridine or of uridine prodrugs are well tolerated in humans with mild osmotic diarrhea being dose-limiting in excessive doses (11–12). Phenotypic HIV-resistance assays and animal data do not indicate that uridine or its metabolites interfere with NRTI at HIV reverse transcriptase and thus would not affect the antiretroviral efficacy of nucleoside analogues (13–15).

In this study we hypothesized that dietary supplementation with uridine improves limb fat content in HIV infected subjects with established clinical lipoatrophy. As a source of uridine, we used NucleomaxX® (Pharma Nord, Vojens, Denmark), a dietary supplement which has been shown to increase the serum concentration of uridine in humans from an average of about 5 μM to more than 150 μM due to its high content (17%) of uridine and triacetyluridine (16) (www.nucleomaxX.com). A further goal of this study was to gather safety data of uridine supplementation in HIV-infected patients, including on HIV disease activity, and to determine if uridine supplementation is associated with changes in the amount of trunk and facial fat and with improvement in fasting lipid and lactate levels. We elected to study the effects of uridine supplementation among subjects who were currently receiving tNRTI containing therapy, because the efficacy of uridine in reversing

mitochondrial toxicity in cell culture was more evident in cells treated with tNRTIs versus other NRTIs, such as purines analogues.

METHODS

Study Design and Population

A5229 was a phase II/III, randomized, double-blind, placebo-controlled study of uridine supplementation in the form of NucleomaxX for the treatment of HIV-associated lipoatrophy. The study was approved by the Institutional Review Board at all participating sites, and a FDA investigational new drug application for the use of NucleomaxX® in HIV lipoatrophy was obtained. All patients provided written informed consent for the DEXA scanning, the collection of samples and subsequent analysis. Eligibility criteria included HIV-infected men and women of at least 18 years of age with established lipoatrophy. Subjects were required to have a plasma HIV-1 RNA level of ≤5000 copies/mL, and be receiving stable thymidine analogue-containing antiretroviral regimen for a minimum of 12 consecutive weeks prior to study entry, with no plan at study entry to significantly alter ART for the duration of the study. For this study, lipoatrophy was defined as patient self-reported and investigator-confirmed fat wasting in at least two of the following areas: face, arms, legs, or buttocks. Exclusion criteria included pregnancy, breastfeeding, liver failure, severe lactose intolerance, diabetes requiring hypoglycemic agents, as well as the use of didanosine, hormonal or immunomodulating therapies. Exclusionary laboratory results were creatinine clearance < 50 mL/min, AST and/or ALT >5 x upper limit of normal (ULN), lipase > 2.5 ULN, hemoglobin <9.0 g/dL, platelet count <50,000/mm^3, or absolute neutrophil count <750/mm^3.

Intervention—The subjects were centrally randomized in a double-blinded fashion to receive either NucleomaxX® or calorie, consistency, color and taste matched placebo for the 48 weeks of the study. NucleomaxX® and placebo were bought in sachets of 36 grams each from Pharma Trade Healthcare AB, Spånga, Sweden and were provided to study participants. Study participants were instructed to drink the entire contents of one sachet after thoroughly mixing it with milk, juice, or water. Since the dosing was on an every other day schedule, instructions were given that if all three sachets were not taken in one day (first 24 hour period), the unused sachet(s) could be taken the next day (second 24 hour period), so that subjects would receive a total of 3 sachets (108 grams total) in a 48-hour period. There were no food restrictions. Antiretroviral drugs were not provided by the study. The subjects were informed to maintain their current antiretroviral therapy, and not modify their exercise or dietary habits during the course of the study period.

Outcome and Follow-up—Study evaluations included physical examination, fasting blood assessments, dietary questionnaires, facial anthropometrics, and whole body dual-energy x-ray absorptiometry (DEXA) scanning at study entry, weeks 24 and 48. Additional safety visits were carried out at weeks 4, 8, 12, 18, and 36 for the purpose of clinical and laboratory monitoring for toxicities, intolerance, and adherence.

Total body DEXA scans were performed at each of the sites, after standardization using a phantom. Central reading occurred at Tufts University, and the readers were blinded to patients' characteristics and treatment allocation. Analysis of overall and body site-specific fat were performed on the basis of the standard protocol for body composition examination.

The metabolic assessments were done in a fasting state of at least 8 hours. They included glucose, insulin, and lipoprotein serum levels. Serum electrolytes, liver enzymes, CD4 cell count, HIV-1 RNA, glucose, lipid panel, and blood lactate were measured per ACTG standards.

All visits included assessment for clinical adverse events, use of concomitant medications, and adherence. Adherence to study medication was determined by available data on sachet count of dispensed versus returned sachets at each study visit, and self-reported missed doses if returned sachet data were not available. Based on these data, an adherence score at each visit was computed at each visit, and scores were averaged over study visits for each treatment group. The adherence score for each visit was computed using: adherence % = [(number of sachets dispensed − number of sachets returned)/number of sachets expected to be taken] ×100. Permanent cessation of the drug was mandatory for grade 4 adverse events, development of diabetes, or pregnancy.

Statistical Analysis—The primary outcome measure was the change in limb fat from baseline to week 48. A sample size of 82 subjects per arm (total of 164) was required to ensure an 85% power to significantly ($p<0.05$) detect a difference of 400 grams in limb fat from baseline to week 48 between the two treatment arms, assuming a standard deviation of 700 grams within groups and allowing for a dropout rate of 20%. Secondary outcome measures included changes in metabolic parameters. The changes from baseline to week 48 were compared between groups using a stratified Wilcoxon rank-sum test, whereas within group changes were tested using a Wilcoxon signed rank test. Four patient populations were considered based on outcome of analysis. (1) An intention-to-treat (ITT) approach with last observation carry forward (LOCF) method was used for primary endpoint analysis along with other secondary endpoints of limb fat change and trunk fat change. (2) As-treated (AT) analysis for limb fat change was performed with completers for DEXA measurements. (3) Study treatment adherence was assessed on ITT with LOCF population, i.e. based on population of primary endpoint analysis. Therefore, limb fat change analysis based on ≥80% adherence was on LOCF population, not completers. (4) Other outcomes such as CD4 change and change in lipid measures are based on ITT principle and completers for the outcomes. Details are presented in Table 2.

RESULTS

Patient Characteristics

A total of 167 subjects were enrolled from October 5, 2006 to January 7, 2008 from 31 ACTG sites. Two subjects never started study drug. Of the 165 subjects who started study treatment, 83 were randomized to receive NucleomaxX. Table 1 shows the baseline characteristics of the study groups. Overall 150 individuals (91%) were male; 102 (62%) were White/Non-Hispanic, and 26 (16%) were previous or current IV drug users. The overall median age at enrollment was 49 years. The baseline median limb fat was 3037 grams, trunk fat 8114 grams, and CD4 count 506 cells/mm^3. At entry, 81% had HIV-1 RNA ≤ 50 copies/mL. The randomization was stratified by type of tNRTI that subjects were receiving at study entry: 126 (76%) were on an AZT-containing regimen, and 39 (24%) were on a d4T-containing regimen. Demographics, clinical and HIV disease parameters were similar between the groups. In particular, there were no statistically significant differences in body mass index (BMI), limb fat, trunk fat, lipids, lactate, or glucose parameters at study entry.

Subject Disposition—Of the 165 subjects who received study treatment, 97 (59%) completed 48 weeks of study treatment. Of these, 49 were randomized to receive NucleomaxX and 48 to placebo. The median (quartile Q1, Q3) follow-up on study treatment was 47 (23, 48) and 47 (18, 48) weeks for the NucleomaxX arm and the placebo arm, respectively. The major reason for discontinuation was bad taste [13(16%) NucleomaxX and 8(10%) placebo; p=0.35]. However, only 3 subjects (1 on NucleomaxX and 2 on placebo) discontinued treatment due to protocol-defined toxicity (diarrhea).

Adherence Assessment—The median adherence score was 97.6% for NucleomaxX compared to 98.8% for placebo for a follow-up period of 48 weeks. There was no significant difference in adherence between the study treatments for either the first 24 weeks of the study (P=0.28) or the entire study (P=0.39).

Primary Endpoint: Changes in Limb Fat—The primary endpoint, change in DEXA-measured limb fat from baseline to week 48, is depicted in Figure 1 and Table 2. By ITT and LOCF, NucleomaxX (N=75) and placebo (N=69) groups had a median (Q1, Q3) change of 74 grams (−206, 344) and 110 grams (−202, 393) in limb fat, respectively from baseline to week 48 (p=0.64), and a median percent change of 1.8% (−6.0, 15.0) and 4.1% (−7.8, 13.4), respectively (p=0.99). The median change in limb fat from baseline to week 24 in the NucleomaxX arm (N=75) was 54g compared with 7g in placebo (N=66) group (p=0.25). The treatment comparison was not statistically significant for percent limb fat change from baseline to week 24 either (2.7% vs. 0.2%; p=0.09).

In the as-treated analyses with DEXA completers, the median percent change in limb fat was greater in the NucleomaxX arm when compared to Placebo (3.4% vs. −0.8%; p=0.01) at week 24 but not at week 48 (1.8% vs. 3.8%; p=0.93). Similar results were obtained from as-treated analysis of absolute change in limb fat, i.e. the median change in limb fat was greater in the NucleomaxX group compared to placebo (89 vs. −36 grams; p=0.012) at week 24, but not at week 48 (74 vs. 107 grams; p=0.71).

The results were similar when the AZT-containing stratum and the d4T-containing stratum were analyzed separately. During the study period, seven subjects in the NucleomaxX arm and six subjects in the placebo arm had discontinued AZT/ZDV or d4T prior to week 48 with a similar duration in the time to discontinuation of tNRTIs in both arms. The results were unchanged when these subjects were excluded from the analysis. The median change in daily caloric consumption from baseline to week 48 was slightly greater for the NucleomaxX arm (12 kcal/day) than for the Placebo arm (−156 kcal/day), but the difference was not statistically significant (P=0.11).

Further analysis of limb fat change from baseline to week 48 and to week 24 based on within group comparisons (using Wilcoxon signed rank test) showed very similar results to between group comparisons. For absolute change, there was some evidence of limb fat gain in NucleomaxX group (P=0.05) but not in placebo group (P=0.88) for week 24, but there was no evidence of significant change from baseline to week 48 in either group (NucleomaxX p=0.21, placebo p=0.13). Results based on percent change limb fat from within group analysis were also in agreement with those of absolute change, i.e. NucleomaxX p=0.008 and placebo p=0.90 at week 24, and NucleomaxX p=0.08 and placebo p=0.132 at week 48.

Subgroup analyses were undertaken to evaluate whether there was any evidence of variation in change of limb fat according to gender, race/ethnicity, and age by randomized treatment arms. No significant interaction effect was found (p>0.05). In addition, change in limb fat was not found to significantly correlate with baseline values of BMI and limb fat (both p>0.05).

After adjustment for adherence, the regression analysis showed that there was no significant difference (p=0.88) between NucleomaxX and placebo for absolute or percent change in limb fat from baseline to week 48. However there was a suggestive relationship (p=0.06) between percent limb fat change from baseline to week 24 and treatment group after adjustment for adherence during the same period. When limiting the analysis to subjects with at least 80% adherence, there was a significant difference in % change in limb fat at

week 24 favoring NucleomaxX (3.4% vs. −0.8%, respectively; p=0.01), but not at week 48 (3.9% vs. 3.8%; p=0.92), and similarly a significant difference in absolute change in limb fat (88.5 vs. −35.5 grams; p=0.02) at week 24 but not at week 48 (105.5 vs. 103 grams; p=0.84).

Changes in Trunk Fat—At week 48, the median change in trunk fat was 274 g for the NucleomaxX arm, and was 550g for the placebo arm (p=0.10). In the as-treated analysis, the median change was 225g for the NucleomaxX arm and 563g for the placebo arm, respectively (p=0.09). No significant differences were found in the response to treatment by gender, race/ethnicity, or age. At week 24, the median change in trunk fat was 299g for the NucleomaxX arm and 330g for the placebo arm (p=0.62). As-treated analysis yielded similar results.

Other Mitochondrial and Metabolic Endpoints

No statistically significant between-arm difference was seen in changes in body mass index. Also no changes were seen in any of the facial anthropometrics measurements (infraorbital, buccal, submandible fat-folds) between groups. No differences in changes from baseline to week 48 were seen in hemoglobin, leukocytes, creatinine kinase, fasting glucose, lactate, or triglycerides between the NucleomaxX and placebo arm. However, notable although modest effects on the cholesterol concentrations were seen. The median change in fasting total cholesterol was significantly greater for the NucleomaxX arm than for the Placebo arm (1 vs. −2 mg/dL, P=0.031) at week 24, but not at week 48 (2 vs. −6 mg/dL; P=0.17). The median change in fasting LDL was marginally smaller for the NucleomaxX arm (−1 vs. −2 mg/dL in placebo; P=0.078) at week 24, and at week 48 (1 vs. −3 mg/dL, P=0.10). The median change in fasting HDL tended to be higher in NucleomaxX compared to placebo (1 vs. −1 mg/dL; p=0.076) at week 24, and was significantly greater (1 vs. −1 mg/dL; P=0.034) at week 48.

Adverse Events/Effect on HIV Disease Activity

Overall, 46/165 (28%) subjects reported grade 3 or above toxicities during the study (31% in the NucleomaxX arm vs. 24% in the placebo arm; p=0.39). The most common (>5 events) Grade ≥3 toxicities were: ache/pain/discomfort (6% in the NucleomaxX arm and 4% in the placebo arm), diarrhea/loose stools (5% in the NucleomaxX arm and 4% in the placebo arm), and abnormal creatine kinase (4% in the NucleomaxX arm and 6% in the placebo arm). There was no difference between the groups in the rate of any of these adverse events.

The protocol defined toxicities were diarrhea and hyperglycemia. Grade 2 or above diarrhea/loose stools was reported in 9 (11%) subjects in the NucleomaxX arm and 6 (7%) subjects in the Placebo arm (p=0.59). Grade 2 or above elevated fasting blood sugar was reported in 5 (6%) subjects in the NucleomaxX arm and 6 (7%) subjects in placebo. Two cases of diabetes occurred during the study, both in the placebo arm, and both had a history of impaired glucose tolerance prior to study enrollment. In addition, NucleomaxX treatment was not found to be associated with higher risk of any diagnosis compared with Placebo.

At entry, 70 (84%) subjects in the NucleomaxX arm and 64 (78%) subjects in the Placebo arm had HIV-1 RNA ≤50 copies/mL. Of the subjects with data available, 59/67 (88%) subjects in the NucleomaxX arm and 54/69 (78%) subjects in the Placebo arm had HIV-1 RNA ≤50 copies/mL at week 48 (p=0.17). The median change in CD4 count from baseline to week 48 was 33 and 28 cells/mm^3 for the NucleomaxX and Placebo arms, respectively (P=0.88).

DISCUSSION

The aim of this study was to determine if the pyrimidine precursor uridine increased limb fat in patients with HIV-lipoatrophy. This study was initiated after several cell culture studies showed that uridine supplementation of hepatocyes and adipocytes abrogated mitochondrial toxicities of tNRTIs (8,17–18)

It has been demonstrated in cultured hepatocytes that uridine or its metabolites compete with tNRTIs at steps of mitochondrial pyrimidine import, degradation or phosphorylation thus countering mtDNA depletion due to tNRTIs and secondary impairment of the electron transport trough the respiratory chain (18). Because the latter is also crucial for the function of dihydroorotate dehydrogenase (DHODH), a key enzyme in the *de novo* synthesis of all intracellular pyrimidines, tNRTI-related mitochondrial toxicity may lead to depletion in building blocks for mtDNA synthesis and thus increase the relative amounts of pyrimidine NRTIs. Through this mechanism, pyrimidine NRTIs may then compete more efficiently at DNA polymerase-gamma. A vicious circle is closed and may contribute to a further loss of mtDNA and oxidative capacity. By providing exogenous uridine from which all intracellular pyrimidines can be salvaged, this vicious circle may be disrupted and mitochondrial DNA and functions restored (18).

In our study, uridine supplementation did not improve limb fat after 48 weeks of treatment, despite a suggestion of a small but statistically significant effect at week 24 in the most adherent subjects. In a previous pilot study of NucleomaxX in HIV lipoatrophy, 20 subjects on AZT or d4T showed a remarkable increase (mean ± SD change of 880 ± 140 grams) in limb fat after only 3 months of NucleomaxX (9). A few differences between this study and the pilot study may explain the discrepancies in the findings. First, although the Finnish pilot study used the same product (NucleomaxX), the dose used was different: 36 grams three times daily for ten days each month, rather than every other day as used in our study. It is possible that more intensive, intermittent courses of uridine supplementation may be more effective. Second, participants in the Finnish study had been receiving ART for a median of 18 months prior to study drug, whereas in our study the cumulative duration of NRTI was unknown. It is possible that our patients had significantly longer exposure to tNRTIs and that like with other lipoatrophy interventions (such as AZT-to-TDF switch), prolonged use of tNRTIs before the lipoatrophy intervention jeopardizes the response of limb fat (19).

Although the safety profile of oral uridine or its prodrugs was reported to be excellent in HIV-negative subjects (20–21), it is important to rule out a negative effect of uridine or its metabolites on the ability of antiretroviral nucleoside analogues to inhibit HIV reverse transcriptase. While such an effect was previously excluded for a number of NRTIs and their combinations in phenotypic HIV-resistance assays and for zidovudine in an animal model (13–15), only small studies have been conducted in HIV-infected subjects (9–10). Consistent with the prior preclinical data, our study failed to detect a significant interaction between uridine and the antiretroviral or immunologic efficacy.

Despite lipoatrophy's frequent association with insulin resistance, the sugar cane derived dietary supplement did not have deleterious effects on glucose metabolism. However, glucose metabolism was only measured by fasting glucose in this study. Therefore, we could have failed to detect pre-diabetes or worsening insulin resistance. Similarly, we found no clinically meaningful changes in fasting lipid levels, despite earlier suggestion of decreased HDL-cholesterol after NucleomaxX treatment (9).

We recognize the limitations of this study, mainly the large number of discontinuations due to low grade toxicities and intolerance to the study drug. In addition, our measure of adherence may be arguably suboptimal, however sachet/pill count has been validated for use

in other ACTG studies. Additionally, 13 subjects (7 on NucleomaxX) changed tNRTI during the study which could significantly confound the results, although the results were unchanged when these subjects were excluded.

In summary, NucleomaxX was safe but not well tolerated by some subjects, mainly due to the bitter taste of pyrimidines. However, even in the most adherent subjects, limb fat did not improve by week 48 despite a suggestion of a modest effect at 24 weeks. Despite the statistical significance, this effect size was very modest and unlikely to be appreciated by the participants. Finally, this study cannot comment on the effect of uridine supplementation in subjects receiving tNRTI-sparing regimen, however the proposed mechanism of action suggests that this strategy should not be effective in these subjects.

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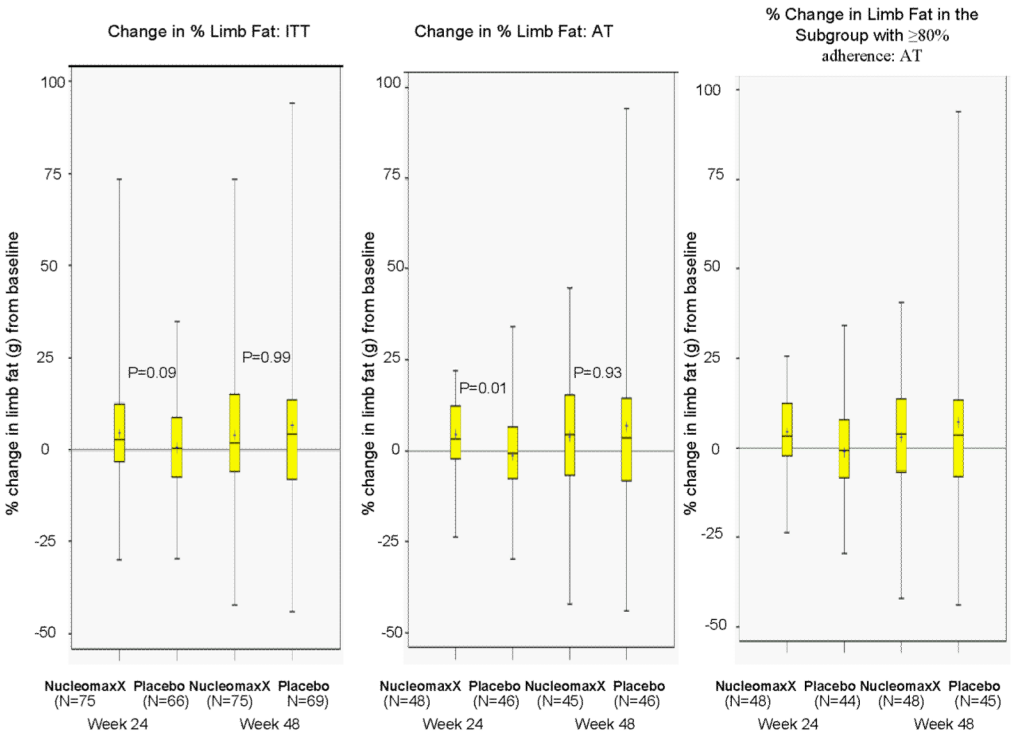

Figure 1.

Changes in limb fat by intent to treat analysis, as treated analysis, and when the analysis restricted to the subgroup with at least 80% adherence

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Table 1

Baseline characteristics by treatment group

		All Subjects (N=165)	NucleomaxX (N=83)	Placebo (N=82)
Gender	Male	150 (91%)	75 (90%)	75 (91%)
	Female	15 (9%)	8 (10%)	7 (9%)
Race/Ethnicity	White	102 (62%)	50 (60%)	52 (63%)
	Black	25 (15%)	11 (13%)	14 (17%)
	Hispanic	27 (16%)	15 (18%)	12 (15%)
	Asian	4 (2%)	3 (4%)	1 (1%)
	American Indian	5 (3%)	3 (4%)	2 (2%)
	Other/Invalid	1 (1%)	1 (1%)	0 (0%)
	Missing/Unknown	1 (1%)	0 (0%)	1 (1%)
IV Drug Use at Baseline	Never	139 (84%)	72 (87%)	67 (82%)
	Currently	1 (1%)	1 (1%)	0 (0%)
	Previously	25 (15%)	10 (12%)	15 (18%)
Age at Baseline (Yrs)	Median (Q1, Q3)	49 (44, 53)	47 (43, 54)	49 (44, 53)
	30–39	19 (12%)	9 (11%)	10 (12%)
	40–49	70 (42%)	38 (46%)	32 (39%)
	50–59	66 (40%)	28 (34%)	38 (46%)
	Over 60	10 (6%)	8 (10%)	2 (2%)
Stratification Factor	AZT-containing	126 (76%)	63 (76%)	63 (77%)
	D4T-containing	39 (24%)	20 (24%)	19 (23%)
CD4 Count	Median (Q1, Q3)	506 (353, 724)	506 (353, 724)	504 (376, 709)
	< 100	1 (1%)	0 (0%)	1 (1%)
	100–199	8 (5%)	6 (7%)	2 (2%)
	200–299	14 (8%)	7 (8%)	7 (9%)
	300–500	55 (33%)	26 (31%)	29 (35%)
	> 500	82 (50%)	41 (49%)	41 (50%)
	Missing/Unknown	5 (3%)	3 (4%)	2 (2%)
HIV-1 R N A ≤50 cp/mL		134 (81%)	70 (84%)	64 (78%)

		All Subjects (N=165)	NucleomaxX (N=83)	Placebo (N=82)
BMI (kg/m^2)	N, Median (Q1, Q3)	161, 23.9 (21.9, 26.0)	81, 23.6 (21.4, 25.9)	80, 24.3 (22.2, 26.5)
Limb fat (grams)	N, Median (Q1, Q3)	165, 3037(2002, 4403)	83, 3149 (1833, 4210)	82, 2995 (2082, 4847)

Note: No statistically significant difference for baseline characteristics between the study arms; Q1=first quartile, Q3=third quartile

Table 2

Summary of outcome variables by treatment group; N, median(Q1, Q3)

Outcome	NucleomaxX	Placebo	P-value
ITT, LOCF results:			
Limb fat (g) change from baseline to week 48	75, 74(−206, 344)	69, 110(−202, 393)	0.64
Limb fat (g) change from baseline to week 24	75, 54(−117, 315)	66, 7(−202, 238)	0.25
Limb fat % change from baseline to week 48	75, 1.8(−6, 15)	69, 4.1(−7.8, 13.4)	0.99
Limb fat % change from baseline to week 24	75, 2.7(−3.4, 12.4)	66, 0.2(−7.3, 8.8)	0.09
Trunk fat (g) change from baseline to week 48	75, 274(−614,1065)	69,550(−248,1296)	0.09
Trunk fat (g) change from baseline to week 24	75, 299(−379, 787)	66, 330(−463, 923)	0.62
As-treated, completer results:			
Limb fat (g) change from baseline to week 48	45, 74(−217, 231)	46, 107(−247, 370)	0.71
Limb fat (g) change from baseline to week 24	48, 89(−65, 325)	46, −36(−203, 144)	0.01
Limb fat % change from baseline to week 48	45, 1.8(−7.2, 11.5)	46, 3.8(−7.8, 14.3)	0.93
Limb fat % change from baseline to week 24	48, 3.4(−2.4, 12.5)	46, −0.8(−7.5, 6.5)	0.01
For at least 80% adherent subjects, LOCF results:			
Limb fat % change from baseline to week 48	48, 3.9(−6.6, 13.7)	45, 3.8(−7.8, 13.4)	0.92
Limb fat % change from baseline to week 24	48, 3.4(−2.4, 12.4)	44, −0.8(−8.2, 7.8)	0.01
ITT, completer results:			
HIV-1 RNA ≤50 cp/mL at week 48	59/67 (88%)	54/69 (78%)	0.17[λ]
CD4 cell count change from baseline to week 48	80, 33(−44, 90)	80, 28(−43, 108)	0.88
Fasting lactate (mmol/L) change from baseline to week 48	67, 0.2(−0.2, 0.6)	62, 0.1(−0.2, 0.4)	0.60
Fasting glucose (mg/dL) change from baseline to week 48	78, 2(−6, 9)	78, 4(−5, 11)	0.13
Fasting total cholesterol (mg/dL) change from baseline to week 48	77, 2(−15, 22)	75, −6(−22, 18)	0.17
Fasting triglycerides (mg/dL) change from baseline to week 48	77, −8(−29, 49)	75, 13(−28, 62)	0.43
Fasting HDL (mg/dL) change from baseline to week 48	77, 1(−3, 4)	73, −1(−6, 2)	0.03
Fasting LDL (mg/dL) change from baseline to week 48	67, 1(−12, 23)	61, −3(−21, 15)	0.10
Fasting non-HDL (mg/dL) change from baseline to week 48	66, 2 (−13, 18)	61, 2 (−18, 17)	0.76
Infraorbital fat- fold (mm) change from baseline to week 48	77, 0.3(−1, 2)	74, 0.3(−0.7, 1)	0.88
Buccal fat-fold (mm) change from baseline to week 48	77, 0.3(−1, 1.3)	74, 0(−0.7, 1.7)	0.94
Submandible fat-fold (mm) change from baseline to week 48	77, 0(−1, 1)	74, 0.3(0, 1.3)	0.06

P-value from stratified Wilcoxon rank sum test,

[λ]P-value from Fisher's exact test