

# A 48 week randomized study of uridine supplementation versus switch to tenofovir (TDF) on limb fat, mitochondrial function, inflammation, and bone mineral density in HIV lipodystrophy

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## Abstract

**Background:** Switch studies have demonstrated that lipodystrophy modestly improve when the thymidine analogue NRTI (tNRTI) is removed. Pilot short trials showed that uridine supplementation (as NucleomaxX®) improves lipodystrophy but the pathogenesis and sustainability of these findings remain uncertain. We compared uridine supplementation in the form of NucleomaxX® to tNRTI switch to TDF in subjects with lipodystrophy on tNRTIs.

**Methods:** All subjects at baseline had lipodystrophy and were on a d4T or AZT-containing regimen with HIV-1 RNA < 400 copies/mL. A randomized, open-label, 48-week study switched patients from the tNRTI to TDF or added uridine (while continuing tNRTI). Baseline and 48 week endpoints were limb fat by DEXA scan, subcutaneous abdominal fat mtDNA and mtRNA, PBMC mtDNA, plasma inflammation markers (sTNF receptors, hsCRP and IL-6), bone mineral density of the hip and lumbar spine, HIV-1 RNA, CD4 counts, and fasting metabolic parameters

**Results:** 50 subjects enrolled (n=24 TDF-switch; 26 uridine). Median age was 48 years; 50% white; 80% males; median limb fat 4494 grams; 80% were receiving AZT at entry. Baseline characteristics were similar between groups. In TDF-switch arm, fat mtDNA, PBMC mtDNA, and inflammation markers did not change although significant increases in mtRNAs (ND1/L13, ND6/L13, CTYB/L13; all p<0.001), limb fat [+409 g (IQR -59; 1155)], CD4 count (p=0.03) and decreases in total-and hip-BMD (median -3.3%; IQR -5.1-0; p=0.005) were seen. In the uridine arm, mtRNAs increased (all < 0.001), hsCRP and IL-6 increased (both p=0.02), while fat mtDNA decreased without changes in limb fat or PBMC mtDNA. Between-group changes were significant for fat mtDNA (p=0.02), hsCRP (p=0.02), IL-6 (p=0.02), limb fat (p=0.04), and total-and hip- BMD (p=0.002). On the TDF-switch, changes in limb fat negatively correlated with baseline fat mtDNA, tNRTI duration and with changes in insulin, and positively with baseline insulin, baseline CD4 and changes in fat mtDNA. No correlation was found between changes in limb fat and those of fat mtRNA, PBMC mtDNA, inflammation markers or PI or NNRTI duration.

**Conclusion:** In subjects with lipodystrophy, switching from a tNRTI to TDF for 48 weeks led to significant increases in limb fat and fat mtRNA. Uridine supplementation did improve mtRNA, but worsened inflammation markers and fat mtDNA and did not change limb fat. Large decreases in total- and hip BMD were seen after TDF switch.

## Background

- Lipodystrophy mildly improves after discontinuation of thymidine NRTI (tNRTI) therapy.

- In vitro, animal studies and a small pilot trial showed that uridine supplementation in the form of NucleomaxX may prevent and even reverse mitochondrial toxicity of tNRTIs.

- To date, no human study has assessed the mitochondrial and adipocyte effect of adding NucleomaxX vs. switching from tNRTI to tenofovir (TDF) in HIV infected subjects with established lipodystrophy.

## Methods

- We enrolled 50 HIV-infected adult subjects with clinical lipodystrophy, on stable tNRTI-containing ART for at least 12 weeks ≥ 18 years old and with HIV-1 RNA < 400 copies/mL.

- All patients were enrolled at the John T Carey Special Immunology Unit, Cleveland, Ohio; Exclusion criteria were diabetes, active endocrine disorders, use of hormonal therapies.

- Patients were randomized 1:1 in an open-labeled fashion to:

- Switch tNRTI for TDF

- Continue tNRTI and add NucleomaxX 36 gram sachet TID every other day

- Patients underwent at baseline and 48 weeks: whole body DEXA scanning, lumbar spine and hip DEXA scanning, blood tests including PBMC mtDNA levels, fasting lipids and insulin, HIV-1 RNA, CD4 counts, and inflammation markers (soluble TNF receptors I and II, hsCRP, and IL-6) and an excisional fat biopsy from the lower abdomen. These biopsies were done under local anesthesia by a plastic surgeon. Fat mtDNA and mtRNA levels were measured in fat tissues by real time PCR. Laboratory personnel were blinded to patients' characteristics.

- Statistical analysis: The level of significance was set at 0.05 for all analyses. All analyses were carried out using SAS, v.8.2 (The SAS Institute, Cary, NC).

**Funding:** The study is supported by the National Institute of Allergy and Infectious Diseases, R01-AI-060484 (GM)

## Results

Median (IQR)	Uridine (n=26)	TDF-switch (n=24)
Age (years)	48 (41,51)	48 (43,51)
Sex (male)	86%	86%
Race		
White	57%	%54.16
African Americans	43%	%33.33
Hispanic	0%	%8.33
Asian	0%	%4.16
BMI (kg/m <sup>2</sup> )	26(19,28)	26(22,28)
CD4+ cell count (cells/mm <sup>3</sup> )	578(439,781)	532(334,858)
Limb fat (kg)	4.4(2.9,6.3)	5.5(3.4,7.0)
Known duration of HIV (months)	146 (78,184)	108 (68,183)
Receiving AZT at entry	73%	83%
Duration of thymidine NRTI (months)	41(24,86)	79(48, 86)
Pi at study entry	38%	50%

Table 1. Baseline Characteristics of Study Participants

\*No significant difference in baseline characteristics between groups

## Correlations

-In the TDF-switch group, changes in limb fat negatively correlated with baseline fat mtDNA, tNRTI duration and with changes in insulin, and positively with baseline insulin, baseline CD4 and changes in fat mtDNA.

-No correlation was found between changes in limb fat and those of fat mtRNA, PBMC mtDNA, inflammation markers or PI or NNRTI duration.

Median (IQR)	Uridine N=26			TDF-switch N=24			Between group p
	Baseline	Change to Week 48	P	Baseline	Change to Week 48	P	
BMI (kg/m <sup>2</sup> )	26(19,28)	0(-0.4,0.5)	0.71	26(22,28)	0(-0.6,0.7)	0.70	0.53
Limb fat (kg)	4.4(2.9,6.3)	0.1(-0.3, 0.3)	0.65	5.5(3.4,7.0)	0.4(-0.06,1.2)	<b>0.007</b>	<b>0.04</b>
Trunk fat (kg)	7.9(5.6,11.6)	0.2(-0.5,0.6)	0.97	7.7(5.8,10.1)	0.7(-0.04,1.4)	<b>0.02</b>	<b>0.02</b>
Fat mtDNA (copies/cell)	662(395,1410)	-169(-778,64)	<b>0.03</b>	641(396,1343)	321(-298,669)	0.37	<b>0.02</b>
PBMC mtDNA (copies/cell)	301(253,424)	-24(-158,91)	0.44	290(225,381)	-52(-105,108)	0.63	0.81
ND1/L13	2.7(2.0,8.9)	3.7(-0.2,8.0)	<b>0.001</b>	6.3(3.1,11.4)	6.3(3.7,10.9)	<b>&lt;0.001</b>	0.07
ND6/L13	0.8(0.5,2.0)	2.2(0.2,5.0)	<b>&lt;0.001</b>	1.5(0.8,4.0)	3.9(1.6,6.4)	<b>&lt;0.001</b>	0.17
CYTBL13	2.2(1.3,4.0)	2.8(0.8,4.5)	<b>&lt;0.001</b>	4.7(2.0,7.1)	7.1(3.9,10.1)	<b>&lt;0.001</b>	<b>0.01</b>
Lumbar spine BMD (g/cm <sup>2</sup> )	1.1(0.9,1.2)	0.39 (-0.96, 1.68)	0.52	1.05(1.0,1.1)	0.0 (-2.9, 1.76)	0.50	0.28
Hip BMD (g/cm <sup>2</sup> )	0.81(0.73,0.97)	0.45 (-0.27, 3.56)	0.14	0.81(0.74,0.94)	-3.3%(-5.1,0.0)	<b>0.01</b>	<b>0.002</b>
IL-6 (pg/ml)	2.6(2.0,3.8)	25.9(10.6,53.7)	<b>&lt;0.001</b>	4.2(2.0,14.2)	2.4(-1.7,55.0)	0.21	<b>0.02</b>
hsCRP (mg/L)	2.0(0.8,4.5)	15.9(4.5,29.9)	<b>&lt;0.001</b>	3.6(1.4,8.4)	-1.1(-4.3,7.1)	0.69	<b>0.02</b>
sTNFR1 (pg/ml)	590(536,831)	48(-137,274)	0.27	615(509,894)	66(-195,169)	0.95	0.63
sTNFR2 (pg/ml)	214(139,411)	724(371,1091)	<b>&lt;0.001</b>	344(133,723)	189(-223,1355)	0.10	0.18
LDL-cholesterol (mg/dL)	123(96,148)	-2(-16,11)	0.43	111(90,127)	-5(-19,20)	0.98	0.78
Triglycerides (mg/dL)	163(109,241)	17(-34,42)	0.65	187(132,363)	-38(-125,32)	<b>0.05</b>	0.07
Insulin (uIU/ml)	10(7,16)	1(-4.0,3.0)	0.60	10(4,12)	-0.5(-3.5,3.0)	0.64	0.54

Table 2. Metabolic results; results expressed in median (IQR)

## Conclusions

- In subjects with lipodystrophy, switching from a tNRTI to TDF for 48 weeks led to significant increases in limb fat and fat mitochondrial RNA levels, and a large decrease in hip BMD.
- Uridine supplementation in the form of NucleomaxX improved mitochondrial RNA levels, but worsened fat mtDNA and did not change limb fat.
- While TDF-switch did not change inflammation markers, the use of NucleomaxX led to large increases in several of the inflammation markers. The etiology of this observation is unclear but is concerning.