Current perspectives on Lipodystrophy

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What is lipodystrophy?

- Lipodystrophies are disorders characterised by loss of adipose tissue
- Two main types:
  - —Familial eg: congenital generalised lipodystrophy, almost total lack of metabolically active adipose tissue since birth
  - —Acquired: generalised loss of subcutaneous fat or partial (limited to face, trunk and upper extremities)
- Autoimmunity underlies both types
- Metabolic complications such as hypertriglyceridemia, diabetes and insulin resistance are related to the degree of fat loss

Lipodystrophy

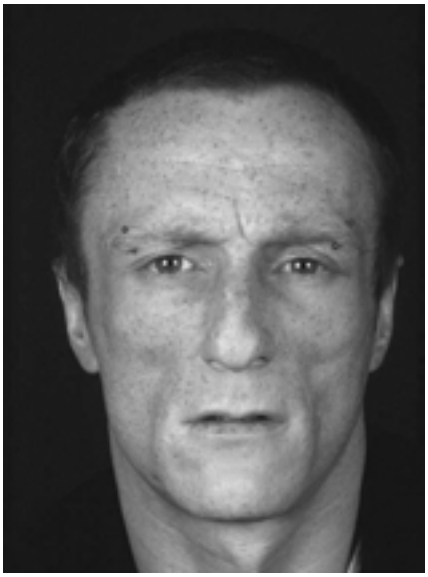
‘Scylla and Charybdis’

or

‘Aunt Spiker and Aunt Sponge’

Defining lipodystrophy

- **Physical body changes associated with fat**
  - **increased (viscceral, buffalo hump, breast enlargement, subcutaneous)**
  - **decreased (subcutaneous layer)**
- **Metabolic changes**
  - **Insulin resistance**
  - **Lactate**
  - **Lipid markers**

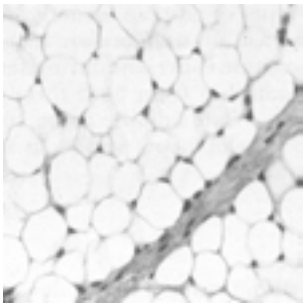


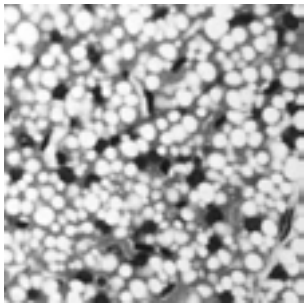
Measurement of Lipodystrophy

Carr et al	Others
Self-assessment	Masked photography
Physician assessment	Single cut MRI
Fasting triglycerides	Anthropometry
C-peptide	
DEXA scans	

White and brown adipose tissue

- White fat - unilocular , widespread subcutaneous and intra-abdominal depots.
- Brown fat - multilocular, widespread in newborn, gradually lost except for some sites eg: kidney, mediastinum





Factors influencing fat distribution

- Genetic factors
  - —Polymorphisms in the many proteins involved in lipid metabolism eg: complement, adrenoceptors, apolipoproteins, lipases, leptin,
  - —Subcutaneous fat correlates with androgen levels in men and breast fat correlates with oestrogen levels in women
- Enviromental factors
  - —Diet - high and low fat
  - —Exercise - correlates more with subcutaneous than visceral fat

Fat wasting

- Face (sunken cheeks, temple hollowness, sunken eyes, prominent zygomatic arch)
- Arms (skinny, prominent veins, muscularity and bones)
- Legs (skinny, symmetrical, prominent non-varicose veins, muscularity and bones)
- Buttocks (loose skin folds, prominent muscles, loss of contour/fat, hollowing)
- Trunk (loss of fat, prominent veins, muscularity and bones)
- Face - sunken cheeks
- Legs - prominent veins
- Buttocks - loss of contour
- Clinical criteria alone are sufficient

Using CT to measure visceral fat

Shaded area is visceral fat

Shaded area is subc. fat

Lipid disturbances

- Lipid disturbances can be assessed using serum TG and total cholesterol levels obtained after an overnight fast (ideally 12 hours).
- Data on LDL and HDL could also be collected.
- Triglyceride levels are significantly raised after feeding
  - —Method for estimating LDL levels using total cholesterol, HDL cholesterol and triglycerides
  - —VLDL = TG / 5
  - —LDLC = Total Cholesterol - HDLC - (TG / 5)

Lipodystrophy syndrome
Cohort Studies

➢ **Australia**	**Carr et al**	**220 patients****
➢ **Australia**	**Mallal et al**	**277 patients(**)**
➢ **Australia**	**Carter et al**	**159 patients**
➢ **France**	**Saint-Marc et al**	**154 patients**,**,****
➢ **France**	**Boufassa et al**	**489 patients**
➢ **Italy**	**Galli et al**	**188 patients**
➢ **Spain**	**Polo et al**	**150 patients**
➢ **USA**	**Lichtenstein et al**	**1,077 patients**
	total	**> 2,700**

John M. - Athens 1999

* = published

NRTIs in lipodystrophy: PROMETHEUS study
van der Valk et al. AIDS; 2001: *15* ***847-55***

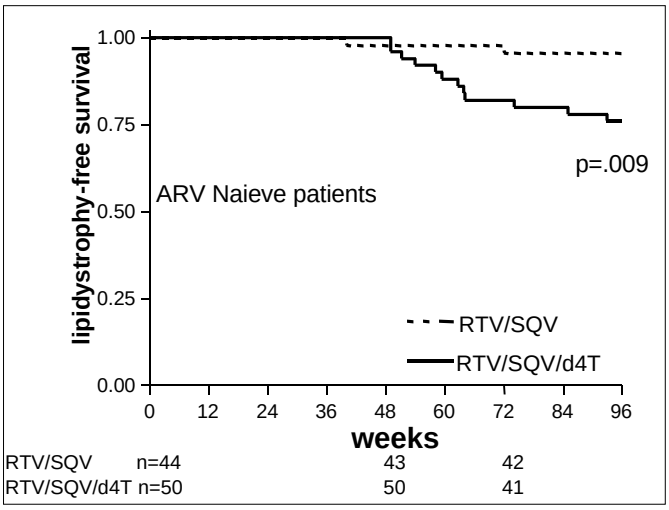
Occurrence of lipodystrophy - 96 weeks follow up

•29/175 pt. (17%) developed lipodystrophy		
RTV/SQV/d4T arm	22/88	(25%) (p=.003, χ2 test)
RTV/SQV arm	7/87	(8%)
•ARVT naive patients		
RTV/SQV/d4T-arm	12/50	(24%) (p=.008, χ2 test)
RTV/SQV - arm	2/44	(8%)
•ARVT experienced patients		
RTV/SQV/d4T-arm	10/38	(26%)
RTV/SQV - arm	5/43	(12%) *

*****median exposure to NRTI's prior to study entry 98 weeks (IQR 53-214)

Role of NRTIs in lipodystrophy ; PROMETHEUS study

van der Valk et al. AIDS ; 2001: *15* ***847-55***



NRTI associated lipodystrophy

Saint Marc *et al.* AIDS 1999; **13 1659-1667**

Prospective study (Inter LIPICO study)

- **43 pts on 2 NRTI (27 d4T, 16 AZT),** no PI´s
- **15 pts naive (controls)**

anthropometric measurements

CT scans: SAT:VAT, TAT

plasma lipid profiles

OGTT

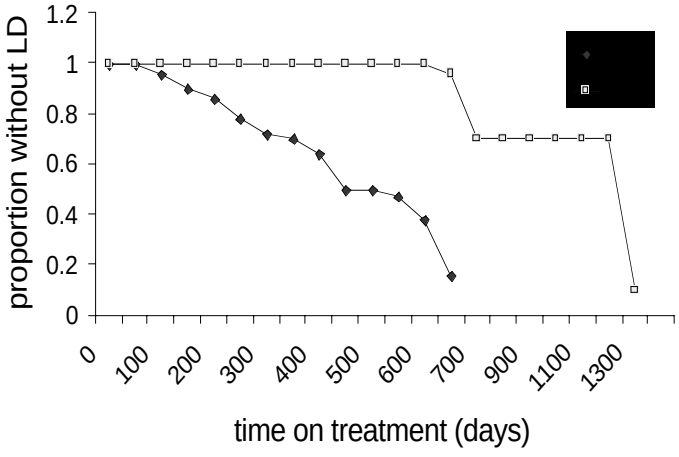
NRTI associated lipodystrophy

Saint Marc *et al.* AIDS 1999; 13 1659-1667

- **anthropometric measurements**
  - **total body fat % (mean) :**
    d4T 12.95 AZT 15.2* controls 17.37*
    ***(p<0,05)**
  - **biceps & scapular skinfolds**
    d4T « AZT = controls (p<0,05)
- **CT scans:**
  - **SAT d4T < AZT = controls (p<0,05)**
  - **SAT:VAT d4T << AZT < controls (p<0,05)**
  - **VAT:TAT d4T > AZT = controls (p<0,05)**

NRTI associated lipodystrophy

Saint Marc *et al.* AIDS 1999; 13 1659-1667



NRTI associated lipodystrophy

Saint Marc *et al.* AIDS 1999; 13 1659-1667

Odds ratio´s for developing lipodystrophy

	adjusted OR (95% CI)	P-value
d4T	**45.26 (3.79-540.9)**	**0.0026**
AZT	**0.022 (0.002-0.26)**	**0.0026**
3TC	**2.60 (0.64 - 10.65)**	**0.18**
ddI	**0.32 (0.08 - 1.32)**	**0.12**

Adjusted for age, HIV-1 RNA, duration of total and current NRTI therapy

LIPOCO study

Saint Marc *et al.* AIDS 2000: 37-49

- **Observational cohort (n=154)**
  - **naive** **n=15: 9.7%**
  - **longterm NRTI** **n=39: 25.3%**
  - **multiple combination (at least 1 PI)** **n=100: 65%**
- **July 1998 - June 1999**
  - ➡ **interim analysis until February 1999**
- **prospective design visits every 6 months**
  - ➡ **clinical chemistry, endocrinology, anthropometrics, CT-scans**

LIPOCO study

Saint Marc *et al.* AIDS 2000: 37-49

Odds ratio´s for developing fat alterations

	adjusted OR (95% CI)		P
NRTI group (n=39)			
d4T	**85.3**	**(3.6-999)**	**0.0058**
AZT	**0.012**	**(0.00-0.27)**	**0.0058**
3TC	**3.90**	**(0.73 - 20.63)**	**0.10**
ddI	**0.24**	**(0.046 - 1.30)**	**0.09**
PI-group (n=100)			
d4T	**4.01**	**(1.2-12.7)**	**0.018**
AZT	**0.25**	**(0.078-079)**	**0.0186**

adjusted for age, HIV-1 RNA, duration of total and current NRTI therapy

Cohort Studies-Sydney, Australia

Carr A, Miller J, Law M, Cooper DA *San Diego 1999*

- **220 patients (mainly male)**
- **cross sectional case-control study:**
  no ART (32) vs NRTI (42) vs NRTI+PI (146)

- **predictors of fat wasting**
  duration of PI, d4T use, total NRTI duration, age
- **predictors of abdominal obesity and buffalo hump**
  3TC, total NRTI
- **NRTI with hepatomegaly, lactic acidemia**
- **PI associated with hyperlipidemia, insulin resistance**

Cohort Studies-Western Australian Cohort Study
Mallal S, John M, Moore C *et al; San Diego 1999*

➢277 patients (82% male)

➢Outcome: subcutaneous fat wasting
(face/arms/legs/abdomen)

➢Assessment
- ✏Australian Lipodystrophy Prevalence Survey 3/98-2/99
  (questionnaire, physician assessment)
- ✏DEXA scans in 161 patients
- ✏Sequential DEXA scans in 77 patients, 6 monthly intervals.

➢Exclusions
- ✏acute, symptomatic NRTI hepatic steatosis/lactic acidosis

Cohort Studies-Western Australian Cohort Study
Mallal S, John M, Moore C *et al; San Diego 1999*

Predictors of subcutaneous fat wasting
multiple logistic regression model

Variable	P value	Odds Ratio
Age	0.0002	1.064
White race	0.0033	6.018
Cumulative time on a PI	0.0427	1.039 per month
Cumulative time on d4T	<0.0001	1.096 per month
Cumulative time on AZT	0.0015	1.021 per month

Cohort Studies-Western Australian Cohort Study
Mallal S, John M, Moore C *et al; San Diego 1999*

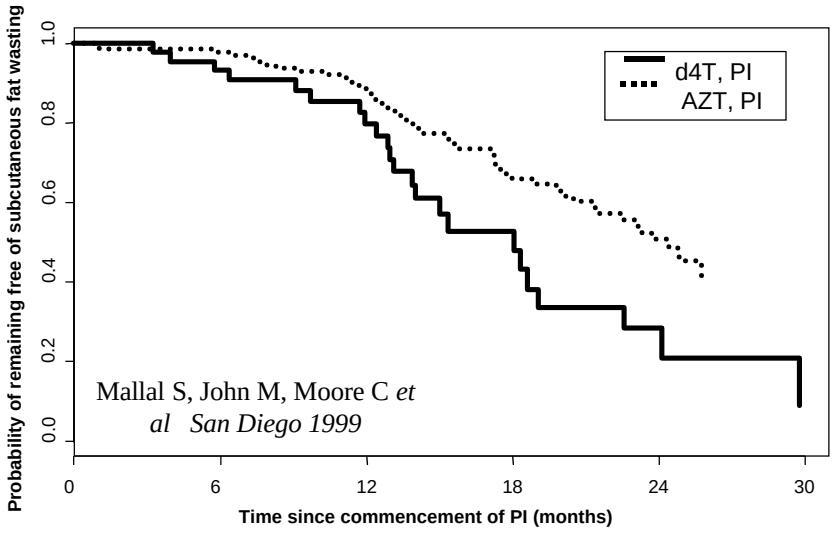
Subcutaneous fat wasting from triple ART

Cox proportional hazards model

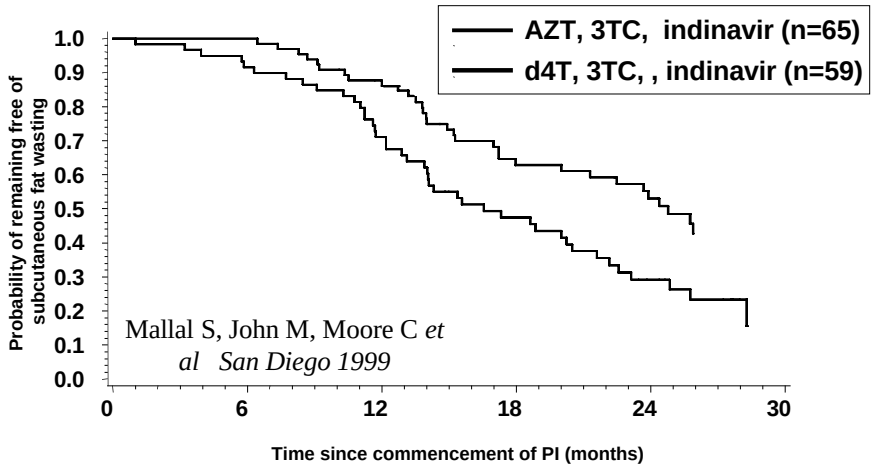
Variable	P value	Relative Risk
Age	<0.0001	1.052
White race	0.023	3.9
Cumulative time on dual NRTI prior to triple therapy	0.0046	1.021 per month
Cumulative time on d4T[1]	<0.0001	1.085 per month
Cumulative time on nevirapine[2]	0.022	0.943 per month

[1] stavudine increases risk by 256% per year compared with AZT
[2] compared with protease inhibitor therapy

Time to fat wasting in PI recipients from start of PIs **concurrent d4T versus AZT**



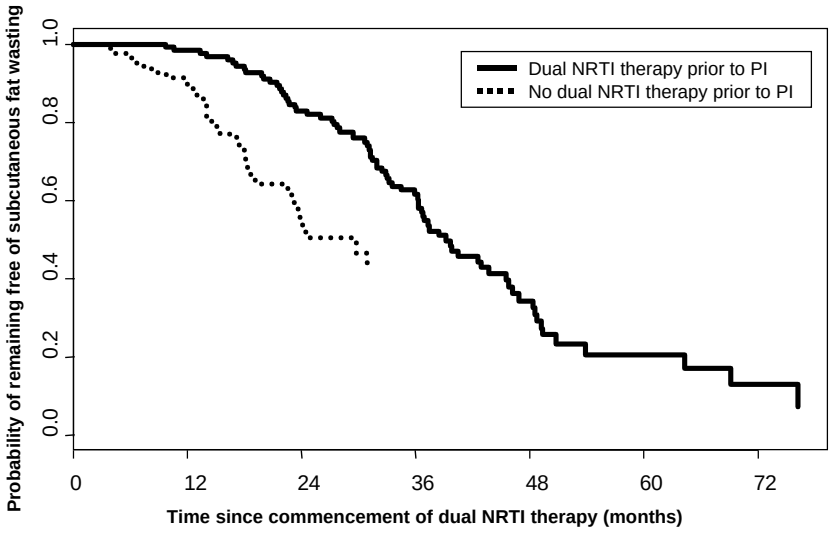
Time to fat wasting in PI recipients
(p<0.0049 Log-Rank Test)



Mallal S, John M, Moore C *et al San Diego 1999*

Accelerated fat wasting after adding PI to NRTIs

Mallal et al AIDS 2000



Lipoatrophy, lactic acidaemia & liver dysfunction

Carr A, Miller J, Law M, Cooper DA ***AIDS*** 2000, 14: F25 - F32 ***I***

- **220 patients (mainly male)**
- **cross sectional case-control study:**
  no ART (32) vs NRTI - PI (42) vs NRTI+PI (146)
- **LD: patient report of lipoatrophy ± fat accumulation**

results

LD symptoms:	**-**	**+**	**(% lipoatrophy)**
no ART	**32**	**0**	**-**
NRTI-PI	**32**	**14**	**(100%)**
NRTI+PI	**44**	**102**	**(100%)**

Lipoatrophy

Carr A, Miller J, Law M, Cooper DA ***AIDS*** 2000, 14: F25 - F32

Factors associated with peripheral lipoatrophy:

	OR	**p-value**
age	**1.23**	**0.01**
current therapy		
- **d4t**	**77.2**	**0.004**
- **ddI**	**1.70**	**0.70**
- **3TC**	**0.63**	**0.69**
- **AZT**	**5.5×10^{-7}**	**-**
duration of ART (per year)		
- **all NRTIs**	**1.73**	**0.03**

Lipoatrophy and lactic acidaemia Carr A, Miller J, Law M, Cooper DA ***AIDS*** 2000, 14: F25 - F32 ***/***

Analysis on all patients (n=220)

Factors associated with LD **(OR ; p-value):**

	LA	**↑ Abdo fat**
➢lactate > 2 mmol/L	**3.3 (0.03)**	**3.97 (0.009)**
➢current therapy		
- **d4t**	**6.69 (< 0.001)**	**2.14 (0.06)**
- **AZT**	**0.37 (0.16)**	**0.19 (0.14)**
➢duration of ART (per year)		
- **all NRTIs**	**1.26 (0.007)**	**1.11 (0.22)**
- **all PIs**	**3.0 (0.007)**	**3.45 (< 0.001)**

Lipoatrophy, lactic acidaemia & liver dysfunction

Carr A, Miller J, Law M, Cooper DA ***AIDS*** 2000, 14: F25 - F32

Lactate:

➢**cases higher lactates than controls**
(4.6 vs 1.2 mmol/L; p < 0.0001)

➢**higher in cases with liver involvement* (n=7)**
(6.8 vs 2.8 mmol/L; p =0.02)

*** hepatomegaly, ascites, peripheral oedema, encephalopathy**

➢**patients with hyperlactatemia**
- **older (44.9 vs 42.2 yrs)**
- **longer on d4T (17 vs 12 months)**
- **longer on ddI (9 vs 7 months)**
- **recent weight loss (40 vs 9 %)**
- **fatigue (58 vs 15%)**
- **nausea (40 vs 10%)**

Changes in HIV-Associated Lipodystrophy Over Time

Kenneth A. Lichtenstein, MD
Chairman, Department of Medicine
Rose Medical Center
Clinical Professor of Medicine
University of Colorado Health Sciences Center
Denver, Colorado, USA

HOPS: HIV Outpatient Study Evaluation of Risk Factors for LD

- HOPS cohort: HIV-infected outpatients from 8 specialty clinics in 7 US cities
- Sponsored by the Centers for Disease Control and Prevention (CDC)
- Two standardized patient/physician surveys:
  - Survey 1 - 1064 patients 4th quarter of 1998
  - Survey 2 - 1244 patients 3rd quarter of 2000
  - 546 patients were in both surveys
- Data collected
  - Demographic
  - Clinical
  - Immunologic
  - Virologic
  - Pharmacologic

HOPS Conclusions

- **Associations determined but not cause and effect relationships[1]**
- **Following risk factors associated with significant fat**

	P	Adjusted OR	95% CI
Age >40 y	**<.001**	**2.42**	**(1.68-3.49)**
HIV ≥7 y/AIDS ≥4 y	**.007**	**1.75**	**(1.17-2.61)**
BMI loss ≥1 kg/m²	**.021**	**1.6**	**(1.07-2.40)**
BMI Δ ≥2 kg/m²	**.009**	**1.68**	**(1.14-2.49)**
d4T ever used	**.004**	**1.82**	**(1.25-3.10)**
IDV ever used	**.003**	**1.97**	**(1.21-2.74)**
d4T ever used & IDV used ≥2 y	**.003**	**1.95**	**(1.25-3.05)**

[1]Lichtenstein. Personal communication 2000. [2]Lichtenstein. 13th IAC; 2000; Durban. Abstract 704.

Factors Associated with Atrophy Only Survey (N=244)

	Adj OR	95% CI	p-value
Host Factors			
Age > 50 yrs	3.17	1.52-6.98	0.003
White Race	4.66	2.55-8.86	0.001
Disease Factors			
Lower CD4%	3.08	1.82-5.31	0.0001
History of AIDS	2.60	1.54-4.49	0.001
BM Index < 21 kg/m²	2.75	1.52-5.08	0.001
Treatment Factors			
Use of d4T > 1 yr (83% use)	3.22	1.94-5.42	0.001

Conclusions

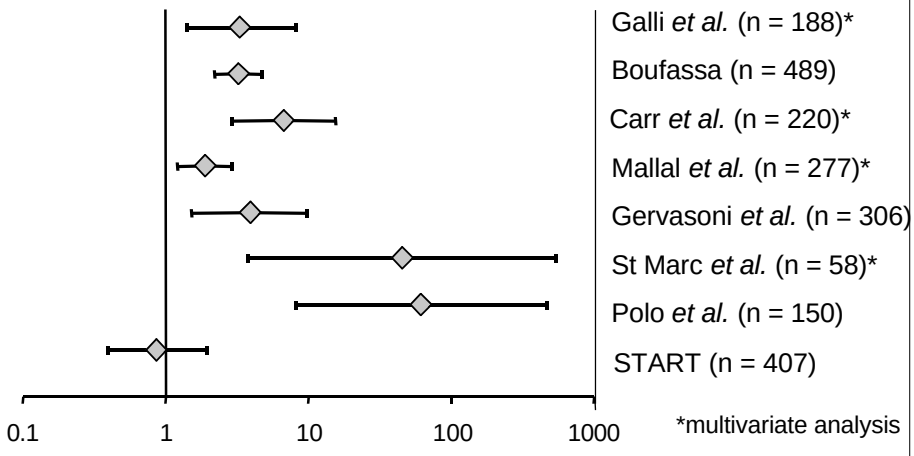
- Host factors such as age and race have strong associations with the development of lipodystrophy. Race is confounded by demographic and psychosocial factors that were not evaluated in the HOPS cohort.
- Measurements of severity of illness are consistently associated with the development of lipodystrophy in both the prevalence and incidence analyses.
- The magnitude of CD4 cell count or viral load response is associated with the development of lipodystrophy.
- Stavudine is strongly associated with lipoatrophy in the prevalence and incidence analyses but it is unclear whether the relationship is etiologic or co-linear (80% of the cohort had received it).
- Changing medications had no influence on improvement of fat maldistribution.
- Poor response to treatment or failure of therapy are associated with improvement in lipoatrophy.

Cohort studies
combined analysis

- **Gender, age and ?race influence risk of developing lipodystrophy and influence clinical phenotype**
- **Lipodystrophy syndrome associated with duration of :**
  - **PI as a class**
  - **NRTIs as a class**
  - **d4T (vs ZDV)**
  - **? 3TC**

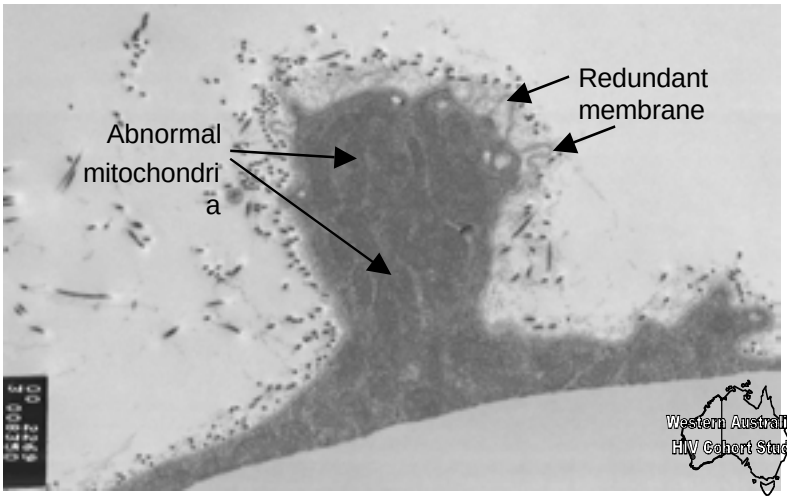
John M. - Athens 1999

Relative risk of lipodystrophy
d4T vs ZDV

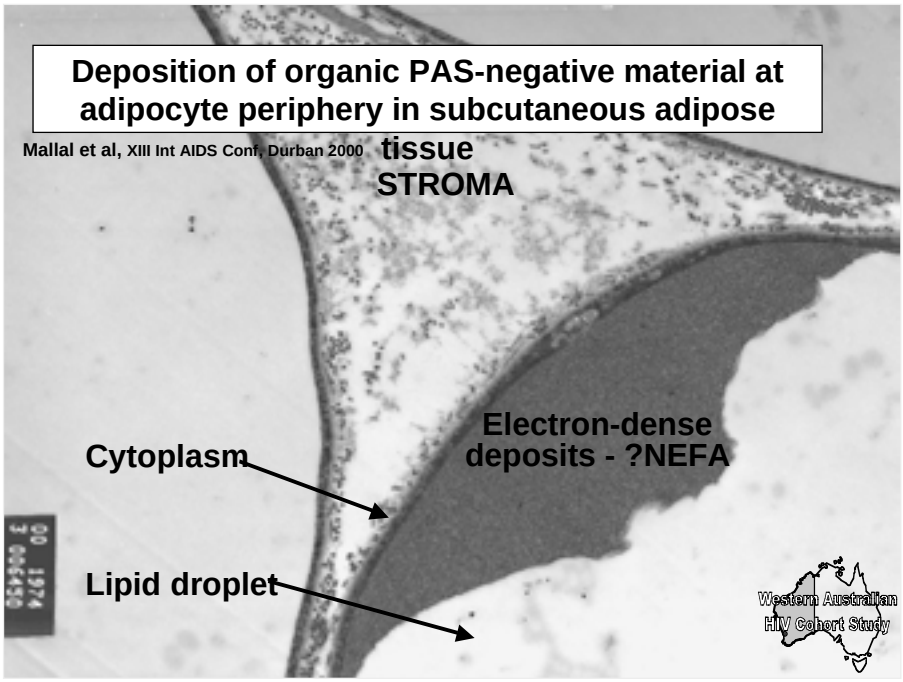


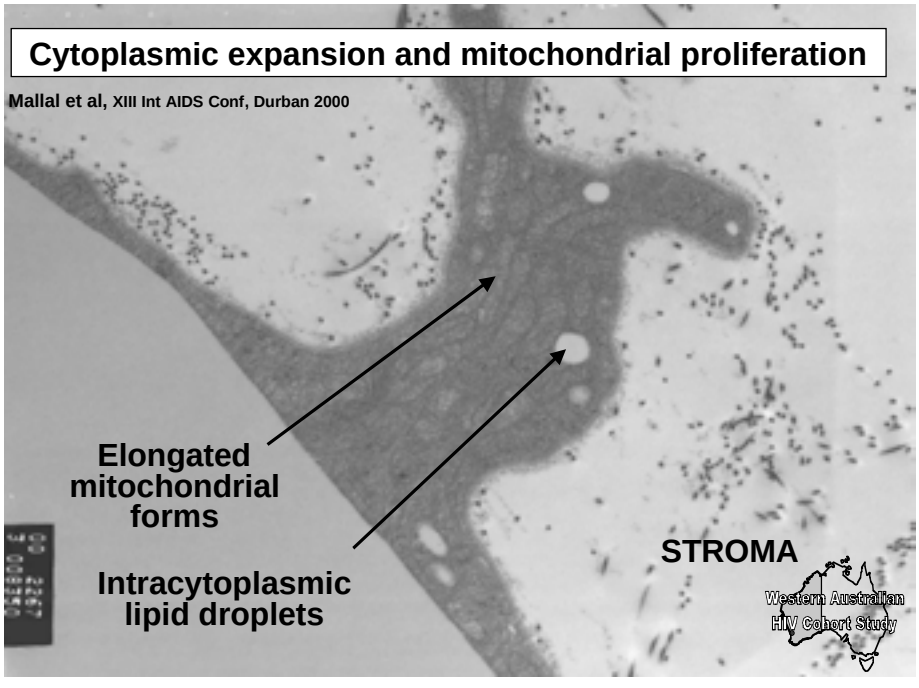
John M. - Athens 1999

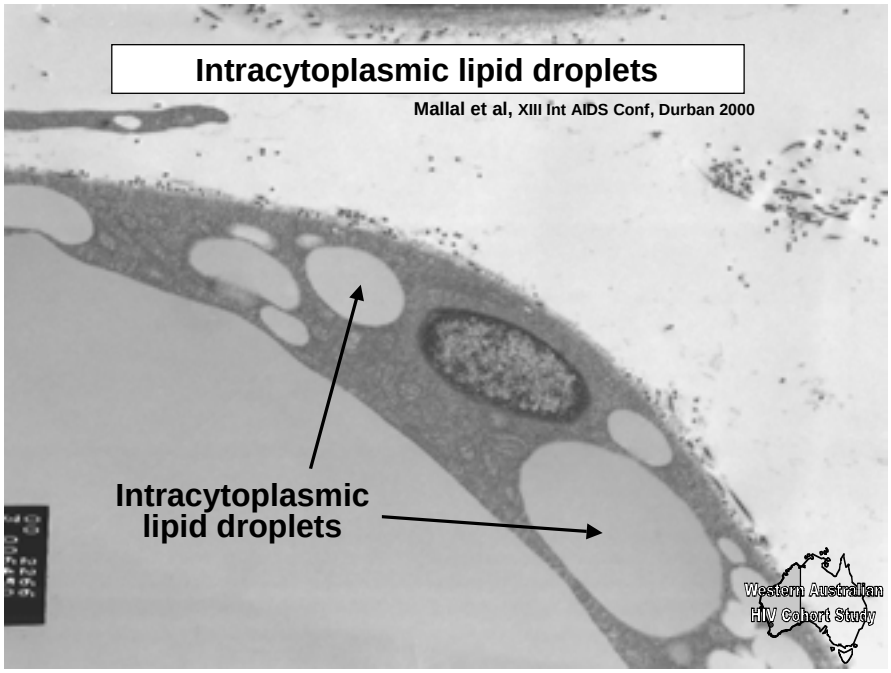
Light and electron microscopy findings from subcutaneous fat in ART-treated and naive pts



Mallal et al, XIII Int AIDS Conf, Durban 2000, Abs LpPeB7054


Deposition of organic PAS-negative material at adipocyte periphery in subcutaneous adipose tissue
Mallal et al, XIII Int AIDS Conf, Durban 2000
STROMA
Electron-dense deposits - ?NEFA
Cytoplasm
Lipid droplet
Western Australian HIV Cohort Study


Cytoplasmic expansion and mitochondrial proliferation
Mallal et al, XIII Int AIDS Conf, Durban 2000
Elongated mitochondrial forms
Intracytoplasmic lipid droplets
STROMA
Western Australian HIV Cohort Study



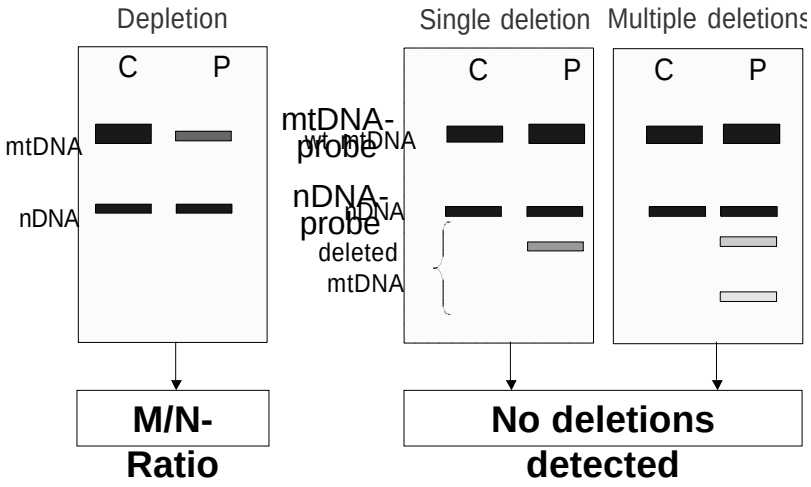
MtDNA-Analysis in HIV-associated lipoatrophy

Crossectional analysis of subcutaneous fat biopsies from the buttocks

Mean time on ART (months)	29.5	64.3		0.001
Current d4T (% of patients)	91	33		0.003
Cumulative Time on d4T (months)	32.5	6.1		<0.001

Walker UA. et al. *Antiviral Therapy* 2

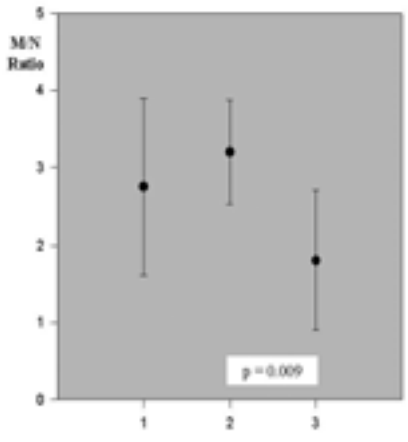
Depletion and deletion in mtDNA - Southern Blot

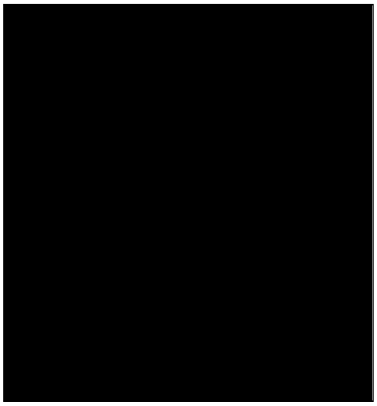


Walker UA. et al. *Antiviral Therapy* 2

mtDNA-depletion in subcutaneous adipose tissue
Association with NRTI-use

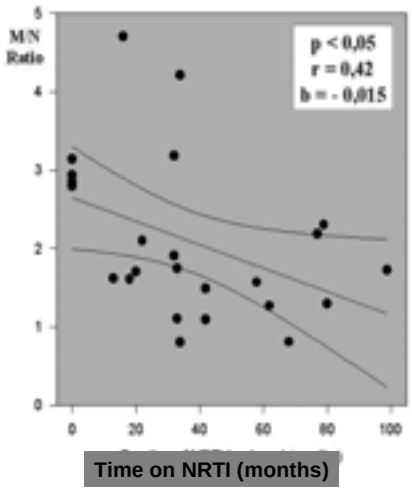
1. HIV-negative controls n = 8
2. HIV-positive, NRTI-naive n = 4
3. HIV-positive, NRTI-treated n = 20





Walker UA. et al. *Antiviral Therapy* 2000

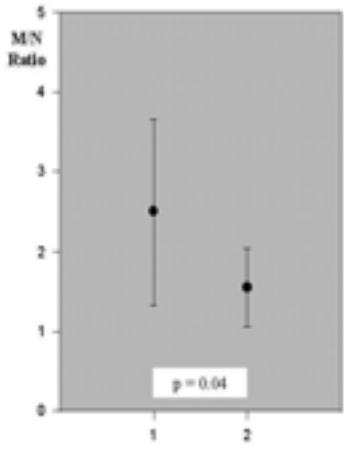
mtDNA-depletion correlates with time on NRTI



- NRTI-treated patients show a significant decline of mtDNA with prolonged NRTI- (but not with PI-) therapy.
- mtDNA-content declined by 0.6% per month of NRTI therapy.

Walker UA. et al. *Antiviral Therapy* 2000

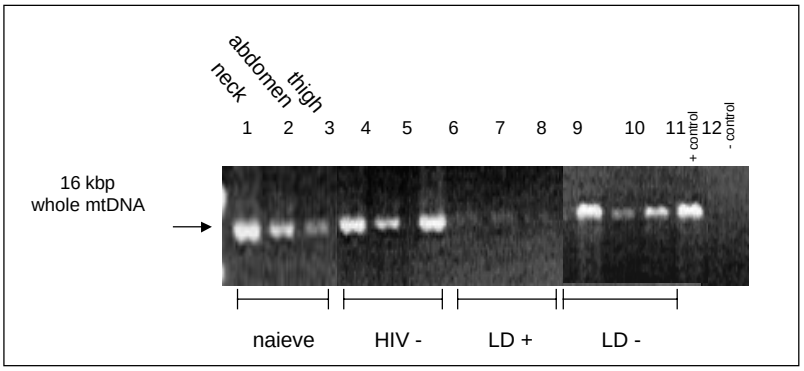
mtDNA-depletion in HIV-associated lipoatrophy



1. NRTI-exposed, LA^- n = 12
2. NRTI-exposed, LA^+ n = 11

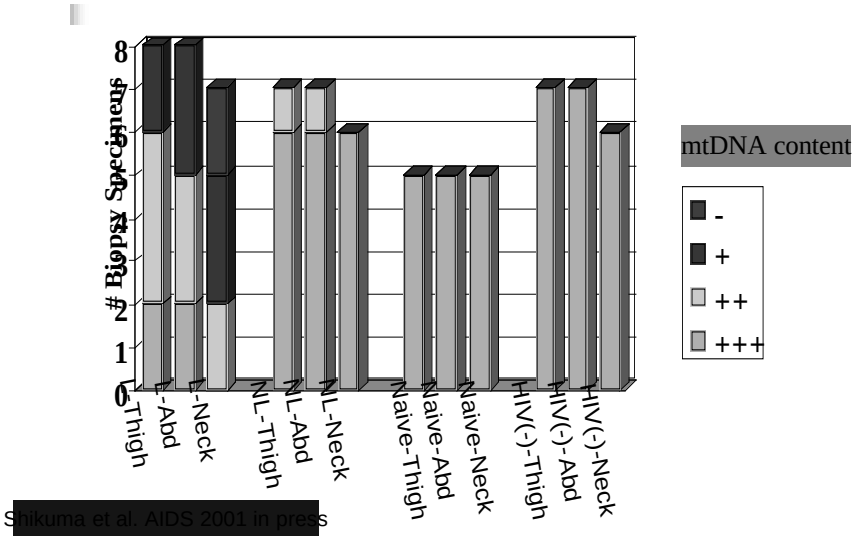
Walker UA. et al. *Antiviral Therapy* 2000

mt DNA decrease in adipose tissue of lipoatrophic patients - 1



Shikuma et al. AIDS 2001 in press

mt DNA decrease in adipose tissue of lipoatrophic patients



Shikuma et al. AIDS 2001 in press

Mitochondrial DNA depletion, assessed by real-time PCR-based quantitative assay, in subcutaneous fat of HIV-infected patients

Cannes, 2001

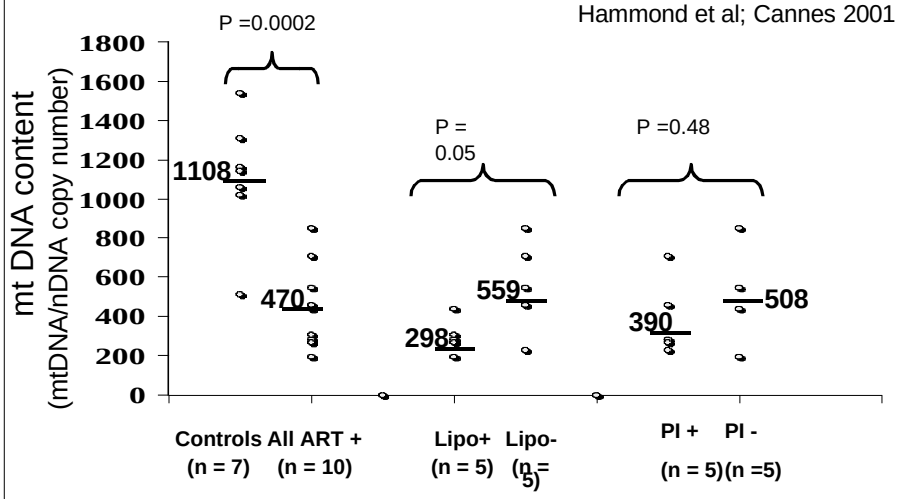
EL Hammond, A Martin, L Taylor, M John, DA Nolan,

SA Mallal

Centre for Clinical Immunology and Biomedical Statistics
Western Australia

mtDNA depletion in ART-treated, and lipoatrophy+ patients

Hammond et al; Cannes 2001



Subcutaneous biopsies in HIV patients

Hammond et al. Cannes 2001

Western Australian HIV Cohort Study

Summary

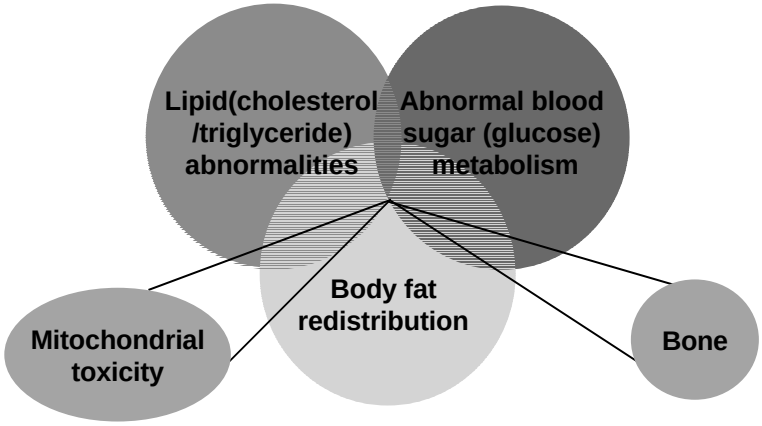
- PCR quantitative assays for mtDNA content- reliable and precise
- mtDNA content - similar in HIV– and HIV+ ART-naive controls
- ↑ Mitochondrial mass correlated with mtDNA depletion (P = 0.02)
- Measures of mtDNA/nDNA content (cf controls):

ART-treated

↓57% (unadjusted) ↓72% (adjusted)

Lipoatrophy +	Non-lipoatrophy
↓73% (unadjusted) ↓84% (adjusted)	↓50% (unadjusted) ↓42% (adjusted)

HIV-Related Metabolic Complications



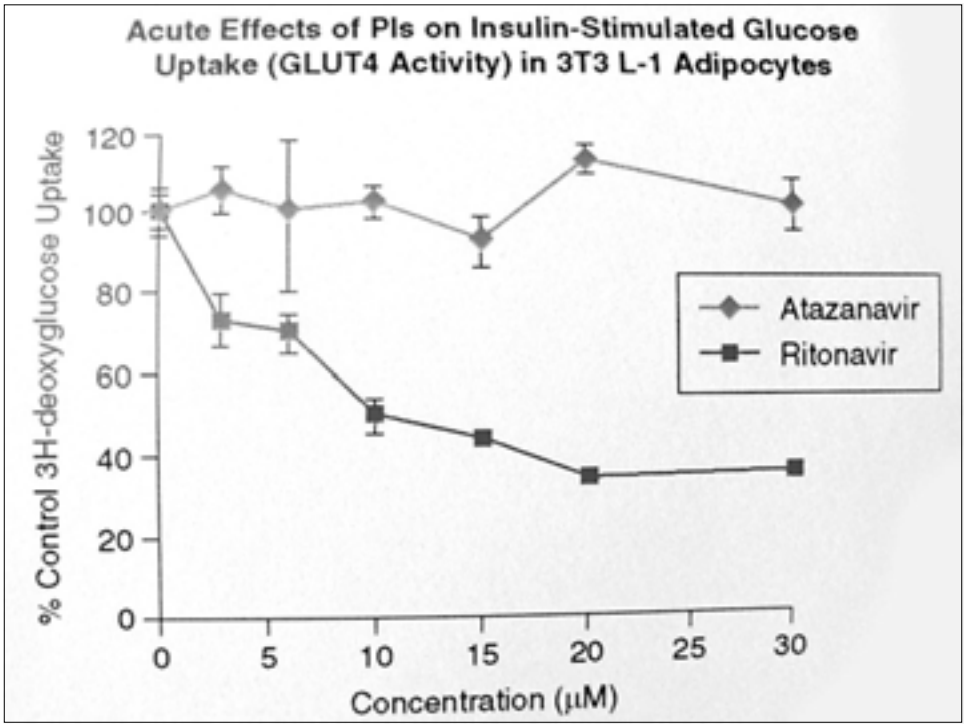
- **One syndrome or several?**
- **One etiology or multifactorial?**

Indinavir Inhibition of Glucose Uptake in Insulin Stimulated Rat Adipocytes

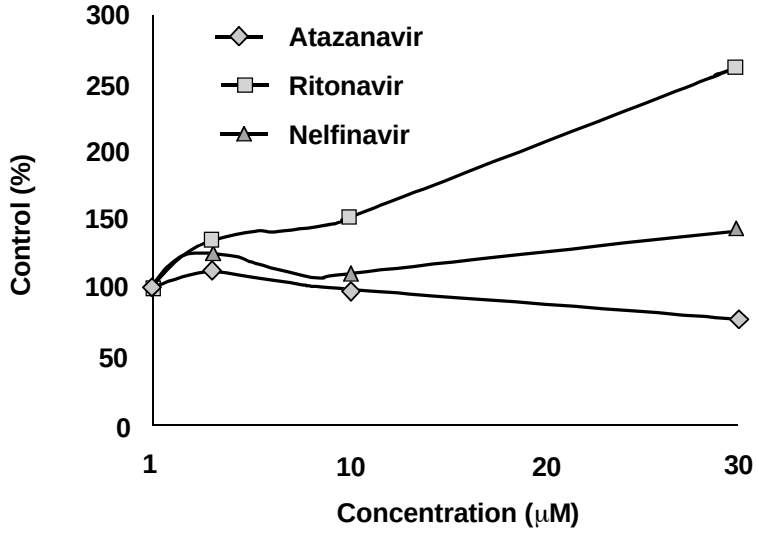
IDV μM	% uptake decreased
1	15.6
5	34.0
10	51.5

Also observed with APV, RTV, LPV in this system
Reproducible with a single 1200 mg of IDV in healthy volunteers
Reversible in rat model with removable of Indinavir

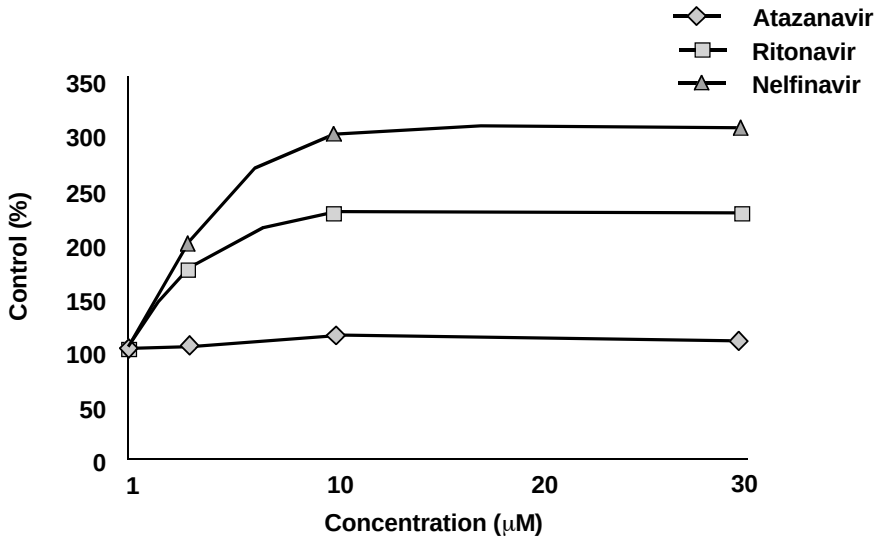
Murata #1 3rd International Workshop on Adverse Drug reactions and Lipodystrophy in HIV



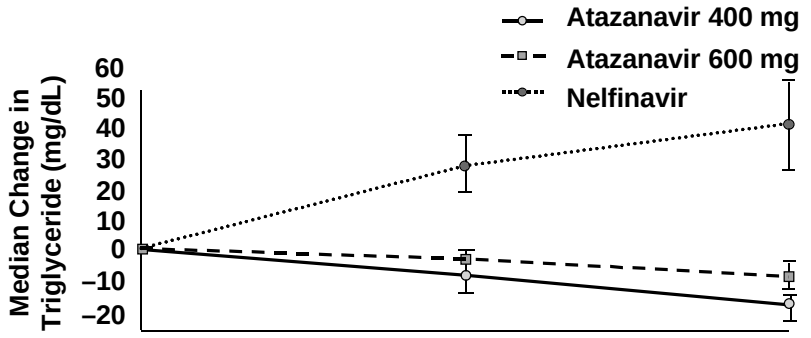
Cholesterol Synthesis in HepG2 Cells



Triglyceride Synthesis in HepG2 Cells



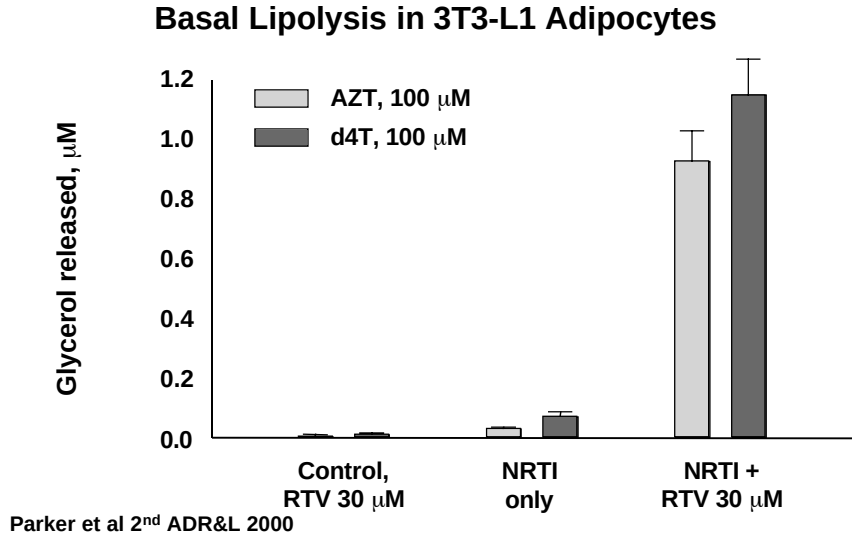
Atazanavir: Median Change in Fasting Triglyceride



400 mg	138	102	78
600 mg	167	130	89
Nelfinavir	77	61	38

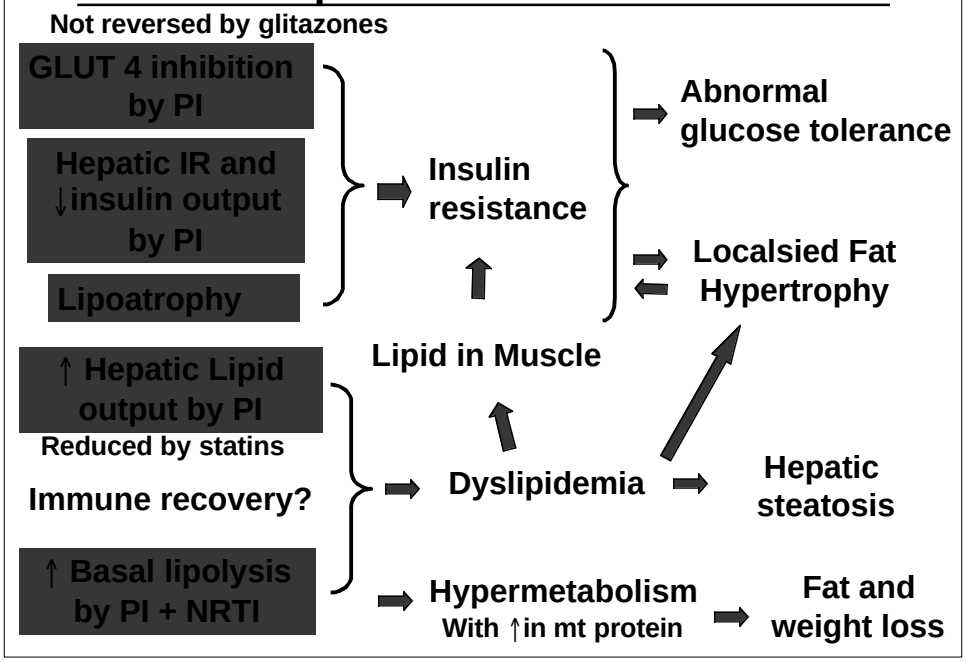
Cahn. 1st IAS; 2001; Buenos Aires. Poster 5.

Synergistic Action of PIs + NRTIs in Adipocytes



Parker et al 2nd ADR&L 2000

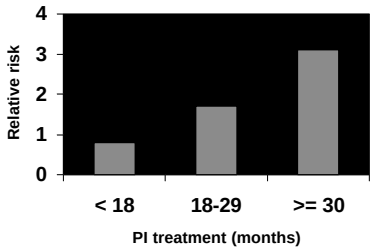
Possible impacts of ART on metabolism



Increased Risk of Cardiovascular Disease in HIV: Effects of HIV/ART?

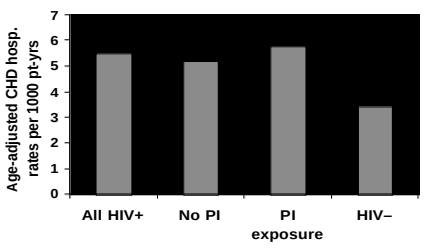
French National Hospital Data Base:

- **19,795 patients received PIs**
- **Increased incidence of MI (per 10,000 pt-yrs) vs HIV- population: 3 x increase with PI for ≥30 months**



Kaiser Permanente Data Base

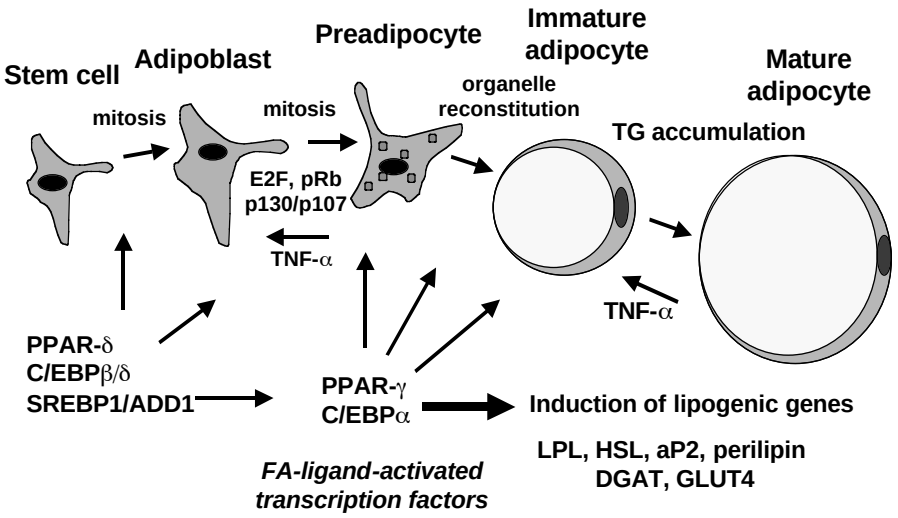
- **4,541 HIV+ vs 41,000 non-HIV+**
- **Hospital D/C codes for CHD events**
- **Among HIV+, 53 CHD events**
- **All HIV+ vs HIV- : significant difference**
- **In HIV+, no difference, PI vs no PI**



1. Mary-Krause M. 8th CROI, Chicago, 2001. #657; 2. Klein D. 8th CROI, Chicago, 2001. #655

Adipocyte Differentiation and Adipogenesis

Opportunities for Interference by Cytokines or Drugs



Inflammation and lipoatrophy

- ⇧ CD4+ lymphocytes and ⇩ HIV RNA in HIV+ subjects with fat redistribution (Engelson AJCN 1999;69:1162)
- Associations between lipodystrophy, nadir CD4, and their rise during HAART (Lichtenstein AIDS 2001;15:1389)
- Immune dysregulation during HAART: more CD8+ lymphocytes contain TNF (Ledru Blood 2000;95:3191)
- Lipoatrophy associated with sTNF receptors (Mynarcik JAIDS 2000;25:312)

mtDNA from biopsies

Inherited mitochondrial disorders

Reductions in functional mtDNA of >80% are required for disease to occur [1,2]

Samples from LD patients

- "modest" changes in mtDNA seen - mean only 44-50% reduction [3]
- some LA samples had normal mtDNA [4]
- some controls had depleted mtDNA [3, 4]
- Madelung's syndrome-associated mtDNA mutation absent. [3]
- Histology same for lipoatrophy and hypertophy

Conclusion: mtDNA reductions in lipoatrophy?

1. not necessary
2. not characteristic
3. not diagnostic [5]

References: 1. Chinnery PF *et al*. J Med Genet 1999; **36**: 425-436
2. Lombes A *et al*. Rev Neurol 1989; **145**: 671-689
3. Walker UA *et al*. 2nd IWADE&L, 2000. Abstract **O6**
4. Shikuma C *et al*. AIDS 2001
5. Moyle G. AIDS 2001; **15**: 413-415

NRTIs + PIs May Synergistically Affect Some Adipocyte Functions

Protease inhibitors [1]

Physiological concentrations:
- Affects triglyceride accumulation

High concentrations:
- Affects lipolysis
- Affects ATP production

d4T or AZT

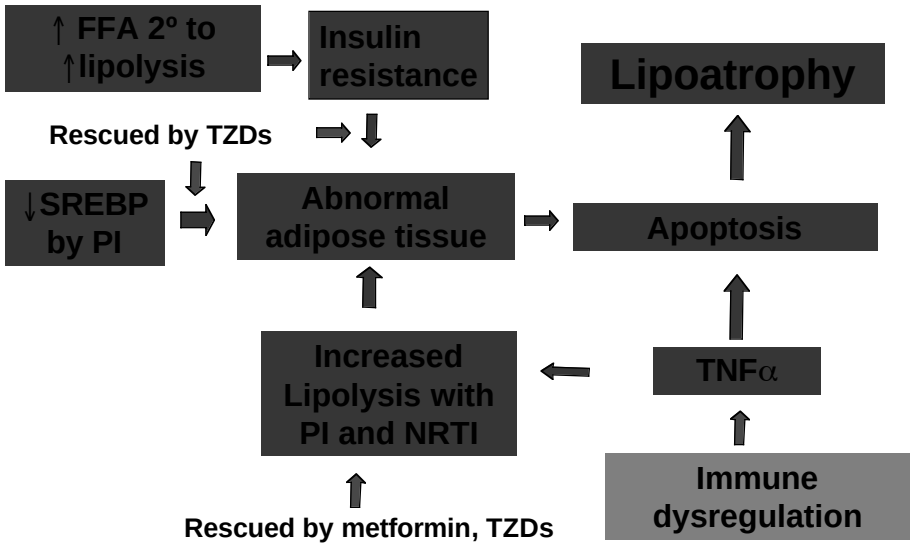
Physiological concentrations:
- No effects observed over 8 weeks[1]

At high concentrations (mice):
- d4T has no effects on adipose tissue mtDNA, limited or transient effects on muscle and liver mtDNA [2]

However, PIs and NRTIs may exert a synergistic effect on adipocytes [3]

References: 1. Parker RA *et al*. IAS 2001
2. Gaou I *et al*.
3. Flint O, et al 3rd ADR&L 2001

Possible impacts of ART on fat mass

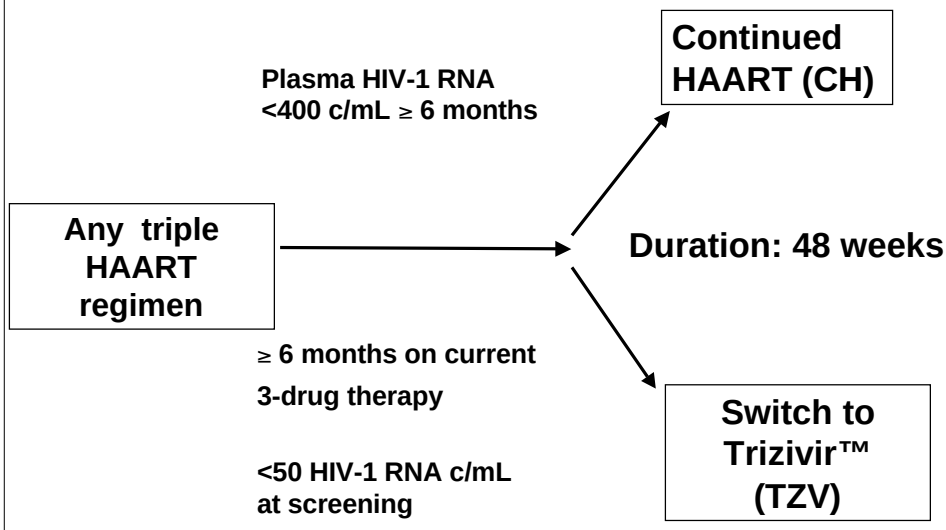


Etiology Can Determine Treatment Choices

- Etiology is not currently established
- Changing treatment response to 'current fashion' risks loss of therapy benefit with no established toxicity management benefit

Protease inhibitor etiology	Switch to NNRTI/triple NRTI regimen
Thymidine analog etiology	Switch to ddI, ABC-based regimen
Nucleoside analog etiology	Switch to PI + NNRTI regimen
Cytokine etiology	Use SIT/pulse therapy; use loose viral control
Multifactorial etiology	Treat individual manifestations
Adipocyte apoptosis etiology	Use glitazones, statins, reduce TNF

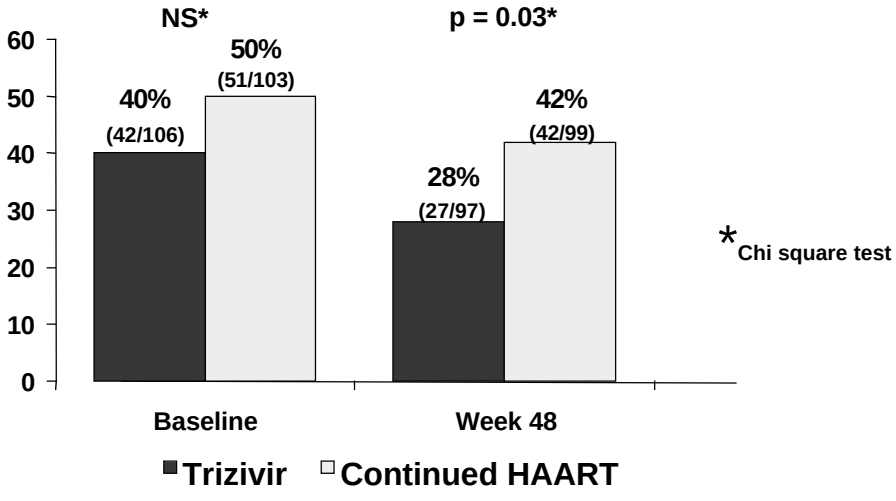
Study design



Lafeuillade A, et al 3rd ADR&L Abstract 28

Lipodystrophy symptoms at week 48

Number of subjects with at least one LD symptom



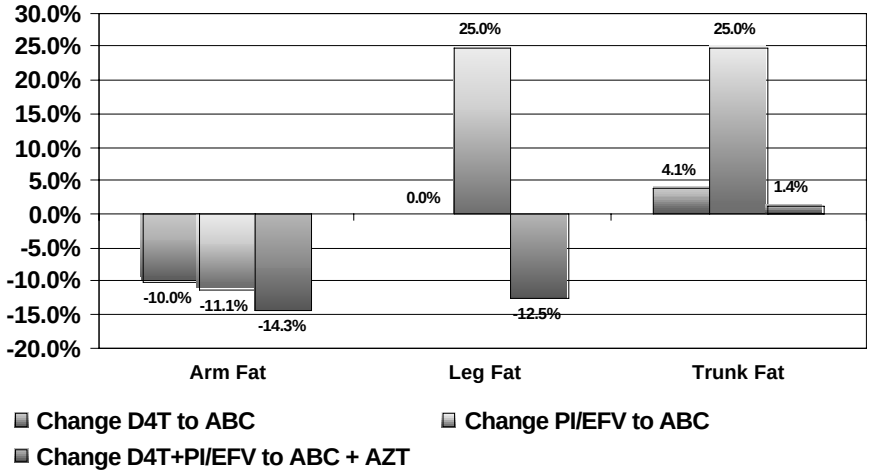
*Chi square test

Emergence/Resolution of Fat accumulation & Fat atrophy symptoms

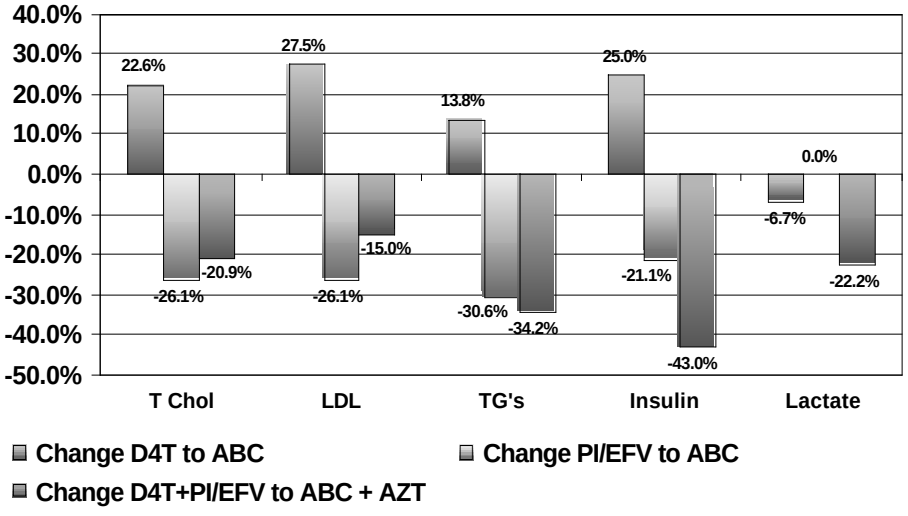
Emergence without any resolution	TZV (n=97) 12 (12%)	CH (n=99) 20 (20%)	p=0.138
Resolution without any emergence	TZV (n=24) 15 (63%)	CH (n=38) 13 (34%)	p=0.029

- Peripheral fat wasting remains the most frequent clinical manifestation at week 48 in both groups.
- Decrease of combined symptoms of central adiposity and peripheral fat wasting was observed in the Trizivir arm.

Randomized Switch of d4T to ABC, PI/EFV to ABC to both to AZT+ABC: 24 week data 10 patients per arm



Randomized Switch of d4T to ABC, PI/EFV to ABC to both to AZT+ABC: 24 week data 10 patients per arm



Conclusions

- Lipoatrophy is part of a complex metabolic and determined syndrome
- It is unclear which agents or what disease process results in lipoatrophy
- Approved PIs cause insulin resistance possible via GLUT4. This is not seen with Atazanavir.
- Increased FFA release with PI+NRTI may further contribute to IR and lipodystrophy
- SREBP inhibition by some PIs may further contribute to abnormal adipose tissue. This may be rescued by TZDs
- Switching away from PIs may improve metabolic parameters. Morphological parameters may also improve. Switch from d4T to ABC does not provide these benefits.