



# Randomised, Controlled, Open Label Study of Revision of Antiretroviral Regimens from Stavudine and/or a Protease Inhibitor to Zidovudine/Lamivudine/Abacavir to Prevent or Reverse Lipoatrophy: 48-Week Data

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## STUDY RATIONALE

There is a need for randomised, controlled studies with objective endpoint measures and long term follow-up to identify which combination of currently licensed ARTs is least likely to induce lipoatrophy ('fat sparing') and/or allow reversal of established lipoatrophy ('fat restoration').

We therefore studied the effects on body fat of taking antiretroviral agents associated with an increased risk of lipoatrophy (d4T and/or any PIs) compared with switching these agents to those associated with lesser risk (ZDV and ABC)<sup>1,2</sup>.

## STUDY DESIGN

Open label study comparing continuation of triple regimens containing d4T or ZDV+ 3TC or ddI + PI (control arm) with revision to ZDV/3TC/ABC (switch arm) in HIV- infected subjects with stable undetectable viral load (<400cps/ml for 8 weeks) and no prior ABC. Clinical lipoatrophy was not required for eligibility.

1:1 randomisation of continue or switch as follows;

ZDV/3TC or ddI/PI → switch PI to ABC

d4T/3TC or ddI/PI → switch PI to ABC and d4T to ZDV

## Primary endpoints

Change from baseline of arm and leg fat (% and kg) on whole body DEXA scan at 24 and 48 weeks.

## Secondary endpoints

- 1-change from baseline of intra-abdominal fat (VAT) on single cut L4 CT scan
- 2-fasting triglyceride, total, LDL and HDL cholesterol and venous lactate levels
- 3-plasma viral load
- 4-adverse events

## RESULTS

Total n=39

Baseline

There were no statistically significant differences between any baseline values for controls vs switch subjects, except for HDL cholesterol (p=0.02).

	Controls d4T+or PI	Switch ZDV/3TC/ABC
n	17	22
male	17	19
regimens(n)	ZDV/3TC/indinavir(9)	(8)
	d4T/3TC/nelfinavir(2)	(7)
	d4T/3TC/indinavir(6)	(7)
mean±SD		
arm fat %	14.81±3.81	18.4±8.75
arm fat kg	1.42±0.52	1.70±0.93
leg fat %	13.25±4.63	15.33±10.70
leg fat kg	3.25±1.45	3.84±4.10
VATcm <sup>2</sup>	129.9±82.23	138.05±55.17
TG mmol/L	3.15±2.49	2.39±1.43
total chol mmol/L	5.65±1.68	5.38±1.09
HDL chol mmol/L	0.91±0.22	1.07±0.21
LDL chol mmol/L	3.23±1.10	3.25±1.15
lactate mmol/L	1.76±0.7	1.65±0.48
median CD4 /mcl	598	627

## VAT and metabolic parameters

Differences in change from baseline between controls & switch for VAT (area and %), serum TGs, total, LDL and HDL cholesterol, and venous lactate were all non-significant at 48 weeks (as treated). At 24 weeks only, LDL cholesterol was significantly lowered in those on baseline d4T/PI (-0.94, p<0.001) and nelfinavir subgroups (-0.72, p=0.03) who switched, versus controls (t-tests).

## Viral load

One subject in the baseline ZDV subgroup who switched from indinavir to ABC, experienced virological failure (2 consecutive viral loads >400 copies/ml). All other study subjects' viral loads have remained undetectable to date.

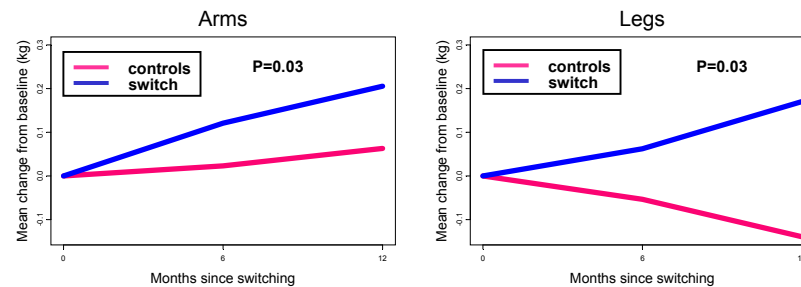
## Adverse events

3 subjects had ABC hypersensitivity reactions which resolved after revision of therapy. One subject had headaches attributed to ZDV which resolved after revision of therapy.

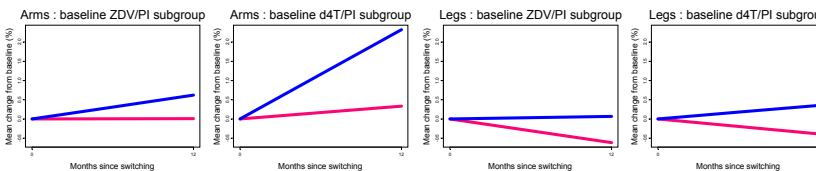
## Limb fat restoration on DEXA is greater in switch group than controls.

All subjects, on-treatment analysis

	Controls (d4T+or PI)	Switch (ZDV/3TC/ABC)	p-value
Mean rate of fat lost or gained from baseline			
<b>Arms</b>			
kg/month	0.005	0.018	p=0.03
%/month	0.012	0.129	p=0.02
<b>Legs</b>			
kg/month	-0.011	0.013	p=0.03
%/month	-0.046	0.020	p=0.07



## Fat restoration versus fat sparing and PI switch versus d4T vs PI switch



	Arms		Legs	
	PI alone switch	d4T+PI switch	PI alone switch	d4T+PI switch
<b>Fat restoration</b> Fat gained (kg) in switch group after 48 weeks	0.15	0.26	0.19	0.06
<b>Fat sparing</b> Change in fat (kg) in controls after 48 weeks	0.01	0.13	-0.23	-0.01

## CONCLUSIONS

ZDV/3TC/ABC was associated with restoration of limb fat compared with regimens containing d4T and/or PI.

Fat restoration appeared to be greater in the arms than the legs, where it was greater after d4T+PI switch versus PI switch alone.

Fat sparing was also evident in the legs (loss of 0.011kg leg fat per month of continued d4T+PI).

Switching did not have significant effects on intra-abdominal fat or on metabolic parameters, which were normal at baseline in most study subjects.

ZDV/3TC/ABC was associated with maintenance of virological control and had no unexpected adverse effects.

## REFERENCES

1.Mallal S, John M, Moore C, James I, McKinnon B. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting (lipoatrophy) in HIV-infected patients. *AIDS* 2000;14(10):1309-1316. 2.John M, Nolan D, Mallal S. Antiretroviral Therapy and the Lipoatrophy Syndrome (review). *Antiviral Therapy* 2001;6:9-20.

## ABSTRACT

**Background:** Treatment with PIs (versus no PIs) and d4T (versus other NRTIs) have been independently associated with higher risk of fat wasting (lipoatrophy) in HIV-infected patients. We sought to determine whether the revision of d4T and/or PI containing regimens to ZDV/3TC/ABC would be safe, efficacious and result in prevention (fat sparing) and/or reversibility (fat restoration) of lipoatrophy.

**Methods:** 40 subjects with stable HIV RNA<400 cps/ml and taking one of three baseline regimens, d4T/3TC/indinavir, d4T/3TC/nelfinavir and ZDV/3TC/indinavir were randomised to continue therapy or switch d4T to ZDV and PI to ABC, such that the universal 'switch' regimen was ZDV/3TC/ABC. Primary endpoints included %change from baseline in fat in the legs and arms in whole body DEXA scans at 24 and 48 weeks. Secondary endpoints were HIV RNA concentration, adverse events, abdominal fat in single cut L4 CT scans, anthropometric and metabolic parameters. **Results:** At 48 weeks in intention to treat analysis, subjects who switched therapy to ZDV/3TC/ABC had a significant mean percent increase from baseline in %leg fat (+0.45) compared with a mean decrease (-0.45) in those who continued any baseline regimens (p=0.03, t-test). There was also an average increase in %arm fat in the switch groups (+0.95 at 24 weeks, +1.73 at 48 weeks) compared with +0.02 at 24 weeks (p=0.05, t-test) and +0.66 at 48 weeks (p=0.08, t-test) in the continue groups. The change from baseline in %arm fat observed on those who switched both d4T and PI was significantly greater than that observed in those who switched PI alone or continued therapy (p=0.01, t-test). For metabolic parameters, there was a mean decrease in LDL cholesterol in those who switched away from indinavir containing regimens (p=0.03, t-test).

**Conclusions:** Switching to ZDV/3TC/ABC maintained virologic control and was associated with objective evidence of fat sparing as well as some fat restoration, compared with continued d4T and/or PI.

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