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The Effect of Individual Antiretroviral Drugs on Body Composition in HIV-Infected Persons Initiating Highly Active Antiretroviral Therapy

Judith C. Shlay, MD, MSPH¹, Shweta Sharma, MS², Grace Peng MS², Cynthia L. Gibert, MD, MSc³, and Carl Grunfeld, MD, PhD⁴ Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT)

¹Denver Community Programs for Clinical Research on AIDS, University of Colorado Denver, Denver, CO

²University of Minnesota, Minneapolis, MN

³Wide-Reaching AIDS Program, Veterans Affairs Medical Center and George Washington University, Washington DC

⁴Veterans Affairs Medical Center and University of California, San Francisco, CA, USA

Abstract

Objectives—To examine the long-term effects of individual antiretroviral drugs on body composition among 416 persons initiating antiretroviral therapy (ART).

Methods—In a substudy of a clinical trial of persons initiating ART, changes in body composition attributable to individual ART were examined. ART assessed were: indinavir, ritonavir, nelfinavir, efavirenz, nevirapine, stavudine (d4T), zidovudine (ZDV), lamivudine (3TC), didanosine (ddI), and abacavir (ABC). Skinfolds and circumferences were measured at baseline and every 4 months. Mid-arm, mid-thigh and waist subcutaneous tissue areas (STAs) and non-subcutaneous tissue areas (NSTAs) were calculated. Rates of change per year of exposure to each individual ART drug were determined using multivariate longitudinal regression.

Results—D4T and ZDV use were associated with losses in STA and skinfold thickness. 3TC use was associated with gains in all STAs and skinfold thickness, while ABC use was associated with an increase in waist STA. Indinavir was associated with gains in waist STA, while indinavir, efavirenz and nevirapine were associated with increases in upper back skinfolds. D4T use was also associated with increases in all NSTAs; 3TC use was associated with the greatest increase in waist NSTA.

Conclusions—In this prospective non-randomized evaluation, the NRTIs d4T and ZDV were associated with decreases in STAs, while 3TC use was associated with increased STAs and waist NSTA.

Introduction

Both lipoatrophy and lipohypertrophy were observed in the NRTI era prior to the availability of highly active antiretroviral therapy (HAART),¹⁻³ with recent studies also linking body composition changes to specific antiretroviral therapies (ART) used as part of HAART⁴⁻⁸ In

particular, thymidine-containing nucleoside reverse transcriptase inhibitor (NRTI) regimens have been associated with the development of lipoatrophy, while thymidine-sparing NRTI regimens have been associated with increasing abdominal fat.^{5, 9-12} For protease inhibitors (PIs) there are conflicting reports as to their contribution to development of lipodystrophy with risk dependent on the type of PI used.^{4, 10-12} Studies suggest less of a role for non-nucleoside reverse transcriptase inhibitors (NNRTIs) in body composition changes.^{13, 14}

Even if specific drugs are related to the development of lipodystrophy, given that HIV-infected persons usually receive multiple drugs, it is difficult to assess the risk associated with individual drugs. To date, standardized long-term comparisons of the role of the individual antiretroviral drugs on body composition have not been well defined. The purpose of our study was to examine the long-term effects attributable to the *cumulative exposure* to specific antiretroviral drugs on body composition among persons initiating ART.

Methods

The data for this paper came from the Metabolic Study,¹⁵ a substudy of a long-term randomized clinical trial, Flexible Initial Retrovirus Suppressive Therapies (FIRST)¹⁶ conducted by the Community Programs for Clinical Research on AIDS (CPCRA)¹⁷

FIRST (CPCRA 058) compared three initial treatment strategies for clinical and immunologic outcomes with the goal of determining whether it was better to initiate ART with a 2-class strategy (PI + NRTI or NNRTI+NRTI) than a 3-class strategy (PI+NNRTI +NRTI) and to determine which of the 2-class strategies, PI or NNRTI, was better for initial therapy. FIRST demonstrated that the 3-class strategy was not superior to the 2-class strategy and was associated with more treatment-limiting toxicity. The study also demonstrated superior virologic response with the NNRTI strategy compared to the PI strategy, but no differences in immunologic or clinical outcomes.¹⁷

Eligibility criteria for the FIRST study included documented HIV infection and being at least 13 years of age. Participants were excluded if they were pregnant or breast feeding, had any prior use of PIs or NNRTIs, or a cumulative total of more than four weeks of NRTI use or more than one week of 3TC use. Participants in FIRST were offered co-enrollment in the metabolic substudy, which required participants to have blood samples drawn in the fasting state and undergo anthropometric measurements. There were no additional eligibility criteria. The metabolic study opened for enrollment in August 1999 and closed for follow-up in September 2005. The demographics of the Metabolic Study participants were similar to that of the overall FIRST cohort, except that triglycerides were lower as they were measured in the fasting state.¹⁵ A consent form approved by the institutional review board of each site was signed by each participant.

The study design, data collection, and results of the metabolic study are published elsewhere.¹⁵ Briefly, this long-term clinical trial assessed changes in metabolic parameters and body composition among 422 ART-naïve persons randomized to one of three HAART strategies. The study demonstrated similar changes in total and regional fat, with no differences among the three ART strategies. Differential effects on lipid metabolism by strategy were seen, with overall increases demonstrated in fasting insulin and insulin resistance for all three strategies.

This study builds on a previously published long-term non-randomized evaluation of the effects of three different NRTI regimens in the presence of similar PI and/or NNRTI therapy.¹⁴ In that study significant subcutaneous tissue differences were identified depending on the NRTI regimen used. All three NRTI regimens, abacavir plus lamivudine (ABC+3TC), stavudine plus lamivudine (d4T+3TC), and zidovudine plus lamivudine (ZDV+3TC), were initially associated with clinical improvements, but with prolonged use of either d4T or ZDV, similar

subcutaneous tissue losses were seen, while with prolonged use of ABC+3TC subcutaneous tissue gains were seen, reflecting differences in the long-term clinical effects of these medications. This current study examines the risks attributable to *cumulative exposure* to specific antiretroviral drugs on body composition.

Participants included in the analyses for this paper met the following criteria: 1) had complete baseline anthropometric data, and 2) had attended at least one follow-up visit where anthropometric data were obtained. Among the 422 participants enrolled in the metabolic substudy, 416 (99%) met inclusion criteria for this analysis.

Body composition measurements were performed by staff that received extensive centralized training and were certified before study initiation and annually.¹⁸ Anthropometric measurements were obtained after an eight-hour fast and included five skinfold measurements using a Lange caliper (i.e., triceps, subscapular, abdomen, suprascapular, thigh) and four body circumference measurements (i.e., midarm, waist, hip, midthigh) using a Dritz sewing tape,¹⁹ all measured twice and averaged for analyses. Four of the measurements (i.e., triceps, subscapular, abdomen, thigh) were performed as previously described.¹⁹ The suprascapular measurement was used to assess changes at the back of neck.²⁰

The anthropometric measures presented in this paper are the subcutaneous and non-subcutaneous tissue areas of the mid-arm, mid-thigh, and waist, and the skinfolds of the subscapular, suprascapular, thigh, triceps, and abdomen. The subcutaneous tissue areas for the mid-arm, mid-thigh, and waist were estimated using skinfold measurements of the triceps, thigh, and abdomen and body circumferences of the mid-arm, mid-thigh, and waist²¹⁻²³ with results expressed in cm². The waist non-subcutaneous tissue area, represents the visceral content of the abdomen (including the intestinal contents and visceral fat), was calculated by subtracting the subcutaneous tissue area from the total area of the cross-section of the abdomen with results expressed as cm². The non-subcutaneous tissue areas for the mid-arm and mid-thigh were calculated as the total cross-section of the limb minus the subcutaneous tissue area and included the muscular and skeletal contents of those areas. Anthropometric measurements were obtained at baseline and every 4 months thereafter. Collection of anthropometric data was stopped on April 2004 at the recommendation of the Data Safety and Monitoring Board for administrative reasons.

Statistical Analysis

Rates of changes in anthropometric measures were estimated using multivariate longitudinal regression models (exposure model) that accounted for updated cumulative exposure time to individual ART drugs.²⁴ The model used is similar to an on-treatment analysis. Cumulative exposure time at each visit for each of the following most commonly prescribed ART during follow-up: PI - indinavir, zidovudine, and zalcitabine; NNRTI - efavirenz and nevirapine, and NRTI - stavudine (d4T), lamivudine (3TC), zidovudine (ZDV), didanosine (ddI), and abacavir (ABC), was determined by noting when changes in antiretroviral medications occurred and accumulating the time spent on each of these drugs. Cumulative exposure time was censored at the visit last attended where anthropometric measurements were taken or April 1, 2004 (when data collection was stopped), whichever came first. All time spent on a specific antiretroviral medication was accounted for irrespective of whether it was continuous. With this censoring time, the analysis dataset had approximately 8% missing data.

Adjusted repeated measures regression analyses with random intercepts were performed with the change from baseline for each of the anthropometric measures (subcutaneous and non-subcutaneous tissue areas and skinfolds) as the dependent variable. The independent variables include updated cumulative time (in years) on each of the three PIs, the two NNRTIs, the five NRTIs, and a continuous variable that denoted follow-up study time (in years) at each visit.

Other variables adjusted for in the models were baseline age, race (black, white, Hispanic/Latino), sex, hepatitis C status, CD4 cell count, HIV-RNA level, and prior AIDS defining event. P-values cited are two-sided.

All statistical analyses were performed using SAS (version 8.2, SAS Institute, Cary, NC).

Results

Among the 416 participants in the metabolic study who met analysis criteria, 23% received indinavir, 25% ritonavir (boosted), 47% nelfinavir, 49% efavirenz, 41% nevirapine, 48% d4T, 63% ZDV, 89% 3TC, 27% ddI, and 34% received abacavir during the study.

Table 1 presents the baseline demographic and anthropometric characteristics of the cohort. The mean age was 38 years with 61% of participants being African American and 22% women. At baseline 14% reported a history of injection drug use (IDU), 36% reported a prior AIDS defining event, 21% had hepatitis C infection by antibody testing, and 62% were cigarette smokers. The baseline CD4 cell count was 214 cells/mm³ and mean log₁₀HIV-RNA level was 5.0 copies/mL.

During the 4 years of follow-up for the metabolic substudy (through April 2004), the overall median follow-up time for anthropometric measures was 3.1 years (IQR: 2.7 – 3.8 years). Table 2 presents the mean and median cumulative exposure times to the commonly used PIs, NNRTIs and NRTIs during the course of the study. For the PIs the median exposure time ranged from 0.58 years (ritonavir) to 1.80 years (nelfinavir). For NNRTIs the median cumulative exposure time was 1.51 years for nevirapine and 1.44 years for efavirenz. The median exposure time for the NRTIs ranged from 1.03 years (ddI) to 2.52 years (3TC).

Subcutaneous tissue areas

In Table 3 the adjusted rates of change for the subcutaneous and non-subcutaneous tissue areas of the mid-arm, mid-thigh, and waist per year of exposure to individual antiretroviral drugs are presented. These rates of change adjust for the time spent on other antiretroviral drugs. For the PIs, only indinavir use was associated with a significant increase in the waist subcutaneous tissue area with the rate of change being positive, indicating fat gain with longer exposure to indinavir. There was no significant association between exposure to either NNRTI and changes in any of the subcutaneous tissue areas.

For the individual NRTIs the adjusted rates per year of exposure to d4T and ZDV for the three subcutaneous tissue areas were negative (tissue loss) and significantly different from zero. The rates of change for 3TC were observed to be positive and significantly different from zero indicating tissue gain. Use of ddI did not have a significant effect on changes in subcutaneous tissue area for any of the sites. The rate of change for exposure to ABC for the waist subcutaneous tissue area was positive and significantly different from zero.

Non-subcutaneous tissue areas

No significant changes in the three non-subcutaneous tissue areas were attributable to cumulative exposure to any of the PIs or NNRTIs (Table 3). The estimated rates of change per year of exposure to d4T or ZDV were positive with the rates for d4T being significantly different from zero and borderline significant for ZDV exposure. For 3TC the three rates were positive with the rate for the waist non-subcutaneous tissue area being highly significant. The three rates for ddI were negative with those for the mid-arm and mid-thigh non-subcutaneous tissue areas being significant. No significant changes in non-subcutaneous tissue area were attributable to cumulative ABC exposure.

Skinfold Thickness

Table 4 summarizes the estimated rates of change in skinfold thickness at five sites (subscapular, suprascapular, abdomen, thigh, and triceps) per year of exposure to each of the antiretroviral drugs after adjusting for the time spent on other antiretroviral drugs. Cumulative exposure to indinavir resulted in increases in the subscapular, suprascapular, and abdominal skinfold thicknesses with the rates of change being significantly different from zero. Cumulative exposure to ritonavir or nelfinavir did not result in significant changes in skinfold thickness at any of the sites. Both efavirenz and nevirapine use resulted in increases in the subscapular and suprascapular skinfolds with the exposure rates of change being significantly different from zero.

The rates of change per year of exposure to d4T or ZDV were negative with most rates being significantly different from zero. For 3TC the rates of change were positive and significant for all of the skinfolds with the exception of the suprascapular skinfold. With ddI exposure the rate of change in the thigh skinfold was positive and significant. Cumulative use of ABC resulted in a significant increase in the abdomen skinfold and a significant decrease in the triceps skinfold.

Discussion

In this study, we assessed the long-term effects of specific antiretroviral drugs on body composition. Using a drug exposure time model, similar to an on-treatment analysis, the cumulative exposure time to individual antiretroviral drugs was used to assess the impact of single components of an ART regimen on changes in body composition. Based on our modeling we determined that the NRTIs have the greatest negative impact on body fat, while the NNRTIs and most PIs have little impact. Additionally, the “positive” impact of 3TC seemed to counterbalance the negative effect of the other NRTIs and likely explains some of the findings previously reported in other studies.²⁵⁻²⁷

Previous PI switch studies (changes from a PI to an NNRTI) have reported conflicting results on the effect of these drug class changes on lipodystrophy,²⁸ with several recent reports attributing significant body composition changes to PIs or NNRTIs.^{4, 12} In our analyses, indinavir was the only PI that had an impact on body composition with a significant increase seen in the waist subcutaneous tissue area as well as abdominal and upper back skinfolds, while the use of either NNRTI resulted in increases in the upper back skinfolds. Thus, based on our findings, PIs and NNRTIs have less of a role in the development of lipoatrophy compared to that of NRTIs.

Among NRTIs, 3TC use has been considered to have little impact on body composition, with most changes in body composition attributed to other NRTIs,^{1, 12} with the exception of one report.² From our assessment of the individual effect of components of an ART regimen we observed increases (positive rates of change) in all three subcutaneous tissue areas as well as a particularly pronounced positive effect in the waist non-subcutaneous tissue area with cumulative 3TC exposure. Previously we had shown that taking ABC combined with 3TC increases waist non-subcutaneous tissue area.⁵ Based on the results from our current cumulative exposure time model the increase in waist non-subcutaneous tissue area with ABC +3TC appears to be mostly due to the 3TC component, with a possible negative effect of ABC. Likewise, we previously reported a somewhat smaller increase in waist non-subcutaneous tissue area in those on ddI+d4T.⁵ The latter results appear to be driven by a smaller increase in waist non-subcutaneous tissue area associated with d4T and perhaps a small negative effect of ddI. However, a limitation of our study is that we did not directly measure visceral fat.

Following the initiation of an antiretroviral regimen that includes either d4T or ZDV in combination with 3TC, initial improvements in body composition and metabolic parameters have been documented.^{15, 29} The development of lipoatrophy with the use of thymidine analogues has been shown to occur with long term exposure.^{5, 7, 11, 12, 29, 30} It is likely that the adverse effects of these drugs begin to occur with their initiation, with these negative effects being offset by the immediate health benefits from initiating ART. With prolonged use of these drugs the beneficial effects of ART diminishes resulting in the development of drug-induced lipoatrophy.

Previous NRTI studies that switched from d4T+3TC to either ZDV+3TC or ABC+3TC in order to examine changes in lipoatrophy have all demonstrated small improvements in body composition with these modifications.²⁵⁻²⁷ In the study with the longest follow-up, the authors demonstrated little change in visceral adipose tissue with these same NRTIs.²⁶ Based on our analyses the minimal change in waist non-subcutaneous adipose tissue reported may be explained by the continued use of 3TC, such that when 3TC is combined with ABC, waist non-subcutaneous fat increases. In the ACTG 384 study which assessed differences between ZDV+3TC and ddI+d4T as well as our previously reported findings that compared ABC+3TC to ddI+d4T, greater reductions in limb fat were associated with use of ddI+d4T than either an ABC+3TC or ZDV+3TC containing regimen.^{4, 5, 29} The mechanism by which these changes in fat mass were seen after d4T substitution has not been fully explained in the literature, but mitochondrial changes may play a role. From our assessment of the individual effects of the NRTIs, stronger induction of lipoatrophy by ddI+d4T compared to ZDV+3TC may be attributable to the effect of 3TC rather than a difference between d4T and ZDV.

As previously reported, it has been shown that NRTI combinations which include d4T or ZDV result in the development of lipoatrophy.^{4, 5, 7, 12, 30} In this study cumulative exposure to d4T was associated with significant increases in the non-subcutaneous tissue areas of the waist, mid-arm, and mid-thigh coupled with losses of subcutaneous tissue in these areas. These findings lend support to the importance of assessing body composition changes with both skinfolds and body circumference measurements (components of subcutaneous and non-subcutaneous tissue area calculations), since by only measuring body circumferences, the reciprocal changes seen in subcutaneous and non-subcutaneous tissue areas would not have been appreciated.

The antiretroviral drugs used in this study reflect those used in the randomized clinical trial which were conducted prior to the availability of newer ART (e.g., atazanavir, tenofovir), which may impact body composition differently. However, these results remain relevant as these drugs are still in use in many parts of the world.³¹ Another limitation of the study is varying exposure times to the different antiretroviral drugs evaluated in this study with some of the new drugs having shorter exposure times. However, in analyses limited to participants with longer exposure time to the drugs, similar trends were found. The non-subcutaneous tissue areas (mid-arm, mid-thigh, waist) were derived based on previously validated formulas,²¹⁻²³ to reflect the specific anatomic sites described in this study. In addition, although more recent studies have used DEXA scanning to assess body composition changes with therapy, anthropometry performed by well-trained individuals using standardized measurement protocols and tools,²⁰ as in our study, has been demonstrated to be a reliable tool for measuring body composition in HIV-infected participants.^{32, 33} Additionally, studies using both methods have shown correlations between DEXA or MRI and anthropometry.³⁴⁻³⁶

It is important to note that the rates of change per year of exposure to each antiretroviral drug presented in this paper were calculated after adjusting for the exposure time to the other drugs in a participant's regimen. Each rate of change should be interpreted as the rate of change per year of exposure to the specific antiretroviral drug in the *presence* of the other drugs.

In conclusion, this study assessed the individual effects of specific antiretroviral drugs on body composition. While no substantial effects on lipoatrophy were seen with use of any of the PIs or NNRTIs, differences were seen with respect to the individual NRTIs. Lipoatrophy was associated with use of d4T and ZDV. 3TC use had a greater impact on body composition than previously recognized with increases demonstrated in all subcutaneous fat areas and in waist non-subcutaneous fat explaining the body composition changes previously reported when 3TC is combined with ABC.⁵ Indinavir, efavirenz and nevirapine were associated with increasing upper trunk fat, while ritonavir and nelfinavir were not. These findings suggest that by examining antiretroviral drugs individually, it enhances our ability to elucidate the impact these drugs have on body composition.

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Table 1

Baseline Characteristics

	Baseline Characteristics
No. participants	416
DEMOGRAPHICS	
Age (mean; years $\pm$ SD)	38.2 $\pm$ 9.7
Race	
Black (%)	60.6
White (%)	26.9
Latino (%)	10.1
Other (%)	2.4
Sex (% Female)	21.9
Prior IV drug use (%)	13.7
Prior AIDS (%)	35.8
PCP prophylaxis (%)	46.2
Hepatitis B (%)	6.8
Hepatitis C (%)	21.2
Smoking (%)	62.3
LABORATORY	
Baseline CD4 [*] (cells/mm ³ ; mean $\pm$ SD)	214.4 $\pm$ 184.3
Baseline HIV-RNA [*] (log ₁₀ copies/mL mean $\pm$ SD)	5.0 $\pm$ 0.8
ANTHROPOMETRIC MEASURES	
Subcutaneous tissue area (cm ² ; mean $\pm$ SD)	
Mid-arm	20.4 $\pm$ 14.0
Mid-thigh	37.1 $\pm$ 25.8
Waist	73.8 $\pm$ 50.9
Non-subcutaneous tissue area (cm ² ; mean $\pm$ SD)	
Mid-arm	56.1 $\pm$ 15.6
Mid-thigh	163.0 $\pm$ 39.7
Waist	512.5 $\pm$ 150.9
Skinfolds (mm; mean $\pm$ SD)	
Subscapular	16.7 $\pm$ 8.3
Suprascapular	16.3 $\pm$ 7.8
Thigh	15.2 $\pm$ 9.0
Triceps	13.9 $\pm$ 8.4
Abdomen	17.2 $\pm$ 10.0

* average of baseline and screening visit

Table 2
Summary Statistics of Cumulative Years of Antiretroviral Drug Use

Antiretroviral Drug	N	%	Mean	S.D.	Quartiles		
					Median	Q1	Q3
PI							
Indinavir (IDV)	96	23.1	1.42	1.24	1.04	0.30	2.32
Ritonavir (RTV)	106	25.5	1.16	1.20	0.58	0.21	1.96
Nelfinavir (NFV)	194	46.6	1.95	1.24	1.80	0.91	3.11
NNRTI							
Efavirenz (EFV)	205	49.3	1.81	1.37	1.44	0.50	3.07
Nevirapine (NVP)	169	40.6	1.79	1.37	1.51	0.55	3.24
NRTI							
Stavudine (d4T)	198	47.6	1.85	1.21	1.67	0.84	3.00
Zidovudine (ZDV)	260	62.3	2.04	1.34	2.07	0.72	3.25
Lamivudine (3TC)	371	89.2	2.34	1.20	2.52	1.21	3.39
Didanosine (ddI)	112	26.9	1.39	1.16	1.03	0.41	2.10
Abacavir (ABC)	141	33.9	1.63	1.27	1.38	0.50	2.70
No of Participants*	416						

* Cohort includes those with non-missing baseline and at least one follow-up measurement for any of the skinfolds, subcutaneous and non subcutaneous fat areas.

Table 3

Rate of Change per Year of Exposure to Antiretroviral Drugs in Subcutaneous and Non-Subcutaneous Tissue Areas of the Mid-arm, Mid-Thigh and Waist using Multivariate Regression Models*

Antiretroviral Drug	Subcutaneous Tissue Area			Non-Subcutaneous Tissue Area		
	Mid-arm (cm ² /yr) (P) †	Mid-thigh (cm ² /yr) (P) †	Waist (cm ² /yr) (P) †	Mid-arm (cm ² /yr) (P) †	Mid-thigh (cm ² /yr) (P) †	Waist (cm ² /yr) (P) †
PI						
Indinavir (IDV)	0.59 (0.16)	0.62 (0.43)	8.23 (<0.0001)	-0.40 (0.39)	1.69 (0.25)	0.91 (0.81)
Ritonavir (RTV)	0.37 (0.39)	0.19 (0.82)	-2.03 (0.27)	-0.61 (0.21)	-1.91 (0.22)	1.32 (0.74)
Nelfinavir (NFV)	-0.30 (0.26)	0.38 (0.45)	0.90 (0.41)	0.50 (0.08)	1.06 (0.26)	1.52 (0.52)
NNRTI						
Efavirenz (EFV)	0.41 (0.14)	0.29 (0.58)	0.60 (0.61)	0.10 (0.75)	-0.99 (0.32)	-0.72 (0.77)
Nevirapine (NVP)	0.34 (0.22)	0.62 (0.24)	1.95 (0.10)	0.23 (0.46)	0.56 (0.58)	2.14 (0.40)
NRTI						
Stavudine (d4T)	-2.15 (<0.0001)	-3.75 (<0.0001)	-4.14 (0.004)	1.08 (0.004)	2.67 (0.03)	6.71 (0.03)
Zidovudine (ZDV)	-2.65 (<0.0001)	-3.07 (<0.0001)	-5.23 (0.0003)	0.66 (0.09)	1.93 (0.13)	5.53 (0.08)
Lamivudine (3TC)	1.46 (<0.0001)	1.40 (0.03)	3.11 (0.03)	0.10 (0.79)	1.65 (0.18)	14.75 (<0.0001)
Didanosine (ddI)	0.12 (0.77)	0.65 (0.41)	0.70 (0.69)	-1.65 (0.0004)	-7.91 (<0.0001)	-3.56 (0.35)
Abacavir (ABC)	-0.59 (0.08)	0.44 (0.48)	2.88 (0.04)	0.29 (0.44)	0.77 (0.53)	-4.37 (0.15)

Note: Cohort (n=416) includes those with non-missing baseline and at least one follow-up measurement for any of the skinfolds, subcutaneous and non subcutaneous fat areas.

* Longitudinal regressions included the following baseline variables: age, race, hepatitis C, CD4 cell count, log10 HIV-RNA, prior AIDS, gender, and cumulative years on specific antiretroviral drugs (i.e., IDV, RTV, NFV, EFV, NVP, d4T, ZDV, 3TC, ddI, ABC).

† P value for comparing rate of change to zero.

Table 4
Rate of Change per Year of Exposure to Drugs in Five Skinfolds using Multivariate Regression Models*

Antiretroviral Drug	Subscapular (mm/yr) (P) [†]	Suprascapular (mm/yr) (P) [†]	Thigh (mm/yr) (P) [†]	Triceps (mm/yr) (P) [†]	Abdomen (mm/yr) (P) [†]
PI					
Indinavir (IDV)	0.71 (0.005)	0.57 (0.03)	0.16 (0.59)	0.37 (0.16)	1.81 (<0.0001)
Ritonavir (RTV)	-0.43 (0.10)	-0.07 (0.79)	0.03 (0.93)	0.31 (0.27)	-0.44 (0.25)
Nelfinavir (NFV)	0.18 (0.27)	0.20 (0.24)	0.01 (0.95)	-0.27 (0.11)	0.13 (0.57)
NNRTI					
Efavirenz (EFV)	0.35 (0.04)	0.44 (0.01)	0.11 (0.56)	0.22 (0.22)	0.18 (0.46)
Nevirapine (NVP)	0.42 (0.01)	0.37 (0.04)	0.19 (0.33)	0.17 (0.35)	0.44 (0.07)
NRTI					
Stavudine (d4T)	-0.07 (0.74)	-0.10 (0.65)	-1.52 (<0.0001)	-1.44 (<0.0001)	-0.97 (0.001)
Zidovudine (ZDV)	-0.49 (0.02)	-0.58 (0.01)	-1.30 (<0.0001)	-1.71 (<0.0001)	-1.31 (<0.0001)
Lamivudine (3TC)	0.44 (0.03)	0.15 (0.51)	0.59 (0.01)	0.99 (<0.0001)	0.65 (0.03)
Didanosine (ddI)	-0.29 (0.24)	0.10 (0.70)	0.73 (0.01)	0.42 (0.11)	0.24 (0.51)
Abacavir (ABC)	0.11 (0.59)	0.22 (0.31)	0.20 (0.39)	-0.41 (0.05)	0.59 (0.04)

Note: Cohort (n=416) includes those with non-missing baseline and at least one follow-up measurement for any of the skinfolds, subcutaneous and non subcutaneous tissue areas.

* Longitudinal regressions included the following baseline variables: age, race, hepatitis C, CD4 cell count, log10 HIV-RNA, prior AIDS, gender, and cumulative years on specific antiretroviral drugs (i.e., IDV, RTV, NFV, EFV, NVP, d4T, ZDV, 3TC, ddI, ABC).

[†] P value for comparing rate of change to zero.