Abstract #99

5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, Paris, France, 8-11 July 2003

Risk Factors for Body Fat Composition Changes in Antiretroviral-Naïve Patients Treated with Lopinavir/ritonavir (LPV/r) or Nelfinavir (NFV)

B da Silva, M King, P Cernohous, C Kelly, R Tressler, and S Brun; Abbott Laboratories, Abbott Park, IL USA

BACKGROUND

Body fat changes have been described in HIV patients receiving antiretroviral therapy. These changes have been described as either lipoatrophy (fat loss), lipohypertrophy (fat gain), or a combination of both of these. The prevalence of lipodystrophy that has been described in the literature varies greatly. The numbers range from as low as 8% to as high as 84%.[1,2] This variation in prevalence may be secondary to differences in the definitions used for the morphologic changes, patient selection, duration of follow-up, and/or the retrospective or cross-sectional study design. These differences make it difficult to compare one study to another and limit the interpretation of the study data.

Prospective evaluation of the possible development of these morphologic changes allows not only for a more accurate assessment of the incidence of these events but also for the evaluation of possible risk factors.

A number of both non-drug (including host and disease state factors) and drug factors have been described in the literature as possible risk factors for the development of body fat changes observed in HIV-infected patients (Table 1).[3,4]

Table 1. Possible Risk Factors for the Development of Body Fat Composition Changes

Non-Drug-Related Factors	Drug-Related Factors
Age	Duration of NRTI use
Body mass index (BMI)	Duration of PI use
CD4 nadir	
Gender	
Duration and severity of HIV	

In order to quantify and better understand the possible risk factors contributing to the development of body composition changes in antiretroviral-naïve patients initiating therapy, we reviewed four clinical trials from the LPV/r (Kaletra) clinical development program (M98-863, M99-056, M97-720, and M00-154). We evaluated the incidence of body fat composition changes as they were reported in these four LPV/r clinical trials. We also describe the risk factors that were found to be associated with the development of these body fat composition changes.

METHODS

Events of fat loss and/or fat gain were recorded from ARV-naïve, HIV-infected adults in 4 clinical trials of LPV/r. The protocols from these studies specifically directed investigators to evaluate patients for body composition changes and to report these events using defined terminology. The following terms were used to search the clinical trials database to identify potential adverse events of body composition changes: buffalo, Cushing, dorsocervical, enlarged, girth, gynecomastia, hump, lipodystrophy, lipoma, moon, and obesity.

Events of fat redistribution identified by the listed terms were sub-categorized as events of fat loss, fat gain, or both based on the verbatim adverse event term (Table 2).

Table 2. Categorization of Body Fat Composition Changes

Fat Loss	Fat Gain	Both
• Lipodystrophy	• Abdominal fat accumulation (central adiposity)	• Fat redistribution
• Peripheral fat wasting	• Breast enlargement (breast hypertrophy) • Dorsocervical fat gain (dorsal fat pad) • Cushingoid appearance without Cushing's disease • Multiple lipomas	• Combinations of both lipodystrophy and abdominal fat accumulation, breast enlargement, or dorsocervical fat gain

Table 3 summarizes the studies included in this analysis:

Table 3. Summary of Studies Included in the Analysis of Body Fat Composition Changes*

Study Number	Phase of Study	Number of Patients Enrolled	Regimen	Patient Population
M98-863	Phase III	326 LPV/r, 327 NFV	LPV/r or NFV + d4T/3TC	ARV-naive
M99-056	Phase IIIb	38	LPV/r QD (n=19) or BID (n=19) + d4T + 3TC	ARV-naive
M97-720	Phase I/II	100	LPV/r + d4T +3TC	ARV-naive
M00-154	Phase I/II	44	LPV/r + EFV + 3TC + tenofovir	ARV-naïve and those with wildtype virus

* Analysis performed through 96 weeks of therapy.

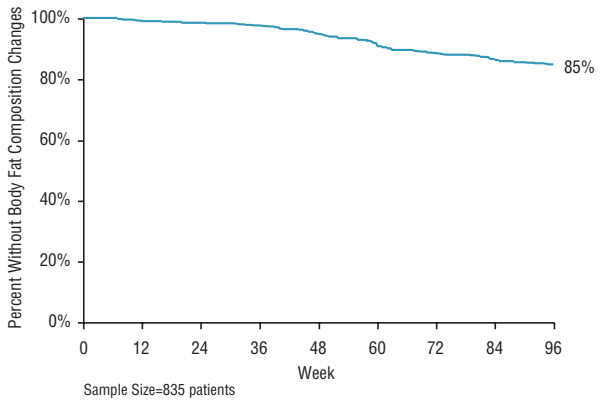
Kaplan-Meier (KM) analysis of the time to body fat composition changes were performed. Individual risk factors were assessed by the Cox proportional hazards model; multivariable risk factors were assessed by stepwise Cox regression (p=0.10 for entry or exit). Analyses assessing the effect of treatment group (LPV/r vs. NFV) were restricted to randomized study M98-863.

RESULTS

Rates of Body Fat Composition Changes Through 96 Weeks of Therapy

508 and 327 patients were treated with LPV/r and NFV, respectively, for a median of over 94 weeks. Through 96 weeks, 15% of patients had body fat composition changes (Figure 1).

Figure 1. Kaplan-Meier Estimates of Time to Onset of Body Fat Composition Changes Through 96 Weeks



There was no statistically significant difference in the proportion of patients with fat gain, fat loss, or both between the two treatment groups. In patients receiving LPV/r from the four studies, 41% of the patients with body fat composition changes had events of fat loss, 37% had events of fat gain, and 22% experienced both.

The Kaplan-Meier analysis of time to onset of fat gain and fat loss for all LPV/r treated patients is displayed in Figures 2 and 3, respectively.

Of male patients receiving LPV/r with body fat composition changes, 41% had events of fat loss, 39% had events of fat gain, and 20% had both. Of female patients receiving LPV/r with body fat composition changes, 42% had events of fat loss, 25% had events of fat gain, and 33% had both (p=0.550).

Figure 2. Kaplan-Meier Estimates of Time to Onset of Fat Gain in LPV/r Patients Through 96 Weeks

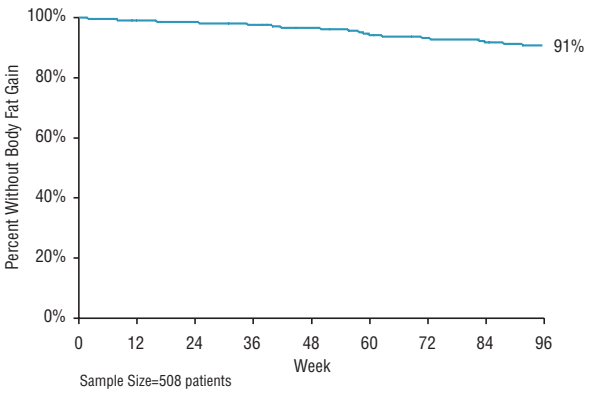
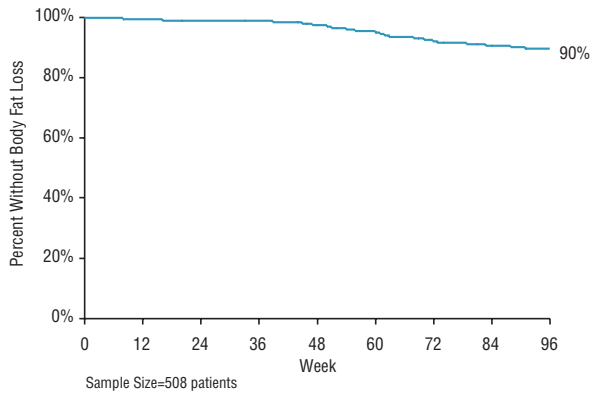


Figure 3. Kaplan-Meier Estimates of Time to Onset of Fat Loss in LPV/r Patients Through 96 Weeks



When LPV/r data from all 4 trials were combined (n=508), no significant differences were observed between patients with or without fat redistribution events in the time to Grade 2+ or Grade 3+ total cholesterol (p=0.124 or p=0.292, respectively).

Likewise, no significant difference was observed in the time to Grade 2+ or Grade 3+ triglyceride levels (p=0.527, p=0.879, respectively.)

Through 96 weeks, when data from all 4 trials are combined, 7 patients (2/508 [<1%] LPV/r and 5/327 [2%] NFV) discontinued therapy due to body fat composition changes.

Risk Factors Associated with Body Fat Composition Changes

In unadjusted analyses, higher baseline (BL) glucose, Caucasian/non-Hispanic race, age, and current alcohol use were significantly associated with the development of body fat composition changes (Table 4). Time to onset of body fat composition by current alcohol usage and race are displayed in Figures 4 and 5, respectively.

Table 4. Cox Proportional Hazard Models for Body Fat Composition Changes

Variable	Hazard Ratio	95% CI	P-value
Caucasian, Non-Hispanic	2.08	1.32-3.28	0.002*
Baseline Glucose (per 10 mg/dL increase)	1.06	1.01-1.12	0.018*
Current Alcohol Use	1.78	1.15-2.75	0.010*
Age at Start of Treatment (per year increase)	1.04	1.02-1.07	<0.001*
Male Gender	0.77	0.46-1.27	0.298
Maximum Triglycerides (per 10 mg/dL increase)	1.00	1.00-1.01	0.854
Maximum Total Cholesterol (per 10 mg/dL increase)	1.02	1.00-1.05	0.120
Maximum Glucose (per 10 mg/dL increase)	1.02	0.99-1.05	0.196
Baseline Total Cholesterol (per 10 mg/dL increase)	1.01	0.96-1.07	0.662
Baseline Triglycerides (per 10 mg/dL increase)	1.00	0.98-1.02	0.721
LPV/r use (vs. NFV)	0.87	0.57-1.32	0.510
Baseline CD4 (per cell/µL increase)	1.00	0.99-1.00	0.912
Years since HIV diagnosis (per year increase)	1.05	1.00-1.10	0.067
Current Smoker	1.07	0.72-1.60	0.730
Positive Smoking History	1.35	0.89-2.04	0.163
Baseline Hypertension (>140 mm Hg systolic and >90 mm Hg diastolic)	2.02	0.74-5.50	0.168
Post-Baseline Hypertension (>140 mm Hg systolic and >90 mm Hg diastolic)	1.28	0.80-2.06	0.303
History of Diabetes	1.25	0.46-3.39	0.667
Baseline Weight (per 1 kg increase)	1.01	0.99-1.02	0.355

* Statistically significant.

Figure 4. Effect of Alcohol Use on Time to Onset of Body Fat Composition Changes

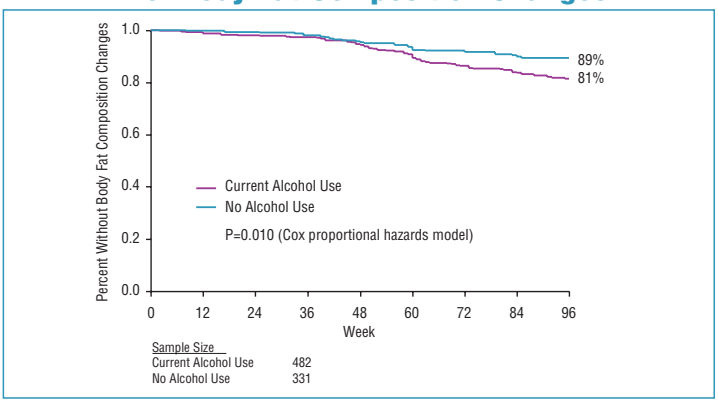
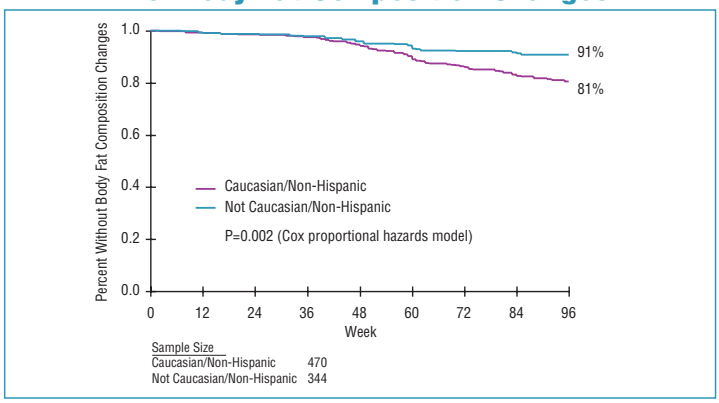


Figure 5. Effect of Race on Time to Onset of Body Fat Composition Changes



Higher baseline glucose values and age were associated with higher risk of body fat composition changes, as illustrated in Figures 6 and 7, respectively.

Figure 6. Effect of Baseline Glucose on Time to Onset of Body Fat Composition Changes

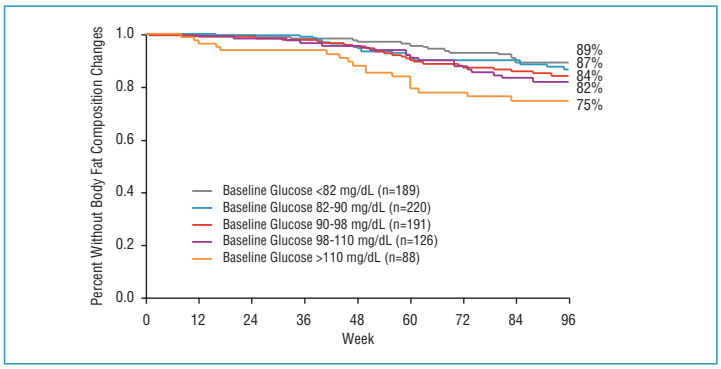
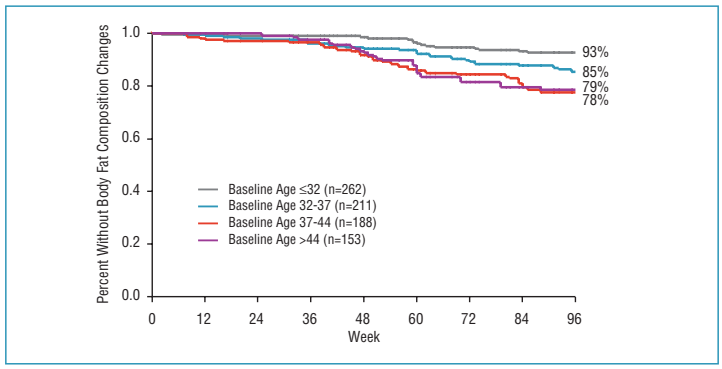


Figure 7. Effect of Age on Time to Onset of Body Fat Composition Changes



In a multivariable analysis, higher BL glucose, Caucasian/non-Hispanic race, higher age, and current alcohol use were associated with higher risk of morphologic changes (Table 5).

Table 5. Multivariable Cox Proportional Hazard Model for Body Fat Composition Changes

Variable	Hazard Ratio	95% CI	P-value
Caucasian, Non-Hispanic	2.14	1.34-3.40	0.001
Age (per year increase)	1.04	1.02-1.06	<0.001
Baseline Glucose (per 10 mg/dL increase)	1.06	1.00-1.13	0.039
Current Alcohol Use	1.74	1.11-2.72	0.025

Maximum on treatment values for total cholesterol, triglyceride, and glucose were not significant risk factors, nor were treatment group, baseline CD4, years since HIV diagnosis, baseline weight, past or current smoking status, or high blood pressure.

CONCLUSIONS

- Through 96 weeks, 15% of patients had body fat composition changes across all four studies. No significant differences were observed between patients receiving LPV/r and NFV.
- For ARV-naïve patients receiving LPV/r who experienced body composition changes, fat loss was the most common event (41%) reported versus fat gain (37%) or both (22%). However, 95% of patients in this analysis received d4T, which has been associated with fat loss.[5]
- In multivariate analyses, higher baseline glucose, higher age, current alcohol use, and Caucasian/non-Hispanic race were associated with a higher risk of fat redistribution events.
- The significance of baseline glucose level, but not on-treatment glucose or lipid values, suggests that the risk of body composition changes is affected by pre-treatment metabolic abnormalities but not by laboratory abnormalities observed during ARV therapy.

REFERENCES

1. Safrin S, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS.* 1999;13:2493-2505.
2. Chen D, Misra A, Garg A. Clinical review 153: lipodystrophy in human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab.* 2002. 87:4845-4856.
3. Lichtenstein KA, Ward DJ, Moorman AC et al. Clinical assessment of HIV-associated lipodystrophy in an ambulatory population. *AIDS* 2001;15:1389-1398.
4. Heath KV, Hogg RS, Singer J et al. Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based cohort. *J Acquir Immune Defic Syndr* 2002;30:440-447.
5. Joly V, Flandre P, Meiffredy V et al. Increased risk of lipoatrophy under stavudine in HIV-1 infected patients: results of a substudy from a comparative trial. *AIDS* 2002. 16:2447-2454.

ACKNOWLEDGMENTS

Abbott Laboratories would like to acknowledge all the study subjects, study coordinators, and investigators who are participating or participated in M97-720, M98-863, M99-056, and M00-154.