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Adherence to the Mediterranean diet is associated with a lower risk of body-shape changes in Croatian patients treated with combination antiretroviral therapy

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Abstract

Background—Lipoatrophy and lipohypertrophy are frequently observed during long-term antiretroviral therapy (ART). We investigated whether consumption of a Mediterranean diet is associated with lower risk of body shape changes in Croatian patients treated with ART.

Methods—Between May 2004 and June 2005, we conducted a cross-sectional study of 136 adults with HIV-1 infection who were treated with ART for at least one year. Lipoatrophy and lipohypertrophy were assessed by self-report and physical examination. Adherence to a Mediterranean diet was determined by a 150-item questionnaire; a 0 to 9-point diet scale was created that stratified respondents as having low adherence (<4 points) and moderate to high adherence (≥ 4 points).

Results—Lipoatrophy was present in 41% and lipohypertrophy in 32% of participants. Non-smokers with a dietary score ≥ 4 had the lowest risk for lipoatrophy. Stavudine use, female gender, and duration of ART were also independently associated with a higher risk of lipoatrophy. A dietary score of ≥ 4 was associated with lower risk of lipohypertrophy (OR 0.3, 95% CI 0.1-0.7; P=0.012). Female gender, longer duration of ART, and longer known duration of HIV infection prior to ART were also independently associated with higher risk of lipohypertrophy.

Conclusions—Croats who did not smoke and moderately or highly adhered to the Mediterranean diet were least likely to have the clinical syndrome of lipoatrophy. Moderate to high adherence to a Mediterranean diet was also associated with a lower risk of lipohypertrophy.

Keywords

HIV; antiretrovirals; lipoatrophy; lipohypertrophy; Mediterranean diet

Introduction

HIV-associated lipodystrophy, also known as fat redistribution syndrome, is a frequent and important side effect of antiretroviral treatment (ART). Lipodystrophy is characterized by sustained changes in body fat distribution (lipoatrophy and lipohypertrophy), and is often accompanied by dyslipidemia and insulin resistance.¹⁻⁴ Peripheral lipoatrophy is characterized by wasting in the face, arms, buttocks and legs, and lipohypertrophy by increased deposition of fat in the abdomen, breasts, and dorso-cervical spine and by the appearance of lipomas.¹

^{5, 6} Recent studies have shown that there is no reciprocal association between peripheral lipotrophy and central lipohypertrophy.^{4, 7-9}

Body fat changes were associated with different host factors, severity of HIV disease, and type of treatment. Only a few studies have investigated the relationship of dietary intake with body fat changes and metabolic abnormalities in HIV-infected patients.¹⁰⁻¹⁴

The traditional Mediterranean diet refers to dietary patterns observed in olive – growing areas of the Mediterranean region.¹⁵ These dietary patterns include a high intake of vegetables, legumes, fresh fruits and nuts, cereals, and olive oil; a moderate intake of fish; a low-to-moderate intake of dairy products and wine; and a low intake of meat and poultry.¹⁶ Most research on the Mediterranean diet has focused on prevention of coronary heart disease and cancer prevention and a recent population-based study found that greater adherence to the traditional Mediterranean diet was associated with a prevention of coronary heart disease and death due to cancer.¹⁷⁻¹⁹ The effect of the Mediterranean diet on lipodystrophy in patients with HIV infection taking ART is unknown. We conducted a cross-sectional study of the relationship between adherence to a Mediterranean diet and body shape changes in HIV infected patients on ART in Croatia.

Methods

Setting

Croatia is a Southeastern European upper-middle-income country with a population of just over 4.4 million. It can be divided into three geographic regions: Mediterranean coastal in the south, Pannonian continental in the north, and mountainous in the center. The Croatian diet can vary by region with persons living along the Adriatic Coast eating a diet more closely resembling the classic Mediterranean diet and those living in the continental and mountain regions eating a more classically Western diet. Between 1985 and 2005 a total of 553 patients were diagnosed with HIV infection in Croatia. Of those 239 had an AIDS-defining illness and 127 died.

Subjects

Patients with documented HIV-1 infection were recruited from the Outpatient HIV/AIDS Department at the University Hospital of Infectious Diseases (UHID) in Zagreb, Croatia from May 2004 to June 2005. Because all HIV-infected patients in Croatia are treated at UHID, we were able to enroll subjects from throughout the country. Included in the study were patients ≥ 18 years old, who had taken ART for at least one year and were willing to provide informed consent to participate in this study. The study protocol was approved by the institutional review boards of UHID and the University of California, San Francisco. Pregnant and breast feeding women, patients with uncontrolled opportunistic infections, and patients with disseminated malignancies were excluded. We had 169 patients who met the eligibility criteria.

Clinical, laboratory and lifestyle data

We administered a standard questionnaire to collect data on age, gender, education, family history of obesity, smoking, mode of infection, diet, current antiretroviral regimen and other treatments during a routine outpatient follow-up visit at UHID. A physical examination was performed that included measurements of waist and hip circumference (in cm), weight (in kg) and height (in cm). Blood was drawn for determination of current CD4 cell count and HIV-1 RNA levels. CD4 cell counts were determined by flow cytometry and HIV-1 RNA levels were determined by polymerase chain reaction (Roche Amplicor Monitor) with the lower limit of detection of 50 copies/ml. Data on the known duration of HIV infection, history of AIDS-defining illness, weight and height prior to HAART, peak HIV RNA level, lowest ever CD4

cell count, and past history of antiretroviral treatment were collected by reviewing patients' medical records. Treatment with a particular antiretroviral drug or drug class was considered present if the drug was administered for more than 6 months.

We assessed physical activity using the short version of the International Physical Activity Questionnaire.²⁰ Energy expenditure was calculated by weighting each type of activity by its energy requirements defined in metabolic equivalents (MET).²¹

Definition and Assessment of body-shape changes Measurements

We defined body-shape changes based on self-report confirmed by subsequent clinical examination by a physician. Body areas were evaluated using criteria developed for the US-based HIV Outpatient Study (HOPS).²² To reduce the influence of mild physical changes, we also used the same grading system.²² Briefly, each participant was asked to report whether he had any changes in fat since starting ART in the face, legs, arms, buttock (atrophy), neck, chest, abdomen, or presence of lipomas (hypertrophy). Each sign of fat accumulation or fat wasting was rated as absent, mild, moderate or severe by the participant and confirmed by the physician. Participants reporting no changes or only mild changes in different body areas were categorized as having “no sign.” Participants were classified in the “lipoatrophy” or “lipohypertrophy” group if they had at least one severe sign or one moderate sign in one area plus at least one subtle or moderate sign in another body area. Participants with mixed patterns were included in both groups.

Dietary Assessment

Dietary intake was assessed through a 150 item food frequency questionnaire provided by Antonia Trichopoulou. The questionnaire was translated into Croatian and one of the authors (DT) interviewed patients. Nutrient intakes were calculated using food composition tables specific to Croatia. For each of the items in the questionnaire, subjects reported frequency of consumption and portion size, and the average monthly intake was divided into daily portions. To assist in accurate determination of portions, we provided 76 photographs depicting typical portion sizes. Items were divided into 12 food groups: potatoes, vegetables, legumes, fruit and nuts, dairy products, cereals, meat, poultry, fish, olive oil, eggs and alcoholic beverages. For each participant, intake of each of the indicated groups in grams per day and total energy intake were calculated. Potatoes were added to the cereal group and poultry was combined with meat to form one category. A ratio of monounsaturated fats to saturated fats was also calculated. We used a 10-point Mediterranean diet scale developed by Trichopoulou A. et al.¹⁶ For each subject, a value of 0 or 1 was determined for each of the 9 components of the Mediterranean diet. The gender specific median consumption value was used as the cutoff point in each food category. For the six beneficial categories (vegetable, legumes, fruits and nuts, cereal, fish and monounsaturated fat to saturated fat ratio) a value of 0 was given to subjects who consumed an amount below the median. For the two detrimental categories (meat which included poultry, and dairy), a value of 1 was assigned to subjects who consumed an amount below the median for each of these categories. For ethanol consumption, a value of 1 was given to men who consumed 10 grams to 50 grams per day and to women who consumed 5 grams to 25 grams per day. The Mediterranean diet score ranged from 0 to 9, with higher scores indicating greater adherence to the traditional Mediterranean diet. Because of the small number of participants in our study, we dichotomized the Mediterranean diet score into below the median (< 4 points, indicating low adherence to the Mediterranean diet) and at or above the median (≥ 4 points, indicating moderate to high adherence to the Mediterranean diet).

Statistical analysis

We used frequency distributions for descriptive analysis and medians and inter-quartile ranges (IQR) for continuous variables such as dietary and energy expenditure. To compare different

characteristics of participants with lipoatrophy or lipohypertrophy to those without these conditions we used the Wilcoxon rank sum test for continuous variables and Fisher's exact test or the chi square test for categorical variables. In a multivariable logistic regression analysis we evaluated factors associated with lipoatrophy and lipohypertrophy separately. The dichotomized Mediterranean diet score was our main independent variable of interest. We screened for potential confounding variables by bivariable analysis and included those with a P-value < 0.25 in the initial models. We applied a stepwise procedure that also included interaction terms and then used backward elimination of terms according to significance of the likelihood ratio test. There was evidence of nonlinearity for the duration of ART in the lipohypertrophy regression model, hence we dichotomized this variable into <25 months and ≥25 months of treatment. Variables with a P-value <0.05 were retained in the final model. The interaction between stavudine (d4T) and non-nucleoside reverse transcriptase inhibitors (NNRTI) use was significant (P= 0.05), suggesting that NNRTIs were associated with lipoatrophy only when d4T was used. Because of this, we did not include the use of NNRTIs in our final lipoatrophy multivariable model. There was a significant interaction between smoking and the Mediterranean diet score in the lipoatrophy model. We assessed the adequacy of the final models by the Hosmer-Lemeshow test and checked for outliers and multicollinearity. All analyses were performed using the SAS statistical package (SAS System for Windows, Release 8.02, SAS Institute, Cary, NC).

Results

Study participants

Of 169 eligible patients, 136 (80%) agreed to interview, examination and review of their medical and database records. All participants were citizens of Croatia with a median age of 43 (IQR 36-50) years, and 108 (79%) were males. Forty-three percent acquired HIV through heterosexual sex, 41% through sex between men and 10% through injecting drugs.

Sixty-five (48%) of the participants were from the Adriatic coastal regions of Croatia, while 71 (52%) were from the continental and mountainous areas of the country. The median Mediterranean diet score was 4 (IQR, 3 to 5.5) and 92 (68%) participants had a Mediterranean diet score ≥ 4. The median lowest ever CD4 cell count was 57.5 cells per mm³ (IQR, 16-145) and the median current CD4 cell count was 356.5 cells per mm³ (IQR, 244.5-486). There was no statistically significant difference in the lowest ever and current CD4 cell count in participants with and without lipoatrophy or lipohypertrophy. The median peak plasma viral load was 5.6 log₁₀ per ml (IQR, 5.1-5.9) and there was no significant difference in peak viral load between participants with and without lipoatrophy and lipohypertrophy.

The median duration of ART was 47 months (IQR, 23-67). There were 45 (33%) participants who used only protease inhibitor (PI) based ART regimens, 34 (25%) who used only NNRTIs regimens and 57 (42%) who used both. Among PI-experienced participants 35% used indinavir, 27% lopinavir/ritonavir and 26% indinavir/ritonavir. More participants had a history of efavirenz (67, 49%) use than of nevirapine (27, 20%). Of the 131 participants taking ART at the time of the interview, 43% were on treatment with a PI, 53% were taking NNRTI-based therapy, and 4% were using both an NNRTI plus a PI. The most common current ART regimen was zidovudine plus lamivudine plus efavirenz (23%), followed by zidovudine plus lamivudine plus lopinavir/ritonavir (16%), zidovudine plus lamivudine plus nevirapine (13%) and abacavir plus lamivudine plus efavirenz (11%).

Body-shape changes

According to our study definitions (Table 1), 56 (41%) participants had lipoatrophy and 44 (32%) had lipohypertrophy. Severe signs of lipoatrophy were found most frequently in the face

(n=14), followed by thighs (n=13) and buttocks (n=12). Severe signs of lipohypertrophy were found most frequently in the abdomen (n=21). Thirty-one participants (23%) had only signs of peripheral fat atrophy, 19 (14%) had only signs of lipohypertrophy and 25 (18%) had both. The main characteristics of participants with and without lipoatrophy or lipohypertrophy are compared on Table 2. Lipoatrophy was seen more frequently in females (17/28, 60.7%) than in males (39/108, 36.1%; $P=0.03$, Table 2). Former and current smokers were more likely to have lipoatrophy. Other factors associated with lipoatrophy were duration of ART and treatment with stavudine and non-nucleosides. Participants with lipoatrophy had a longer known duration of HIV infection and a lower weight before initiation of combination ART compared to participants without lipoatrophy, but these differences were not statistically significant ($P=0.09$ and $P=0.064$, respectively) (Table 2). There was no association between the Mediterranean diet score and lipoatrophy on bivariable analysis.

Of the 44 participants with lipohypertrophy 95% had fat deposition in the abdomen, and 84% reported fat deposition in the thorax. Of 28 females 19 (67.9%) had signs of lipohypertrophy whereas out of 108 males, 25 (23.2%) had lipohypertrophy ($P<0.001$, Table 2). Participants with moderate to high adherence to the Mediterranean diet (score ≥ 4) had less frequently lipohypertrophy ($P=0.031$, Table 2). NNRTI use was more frequently associated with lipohypertrophy than PI use on bivariable analysis (Table 2). Of 45 patients who used PIs only 9 (20%) had lipohypertrophy, while of 34 participants who used NNRTIs 16 (47%) had lipohypertrophy. We also found that the following factors were associated with lipohypertrophy: longer known duration of HIV infection before combination ART was given, greater waist-to-hip ratio and a greater change in body mass index (Table 2).

Diet, energy intake and energy expenditure

Because of the gender difference in dietary intake and because of the low number of women in our study we report dietary intake only for 108 men. There was no statistically significant difference in consumption of the six beneficial diet categories (vegetable, legumes, fruits and nuts, cereal, fish and monounsaturated fat to saturated fat ratio) between men with and without lipoatrophy or lipohypertrophy. However, participants without lipoatrophy consumed more fish than participants with lipoatrophy (median 38 g/day, IQR 25-45; versus 28 g/day, IQR 17-45; $P=0.062$). For the two detrimental categories (meat, which included poultry, and dairy) there was also no significant difference although men with lipoatrophy consumed more meat than men without lipoatrophy (134 g/day, IQR 100-153 versus 114 g/day, IQR 89-140; $P=0.08$). Men without lipohypertrophy consumed more cereals than those with lipohypertrophy (282 g/day, IQR 246-325; versus 256 g/day, IQR 240-281; $P=0.021$). There was no statistically significant difference in other food categories, however, men with no lipohypertrophy consumed more vegetables (364 g/day, IQR 260-447) and monounsaturated fat (36 g/day, IQR 29-44) than men with lipohypertrophy (302 g/day, IQR 247-374; $P=0.081$, and 32 g/day, IQR 26-39; $P=0.08$ respectively). Fifty-one participants did not consume olive oil. Of 69 men without lipoatrophy, 48 (70%) consumed olive oil, whereas of 39 men with lipoatrophy 20 (51%) consumed olive oil ($P=0.066$). Of 83 men without lipohypertrophy 58 (70%) consumed olive oil, whereas of 25 men with lipohypertrophy 15 (40%) consumed olive oil ($P=0.009$). The median consumption of olive oil for men who used it was 17.7 grams/day, IQR 13.5 to 24.8. The consumption of ethanol was similar in participants with and without lipoatrophy or lipohypertrophy, and there was also no difference in energy intake and energy expenditure.

Multivariable analysis

Lipoatrophy was associated with stavudine use, gender, and duration of ART (Table 3). There was also a significant interaction between smoking and the Mediterranean diet score. Non-smokers who moderately or highly adhered to the Mediterranean diet (score ≥ 4) were less

likely to have lipoatrophy than other subgroups (Table 3). Lipohypertrophy was associated with a Mediterranean diet (score ≥ 4), gender, known duration of HIV infection prior to combination ART and duration of ART (Table 3). Because the addition of PI or NNRTI use to the model gave a non-significant result we removed those variables from the final analysis.

Discussion

We found that non-smokers who moderately or highly adhered to the Mediterranean diet were least likely to have the clinical syndrome of lipoatrophy. Participants without the clinical syndrome of lipohypertrophy adhered to the Mediterranean diet more frequently than did participants with lipohypertrophy. Among individual components of the Mediterranean diet, only olive oil consumption showed a significant association with body fat change; those who consumed olive oil were less likely to have lipohypertrophy. This finding supports the use of a combined Mediterranean diet score, since individual components may each have only a small effect.

Except for the consumption of olive oil which was very low in our study population the median consumption of other food categories was similar to those reported from Greece by Trichopoulou et al.¹⁶ We did not use the polyunsaturated fat in the numerator of the lipid ratio as suggested by Trichopoulou et al. for populations with a low intake of olive oil²³ because the beneficial effects of polyunsaturated fat are still debated.²⁴ Participants with moderate to high adherence to the Mediterranean diet consumed more legumes, fish, fruit and nuts, vegetables and had a higher ratio of monosaturated to saturated fat intake than participants with low adherence to the Mediterranean diet.

Data on diet and body shape changes in HIV-infected patients are limited, and none of the previous studies has looked specifically at different food categories. An Australian study found no relationship between either saturated fat or total fat intake and body composition parameters characteristic of lipodystrophy in patients on ART.¹⁰ Hadigan et al. reported that HIV-infected men, with or without fat redistribution, had similar dietary habits and did not differ from one another in total energy intake or macronutrient composition.¹¹ A nested case control study from the US found that HIV patients on ART without fat deposition had greater overall energy intake, protein consumption and total dietary fiber intake than patients with HIV-related fat deposition.¹⁴ Roubenoff et al. described a patient in whom an exercise program and moderate-fat, low glycaemic, high-fiber diet reversed central obesity.¹³ We found that men without lipoatrophy tended to consume more fish and less meat than men with lipoatrophy. Men without lipohypertrophy consumed significantly more cereals than men with lipohypertrophy.

Only a few studies have looked at smoking as a risk factor for body shape changes in HIV infected patients. In a cross-sectional study of body composition measured by dual energy x-ray absorptiometry (DEXA), Forrester and Gorbach found that Hispanic men who smoke had less total fat, less trunk fat and more appendicular fat than nonsmokers.²⁵ Hendricks et al. reported that those without fat deposition tended not to be current smokers.¹⁴ Smoking was associated with less visceral adipose tissue in women in the US-based Study of Fat Redistribution and Metabolic Change in HIV infection.⁹ We found that lipoatrophy was more prevalent in current and former smokers compared to nonsmokers. When this was adjusted for stavudine use, gender, and duration of ART there was a significant interaction between the smoking status and Mediterranean diet (Table 3) suggesting that diet and smoking habits combined may exert an effect on fat loss.

A number of risk factors for lipoatrophy have been identified in observational studies using multivariable analysis. They include, exposure to and duration of stavudine use,^{22, 26-30} age,^{2, 4, 7, 9, 22, 26, 27, 29, 31, 32} presence of markers of severity of HIV disease,^{9, 22, 26, 27, 31-33}

duration of therapy,^{2, 22, 26, 27, 31} and white race^{9, 22, 31, 33} We confirmed the role of stavudine and duration of ART as risk factors in our study. The role of stavudine and, to a lesser extent zidovudine, in lipodystrophy has been further established by findings from randomized controlled trials using lamivudine or emtricitabine with efavirenz and a thymidine analogue or tenofovir. Total limb fat was significantly less in patients treated with stavudine³⁴ and zidovudine³⁵ compared to tenofovir in a subgroup of patients with DEXA measurements. Several factors have been associated with lipohypertrophy: duration of therapy,^{22, 26, 27, 31} markers of disease severity,^{22, 27, 29} and age.^{22, 26, 27, 30} Early studies found that PI use was associated with lipohypertrophy.^{27-29, 31} However, we did not find an association of PI use compared to NNRTI use in lipohypertrophy, a finding also reported in other more recent studies.^{7, 9, 32}

The principal limitation of our study was the cross-sectional design. Hence, we have not studied the change in adipose tissue over time. Confounding is inherent in any observational study especially when the sample size is relatively small.

However, we were able to adjust for the majority of known confounders for fat loss and fat gain and we report results consistent with the majority of findings from larger studies. Also, the median duration of combination ART was long (47 months) which allowed us enough time to observe body fat changes. We included in our study 80% of all HIV infected Croatian patients who have been on ART for at least 12 months. This in our view enables us to draw valid inferences for Croatians. Our findings, however, may not apply to other populations.

In summary, we found that the risk of lipodystrophy was lowest in Croatians who did not smoke and were at least moderately adherent to a Mediterranean diet. Moderate to high adherence to a Mediterranean diet was associated with a lower risk of lipohypertrophy.

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Table 1
Number and severity of lipoatrophy and lipohypertrophy in 136 Croatian HIV-infected patients

Severity and number of signs	Lipoatrophy	Lipohypertrophy
None	48 (35%)	51 (38%)
Only Subtle		
1	10	30
> 1	14	1
Moderate		
1	8	10
> 1 ^a	24	20
Severe		
1	3	3
> 1 ^b	29	21
Total	136	136

^a One moderate sign plus at least one subtle or one moderate

^b One severe sign plus at least one subtle, one moderate or one severe sign.

The gray shading indicates patients included in the lipoatrophy group (56/136, 41%) and in the lipohypertrophy group (44/136, 32%). Twenty-five patients had both lipoatrophy and lipohypertrophy.

Table 2
Main characteristics of 136 HIV-infected patients with and without lipoptrophy and lipohypertrophy*

Characteristics	Lipoatrophy			Lipohypertrophy		
	Yes N=56	No N=80	P	Yes N=44	No N=92	P
Male gender	70	86	0.030	57	90	<.001
Age at study inclusion, years	44 (39-52)	43 (37-50)	0.305	44 (39-53)	44 (37-50)	0.421
Former or current smoker	77	58	0.042	71	64	0.562
Mode of infection						
Heterosexual	46	40	0.400	46	41	0.677
Male who has sex with men	34	46		39	42	
Injecting drug user	9	10		9	10	
Hemophilic	4	1		5	1	
Unknown	7	3		2	5	
Mediterranean diet score ≥ 4	62	71	0.352	55	74	0.031
Disease severity						
Known duration of HIV infection prior to start of ART, months	9 (1-53)	3 (0-33)	0.090	29 (1-65)	3 (0-26)	0.011
History of AIDS defining illness	52	44	0.386	50	46	0.714
Current HIV RNA count < 50 copies/ml	84	88	0.619	84	87	0.792
Peak HIV RNA $\geq 300\,000$ copies/ml	59	53	0.488	52	57	0.714
Lowest ever CD4 count (cell/mm ³) ≤ 50	48	40	0.382	43	43	1.000
Treatment						
Duration of ART, months	53 (36-72)	37 (20-56)	0.001	49 (31-71)	44 (21-62)	0.053
Protease inhibitor use ≥ 6 months	71	78	0.429	64	80	0.055
Non-nucleoside use ≥ 6 months	79	59	0.017	80	61	0.034
Stavudine use ≥ 6 months	73	46	0.003	61	55	0.580
Body measurements						
Waist-to-hip ratio, males > 0.95 or female > 0.8	84	71	0.103	89	71	0.030
Change in BMI > 2 kg/m ²	61	54	0.483	71	50	0.028
Weight prior to ART, kg	63 (54-72)	68 (60-78)	0.064	62 (54-75)	66 (57-74)	0.243

* Values are percentages or medians (25th–75th percentile)

Table 3

Factors associated with lipoptrophy or lipohypertrophy

Lipoatrophy	OR	95% CI	P
Stavudine use			
Yes	3.99	1.72-9.28	0.001
No	1.00		
Gender			
Male	0.33	0.133-0.86	0.023
Female	1.00		
Duration of HAART (per 12 months)	1.47	1.17-1.85	0.001
Interaction of smoking* and Mediterranean diet score			
Non-smoking in participants with Mediterranean diet score ≥ 4	1.00		
Non-smoking in participants with Mediterranean diet score < 4	4.53	0.86-23.92	0.076
Smoking in participants with Mediterranean diet score ≥ 4	3.42	1.21-9.67	0.014
Smoking in participants with Mediterranean diet score < 4	4.39	1.35-14.26	0.021
Mediterranean diet score			
< 4	1.00		
≥ 4	0.30	0.12-0.75	0.010
Gender			
Male	0.09	0.03-0.26	< 0.001
Female	1.00		
Known duration of HIV infection before start of HAART (per 12 months)	1.17	1.05-1.31	0.004
Duration of HAART			
< 25 months	1.00		
≥ 25 months	6.19	1.76-21.74	0.005

* current or former smoking