

Morphologic Alterations in HIV-Infected People with Lipodystrophy Are Associated with Good Adherence to HAART

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Objective: To evaluate the association between adherence to drugs and morphologic alterations (MOA) in a cohort of HIV-infected patients on HAART.

Method: This was a cross-sectional multicenter cohort study in eight tertiary Clinical Centers of Northern and Central Italy. Consecutive outpatients taking HAART were enrolled from August 2000 to March 2001. They completed a self-administered questionnaire for the evaluation of signs of MOA and the self-reported adherence to drugs. Main outcome measures were MOA according to the Multicenter AIDS Cohort Study (MACS) definition and adherence to drugs. **Results:** One hundred seventy-five persons were enrolled into the study. Median CD4 cell count was 522 (interquartile range [IQR] 306–720); 35% of people had undetectable HIV RNA. Patients had been taking HAART for a median of 53 months (IQR 33–62). Among enrolled patients, 83 (47%) had a diagnosis of self-reported MOA; 57 of them reported body changes of more than 12 months duration. Forty persons (23%) self-reported nonadherence in the previous week. Mean time on HAART was 48.7 months ($SD = 19.7$) for people with MOA and 42.1 months ($SD = 21.8$) for those without MOA ($p = .043$). The odds of adherence for people with MOA was 2.36 times (95% CI 1.11–5.00) higher than for people without MOA. On multivariate analysis, being older and female, having an undetectable HIV RNA, longer duration on HAART, and self-reported adherence were independently associated with the presence of MOA. In people with MOA, adherence seems to decrease over time.

Conclusion: Longer time on HAART and self-reported adherence were correlated to MOA. MOA was also associated with older age and female gender. **Key words:** adherence, HAART, morphologic alterations

The recent introduction of highly active antiretroviral therapy (HAART) has led to impressive benefits in terms of morbidity and mortality. However, adverse events of antiretrovirals are common and can have a major impact on patients' quality of life. Toxicity is the most frequent cause for discontinuation in people taking HAART,¹ and adverse drug effects (ADEs), such as nausea, vomiting, and sexual dysfunctions, are recognized as important determinants of nonadherence to drugs.^{2–4}

In the last few years, morphologic alterations (MOA) have emerged as a new antiretroviral-related ADE. However, other factors in addition to drugs may also be related to this syndrome, such as

age, race, gender, duration of HIV infection, and CD4 cell count.⁵ Clinical manifestations include lipoatrophy, lipohypertrophy, or both in localized areas. Sometimes the syndrome is associated with metabolic abnormalities such as hyperglycemia, hypertriglyceridemia, and hypercholesterolaemia.⁶

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The incidence of MOA was 49%–53% in three large cohorts for investigation on this condition.^{6–9}

MOA may have a negative impact on the patient's well-being^{10,11} due to the important body changes and changes in self-image. Physical changes can also stigmatize patients as "sick" and likely HIV infected.¹² Some patients may refuse to start or to continue therapy for fear of developing unsightly morphological changes.¹³

Published results have shown that MOA is significantly correlated with increased duration of antiretroviral therapy and with lower plasma HIV RNA^{14,15} and is thus related to good adherence. On the other hand, other authors¹⁶ have suggested that the number of MOA symptoms is significantly related to self-reported nonadherence 20 months after starting HAART. However, no clinical trials assessing the direct relationship between MOA and adherence have been published so far.

We hypothesized that MOA would be significantly associated with adherence to HAART and that adherence would decline with time since MOA diagnoses. The objective of the study was to evaluate the association between adherence and MOA in a cohort of patients with HIV infection who were taking HAART.

METHOD

Design and Population

A cross-sectional multicenter cohort study (Gruppo Regionale di Analisi dell'Aderenza nella Lipodistrofia - GRAAL Study) was designed to evaluate the impact of MOA on adherence to HAART. This study was a cross-sectional analysis of data collected at study enrollment.

HIV-infected outpatients were consecutively enrolled in eight Clinical Centers of Northern and Central Italy from August 2000 to March 2001. Inclusion criteria were HIV infection, age ≥ 18 years, and being prescribed antiretroviral therapy (defined as two nucleoside-analogue reverse transcriptase inhibitors [NRTIs] + one or two protease inhibitors [PIs], two NRTIs + one nonnucleoside-analogue reverse transcriptase inhibitor [NNRTI], or three NRTIs) for at least 6 months and up to a maximum of 72 months. Exclusion criteria were CDC C group classification, a diagnosis of AIDS dementia complex >2 according to the Price classification, isolated metabolic abnormalities not asso-

ciated with MOA, hospitalization at the time of enrollment, and inability to complete the questionnaire. We excluded patients with advanced AIDS who may have had morphological abnormalities similar to those of MOA. No treatments for MOA were suggested by protocol. The protocol was approved by each of the local ethics committees of the participating clinical centers.

Data Collection

At enrollment, a questionnaire on self-reported signs of MOA¹⁷ was administered. The questionnaire asks about body changes of 12 regions (presence of a buffalo hump; subcutaneous fat accumulation; fat wasting in cheeks, arms, buttocks, and legs; fat accumulation in neck, abdomen, breast, and sacral region; prominent veins in arms or legs). It also investigated the self-reported degree of MOA in any area (absent, mild, moderate, severe). Weight, body mass index, and waist-to-hip ratio were measured by physicians at each visit. Blood analysis included fasting glucose, triglycerides, and total and HDL cholesterol levels.

For the purpose of the study, we used the Multicenter AIDS Cohort Study (MACS) criteria for MOA.¹⁸ MOA was defined as patient self-reported moderate or severe peripheral lipoatrophy (thinning of arms or legs), moderate or severe subcutaneous fat hypertrophy (dorsocervical region, neck, lipoma), or the combination of central fat accumulation (increase in abdomen or breast) and lipoatrophy. This definition appeared to best minimize diagnosis prevalence of MOA in HIV-negative men. The MACS definition excludes isolated metabolic alterations and discriminates populations with or without MOA.

Adherence Measures

At enrollment, participants in the study were asked to complete a previously tested self-administered questionnaire.¹⁹ The questionnaire investigates knowledge about the current HAART scheme (being able to correctly recall name, colour, and timing of current drugs), adherence behaviour (missing doses), interruptions in drug supply (sometimes running out of pills between visits), knowledge of current HIV disease stage (most recent CD4+ cell count and plasma HIV RNA), and reasons for missing or discontinuing drugs.

For this study, self-reported nonadherence was defined as missing one or more doses of antiretroviral drugs during the preceding week. The questionnaire also asked about perceived functional status and psychological well-being using the MOS-HIV Health Survey,²⁰ symptoms, satisfaction with health care, patient-provider relationship, treatment with complementary medicine, use of alcohol or recreational drugs, level of education, type of housing, type of profession and time of unemployment, monthly income, children, and living with other HIV-positive persons. On average, it took 15 minutes to fill out the questionnaire. The questionnaires were collected in sealed anonymous envelopes and were delivered unopened to the data center.

Other Measures

Demographic characteristics (age, gender), clinical characteristics (HIV disease stage, antiretroviral therapy, previous cardiovascular events), and behavioural variables (alcohol intake, physical activity, smoking status) were collected from medical records.

At each study visit, samples for CD4+ cell count and plasma HIV RNA level were also collected. Plasma HIV RNA levels were determined using a branched chain DNA technique (Quantiplex 2.0; Chiron, Emeryville, California, USA) with a detection limit of 50 copies/mL.

Statistical Analysis

A descriptive analysis of the study population was carried out. We compared the relationships of dichotomized and continuous independent variables to MOA using bivariate logistic regression. Results are presented using odds ratios (ORs) with 95% confidence interval (95% CI). A *p* value of <.05 was considered statistically significant. Multivariate logistic regression analyses included all variables found to be significantly associated with MOA at univariate analysis after controlling for clinical center. Data were analyzed with the SPSS software statistical package (version 9.0; SPSS Inc., Chicago, Illinois, USA).

RESULTS

As of March 2001, 175 patients were enrolled into the study. Mean age was 40 years, 40% were fe-

male, and 33% were former intravenous drug users (IDUs; **Table 1**). Median CD4 cell count was 522 (interquartile range [IQR] 306–720); 35% of people had undetectable HIV RNA (< 50 copies/mL). Patients had been taking HAART for a mean of 45.3 months (± 21); 95 (54%) had been taking HAART for more than 4 years.

When compared to men, women were younger (*p* < .0001), had lower weight (*p* < .0001), lower

Table 1. Characteristics of patients on HAART (N = 175)

Demographic variables	
Age, years (median, IQR)	39 (35–43)
Female, <i>n</i> (%)	70 (40)
Epidemiological and clinical variables	
CDC group A, <i>n</i> (%)	80 (45.7)
Intravenous drug user, <i>n</i> (%)	33.3
Previous cardiovascular events, <i>n</i> (%)	6 (3.4)
CD4 cell count/ μ L (<i>SD</i>)	543 (305)
Plasma HIV RNA log, copies/mL (median, IQR)	2.5 (1.69–3.29)
Undetectable plasma HIV RNA (%)(<50 copies/mL)	64 (36.6)
Duration of HAART, months (<i>SD</i>)	48.8 (31.5)
Metabolic variables	
Glucose, mg/dL (median, IQR)	90 (83–101)
Triglycerides, mg/dL (median, IQR)	177 (113–299)
Total cholesterol, mg/dL (median, IQR)	204 (165–245)
HDL cholesterol, mg/dL (median, IQR)	41 (35–50)
Anthropometric measures	
Weight, kg (<i>SD</i>)	67 (12)
Body mass index, kg/m ² (<i>SD</i>)	23.2 (3.7)
Waist-to-hip ratio (median, IQR)	0.92 (0.83–0.98)
Behavioural variables	
Alcohol intake (more than half a liter of wine/beer or more than one glass of liquor daily), <i>n</i> (%)	63 (36.0)
Moderate/severe physical exercises (activities more than 5 times a week for more than 30 minutes each time), <i>n</i> (%)	88 (50.3)
Currently smoker (%)	109 (62.3)

Note: IQR = interquartile range.

Table 2. Self-reported degree of changes in 14 body areas according to gender

Self-reported fat redistribution	Men				Women			
	Absent (%)	Mild (%)	Moderate (%)	Severe (%)	Absent (%)	Mild (%)	Moderate (%)	Severe (%)
Neck enlargement	102 (97.1)	1 (1)	1 (1)	1 (1)	62 (88.6)	4 (5.7)	1 (1.4)	3 (4.3)
Buffalo hump**	101 (96.2)	2 (1.9)	0 (0)	2 (1.9)	56 (80)	5 (7.1)	5 (7.1)	4 (5.7)
Fat wasting in the cheeks	67 (63.8)	12 (11.4)	13 (12.4)	13 (12.4)	41 (58.6)	14 (20)	8 (11.4)	7 (10)
Fat wasting in the arms	74 (71.2)	13 (12.5)	11 (10.6)	6 (5.8)	41 (58.6)	12 (17.1)	11 (15.7)	6 (8.6)
Fat wasting in the buttocks	63 (60)	17 (16.2)	10 (9.5)	15 (14.3)	35 (50)	10 (14.3)	12 (17.1)	13 (18.6)
Fat wasting in the legs*	66 (62.5)	13 (12.5)	12 (11.5)	13 (12.5)	30 (42.9)	8 (11.4)	15 (21.4)	17 (24.3)
Abdominal fat accumulation*	61 (58.1)	24 (22.9)	13 (12.4)	7 (6.7)	28 (40)	17 (24.3)	10 (14.3)	15 (21.4)
Breast enlargement*	91 (86.7)	7 (6.7)	5 (4.8)	2 (1.9)	47 (67.1)	9 (12.9)	9 (12.9)	5 (7.1)
Increased hip girth**	99 (94.3)	1 (1)	4 (3.8)	1 (1)	56 (80)	7 (10)	4 (5.7)	3 (4.3)
Subcutaneous fat accumulation	96 (91.3)	1 (1)	3 (2.9)	5 (4.8)	62 (88.6)	0 (0)	7 (10)	1 (1.4)
Prominent arm veins	82 (78.1)	13 (12.4)	8 (7.6)	2 (1.9)	47 (67.1)	8 (11.4)	8 (11.4)	7 (10)
Prominent leg veins***	63 (60)	21 (20)	15 (14.3)	6 (5.7)	35 (50)	13 (18.6)	7 (10)	15 (21.4)

* $p < .05$; chi-square test. ** $p < .01$; chi-square test. *** $p = .02$.

body mass index ($p = .01$), lower waist-to-hip ratio ($p = .001$), higher CD4 cell counts ($p = .03$), and higher HDL cholesterol levels ($p = .01$) and triglycerides levels ($p = .03$).

Eighty-three people (47%) had a diagnosis of MOA. Of these, 57 people reported body changes of more than 12 months duration. **Table 2** shows self-reported degree of body changes in the 12 explored areas. The most frequent body changes reported as severe were fat wasting in legs (18%), buttocks (16%), cheeks (11%); abdominal fat accumulation (13%); and prominent leg veins (12%). Mean time on HAART was 48.7 months ($SD = 19.7$) for people with MOA and 42.1 months ($SD = 21.8$) for those without ($p = .043$).

The response rate to the adherence questionnaire was 93.2%. Forty people (23%) reported having missed at least one dose of antiretroviral therapy during the previous week. Thirty-one patients (18%) reported sometimes running out of drugs between clinic visits.

In bivariate analysis, factors significantly related to self-reported MOA were older age, longer duration on HAART, undetectable HIV RNA, self-reported adherence, higher HDL, and higher blood glucose levels (**Table 3**).

The probability of being adherent was 2.36 times higher (95% CI 1.11-5.00) for people with MOA than for people without MOA.

On multivariate analysis, being older and female, having an undetectable HIV RNA, longer duration on HAART, and self-reported adherence were independently associated with the presence of MOA (**Table 4**).

Figure 1 shows rates of optimal and suboptimal adherence according to the duration of MOA. For the 83 people with self-reported MOA, the probability of optimal adherence is 0.97 (95% CI 0.95-1.00, $p = .09$) for each additional month since MOA diagnosis.

DISCUSSION

In this study, self-reported adherence to HAART was independently associated with MOA. This was accompanied by the expected independent association with undetectable HIV RNA and longer duration of HAART therapy. In addition, MOA was associated with older age and female gender. In people with MOA, optimal adherence to

Table 3. Variables associated with presence of self-assessed fat redistribution (using the Multicenter AIDS Cohort Study definition); bivariate analysis

Variables	OR (95% CI)	<i>p</i>
Demographic variables		
Age	1.05 (1.009-1.100)	.017
Female	1.78 (0.97-3.29)	.06
Epidemiological and clinical variables		
CDC group B	1.72 (0.93-3.20)	.08
Cardiovascular events in past 6 months	5.70 (0.65-49.90)	.08
CD4 cell count/ μ L	1.000 (0.999-1.002)	.24
Undetectable HIV RNA	2.06 (1.08-3.93)	.028
Time on HAART (for each month)	1.01 (1.00-1.03)	.04
Metabolic variables		
Glucose	1.02 (1.00-1.04)	.017
Triglycerides	1.00 (0.99-1.001)	.84
Total cholesterol	1.001 (0.99-1.005)	.27
HDL cholesterol	0.94 (0.90-0.98)	.004
Anthropometric measures		
Body mass index	1.01 (0.92-1.11)	.81
Waist-to-hip ratio	5.52 (0.50-60.73)	.16
Weight	0.99 (0.96-1.01)	.38
Behavioural variables		
Drinking alcohol (>0.5 L wine/beer or >1 glass of liquor/day)	0.80 (0.43-1.49)	.48
Smoking	1.12 (0.57-2-20)	.73
Not physical activity	0.73 (0.35-1.52)	.40
Adherence-related variables		
Self-reported adherence (no missed doses in past week)	2.36 (1.11-5.00)	.023
Running out of drugs before clinic visit	0.77 (0.35-1.70)	.52

antiretrovirals was related to the duration of awareness of MOA.

Other studies have found an association between viral suppression related to HAART and the development of MOA.^{14,15,21,22} A possible explanation could be that adequate adherence results in bigger exposure to antiretroviral drugs,^{19,23} which may imply a higher probability of long-term metabolic side effects. Others investigators have noted a relationship between time on HAART and MOA, arguing for a role of the cumulative toxicity of antiretroviral drugs.^{7,8,22,24-27}

Longitudinal studies are needed to confirm the finding of previous reports that suggests that treatment-related adverse events can be a barrier to

adherence or sustained adherence to antiretroviral therapy.²⁻⁴ Duran et al.¹⁶ demonstrated that the number of symptoms related to MOA was significantly related to self-reported nonadherence after 20 months from initiation of HAART. However, since their study was not designed to assess the association between MOA and adherence, it was not possible to examine the relationship between adherence and MOA for people with more recent onset of MOA.

In our study, a trend of decreasing adherence since MOA diagnosis emerged. To significantly correlate time since MOA diagnosis to poorer adherence, it would be useful to demonstrate that decreasing adherence is not merely a matter of

Table 4. Variables independently associated with self-assessed fat redistribution (according to MACS definition); multivariate analysis

Variables	OR (95% CI)	<i>p</i>
Age	1.08 (1.02-1.14)	.007
Time on HAART	1.02 (1.001-1.04)	.037
Female	2.65 (1.21-5.80)	.015
CDC group B	1.46 (0.69-3.06)	.32
HIV RNA <50 copies/mL	2.10 (1.01-4.37)	.048
No missed doses in past week	2.46 (1.06-5.71)	.035

prolonged time on HAART. In our sample, the difference in mean time on HAART between people with MOA and people without MOA was 6.6 months. It is likely that this difference is too small in respect to the long duration of treatment exposure to interfere with the adherence outcome.

Future studies can verify whether the relationship between MOA and adherence is an inverted U-shaped function. Initially, MOA results from good adherence. However, the development of MOA, which the patient attributes to HAART, and the consequent dissatisfaction with body image can put the patient at risk for decreased adherence. Suboptimal adherence may in turn lead to virological failure.²⁸

In the present cohort, several other factors were associated with MOA. Older age has also been identified as a risk factor by other authors,^{7,22,24,26,29} which supports the theory that MOA may be associated with accumulated mitochondrial abnormalities that may accrue with age.³⁰⁻³³ Physiologic reduction of lean body mass and an increase in fat mass as well as a decrease in limb fat may also be seen with increasing age.³² In addition, in some studies, older age has been associated with better adherence.^{3,33,34} Thus, it is possible that older age may also account for unmeasured superiority in adherence.

Females were also at higher risk of having MOA. These results confirm previous reports in literature.^{6,14,22,27,35,36} The explanation for this result is not clear. MOA may occur secondary to endocrinological or hormonal alterations induced by antiretrovirals, although this has not been confirmed in all the studies on the assessment of risk factors for MOA.²⁷ In a recent study, Hadigan et al.³⁷ found that women with MOA had a significantly higher level of total and free testosterone compared to women without MOA. It is also possible that women might be more aware of their body changes compared to men and more likely to report their occurrence.

Our study had some limitations. Given the cross-sectional design, it is not possible to draw causal inferences between adherence and MOA. Longitudinal studies are needed to further examine the

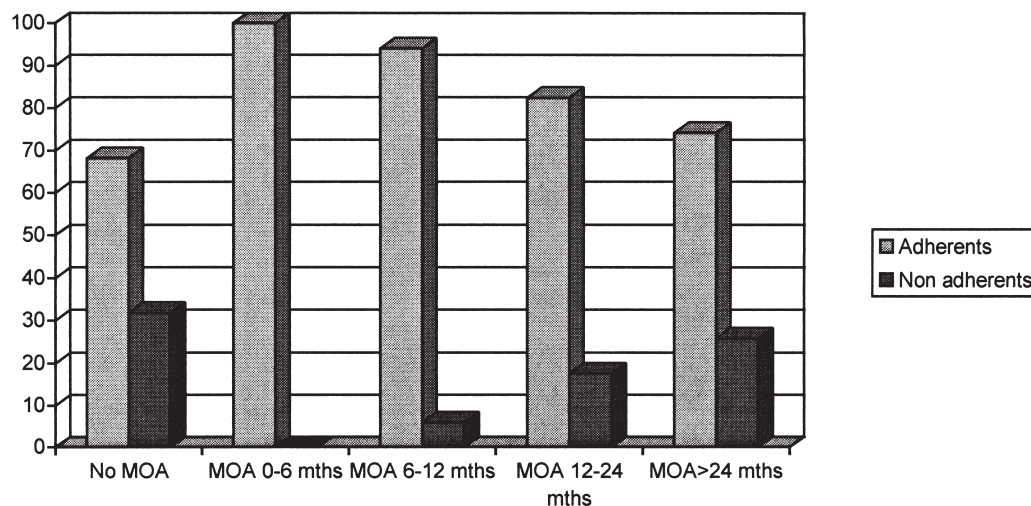


Figure 1. Adherence rate according to the duration of morphological alterations (MOA).

relationship of MOA to adherence. Moreover, we did not assess the association of each single antiretroviral agent or each single class of drugs to MOA. It is important to note that, in the present study, both MOA and adherence were assessed through self-report. This could have increased the variability of our results. Moreover, since both were binary variables, statistical power can be affected. Finally, results of the present study are not generalizable in populations different from ours.

The etiology of HIV-related MOA remains to be elucidated, and relationships among all causative factors should be assessed.⁶ Antiretrovirals seem to play an important role, but pathogenesis is multifactorial and nonpharmacologic factors also appear to contribute to MOA.

Data from the present study have a number of clinical implications for the management of antiretroviral therapy in HIV-infected patients in helping them to know what they have to expect and potentially in improving their adherence to antiretroviral therapy. First, the possibility of developing MOA after the prescription and maintenance of HAART with optimal adherence should be discussed with the patient at the time of choosing a first or new HAART regimen. It should be noted that some groups are at increased risk for MOA, including older persons and women. This may serve to help calibrate patients' expectations, reduce the surprise if MOA develops, and facilitate an ongoing dialogue about the benefits of HAART, adverse drug effects, and adherence.

Second, a careful screening of the MOA occurrence is mandatory for an early recognition of the syndrome itself. Unfortunately, there is no international consensus on methods of assessment and on the MOA definition or diagnostic criteria. However, since the subjective perception of morphologic changes by those receiving therapy is of great importance, we suggest the use of a patient-reported questionnaire. The validity of patient-reported body changes has been demonstrated through the assessment of a high concordance between patient self-report with a systematic enquiry and the findings of clinical examination.¹⁷

Third, since adherence is not a static phenomenon and since MOA patients might be at higher risk of suboptimal adherence, it is of crucial importance to implement strategies early that are designed to maintain or increase adherence over time. Unfortunately, there are no treatments of

proven efficacy to reduce MOA yet. In conclusion, MOA was more frequent in HAART-adherent patients. Morphologic abnormalities can be disfiguring and frightening, and they subject patients to increased risk of disclosure of their HIV status. All of these factors put MOA patients at higher risk of impaired adherence over time. The benefits of HAART may be offset if patients decide to alter or abandon HAART because of the occurrence or fear of MOA. Studies are needed to determine ways to detect MOA early in its course, ways to maintain or improve adherence over time, and methods for its effective treatment.

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