Published in final edited form as:

Alcohol. 2009 February ; 43(1): 65–71. doi:10.1016/j.alcohol.2008.09.004.

Alcohol Consumption and Lipodystrophy in HIV-infected Adults with Alcohol Problems

Debbie M. Cheng, ScD^{1,2}, Howard Libman, MD³, Carly Bridden, MA, MPH², Richard Saitz, MD, MPH^{2,4}, and Jeffrey H. Samet, MD, MA, MPH^{2,5}

¹Department of Biostatistics, Boston University School of Public Health, Boston, MA 02118 USA

²Clinical Addiction Research and Education (CARE) Unit, Section of General Internal Medicine, Department of Medicine, Boston Medical Center and Boston University School of Medicine, Boston, MA 02118 USA

³Divisions of General Medicine and Primary Care and Infectious Diseases, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215 USA

⁴Department of Epidemiology and Youth Alcohol Prevention Center, Boston University School of Public Health, Boston, MA 02118 USA

⁵Department of Social and Behavioral Sciences, Boston University School of Public Health, Boston, MA 02118 USA

Abstract

Lipodystrophy is a common long-term complication of HIV infection that may lead to decreased quality of life and less adherence to antiretroviral therapy (ART). A complete understanding of the etiology of HIV-associated lipodystrophy has not as yet been achieved, although factors related to the virus, per se, and use of ART appear to be related. Alcohol use is common among HIV-infected patients and has biological effects on fat distribution, yet alcohol's relationship to HIV-associated lipodystrophy has not been examined. The goal of this clinical study was to assess the effect of alcohol consumption on lipodystrophy in HIV-infected adults with alcohol problems. This was a prospective study (2001 - 2006) of 289 HIV-infected persons with alcohol problems. The primary outcome was self-reported lipodystrophy, which was assessed at one timepoint (median 29 months after enrollment). Alcohol use was assessed every 6 months and classified as: abstinent at all interviews; ≥ 1 report of moderate drinking but no heavy drinking; 1 or 2 reports of heavy drinking; or ≥ 3 reports of heavy drinking. Multivariable logistic regression models were fit to the data. Fifty-two percent (150/289) of subjects reported lipodystrophy. Alcohol consumption was: 34% abstinent at all interviews; 12% ≥ 1 report of moderate drinking, but no heavy drinking; 34% 1-2 reports of heavy drinking; 20% ≥ 3 reports of heavy drinking. Although not statistically significant, subjects with alcohol use had a higher odds of lipodystrophy [adjusted odds ratios and 95% CI: ≥ 1 report of moderate drinking, 2.36 (0.89, 6.24); 1-2 reports of heavy drinking, 1.34 (0.69, 2.60); ≥ 3 reports of heavy drinking, 2.07 (0.90, 4.73)]. Alcohol use may increase the odds of developing HIV-associated lipodystrophy among subjects with alcohol problems. However, larger studies are needed to elucidate fully the role and impact of alcohol consumption on the development of this common long-term complication of HIV infection and its treatment.

Keywords

lipodystrophy; HIV; alcohol consumption

INTRODUCTION

Despite dramatic improvements in morbidity and mortality of HIV-infected patients on antiretroviral therapy (ART), several important long-term complications of the disease and its treatment, including lipodystrophy syndrome, have been described. HIV-associated lipodystrophy (abnormal body fat distribution, often with hyperlipidemia and/or glucose intolerance) is common, with a prevalence ranging from 20-80% in patients on ART (Sattler, 2003). Between 20-50% of HIV-infected patients will report at least one sign of lipodystrophy within the first two years of starting ART (Galli et al., 2002; Heath et al., 2002). The abnormal fat distribution is typically characterized by fat accumulation in the neck, breasts, and abdomen, and fat loss in the face, buttocks, and extremities. Hyperlipidemia and glucose intolerance may contribute to the risk for cardiovascular and other atherosclerotic disease as patients age. In addition, patient quality of life and adherence to ART may be adversely affected by lipodystrophy through decreased self-esteem and stigmatization (Blanch et al., 2004).

The cause of HIV-associated lipodystrophy is unclear, but it appears to be multifactorial in origin, involving host factors (Martinez et al., 2001b), HIV itself (Mujawar et al., 2006), and ART drug effects. The latter are particularly notable with use of the nucleoside analogue reverse transcriptase inhibitors (NRTIs) and protease inhibitors (Caron et al., 2001). ART may have an impact on liver lipid transport, glucose homeostasis (Ben-Romano et al., 2003), and adipose tissue directly (Caron et al., 2001). The NRTIs specifically affect mitochondrial DNA replication (McComsey and Walker, 2004), which may explain the prominence of abnormal fat distribution in this syndrome because of the central role of mitochondria in fat cells and the high content of mitochondria in brown fat in particular (Brinkman et al., 1999; Villarroya et al., 2007).

Alcohol use is common among HIV-infected patients, and there are reasons to hypothesize that it may affect the development of lipodystrophy. Alcohol has multiple effects on metabolism including changes in energy intake (Armellini et al., 1993). An intriguing link can be found between alcohol use and mitochondrial DNA replication in an uncommon disease referred to as multiple symmetrical lipomatosis (MSL). First described by Madelung in 1888 as a case series of lipomas in patients with chronic alcoholism, MSL is characterized by nonencapsulated lipomas in a symmetrical distribution, typically in the subcutaneous fat of the back of the neck and the proximal legs and arms (Brinkman et al., 1999; Enzi et al., 1977), with sparing or wasting of fat in the distal arms and legs (Coin et al., 2005). In a more recent case series, alcohol intake of over 50 ml per day was observed in 29 of 31 patients with MSL (Enzi et al., 2002). However, it is now known that many patients with MSL also have either mutations in mitochondrial DNA or abnormal mitochondrial function (Klopstock et al., 1997; Schoffer and Grant, 2006), which leads to the hypothesis that heavy alcohol use in people with reduced mitochondrial function produces an increased risk of abnormal fat growth. In addition, several investigators have suggested that HIV-associated lipodystrophy itself resembles MSL because of the similar patterns of abnormal fat distribution (Brinkman et al., 1999; Hengel et al., 1997; Teplitzky and Halabe, 1999), and Brinkman et al (Brinkman et al., 1999) have hypothesized that mitochondrial toxicity underlies both syndromes. This association between alcohol use and MSL suggests the need to investigate whether heavy alcohol consumption contributes to the development of HIV-associated lipodystrophy.

The goal of this study was to assess the association between alcohol consumption and lipodystrophy in HIV-infected adults with alcohol problems. The relationship of these two common conditions has received little attention in this patient population. We examined this issue using data from a prospective cohort of HIV-infected persons with current or past alcohol problems.

MATERIALS AND METHODS

Study Design and Participant Recruitment

Subjects were participants in HIV-LIVE (HIV - Longitudinal Interrelationships of Viruses and Ethanol), a prospective, observational cohort study of HIV-infected patients with current or past alcohol problems. Data were collected at baseline and every 6 months thereafter for up to 42 months.

Four hundred subjects were recruited from the following sources: 1) 38% (n=154) from the HIV-ALC (HIV-Alcohol Longitudinal Cohort) study, a previous cohort study at Boston Medical Center (BMC) with identical inclusion and exclusion criteria (Samet et al., 2004); 2) 22% (n=88) from the Diagnostic Evaluation Unit (Samet et al., 1995), an intake clinic for HIV-infected patients at BMC; 3) 8% (n=31) from the HIV Primary Care and Specialty Clinics at Beth Israel Deaconess Medical Center (BIDMC); and 4) 32% (n=127) through flyers distributed in health care centers, homeless shelters, and drug treatment programs, advertisements in newspapers, and referrals from other HIV-LIVE subjects.

Eligibility criteria were: 1) documented HIV antibody test by ELISA confirmed by Western blot; 2) ≥ 2 affirmative responses to the CAGE alcohol screening questionnaire (Buchsbbaum et al., 1991; Mayfield et al., 1974) or diagnosis of lifetime alcohol abuse or dependence based on a study physician investigator clinical assessment; 3) ability to speak English or Spanish; and 4) at least one contact person. Exclusion criteria were: 1) score of <21 on the 30-item Folstein Mini-Mental State Examination (Folstein et al., 1975; Smith et al., 2006); or 2) trained interviewer assessment that the patient could not comprehend informed consent or answer the interview questions. In addition to the exclusion criteria noted for the HIV-LIVE study, the current analyses also excluded patients reporting moderate or severe isolated abdominal obesity in order to avoid confounding by age-related central adiposity. Enrollment began August 2001 and ended July 2003. Eligible subjects who wished to participate provided written informed consent prior to enrollment. Most interviews took place at General Clinical Research Centers. The Institutional Review Boards of BMC and BIDMC approved this study. Additional privacy protection was secured with a Certificate of Confidentiality from the Department of Health and Human Services to protect subjects from release of research data under court order or subpoena.

Subject Assessment

Subjects received an interviewer-administered assessment at baseline and 6-month intervals, conducted in English or Spanish, including questions on demographics, HIV risk behaviors, alcohol consumption, and ART use in the past 30 days. Lipodystrophy was evaluated at a single follow-up visit using a questionnaire developed by Carr et al (Carr et al., 2003). These questions supplemented the standard assessment and were instituted in 2004. Due to the sequential study accrual, subjects were administered the supplemental assessment at different follow-up times. Fat loss and/or fat gain in the face, front or sides of neck, back or base of neck, arms, breasts, waist, buttocks, and legs were assessed. The severity of any reported fat gain/loss was rated as mild, moderate, or severe. The presence and location of any fat lumps was also evaluated by research associate administered subject questionnaire. Past month alcohol consumption was assessed using a validated calendar method (Sobell and Sobell, 1996). The Composite

International Diagnostic Interview (CIDI) Alcohol Module (Robins et al., 1988) was administered following study enrollment to determine current (past 6 months) and lifetime diagnoses of alcohol abuse and dependence. We recorded CD4 cell counts and HIV RNA levels at each interview. Values were obtained by phlebotomy if not available from clinical records within 4 months of the interview. HCV RNA was measured using commercially available assays, either by branched-chain DNA or PCR-based assays. Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D); a cut-off of ≥ 23 was used to denote substantial depressive symptoms in persons with chronic diseases (Cook et al., 2002). ART use was assessed with the question, “Have you ever taken antiviral medications for your HIV?”

Outcomes

The primary outcome was self-reported lipodystrophy since diagnosis of HIV infection. It was defined as a response of moderate or severe changes in any of the following parameters: fat loss in the face or arms; fat gain in the back or base of the neck; increase in breast size; decrease in fat on buttocks or legs; or lipomatosis. The presence of lipodystrophy was based on an objective case definition previously developed and validated by Carr et al (Carr et al., 2003) but excluded clinical characteristics not generally recognized as manifestations of HIV-associated lipodystrophy (i.e., fat gain in face, fat loss/gain in the front or sides of neck, fat loss in the back or base of neck, fat gain in arms, decrease in breast size, increase in fat on buttocks or legs, and decrease in waist size). Consistent with the definition by Carr et al, patients reporting “moderate or severe isolated abdominal obesity” were excluded from analyses in order to avoid confounding by age-related central adiposity. Three secondary outcomes were also examined: lipohypertrophy (defined as a response of moderate or severe fat gain in the back or base of the neck or increase in size of breast); lipoatrophy (defined as a response of moderate or severe fat loss in the face or arms, or decrease in fat on buttocks or legs); and reporting both fat gain (i.e., lipohypertrophy or lipomatosis) and fat loss (i.e. lipoatrophy) since the diagnosis of HIV infection. The last outcome is a more stringent definition of lipodystrophy as it requires a report of both fat gain and fat loss, while the primary definition requires a report of either fat gain or fat loss.

Primary Independent Variable

At each study interview, alcohol use in the past 30 days was classified as heavy, moderate, or abstinent. Heavy alcohol use was defined as >14 drinks/week or ≥ 5 drinks on one occasion for men <66 years old, and >7 drinks/week or ≥ 4 drinks on one occasion for men ≥ 66 years old and all women (National Institute on Alcohol Abuse and Alcoholism, 2005). Moderate alcohol use was defined as any drinking less than heavy amounts. The main independent variable was alcohol consumption, measured across all available study interviews between study enrollment and the follow-up visit when lipodystrophy was assessed. The longitudinal information collected on alcohol use was combined, and subjects were classified into one of the following four alcohol consumption categories: abstinent at all available interviews; at least one report of moderate drinking but no heavy drinking; 1 or 2 interviews in which heavy drinking was reported; 3 or more interviews in which heavy drinking was reported. Based on the definition of the highest drinking category, subjects who did not complete at least 3 study interviews were excluded from analyses.

Potential Confounding Factors

The following potential confounders were included in the analyses: gender; age; race/ethnicity (black, white, other); hepatitis C RNA status (positive vs. negative); current depressive symptoms (yes vs. no); ART use (ever vs. never); cocaine use past 6 months (yes vs. no); CD4 cell count; and lifetime alcohol dependence diagnosis (no diagnosis, abuse, dependence).

Covariate values for depressive symptoms, CD4 cell count, and cocaine use were taken from the follow-up interview at which lipodystrophy was assessed. All other covariates were taken from study enrollment.

Statistical Analysis

Descriptive statistics were used to assess the bivariate relationship between subject characteristics and lipodystrophy for the study sample at enrollment. Chi-square and Fisher's exact tests were used as appropriate to assess the bivariate associations. We examined the relationship between alcohol consumption and lipodystrophy by fitting multivariable logistic regression models. Unadjusted and adjusted models controlling for all potential confounding factors were fit to the data. Analyses of all secondary outcomes were also conducted using logistic regression models. To minimize the potential for collinearity, we assessed correlation between pairs of independent variables and verified that no pair of variables included in the same regression model was highly correlated (i.e., $r > 0.40$). All analyses were conducted using two-sided tests and a significance level of 0.05. Analyses were performed using SAS software (version 9.1; SAS Institute, Cary, NC).

Sample Size Considerations

Among the 289 study subjects, 99 reported past month abstinence at all study visits, 34 had at least one report of past month moderate drinking but no heavy drinking, 98 had 1-2 reports of heavy drinking during the past month, and 58 had 3 or more such reports of heavy drinking. Consistent with the observed proportion of 50% reporting lipodystrophy among the reference group of those abstinent at all visits, the available sample sizes allow our study 80% power to detect an odds ratio as small as 2.8 for ≥ 3 episodes of heavy drinking, 2.4 for 1-2 episodes of heavy drinking, and 3.7 for moderate but no heavy drinking. Power calculations were based on chi-square tests using a significance level of 0.05.

RESULTS

Of the 400 HIV-LIVE subjects, 326 (82%) completed the follow-up study interview in which lipodystrophy was assessed. Of the 326 subjects who completed the lipodystrophy questionnaire, 30 were excluded because of isolated abdominal obesity and 7 were excluded for having fewer than 3 study visits at the time lipodystrophy was assessed. This resulted in a final study sample of 289 HIV-infected subjects with current or past of alcohol problems. Among the study sample, the proportion that was assessed at the baseline, 6, 12, 18, 24, 30, 36, and 42 month study visits was 100%, 89%, 88%, 89%, 88%, 89%, 77%, and 60%, respectively.

Characteristics of the study sample at study enrollment are shown in Table 1. The majority were male (74%) and non-white (68%). The age range of the subjects was 20.9 - 70.7 years, with a mean of 42.9. At study enrollment, 46% reported cocaine use in the past 12 months, 48% had substantial current depressive symptoms ($\text{CES-D} \geq 23$), 50% were hepatitis C RNA-positive, and 87% had ever taken ART. CD4 cell count ranged from 8-1809 cells/mm³, with a median of 404. The proportions in each alcohol consumption category were as follows: 34% were abstinent at all interviews; 12% had at least one report of past month moderate drinking, but no heavy drinking; 34% had 1-2 reports of past month heavy drinking; 20% had ≥ 3 reports of past month heavy drinking. Among the 289 study subjects, 150 (52%) had self-reported lipodystrophy, 115 (40%) lipoatrophy, 48 (17%) lipohypertrophy, and 42 (15%) both fat gain and loss. The median follow-up time at which lipodystrophy was assessed was 29 months after study enrollment (interquartile range 20 - 31 months). The mean and median number of interviews that occurred between enrollment and the time that lipodystrophy was assessed was five (interquartile range 4-6 interviews) and the mean and median number of interviews that

occurred overall (i.e. including interviews that occurred following assessment of lipodystrophy) was seven (interquartile range 6-8 interviews).

In multiple logistic regression models controlling for potential confounders, the adjusted odds ratios (AOR) and 95% confidence intervals (CI) for lipodystrophy were 2.07 (0.90,4.73) for ≥ 3 reports of any past month heavy drinking; 1.34 (0.69,2.60) for 1-2 reports of any past month heavy drinking; and 2.36 (0.89,6.24) for any past month moderate but no heavy drinking (Table 2). Factors significantly associated with lipodystrophy were substantial depressive symptoms (AOR 2.32 [95% CI 1.30, 4.15] for CES-D ≥ 23 vs. CES-D < 23), ART use ever (AOR 2.64 [95% CI 1.10, 6.36]), and CD4 cell count (AOR 1.13 [95% CI 1.02, 1.25] per 100 unit increase). Secondary analyses excluding depressive symptoms as a covariate produced similar results [AOR (95% CI): ≥ 1 report of moderate drinking, 2.23 (0.86, 5.78); 1-2 reports of heavy drinking, 1.46 (0.76, 2.80); ≥ 3 reports of heavy drinking, 2.14 (0.95, 4.82)]. In secondary analyses of the effect of any reports of past month drinking (yes vs. no), the AOR and 95% CI for lipodystrophy was 1.63 (0.89, 3.22).

The estimated associations between alcohol consumption and each of the secondary outcomes are reported in Table 3. For lipohypertrophy, subjects in each drinking category had a higher odds of reporting lipohypertrophy compared to those who were abstinent at all interviews (AOR [95% CI]: 2.51 [0.82, 7.66] for ≥ 3 reports of heavy drinking; 1.31 [0.53, 3.25] for 1-2 reports of heavy drinking; and 3.52 [1.07, 11.54] for moderate but no heavy drinking), with the last comparison being statistically significant. For lipoatrophy, the adjusted odds ratios [95% CI] were 1.77 [0.76, 4.12] for ≥ 3 reports of heavy drinking; 0.92 [0.46, 1.84] for 1-2 reports of heavy drinking; and 1.15 [0.44, 3.01] for moderate but no heavy drinking. For reporting both fat gain and fat loss, subjects with 1-2 reports of heavy drinking had increased odds of the outcome, but no association was statistically significant.

DISCUSSION

Lipodystrophy syndrome is common in HIV-infected patients, multifactorial in origin, and associated with decreased self-esteem, stigmatization, and possibly an increased risk of cardiovascular and other atherosclerotic disease. Alcohol use is also frequent among HIV-infected persons. Based on the link between chronic alcoholism and the development of abnormal fat growth in patients with mitochondrial replication deficits, as seen in multiple symmetrical lipomatosis, we hypothesized that alcohol use increases the risk of HIV-associated lipodystrophy. Exploration of this association has not been an active area of clinical HIV investigation. Our results suggest the potential of a clinically important relationship between alcohol and lipodystrophy among a cohort of HIV-infected subjects with alcohol problems. Subjects with multiple reports of heavy drinking had twice the odds of reporting lipodystrophy compared with those reporting abstinence, although these findings were not statistically significant. Alcohol consumption may be associated with the secondary outcome lipohypertrophy, where a statistically significant result was observed for moderate drinking compared to abstinence.

In the current study, alcohol use was prospectively examined at 6-month intervals using a comprehensive, validated instrument. In addition, we used a definition for lipodystrophy based on the objective case definition validated by Carr et al (Carr et al., 2003). Several factors that may be associated with HIV-associated lipodystrophy, such as ART use, depressive symptoms, and cocaine use, were accounted for in the regression analyses to minimize the potential for confounding. The findings that both ART use and depressive symptoms were associated with lipodystrophy provide face validity for the cohort and the definition employed to examine the association between alcohol use and lipodystrophy. These findings are consistent with the medical literature that suggests that ART use likely plays an etiologic role in the development

of lipodystrophy (Ben-Romano et al., 2003; Caron et al., 2001); depressive symptoms may be a consequence of the undesirable bodily changes that define this syndrome (Blanch et al., 2004; Martinez et al., 2001a).

The primary limitation of the current study is that our definition of lipodystrophy relied solely on self-report and did not include a physical assessment by a clinician. The potential for measurement error from the self-reported outcome may have biased our estimates. However, if there is reporting bias, we would expect an underreporting of lipodystrophy. Thus if there was a positive association between alcohol use and lipodystrophy, such underreporting would bias our results towards the null hypothesis of no association. A second limitation of the study was a lack of power to detect associations of the observed magnitude. This study is a secondary data analysis and was not designed to determine the impact of alcohol on lipodystrophy. However, these data provide estimates of the magnitude of the alcohol effect and will be useful in designing future studies that will more definitively assess the effect of alcohol use on HIV-associated lipodystrophy.

Another limitation of the study is the potential for misclassification of alcohol consumption status given that subjects were observed for the past 30 days rather than the past 6 months at each study visit. However, we used a validated measure for assessing alcohol consumption and one that has been shown to be correlated with assessments of longer timeframes (Carey et al., 2004; Koppes et al., 2000). There is also the potential for residual confounding due to uncontrolled confounders or misclassification of confounders, which may have biased the results of this study. Finally, the observational study design and the possibility that lipodystrophy could have occurred prior to alcohol consumption limit our ability to establish a causal relationship between alcohol consumption and development of lipodystrophy. Instead, the results describe the association between the pattern of alcohol use prior to the assessment of lipodystrophy. Of note, if subjects decreased their consumption after developing lipodystrophy, we would expect to see a negative association between drinking and lipodystrophy, not the positive association observed in the study. Nonetheless this study, novel for its evaluation of this research question, provides preliminary, hypothesis-generating data that may be useful in planning future, clinical studies.

Alcohol use in HIV-infected patients with alcohol problems may increase the likelihood of developing HIV-associated lipodystrophy. However, larger studies are needed to elucidate fully its role and impact on the development of this common long-term complication of HIV infection and its treatment.

ACKNOWLEDGEMENTS

We appreciate the contributions of the research associates and data managers. Support came from the National Institute of Alcohol Abuse and Alcoholism (NIAAA) of the NIH: R01-AA13216 (Clinical Impact of HCV and Alcohol in HIV-Infected Persons); R01-AA11785 (Medication Adherence in Alcohol Abusing HIV Patients); R01-AA10870 (Enhanced Linkage of Alcohol Abusers to Primary Care); and K24-AA015674 (Impact of Alcohol Use on HIV Infection—In US and Russia). Research was conducted in part in the General Clinical Research Centers at Boston University School of Medicine, USPHS Grant M01 RR00533 and Beth Israel Deaconess Medical Center, USPHS Grant M01 RR01032.

Supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the NIH: R01-AA13216; R01-AA11785; R01-AA10870; K24-AA015674; and USPHS Grants M01 RR00533 and M01 RR01032

References

- Armellini F, Zamboni M, Frigo L, Mandragona R, Robbi R, Micciolo R, Bosello O. Alcohol consumption, smoking habits and body fat distribution in Italian men and women aged 20-60 years. *Eur J Clin Nutr* 1993;47:52–60. [PubMed: 8422873]

- Ben-Romano R, Rudich A, Torok D, Vanounou S, Riesenber K, Schlaeffer F, Klip A, Bashan N. Agent and cell-type specificity in the induction of insulin resistance by HIV protease inhibitors. *AIDS* 2003;17:23–32. [PubMed: 12478066]
- Blanch J, Rousaud A, Martinez E, De Lazzari E, Milinkovic A, Peri JM, Blanco JL, Jaen J, Navarro V, Massana G, Gatell JM. Factors associated with severe impact of lipodystrophy on the quality of life of patients infected with HIV-1. *Clin Infect Dis* 2004;38:1464–70. [PubMed: 15156486]
- Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;354:1112–5. [PubMed: 10509516]
- Buchsbaum DG, Buchanan RG, Centor RM, Schnoll SH, Lawton MJ. Screening for alcohol abuse using CAGE scores and likelihood ratios. *Ann Intern Med* 1991;115:774–7. [PubMed: 1929025]
- Carey KB, Carey MP, Maisto SA, Henson JM. Temporal stability of the timeline followback interview for alcohol and drug use with psychiatric outpatients. *J Stud Alcohol* 2004;65:774–81. [PubMed: 15700516]
- Caron M, Auclair M, Vigouroux C, Glorian M, Forest C, Capeau J. the HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* 2001;50:1378–88. [PubMed: 11375339]
- Carr A, Emery S, Law M, Puls R, Lundgren JD, Powderly WG. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet* 2003;361:726–35. [PubMed: 12620736]
- Coin A, Sergi G, Enzi G, Busetto L, Pigozzo S, Lupoli L, Strater D, Peruzza S, Meral Inelmen E. Total and regional body composition and energy expenditure in multiple symmetric lipomatosis. *Clin Nutr* 2005;24:367–74. [PubMed: 15896422]
- Cook JA, Cohen MH, Burke J, Grey D, Anastos K, Kirstein L, Palacio H, Richardson J, Wilson T, Young M. Effects of depressive symptoms and mental health quality of life on use of highly active antiretroviral therapy among HIV-seropositive women. *J Acquir Immune Defic Syndr* 2002;30:401–9. [PubMed: 12138346]
- Enzi G, Busetto L, Ceschin E, Coin A, Digito M, Pigozzo S. Multiple symmetric lipomatosis: clinical aspects and outcome in a long-term longitudinal study. *Int J Obes Relat Metab Disord* 2002;26:253–61. [PubMed: 11850759]
- Enzi G, Inelmen EM, Baritussio A, Dorigo P, Prosdocimi M, Mazzoleni F. Multiple symmetric lipomatosis: a defect in adrenergic-stimulated lipolysis. *J Clin Invest* 1977;60:1221–9. [PubMed: 199616]
- Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;12:189–98. [PubMed: 1202204]
- Galli M, Cozzi-Lepri A, Ridolfo AL, Gervasoni C, Ravasio L, Corsico L, Gianelli E, Vaccarezza M, Vullo V, Cargnel A, Minoli L, Coronado O, Giacometti A, Antinori A, Antonucci G, D’Arminio Monforte A, Moroni M. Incidence of adipose tissue alterations in first-line antiretroviral therapy: the LipoICoNa Study. *Arch Intern Med* 2002;162:2621–8. [PubMed: 12456235]
- Heath KV, Hogg RS, Singer J, Chan KJ, O’Shaughnessy MV, Montaner JS. Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based cohort. *J Acquir Immune Defic Syndr* 2002;30:440–7. [PubMed: 12138351]
- Hengel RL, Watts NB, Lennox JL. Benign symmetric lipomatosis associated with protease inhibitors. *Lancet* 1997;350:1596. [PubMed: 9393341]
- Klopstock T, Naumann M, Seibel P, Shalke B, Reiners K, Reichmann H. Mitochondrial DNA mutations in multiple symmetric lipomatosis. *Mol Cell Biochem* 1997;174:271–5. [PubMed: 9309699]
- Koppes LL, Kemper HC, Post GB, Snel J, Twisk JW. Development and stability of alcohol consumption from adolescence into adulthood: the Amsterdam Growth and Health Longitudinal Study. *Eur Addict Res* 2000;6:183–8. [PubMed: 11124571]
- Martinez E, Garcia-Viejo MA, Blanch L, Gatell JM. Lipodystrophy syndrome in patients with HIV infection: quality of life issues. *Drug Saf* 2001a;24:157–66. [PubMed: 11347720]
- Martinez E, Mocroft A, Garcia-Viejo MA, Perez-Cuevas JB, Blanco JL, Mallolas J, Bianchi L, Conget I, Blanch J, Phillips A, Gatell JM. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet* 2001b;357:592–8. [PubMed: 11558485]

- Mayfield D, McLeod G, Hall P. The CAGE questionnaire: validation of a new alcoholism screening instrument. *Am J Psychiatry* 1974;131:1121–3. [PubMed: 4416585]
- McComsey GA, Walker UA. Role of mitochondria in HIV lipoatrophy: insight into pathogenesis and potential therapies. *Mitochondrion* 2004;4:111–8. [PubMed: 16120376]
- Mujawar Z, Rose H, Morrow MP, Pushkarsky T, Dubrovsky L, Mukhamedova N, Fu Y, Dart A, Orenstein JM, Bobryshev YV, Bukrinsky M, Sviridov D. Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. *PLoS Biol* 2006;4:e365. [PubMed: 17076584]
- National Institute on Alcohol Abuse and Alcoholism. Helping Patients who Drink Too much: A Clinician's Guide. National Institute on Alcohol Abuse and Alcoholism; Washington, D.C.: [Accessed October 24, 2007]. Updated 2005 edition Available at <http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/guide.pdf>
- Robins LN, Wing J, Wittchen HU, Helzer JE, Babor TF, Burke J, Farmer A, Jablenski A, Pickens R, Regier DA, et al. The Composite International Diagnostic Interview. An epidemiologic instrument suitable for use in conjunction with different diagnostic systems and in different cultures. *Arch Gen Psychiatry* 1988;45:1069–77. [PubMed: 2848472]
- Samet JH, Horton NJ, Meli S, Freedberg KA, Palepu A. Alcohol consumption and antiretroviral adherence among HIV-infected persons with alcohol problems. *Alcohol Clin Exp Res* 2004;28:572–7. [PubMed: 15100608]
- Samet JH, Libman H, LaBelle C, Steger K, Lewis R, Craven DE, Freedberg KA. A model clinic for the initial evaluation and establishment of primary care for persons infected with human immunodeficiency virus. *Arch Intern Med* 1995;155:1629–33. [PubMed: 7618986]
- Sattler F. Body habitus changes related to lipodystrophy. *Clin Infect Dis* 2003;36:S84–90. [PubMed: 12652376]
- Schoffer K, Grant I. Multiple lipomas, alcoholism, and neuropathy: Madelung's disease or MERRF? *Muscle Nerve* 2006;33:142–6. [PubMed: 16007676]
- Smith KL, Horton NJ, Saitz R, Samet JH. The use of the mini-mental state examination in recruitment for substance abuse research studies. *Drug Alcohol Depend* 2006;82:231–7. [PubMed: 16256278]
- Sobell, LC.; Sobell, MB.; Alcohol Timeline Followback (TFLB), in American Psychiatric Association. *Handbook of Psychiatric Measures*. American Psychiatric Association; Washington DC: 1996. p. 477–479.
- Teplitzky V, Halabe A. Fat distribution in AIDS. *N Engl J Med* 1999;340:969–70. [PubMed: 10094652]
- Villarroya F, Domingo P, Giral M. Lipodystrophy in HIV 1-infected patients: lessons for obesity research. *Int J Obes (Lond)* 2007;31:1763–76. [PubMed: 17653062]

Table 1

Characteristics of the subjects at study enrollment and bivariate associations with lipodystrophy (N=289)

Variable	Number (%)	Number (%) reporting lipodystrophy by characteristic
Alcohol Consumption^a		
Abstinent at all interviews	99 (34%)	50 (51%)
≥1 report of moderate drinking	34 (12%)	18 (53%)
1-2 reports of heavy drinking	98 (34%)	49 (50%)
≥3 reports of heavy drinking	58 (20%)	33 (57%)
Gender		
Male	214 (74%)	104 (49%)
Female	75 (26%)	46 (61%)
Hepatitis C RNA		
Positive	143 (49%)	79 (55%)
Negative	145 (51%)	70 (48%)
CES-D[*]		
<23	151 (52%)	70 (46%)
≥23	138 (48%)	80 (58%)
Race		
White	92 (32%)	55 (60%)
Black	138 (48%)	69 (50%)
Other	59 (20%)	26 (44%)
ART use[*]		
Never	37 (13%)	12 (32%)
Ever	251 (87%)	137 (55%)
Recent Cocaine Use		
No	156 (54%)	83 (53%)
Yes	133 (46%)	67 (50%)
Age (years)^b		
21-40	117 (40%)	59 (50%)
41-48	101 (35%)	46 (46%)
49-71	71 (25%)	45 (63%)
CD4 Cell Count^{b,c}		
8-277	77 (28%)	37 (48%)
278-518	98 (36%)	52 (53%)
519-1809	96 (35%)	52 (54%)
Lifetime Alcohol Diagnosis		
No diagnosis	37 (13%)	19 (51%)
Abuse	55 (19%)	25 (45%)
Dependence	193 (68%)	104 (54%)
Recent Alcohol Diagnosis		
No diagnosis	249 (87%)	131 (53%)

Variable	Number (%)	Number (%) reporting lipodystrophy by characteristic
Abuse	7 (2%)	3 (43%)
Dependence	29 (10%)	14 (48%)

^a Report is based on assessment of alcohol use in the past month at each research interview

* p<.05 for bivariate association with lipodystrophy

^b Based on tertiles from study sample

^c n=271

Table 2

Adjusted odds ratios for lipodystrophy based on multivariable logistic regression analyses of 289 HIV-infected subjects with current or past alcohol problems

Variable	Adjusted OR (95% CI)
Alcohol Consumption^a	
Abstinent at all interviews	1.00
≥1 report of moderate drinking	2.36 (0.89, 6.24)
1-2 reports of heavy drinking	1.34 (0.69, 2.60)
≥3 reports of heavy drinking	2.07 (0.90, 4.73)
Gender	
Male	1.00
Female	1.83 (0.95, 3.53)
Hepatitis C RNA	
Positive	1.00
Negative	0.90 (0.50, 1.62)
CES-D	
<23	1.00
≥23	2.32 (1.30, 4.15) *
Race	
White	1.00
Black	0.64 (0.34, 1.19)
Other	0.60 (0.28, 1.29)
ART use	
Never	1.00
Ever	2.64 (1.10, 6.36) *
Recent Cocaine Use	
No	1.00
Yes	1.36 (0.69, 2.68)
Age (per 10 year increase)	1.42 (0.95, 2.13)
CD4 Count (per 100 cells/mm³ increase)	1.13 (1.02, 1.25) *
Lifetime Alcohol Diagnosis	
No diagnosis	1.00
Abuse	0.42 (0.16, 1.10)
Dependence	0.72 (0.32, 1.61)

^a Report is based on assessment of alcohol use in the past month at each research interview

* p < 0.05.

Table 3

Adjusted odds ratios for the secondary outcomes lipohypertrophy, lipoatrophy, and report of both fat gain and fat loss

Alcohol Consumption ^a	Adjusted OR ^b (95% CI)		
	Lipohypertrophy	Lipoatrophy	Report of both Fat Gain and Fat Loss
Abstinent at all interviews	1.00	1.00	1.00
≥1 report of moderate drinking	3.52 (1.07, 11.54)	1.15 (0.44, 3.01)	0.87 (0.25, 2.99)
1-2 reports of heavy drinking	1.31 (0.53, 3.25)	0.92 (0.46, 1.84)	1.38 (0.53, 3.58)
≥3 reports of heavy drinking	2.51 (0.82, 7.66)	1.77 (0.76, 4.12)	0.87 (0.27, 2.80)

^a Report is based on assessment of alcohol use in the past month at each research interview^b All logistic regression models adjusted for gender, age, race, hepatitis C status, depressive symptoms, ART use, CD4 cell count, lifetime alcohol diagnosis, and cocaine use