

Visceral abdominal-fat accumulation associated with use of indinavir

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Summary

Background After the addition of the protease inhibitor indinavir to combination drug regimens for HIV-1 infection, some patients have experienced an increase in abdominal girth with symptoms of abdominal fullness, distension, or bloating. We aimed to find out whether this collection of symptoms was associated with changes in abdominal fat and whether such changes were associated with indinavir use.

Methods Abdominal computed tomography was used in ten HIV-1-positive patients who had such abdominal symptoms to measure total adipose tissue (TAT) and visceral adipose tissue (VAT) at the umbilicus (L4 vertebral level). The VAT:TAT ratio in the ten cases was compared with that in ten HIV-1-infected patients who had been using indinavir without abdominal symptoms for at least 6 months and ten HIV-1-infected patients who were not using indinavir.

Findings The mean VAT:TAT ratios for the three groups—non-users, symptom-free indinavir users, and symptomatic indinavir users—were 0.40 (SD 0.15), 0.59 (0.18), and 0.70 (0.20), respectively ($p=0.004$). The VAT:TAT ratio correlated with duration of indinavir use ($r=0.47$, $p=0.01$). The mean areas of VAT for the three groups were 106 cm² (SD 72), 141 cm² (65) and 202 cm² (93), respectively ($p=0.03$). The mean body-mass index of the groups was similar, and patients in the two indinavir groups did not gain a significant amount of weight after starting the drug. Serum triglyceride values increased after starting indinavir and correlated with VAT:TAT ratios.

Interpretation Our data suggest that some HIV-1-infected patients on indinavir treatment accumulate intra-abdominal fat that may cause abdominal symptoms. Recent evidence suggests that other HIV-1 protease inhibitors may be associated with changes in body-fat distribution. Larger studies of protease-inhibitor treatment are needed to investigate this association further and to investigate metabolic or endocrine mechanisms that may underlie this phenomenon.

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Introduction

Protease inhibitors are a major advance in the treatment of HIV-1 infection.^{1–3} Of four such agents currently available in the USA, indinavir (Crixivan; Merck, West Point, PA, USA) is the most commonly prescribed. Although indinavir is usually well tolerated, premarketing trials and reports published since the drug became available in 1996 have linked use to hyperbilirubinaemia, hepatitis, hyperglycaemia, and a range of urological abnormalities⁴ (and Crixivan package insert).

Within several months of adding indinavir to their antiretroviral regimens, some of our patients began to complain of increased abdominal girth, usually without substantial weight gain. In addition, these patients sometimes complained of other abdominal symptoms such as distension, fullness, and bloating. At the same time, monitoring of an Internet bulletin board for indinavir users (crix-list@pinkpage.com) suggested an increase in the number of postings from individuals with similar complaints.

In several patients with these symptoms, abdominal computed-tomography (CT) scans suggested an excess amount of intra-abdominal (omental, mesenteric, and retroperitoneal) fat and a relative paucity of subcutaneous fat. In other clinical settings, accumulation of intra-abdominal fat has been associated with various disorders that have been linked with adverse long-term health consequences.^{5–7}

CT is a convenient and reliable non-invasive method for measuring body fat.^{8–12} To study any possible association between indinavir use and increased intra-abdominal fat, we compared CT measurements of abdominal fat in HIV-1-infected patients who had used indinavir with those for similar patients who had not used the drug.

Methods

Patients

The patients described here participated in clinical studies at the National Institute of Allergy and Infectious Diseases/Critical Care Medicine Department HIV Research Clinic at the National Institutes of Health in Bethesda, MD, USA. Between April and November, 1997, ten HIV-1-infected men who complained of increasing abdominal girth after starting protease-inhibitor therapy with indinavir (group A) were assessed by abdominal CT. CT scans were compared with those from ten HIV-1-infected men who had taken indinavir for at least 6 months without abdominal symptoms (group B) and with those from ten HIV-1-infected men who were not taking indinavir (group C). The CT scans used for comparison with those from group A were identified by review of clinic radiology records—the most recent scans of patients who met group definitions were chosen. Patients with clinically important intra-abdominal pathology—such as marked organomegaly, masses, or ascites—were excluded. These patients had had abdominal CT between March, 1996, and October, 1997. The patients were selected and their CT scans referred for abdominal-fat

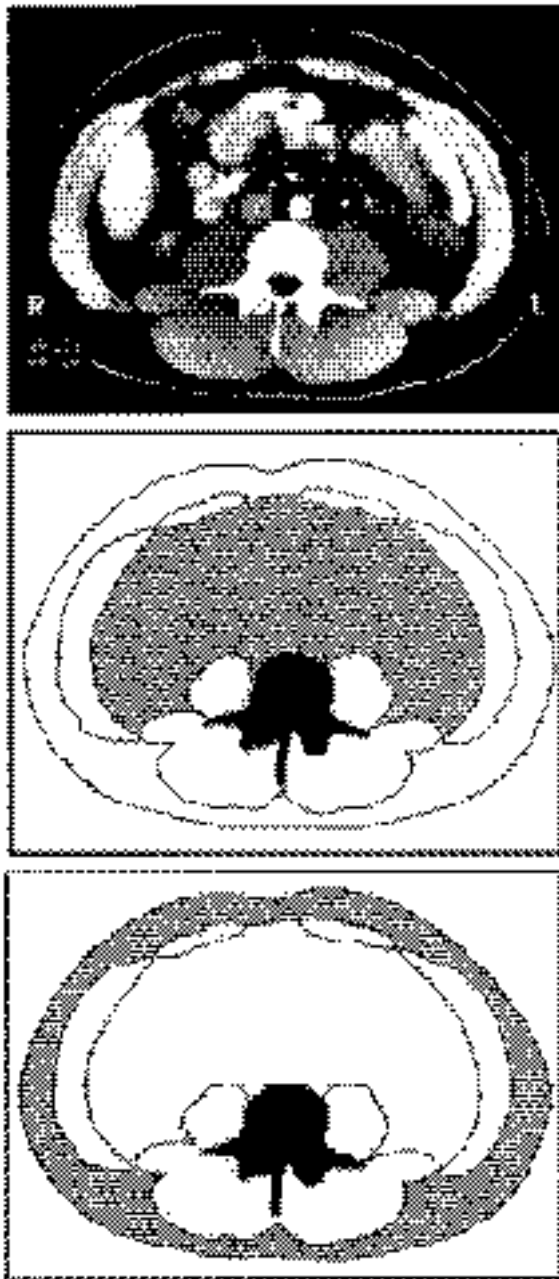


Figure 1: **CT scan of patient not taking indinavir (group C)**
 1A: cross-sectional area within which total adipose tissue is measured (223 cm²) 1B: intra-abdominal area (shaded) within which visceral adipose tissue is measured (79 cm²). 1C: subcutaneous area (shaded) for which subcutaneous adipose tissue is calculated by subtracting visceral from total adipose tissue. Ratio of visceral to total adipose tissue is 0.35.

measurement without knowledge of their abdominal fat status.

CD4-lymphocyte counts, quantitative HIV-1-RNA (viral-load) measurements, serum lipid values, and anthropometric data were collected from clinic databases and patients' charts. Some patients described here began receiving indinavir before US Food and Drug Administration approval as part of a therapeutic trial. No patient received more than the recommended indinavir dose of 2400 mg daily divided into three or four doses.

CT measurement of abdominal fat

CT was done on General Electric HiSpeed helical CT scanners (GE Medical Systems, Milwaukee, WI, USA). Exposure parameters were Kvp 120, mAs 210, and pitch 1:1. Imaging

data were reconstructed every 10 mm. The scout image was used to approximate a level at the umbilicus or the fourth lumbar vertebra, which is a valid predictor of total abdominal fat in men.¹³⁻¹⁵ Tissue compartments were measured by planimetry with a trackball-controlled cursor. The area of adipose tissue in each compartment was quantified by manufacturer-supplied software that sums the area of pixels in the digital image with CT values from -150 and -50 Hounsfield Units (HUs), which correspond to adipose tissue (figure 1). Total adipose tissue (TAT; figure 1A) and visceral adipose tissue (VAT; figure 1B) were measured directly. Subcutaneous adipose tissue (SAT; figure 1C) and VAT:TAT ratio were calculated. All CT fat measurements were made by individuals who were unaware of whether or not the patient had been taking indinavir.

Statistical analysis

ANOVA was used to assess the differences in mean VAT:TAT ratios and mean areas of VAT and SAT between the study groups. Patients' age, laboratory data, and anthropometric data were similarly analysed. Change in mean body weight and serum lipid values were assessed by paired Student's *t* tests (two-tailed); an unpaired *t* test was used for other two-group comparisons. Correlation of serum lipids and duration of indinavir use with the VAT:TAT ratio was assessed by linear regression. The χ^2 test was used to compare nucleoside antiretroviral use between groups.

Results

Characteristics of the patients are shown in the table. No patient in group A had CT findings—such as distended bowel, marked hepatosplenomegaly, masses, or ascites—to explain their abdominal symptoms. Indications for abdominal CT in the 20 patients in groups B and C were: raised serum aminotransferases (eight patients); urological symptoms or signs (six patients); raised pancreatic enzymes (three patients); and other disorders (three patients).

Patients in the three groups were of similar ages. Mean CD4-lymphocyte counts were higher and viral-load measurements were lower in the two indinavir groups (A, B) than in the non-user group (C) but these differences were not significant. Patients in group A had

	Group A (n=10)	Group B (n=10)	Group C (n=10)	p
Age (years)	43.3 (5.7)	43.6 (7.0)	41.7 (8.8)	0.82
CD4 lymphocytes				
Count (cells/ μ L)	797 (337)	796 (626)	544 (343)	0.37
Proportion of total lymphocytes, %	30%	33%	27%	0.65
HIV-1 RNA (copies/mL)*				
Geometric mean	1123	1176	4172	0.28
Range	499-125 000	499-53 000	499-318 000	..
Concurrent nucleoside analogues				
Zidovudine and lamivudine	2	3	2	0.83
Stavudine and lamivudine	8	6	7	0.62
Body-mass index (kg/m²)	24.7 (2.6)	26.2 (2.4)	25.0 (3.2)	0.46
CT abdominal-fat measurements				
SAT (cm ²)	112 (98)	106 (64)	131 (63)	0.75
VAT (cm ²)	202 (93)	141 (65)	106 (72)	0.03

Group A=HIV-1-infected patients who were using indinavir and had abdominal symptoms.

Group B=HIV-1-infected patients who were using indinavir for more than 6 months without abdominal symptoms.

Group C=HIV-1-infected patients who were not using indinavir.

Data are mean (SD) unless otherwise stated.

*Lower limit of sensitivity of the bDNA assay was 500 HIV-1 copies/mL; values below that were assigned a value of 499 copies/mL.

Characteristics of patients and CT abdominal-fat measurements

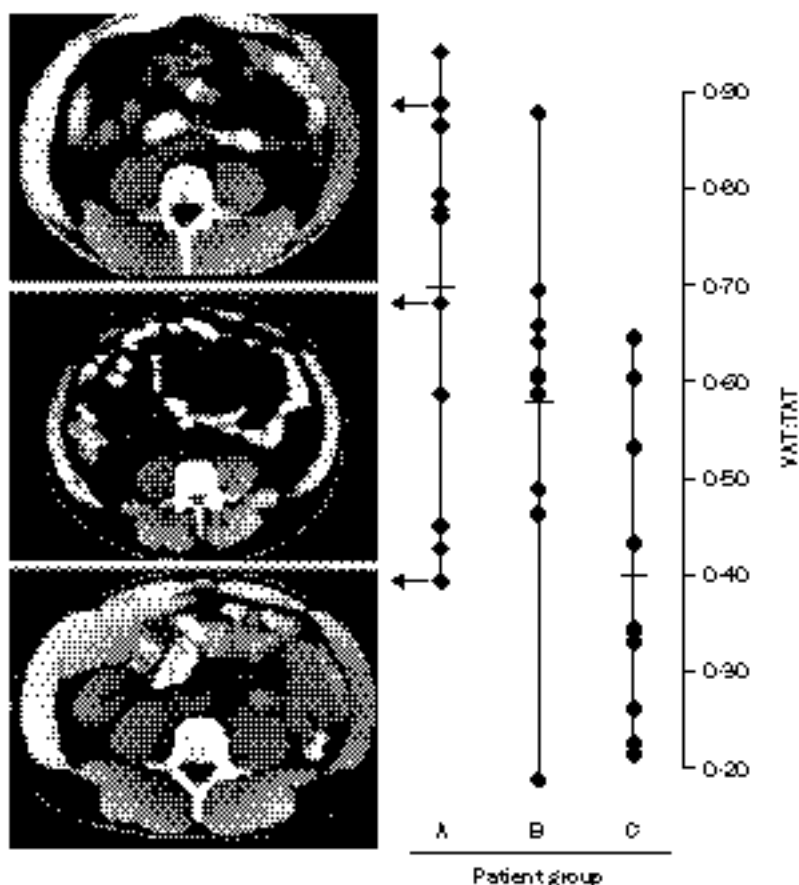


Figure 2: Distribution of visceral to total abdominal fat ratios (VAT:TAT), by patient group.

Horizontal bars indicate group means that are significantly different ($p = 0.004$). Group A patients were symptomatic indinavir-users; group B patients were symptom-free indinavir-users; and group C patients were non-users. The three panels on the left show CT scans of the three Group A patients indicated by arrows.

been taking indinavir for 3–27 months (mean 14.1 [SD 6.9] months); two of these patients had CT done after indinavir was discontinued (for 1 month and 2 months, respectively) and were taking a combination of zidovudine and zalcitabine. Patients in group B had been taking indinavir for 6–18 months (mean 9.7 [3.7] months). Use of nucleoside antiretroviral drugs was similar in the three groups. Although these patients used a wide variety of other drugs, no clear differences in concomitant drug use between the groups emerged (data not shown). No patient was using systemic corticosteroids; one group-A patient, two group-B patients, and one group-C patient received testosterone replacement. 23 patients (eight in group A, ten in group B, and five in group C) had been participating in studies of intermittent interleukin-2 infusions for the treatment of HIV-1 infection.

Anthropometric, CT, and lipid data

Mean body-mass index for the three groups was similar (table). Bodyweights before the start of indinavir therapy were available for eight of ten patients in group A and nine of ten patients in group B. Bodyweight data at the time of CT and 6 months earlier were available for nine patients in group C. During this interval, the group-A patients had a mean weight increase of 1.7 kg (SD 2.8; $p=0.25$). Group-B patients had a mean decrease in body weight of 0.6 kg (3.8; $p=0.55$). The group-C patients

had a mean weight increase of 1.3 kg (2.6; $p=0.17$). Weight changes did not differ significantly between the groups ($p=0.80$).

Group A had the most VAT, group C the least, and group B had an intermediate amount of intra-abdominal fat (table). Although patients in groups A and B had less subcutaneous fat than patients in group C, these differences were not significantly different. Mean VAT:TAT were 0.70 (0.20), 0.59 (0.18), and 0.40 (0.15) for groups A, B, and C, respectively (figure 2; $p=0.004$). When VAT:TAT was compared between groups, the differences between groups A and C ($p=0.002$) and groups B and C ($p=0.03$), were significant but that between groups A and B ($p=0.20$) was not. VAT:TAT correlated with duration of indinavir use ($r=0.47$, $p=0.01$).

For 18 patients in groups A and B for whom serum lipid data were available, VAT:TAT correlated with triglyceride values ($r=0.57$; $p=0.01$) but not with cholesterol ($r=0.17$; $p=0.51$). Serum lipid data before starting indinavir were available for 15 of the 20 patients in groups A and B. Mean cholesterol values increased from 4.7 to 5.5 mmol/L at the time of CT ($p=0.006$) and mean triglyceride values increased from 3.4 to 4.2 mmol/L at the time of CT ($p=0.05$). Serum lipid data at the time of CT and 6 months earlier were available for six patients in group C. During this period, serum lipid concentrations did not change significantly, triglyceride values

decreased from 1.9 to 1.7 mmol/L ($p=0.30$), and cholesterol values decreased from 4.4 to 4.1 mmol/L ($p=0.84$).

Discussion

We report ten men who developed a similar pattern of abdominal symptoms 3 or more months after starting indinavir for HIV-1 infection. Symptoms included increased girth in the absence of substantial overall weight gain and symptoms of distension, fullness, and bloating. Although news of this syndrome has begun to circulate widely among HIV-1-positive patients who are using protease inhibitors, and reports have appeared in the AIDS-activist press, underlying mechanisms have not been elucidated.¹⁶ Abdominal CT in our symptomatic patients suggests that an increased amount of visceral fat is the cause of these symptoms. Comparison of these scans with those from HIV-1-infected men who have not used indinavir confirm the increase in intra-abdominal fat in symptomatic indinavir users; an association strengthened by the finding of an intermediate amount of intra-abdominal fat in indinavir users without abdominal symptoms. Despite the small number of patients studied, these group differences are statistically significant. The finding that abdominal visceral fat increased with duration of indinavir use lends additional support for such an association. Since completion of our study in November, 1997, another patient has presented



Figure 3: **Abdominal CT scans taken 10 days before (3A) and 5 months after (3B) patient with abdominal symptoms had started indinavir.**

Visceral adipose tissue increased from 147 cm² to 201 cm².

to us with abdominal distension and occasional sensations of bloating. After starting indinavir, zidovudine, and lamivudine 5 months earlier, his weight had increased from 79.6 kg to 81.2 kg. A CT scan suggested abundant visceral fat. Comparison with a CT scan that the patient had undergone 10 days before starting indinavir (to investigate mild abnormalities in serum aminotransferases) showed a 37% increase in visceral fat (figure 3).

Several studies have established normal values for abdominal fat as measured by CT. Data from these studies suggest that normal, healthy men of ages similar to those in this report have mean VAT:TAT of about 0.40.^{13,14} This value is similar to that in our patients who were not using indinavir and significantly less than that found in the two indinavir-treated groups. These previous studies found mean VAT values of 93 cm² (SD 49) and 90 cm² (53). Seven patients in group A (70%) and five patients in group B (50%) had values above those means plus one SD (143 cm²), whereas three patients in group C (30%) had values above this level.

Patients in the two indinavir groups (groups A and B) had higher CD4-lymphocyte counts and lower viral load than the patients who were not treated with indinavir (group C), although these differences might be expected since an antiretroviral regimen that includes indinavir is more effective than nucleoside analogues alone. Also, a smaller proportion of patients in group C had participated in studies of interleukin-2 for the treatment of HIV-1 infection. Thus, there were differences between groups other than indinavir exposure. Larger studies are

needed to confirm our findings and further investigate the role of potential cofactors and to eliminate bias and possible confounding variables.

Increased intra-abdominal fat might simply reflect improved health because of HIV-1 suppression in patients on highly active antiretroviral therapy. This explanation is unlikely because patients in the three groups had similar body-mass indices, and because the indinavir-treated patients did not experience significant weight gain after starting the drug. The disproportionate amount of VAT, as opposed to SAT, also argues against this possibility.

In 1982, Borkan and colleagues⁸ first described the use of CT for assessment of intra-abdominal fat. Other studies have since validated this method and have shown the usefulness of measuring intra-abdominal fat in various disorders. CT digital images are reconstructed from many measurements of tissue attenuation by X-rays. Each pixel within the image has a numerical CT value that corresponds to tissue attenuation, and each pixel in the image is of known size, based on matrix size and field of view. Thus, the number of pixels and the corresponding area within a set range of CT values can be calculated. Such CT-derived data have contributed substantially to the refinement of the concept of "central" obesity into the concept that overabundance of visceral fat is associated with various metabolic and endocrine abnormalities.^{10,17-19} These disorders include hyperlipidaemia and glucose intolerance, which have been associated with the use of protease inhibitors.

Our data suggest an association between the development of visceral obesity and hyperlipidaemia in indinavir-treated patients. In other clinical settings, these abnormalities are thought to reflect the high lipolytic activity of omental adipocytes, which leads to elevated free fatty acids in the portal circulation and increased hepatic lipid synthesis.²⁰ Increased visceral fat is one of the hallmarks of Cushing's syndrome, other features of which have also been reported among users of protease inhibitors; however, an abnormality in the hypothalamic-pituitary-adrenal axis has not been found.²¹⁻²⁵

If confirmed, our findings raise important questions. What are the mechanisms by which visceral fat accumulation is induced? Could this change be a direct drug effect, or a drug interaction or rather is it an unusual byproduct of effective control of the virus? Are other HIV-1 antiretroviral regimens associated with similar changes? The pattern of protease-inhibitor use in our clinic did not allow a similar assessment of patients using other drugs of this class. There is preliminary evidence that HIV-1-infected patients using other protease inhibitors, and occasionally antiretroviral regimens that do not contain a protease inhibitor, experience changes in body-fat distribution.^{21,25} Are women similarly affected? Are children? Does such accumulation of fat persist and is it associated with the same range of metabolic abnormalities that is seen in non-HIV-1-infected patients? Are there potential treatments? Several contributors to the Crixivan "chat list" report having had liposuction, a less than satisfactory solution given the intra-abdominal rather than subcutaneous location of the excess adipose tissue. If there are metabolic abnormalities, do they have long-term health consequences?

New therapies, such as the protease inhibitors, are transforming HIV-1 infection into a chronic disease

amenable to long-term treatment, at least in some patients. Life expectancies are increasing, and, eventually, may reach normal ranges. Answers to the questions raised by our findings are needed so that long-term side-effects of antiretroviral therapy do not interfere with these hopes.

Contributors

The research was carried out under the general direction of Kirk Miller and Judith Falloon. Elizabeth Jones, Irwin Feuerstein, and Rani Shankar were responsible for radiological aspects of the study as was Jack Yanovski for metabolic and anthropometric aspects. All investigators participated in writing the paper through the standard drafting and review process.

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