

Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial

Véronique Joly^a, Philippe Flandre^b, Vincent Meiffredy^b,
Nicolas Leturque^b, Marine Harel^b, Jean-Pierre Aboulker^b
and Patrick Yeni^a

Objectives: To compare the incidence of clinical lipodystrophy in HIV-1-infected patients receiving zidovudine or stavudine, in combination with indinavir and lamivudine, in a randomized trial.

Methods: NOVAVIR was a randomized multicentre trial comparing stavudine/lamivudine/indinavir and zidovudine/lamivudine/indinavir in 170 patients pretreated with zidovudine, didanosine or zalcitabine (> 6 months), but naive for lamivudine, stavudine and protease inhibitors. The incidence of clinical lipodystrophy and metabolic abnormalities was assessed in a subgroup of 101 patients after 30 months of follow-up.

Results: The incidence of lipoatrophy was increased in the stavudine arm versus the zidovudine arm, as followed: facial atrophy: 48 versus 22% of patients, $P = 0.011$, lower limb atrophy: 49 versus 22% of patients, $P = 0.006$, buttock atrophy: 47 versus 20% of patients, $P = 0.009$, venomegaly: 57 versus 24% of patients, $P = 0.001$. There was no significant difference in the incidence of clinical signs of central fat accumulation nor in fasting metabolic parameters at month 30 between the two arms. In multivariate analyses, the stavudine arm, previous therapy with didanosine, and a lower CD4 cell count at study entry were associated with an increased risk of lipoatrophy, whereas older patients and women had an increased risk of lipohypertrophy.

Conclusion: Patients receiving stavudine/lamivudine/indinavir had a greater rate of clinical lipodystrophy, mainly lipoatrophy, than those treated with zidovudine/lamivudine/indinavir.

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Introduction

Highly active antiretroviral therapy (HAART) for HIV-1 therapy has decreased AIDS-related mortality [1,2]. However, coincident with these advances, was described a lipodystrophy syndrome occurring in

HIV-infected individuals receiving HAART [3]. This syndrome is characterized by body fat redistribution leading to peripheral fat wasting and central adiposity. Metabolic abnormalities have also been reported, such as elevated triglyceride and cholesterol levels, and insulin resistance or type 2 diabetes mellitus. It is still

From the ^aService de Maladies Infectieuses et Tropicales A, Hôpital Bichat Claude Bernard, Paris, France; and ^bINSERM SC 10, Hôpital Paul Brousse, Villejuif, France.

Correspondence to: Véronique Joly, Maladies Infectieuses et Tropicales A, Hôpital Bichat Claude Bernard, 46 rue Henri Huchard, Paris, France.

Tel: +33 1 40 25 78 07; fax: +33 1 40 25 67 75; e-mail: veronique.joly@bch.ap-hop-paris.fr

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unclear whether morphological changes and metabolic abnormalities are related or if they represent several distinct conditions.

The prevalence of lipodystrophy varies widely, because of the lack of a consistent definition, variability in diagnostic techniques, and various durations of follow-up. It ranges from 5 to 83% in patients receiving a protease inhibitor (PI) [3,4]. Although the initial identification of this syndrome was coincident with the widespread use of PI-containing regimens, more recent reports have concluded that it may occur in the absence of PI [5,6], and the aetiology of this syndrome remains unclear. The clinical changes, particularly lipodystrophy, have a major psychological impact that may alter the desire to continue antiretroviral therapy.

In both PI-sparing or in PI-containing regimens, the role of nucleoside reverse transcriptase inhibitors (NRTI) in the occurrence of lipodystrophy has been studied in retrospective, non-randomized studies. Stavudine was shown in different studies to be associated with a higher relative risk for the development of lipodystrophy (primarily fat loss) [4,7–9]. Few randomized studies have evaluated the role of NRTI in lipodystrophy [10–12].

NOVAVIR is a randomized multicentre trial comparing the activity and toxicity of lamivudine and indinavir, in combination with zidovudine or stavudine, in patients previously exposed to zidovudine, didanosine or zalcitabine, but naive for stavudine, lamivudine and PI. Antiviral activity and toxicity were similar in both arms after 18 months follow-up [13]. The incidence of clinical lipodystrophy and metabolic abnormalities was assessed in a subgroup of patients after 30 months of follow-up. As the two arms differed only by the NRTI, zidovudine or stavudine, associated with lamivudine and indinavir, this trial gives the opportunity to assess the influence of stavudine versus zidovudine on the occurrence of lipodystrophy in a randomized trial.

Materials and methods

NOVAVIR trial

The NOVAVIR design has been described elsewhere [13]. Briefly, NOVAVIR was a randomized, multicentre open-label trial that compared the safety and efficacy of stavudine versus zidovudine in combination with lamivudine plus indinavir in patients pretreated with zidovudine, didanosine, or zalcitabine, but naive for stavudine, lamivudine and PI. Randomization was performed centrally in a 1:1 ratio, with stratification according to the HIV-RNA copy number in the plasma at the time of screening (10 000 copies/ml or fewer versus more than 10 000 copies/ml). Patients

who completed 18 months of study were allowed to continue in an extension phase that followed patients for 12 additional months. Zidovudine was given as 250–300 mg twice a day, lamivudine as 150 mg twice a day, stavudine as 40 mg twice a day (30 mg for patients weighing less than 60 kg) and indinavir as 800 mg every 8 h. Patients were advised to take indinavir on an empty stomach. The patients enrolled had documented HIV-1 infection, as determined by positive enzyme-linked immunosorbent assay confirmed by Western blot, were aged 18 years or older, and had more than 6 months previous zidovudine, didanosine or zalcitabine cumulative treatment, either as monotherapy or in combination. Patients had HIV-1 plasma RNA levels between 5000 and 200 000 copies/ml. The primary measure of antiretroviral activity was the time to virological failure, defined as the first HIV-RNA level greater than 5000 copies/ml after at least 8 weeks of therapy, confirmed in a second specimen. The trial was run in 43 centres in France.

Lipodystrophy substudy

The lipodystrophy substudy was a cross-sectional study performed at the end of extended follow-up, i.e. 30 months after the initiation of a PI-containing regimen. The study was run from January 2000 to May 2001. Demographic factors, body mass index, CDC stage, drug treatment history, baseline CD4 cell count and viral load were obtained from the NOVAVIR database. Fasting glucose, triglyceride and cholesterol blood levels and body shape changes were assessed. Fat redistribution was evaluated through a standardized questionnaire. Body areas evaluated included buffalo neck, increased breast size, increased waist size, increased abdomen wall thickness, increased neck size, sunken cheeks, lower limb atrophy, upper limb atrophy, buttock atrophy and veinomegaly. The presence of these signs was based on patient and physician agreement. We could thus determine the proportion of patients with none or at least one symptom of peripheral atrophy or fat accumulation. Because of a lack of clear definition of the lipodystrophy syndrome, we also investigated prognostic factors in patients with one or two symptoms (moderate) and with three or more symptoms (severe) of peripheral atrophy or fat accumulation. Cholesterol, triglyceride and glucose blood levels, CD4 cell count and viral load were routinely determined in each clinical site at the time of lipodystrophy evaluation.

Statistical analysis

The Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables were used to compare baseline characteristics between groups of patients. The Wilcoxon two-sample test was used to test for no differences in continuous variables (metabolic parameters) by categorical variables (treatment groups). Fisher's exact test was used to test the ass-

ociation between categorical variables (body shape changes). Risk factors of lipoatrophy, and lipohypertrophy were assessed using logistic regression models. Response variables in regression models were either a binary response (none versus at least one sign), or an ordinal response (none, one or two, or three or more signs). For an ordinal response with three response levels, we used a polytomous regression model with two cumulative logits to determine predictors of more signs of lipoatrophy or lipohypertrophy [14]. These cumulative logits are the log odds of three or more signs of lipoatrophy or lipohypertrophy to one or two signs or no signs, and the log odds of one or more signs of lipoatrophy or lipohypertrophy to no signs. Many variables were considered in univariate analyses, including sex, randomized group, age, HIV-1-RNA level in log₁₀ copies/ml at baseline, CD4 cell count at baseline, changes in CD4 cell count from baseline to month 30, duration of previous therapy, and previous NRTI received (zidovudine plus didanosine versus zidovudine plus zalcitabine). Stepwise logistic regression was used to determine independent prognostic factors among those in which the univariate *P*-value was lower than 0.20. All data were analysed using the SAS statistical analysis software (version 8; SAS Institute, Cary, NC, USA).

Results

Background

One hundred and seventy patients were randomly assigned in NOVAVIR into stavudine/lamivudine/indinavir or zidovudine/lamivudine/indinavir and were followed for 18 months. Before month 18, virological failure occurred in 14 patients (16%) receiving stavudine plus lamivudine plus indinavir and 15 patients (18%) receiving zidovudine plus lamivudine plus indinavir, with no statistical difference between the treatment arms (log-rank test, *P* = 0.98) [13]. As recommended by the Data Safety Monitoring Board, patients who did not fail and who had HIV-1-RNA levels below 5000 copies/ml at month 18 were asked to participate in a 12 month extended follow-up, in an attempt to assess the duration of the antiviral activity of treatment. The primary endpoint was reached in a further six patients during the extended follow-up, three failures in each arm, with again no statistical difference between both groups (log-rank test *P* = 0.98). At month 18, 67 and 73% of patients had HIV-1-RNA levels below 500 copies/ml in the stavudine and the zidovudine arms, respectively, with no statistical difference between the two groups (*P* = 0.50). At the end of the extended follow-up, the proportion of patients with less than 500 copies/ml was 76 and 78% in the stavudine and the zidovudine arms, respectively.

Population of patients

The 12 months extended follow-up was run in 115 patients (68%) out of the 170 patients. One hundred and one patients were included in the lipodystrophy substudy: 47 patients in the stavudine arm and 54 patients in the zidovudine arm. Characteristics at baseline, i.e. at day 0 (start of NOVAVIR study), were well balanced across treatment arms of the lipodystrophy substudy, and did not differ from baseline characteristics of the whole population of the trial (Table 1).

At the time of lipodystrophy evaluation, 30 months after randomization, the median CD4 cell counts were 551 and 507 cells/mm³, in the stavudine and the zidovudine arms, respectively, consecutive to a median increase from baseline of 272 and 237 cells/mm³, respectively. Similar increases in CD4 cell counts in the whole NOVAVIR population were observed with 260 and 237 cells/mm³ in the stavudine and zidovudine arms, respectively. The HIV-RNA level was below 500 copies/ml in 81% of patients in both the stavudine and zidovudine arms, compared with 78 and 84% of the whole population of patients, in the stavudine and the zidovudine arms, respectively. At month 30, 45 (96%) and 47 (87%) patients in the lipodystrophy substudy were still assigned to stavudine and zidovudine in the stavudine and zidovudine arms, respectively. Forty (85%) and 47 (87%) patients were still receiving indinavir in the stavudine and zidovudine arms, respectively.

Metabolic parameters

At month 30, there was no significant difference between the two arms in the median value of blood levels of fasting cholesterol [5.29, interquartile range (IQR) 4.3–6.3, and 5.40, IQR 4.6–6.3 mmol/l in the stavudine and the zidovudine arms, respectively; *P* = 0.73], triglycerides (1.5, IQR 1.1–2.3, and 1.6, IQR 1.1–2.4 mmol/l in the stavudine and zidovudine arms, respectively; *P* = 0.98) and glucose (5.1, IQR 4.7–5.8, and 5.1, IQR 4.7–5.7 mmol/l in the stavudine and zidovudine arms, respectively; *P* = 0.62). The percentages of patients with the occurrence of minor (grade 1) or worse increases of cholesterol, triglyceride, and glucose levels were no different between the two treatments arms. Eight patients (8%) received lipid-lowering agents (seven and one in the stavudine and zidovudine arms, respectively, Fisher's exact test *P* = 0.024).

Body shape changes

Twenty-three patients had only lipoatrophy, 11 patients had only lipohypertrophy, and 33 patients had mixed lipodystrophy. Eight patients had three or more clinical signs of both peripheral fat depletion and central fat accumulation.

Table 1. Characteristics of patients at baseline (start of NOVAVIR study).

	Lipodystrophy substudy		NOVAVIR study
	d4T + 3TC + IDV (n = 47)	ZDV +3TC + IDV (n = 54)	Total (n = 170)
Sex, no. (%) male	38 (81)	44 (81)	135 (79)
Age, years			
Median	38	39	37
25–75%	32–42	34–49	33–44
Previous NRTI			
Median duration (months)	21.6	24.0	19.5
25–75%	12–47	13–49	12–37.9
N (%) patients exposed to:			
ZDV/ddI	32 (68)	32 (59)	89 (52)
ZDV/ddC	16 (34)	27 (50)	64 (38)
ZDV/ddC and ZDV/ddI	1 (2)	6 (11)	13 (8)
CDC status, no. (%)			
CDC-A	22 (47)	20 (37)	80 (47)
CDC-B	19 (40)	29 (54)	72 (42)
CDC-C	6 (13)	5 (9)	18 (11)
CD4 cells/mm ³			
Median	295	283	291
25–75%	231–358	221–347	221–368
HIV-RNA level, log ₁₀ copies/ml			
Median	4.39	4.29	4.36
25–75%	4.07–4.68	4.05–4.63	4.08–4.66

CDC, Centers for Disease Control and Prevention; ddC, zalcitabine; ddI, didanosine; d4T, stavudine; IDV, indinavir; NRTI, nucleoside reverse transcriptase inhibitors; 3TC, lamivudine; ZDV, zidovudine.

When considering the symptoms of central adiposity there was no difference in the proportion of patients with buffalo neck, increased breast size, increased waist size, increased abdominal wall thickness or increased neck size (Fig. 1a). Overall, 44% of patients had at least one clinical sign of central fat accumulation. When considering symptoms of peripheral fat depletion, patients in the stavudine arm more frequently had facial atrophy (48 versus 22%, $P = 0.011$), lower limb atrophy (49 versus 22%, $P = 0.006$), buttock atrophy (47 versus 20%, $P = 0.009$) and venomegaly (57 versus 24%, $P = 0.001$) than patients in the zidovudine arm (Fig. 1b). In the stavudine arm, patients less frequently had no sign of lipoatrophy than in the zidovudine arm (30 versus 57% of patients, $P = 0.009$). Overall, the proportion of patients with none, one or two, or three or more clinical signs of lipoatrophy was different between the two arms (Fig. 2a, $P = 0.013$). In the stavudine arm, there was a trend towards more patients with one or two clinical signs of fat accumulation than in the zidovudine arm (Fig. 2b; $P = 0.14$).

The median body mass indexes were 22.2 (IQR 20.3–23.9) and 22.5 (IQR 20.7–24.7) in the stavudine and zidovudine arms, respectively, with no statistical difference ($P = 0.49$).

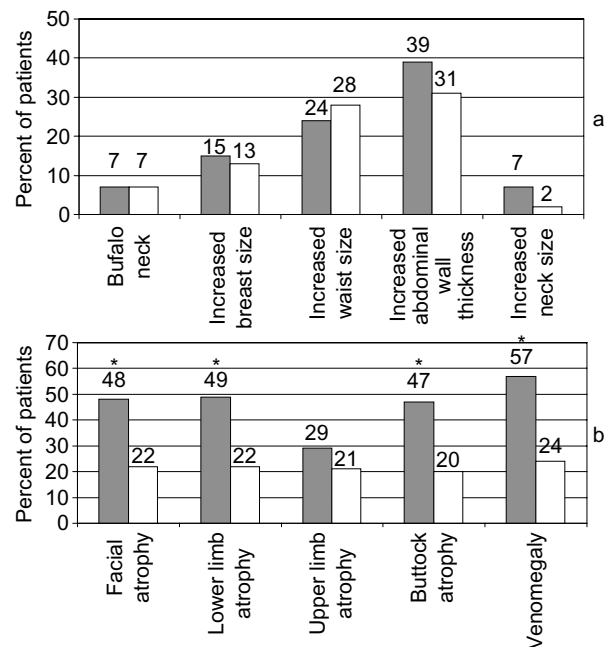


Fig. 1. Proportion of patients with central fat accumulation (a) or peripheral fat depletion (b) according to each body area, in the zidovudine and stavudine arms. □ Zidovudine arm; ■ stavudine arm. *Means significantly different from zidovudine arm, $P < 0.05$.

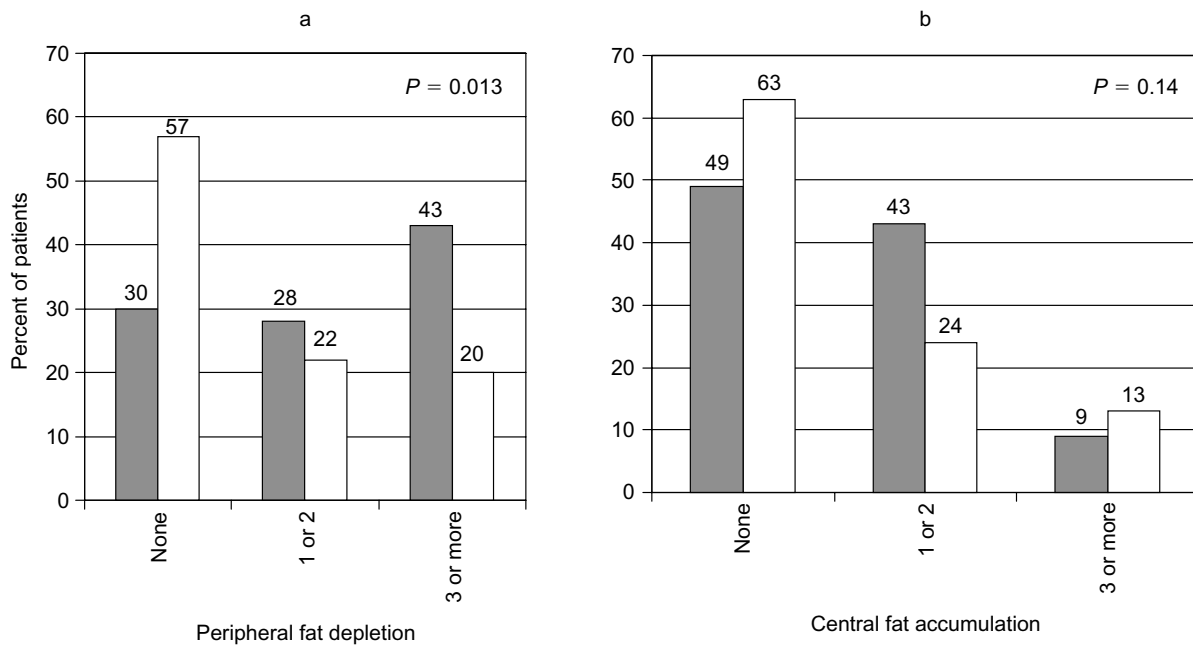


Fig. 2. Proportion of patients with none, one or two, or three or more body sites with peripheral fat depletion (a) or central fat accumulation (b), in the zidovudine and stavudine arms. □ Zidovudine arm; ■ stavudine arm. Body sites with peripheral fat depletion or central fat accumulation are those reported in Fig. 1.

Risk factors of lipodystrophy

In multivariate analysis, using a binary response to define the occurrence of lipoatrophy, patients in the stavudine group were significantly more likely to develop peripheral fat depletion than patients in the zidovudine group, as patients who had received previous therapy with didanosine compared with zalcitabine and patients with lower CD4 cell counts at study entry. When an ordinal response was investigated for lipoatrophy, the final model provided that the stavudine arm, and previous therapy with didanosine were independently associated with the development of peripheral fat depletion. For example, patients randomly assigned into the stavudine arm had 3.26 times higher odds of having more signs of lipoatrophy as patients randomly assigned into the zidovudine arm, both for three or more signs versus two or less signs and for one or more signs versus no sign of lipoatrophy (Table 2).

Univariate analysis of the occurrence of lipohypertrophy resulted in a significant association with age when a binary response was used, and in addition, with sex, randomization group and CD4 cell count at baseline when an ordinal response was modelled. Final models indicated that the increased risk of older patients remained statistically significant when a binary response was used, and that older patients and women had an independent increased risk of central fat accumulation when an ordinal response was modelled (Table 2).

Discussion

The lipodystrophy syndrome was described less than 2 years after the introduction of PI into routine clinical practice. Initially assumed to be an effect of PI, this syndrome was also reported in patients who were PI-naïve.

Different studies have suggested that stavudine could favour the occurrence of lipoatrophy, but most of them are cohort studies, and some results are conflicting. As stavudine had not been used for as long as zidovudine, didanosine and zalcitabine, there is potential bias in cohort studies. Few randomized studies evaluated the role of NRTI in lipoatrophy. The ALBI study [10] compared the toxicity of zidovudine/lamivudine and stavudine/didanosine, and thus could not assess the toxicity of stavudine itself. The Prometheus study [11] showed an increased risk of lipodystrophy in patients receiving stavudine in combination with saquinavir/ritonavir, compared with patients receiving saquinavir/ritonavir only, but did not assess the specific risk linked to stavudine compared with other NRTI. Law *et al.* [12] compared the risk of lipodystrophy during treatment with three NRTI combinations (zidovudine/lamivudine, stavudine/lamivudine, stavudine/didanosine), with or without indinavir or nevirapine in a comparative randomized trial. The combination of stavudine and didanosine was associated with an increased risk of peripheral lipoatrophy, but no specific

Table 2. Multivariate analysis of factors associated with progression to lipoatrophy or lipohypertrophy.

	Odds ratio	95% CI	P value
Risk factors of lipoatrophy			
Binary regression model			
Randomized group (d4T versus ZDV)	3.12	1.24–7.81	0.015
CD4 cell count baseline (per 100 cells increase)	0.58	0.36–0.93	0.023
Previous therapy (ZDV + ddI versus ZDV + ddC)	2.54	1.01–6.39	0.047
Polytomous regression model			
Randomized group (d4T versus ZDV)	3.26	1.43–7.44	0.005
Previous therapy (ZDV = ddI versus ZDV + ddC)	2.46	1.05–5.76	0.04
Risk factors of lipohypertrophy			
Binary regression model			
Age (per 10 years older)	1.73	1.11–2.69	0.015
Polytomous regression model			
Sex (female versus male)	3.68	1.33–10.17	0.012
Age (per 10 years older)	1.77	1.18–2.66	0.006

CI, Confidence interval; ddC, zalcitabine; ddI, didanosine; d4T, stavudine; ZDV, zidovudine.

risk was associated with stavudine itself. The small size of the sample (21–35 patients per group) may have precluded the authors from observing a role of stavudine independently from its combination with didanosine.

The long-term follow-up of patients enrolled in the Novavir study provided a unique opportunity to assess the relative contribution of stavudine in the development of the lipodystrophy syndrome, because patients in that trial had never received stavudine nor PI, had the same duration of previous antiretroviral therapy with zidovudine, didanosine or zalcitabine, and were randomly assigned between stavudine and zidovudine. All patients received indinavir and had the same duration of treatment with PI at the time of lipodystrophy evaluation, thus reducing heterogeneity related to antiretroviral treatment duration and type of PI between the two groups.

In our study, the evaluation of body shape changes was subjective. Other studies, however, have found good agreement between lipodystrophy, as assessed by physicians and the use of objective measurements such as dual energy X-ray absorptiometry [15] or sonography [16]. The overall frequency of any lipodystrophy detected in our population was relatively high, but in agreement with that of other published studies [9,17]. This could result from the inclusion of many distinct parameters in the body shape evaluation, with lipodystrophy being reported present as soon as one clinical symptom was reported.

We found a significantly increased incidence of peripheral fat depletion in the stavudine arm. Results obtained through the standardized questionnaire were confirmed by measurement of the thigh skinfold thickness in a subgroup of patients (data not shown). By contrast, the

incidence of metabolic abnormalities did not differ between the two arms, and the occurrence of lipohypertrophy was not significantly associated with stavudine treatment in multivariate analysis.

Several uncontrolled studies have evaluated the role of stavudine in the occurrence of lipodystrophy. In a cohort study, Mallal *et al.* [18] found that increased cumulative time on a regimen containing stavudine significantly increased the risk of fat wasting, compared with time on a regimen containing zidovudine. Martinez *et al.* [9] found that, even after adjusting for the increased risk associated with increasing exposure to HAART, there was a 16% increased risk of lipoatrophy associated with each additional exposure to stavudine. Carr *et al.* [19] showed the use of stavudine to be associated with peripheral lipoatrophy, and lamivudine duration to be associated with abdominal obesity. Heath *et al.* [7] reported that, in multivariate analysis, lipodystrophy was associated with having ever used a PI and with the duration of stavudine therapy.

Some studies found that fat wasting was more frequent in patients receiving PI and nucleosides than in patients receiving nucleosides only [18]. It has also been suggested that lamivudine causes fat wasting [20]. As in our study, all patients received indinavir, the synergistic toxicity of PI and nucleosides could not be evaluated. It is likely that the backbone treatment of indinavir and lamivudine increased the toxicity of stavudine.

Mulligan *et al.* [21] reported that metabolic parameters and lipoatrophy were independent, but that in patients with any sign of hypertrophy, a higher maximum for cholesterol serum levels was observed. This is in agreement with our data, showing the lack of a difference in fasting triglyceride, cholesterol and glucose blood levels between the two arms, in spite of an

increased incidence of lipoatrophy in the stavudine arm.

The multivariate analysis confirmed the role of the randomized arm (stavudine versus zidovudine) in the risk of lipoatrophy. We did not find the duration of previous antiretroviral therapy exposure to be an additional independent risk factor for the development of lipodystrophy, in contrast to many other observational studies [4,18,20,22]. This may be explained by the relatively short median time of previous NRTI exposure in our study population, compared with some observational studies, and is in agreement with data reported by van der Valk *et al.* [11], who studied patients previously exposed to NRTI for a median time of 94 weeks. We found that previous treatment with zidovudine plus didanosine increased the risk of lipoatrophy compared with zidovudine plus zalcitabine. This finding had not been reported previously, and cannot be explained by a longer exposure to didanosine because we found no difference in the duration of previous therapy between patients who had received zidovudine plus didanosine or zidovudine plus zalcitabine. Our results confirmed the role of factors other than drug toxicity in the development of lipodystrophy, such as the severity of HIV disease and age, previously discussed in other studies [4,9,7,17,18]. Drug-induced mitochondrial dysfunction in adipocytes has been suggested as a potential mechanism for the induction of lipodystrophy by NRTI [23,24]. As mitochondrial DNA defects would be expected to increase with age [25], our finding of age as a predictor of wasting is consistent with this hypothesis.

There are some caveats in our study. First, this is a cross-sectional study. Second, the study was based on a subjective evaluation of body shape changes and was not blinded; thus, we cannot exclude the possibility that our findings have been biased by physicians being more likely to report lipodystrophy in the stavudine-containing arm. Third, these results were obtained in only 59% of the trial population, and this may have introduced some bias and reduced the value of randomization. Finally, these results were observed in the context of previous exposure to zidovudine, didanosine or zalcitabine for a median duration of 21.6 months, and results could be different in a population of antiretroviral-naïve patients.

Conclusion

Patients receiving stavudine/lamivudine/indinavir had a greater rate of clinical lipodystrophy, mainly lipoatrophy, than those treated with zidovudine/lamivudine/indinavir. The risk of lipoatrophy was enhanced in patients previously exposed to zidovudine/didanosine

compared with those exposed to zidovudine/zalcitabine. The mechanisms involved in stavudine toxicity and the effect of treatment interruption warrants further investigations.

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Appendix: NOVAVIR study organization

Scientific committee

J.-P. Aboulker, B. Bazin, F. Brun-Vézinet, I. Carrière, A. Certain, J. Dormont, Y. Esnault, P. Flandre, P.-M. Girard, V. Joly, C. Katlama, V. Meiffredy, C. Michelet, J.-M. Molina, A. Prieur, F. Raffi, D. Séréni, P. Yeni.

Participating clinical centres

Centre Hospitalier de Belfort, Belfort (J.-P. Faller, P. Elinger); Centre Hospitalier La Milétrie, Poitiers (J.-P. Breux, M. Duballet); CHRU Pointe à Pitre-Abymes, Guadeloupe (B. Contamin, M. Strobel); Hôpital Robert Debré, Reims (I. Beguinot, G. Remy); Hôpital Corvisart, Charleville Mézières (M. Bouvier-

Alias, P. Lanoux, C. Penalba); Hôpital Avicenne, Bobigny (B. Jarrousse, P. Honoré); Hôpital Saint-Jacques, Besançon (G. Achard, C. Drobacheff, H. Gil, B. Hoen, C. Roche); Hôpital André Mignot, Le Chesnay (J. Doll); Hôpital Cochin, Paris (J. Krulik, D. Sicard, D. Séréni, B. Silbermann); Hôpital Bicêtre, Le Kremlin Bicêtre (J.-F. Delfraissy, C. Goujard, M. Mole, M.-T. Rannou); Hôpital Lariboisière, Paris (J.-M. Salord, V. Vincent, M. Parrinello); Hôpital Henri Duffaut, Avignon (G. Brun, G. Lepeu); Hôpital Jean Verdier, Bondy (V. Jeantils, C. Thaleb); Hôpital Rothschild, Paris (N. Adda, T. Nguyen, W. Rozenbaum); Hôpital Antoine Bécclère, Clamart (F. Boue, V. Chambrin, G. Lubart); (Hôpital Bichat Claude-Bernard, Paris (Y. Bennai, L. Belardi, E. Bouvet, I. Fournier, C. Gaudebout, v. Joly, C. Mandet, S. Masson, P. Yeni); Centre Médico-Chirurgical Foch, Suresnes (I. Vergne, D. Zucmann); Hôpital Henri Mondor, Créteil (M. Lechevallier, A. Sobel); Hôpital Pitié-Salpêtrière, Paris (C. Katlama, S. Maury, H. Schoen); Hôpital Saint-Louis, Paris (J. Modai, M.-N. Sombardier); Hôpital Pierre Zobda-Quitman, Fort de France (A. Cabie, V. Beaujolais, G. Sobesky); Hôpital d'Angers, Angers (J.-M. Chennebault, P. Fialaire, E. Vivien); CHR Pellegrin, Bordeaux (T. Galperine, J.-M. Ragnaud); Hôpital Saint-André, Bordeaux (M. Bonarek, Ph. Morlat); Hôpital Hôtel Dieu, Lyon (C. Carré, L. Cotte, C. Trépo); Hôpital Sainte Marguerite, Marseille (T. Dinh, G. Fabre, J.-A. Gastaut); CHU Gui de Chauiac, Montpellier (C. Merle, J. Reynes, M. Vidal); Hôpital Hôtel Dieu, Nantes (M.-F. Charonnat, A. Huart, F. Raffi, M. Sicot); Hôpital De L'Archet, Nice (Ph. Clevenbergh, P. Dellamonica); Hôpital Pontchaillou, Rennes (C. Arvieux, F. Cartier, F. Souala); Centre Hospitalier La Beauchée, Saint Briec (C. Devaurs, C. Hascoet); CHRU de Strasbourg, Strasbourg (V. Krantz, J.-M. Lang); Hôpital de Purpan, Toulouse (M.-F. Garbay, P. Massip); CHU Côte de Nacre, Caen (C. Bazin, P. Goubin, M. Six); Hôpital de Tourcoing, Tourcoing (Y. Mouton); Hôpital de Brabois, Vandoeuvre les Nancy (C. Burty, Ph. Canton, Th. May); Hôpital Charles Nicolle, Rouen (F. Borsa-Lebas, Y. Debab); Centre Hospitalier de Compiègne, Compiègne (L. Geffray, D. Merrien).

Data and safety monitoring board

E. Hirsch, J. Puel, M. Seligmann, M. Vray.

Coordinating trial centre

INSERM SC10: J.-P. Aboulker, B. Bazin, P. Flandre, M. Harel, S. Hazebrouck, N. Leturque, V. Meiffredy, A. Prieur, Y. Saïdi.

ARCAM: R. Léonard, A. Dauphin, R. Laillier.