

ASSOCIATION BETWEEN NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR (NNRTI) USE AND HIV-ASSOCIATED LIPODYSTROPHY SYNDROME (HALS) IN THE DAGNÄ-LIPART COHORT STUDY

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ABSTRACT

Background of study: The DAGNAE LipART cross-sectional study drew patients from the ART 96 trial, a closed, prospective, multicentre (n = 81) cohort of HIV-positive and therapy-naïve patients (n = 828), who had started ART in mid 1996. Encompassing 27 centres meeting defined selection criteria to represent the cohort as a whole and 221 patients, LipART addressed the effects of 3-year antiretroviral use on HALS.

Objective: As part of LipART, to analyze the effect of NNRTI use on fat redistribution and lipid levels.

Design: cross-sectional, multicentre. Standardized physician and patient questionnaires, including linear analog scales, laboratory parameters such as lipid levels and antiretroviral therapy history, were applied for lipodystrophy reporting.

Results: 73 (33%) of 221 subjects in the LipART study received NNRTIs (for a mean duration of 8.5 months). 39 patients took Nevirapine (NVP, mean 9.7 months) and 38 took Efavirenz (EFV, mean 5.8 months). No significant differences in demographics were noted. A > 12 months-use of NNRTIs was found to be independently and significantly associated with a decreased risk for lipodystrophy (odds ratio = 0.22, p < 0.05). Use of NNRTIs was not significantly associated with hypertriglyceridemia (rel. risk = 0.87, p = 0.49), but was linked to hypercholesterolemia (rel. risk = 1.63, p = 0.01). Differentiating between individual substances: NVP use was sub-significantly associated with a decreased risk for hypertriglyceridemia (rel. risk = 0.55, p = 0.06). EFV, on the other hand, was associated with hypercholesterolemia (rel. risk = 2.35, p < 0.01). This was confirmed using serum levels and t-test analysis.

Conclusions: Use of NNRTIs for > 12 months resulted in a decreased risk for lipodystrophy. NNRTI use was not associated with the occurrence of hypertriglyceridemia, but was linked to hypercholesterolemia secondary to the effects of EFV.

METHODS

Study population

The German closed multicenter (n = 79) cohort study "ART 96" followed a total of 828 HIV-seropositive individuals who started their first antiretroviral therapy between July and September 1996. Of these 79 centres, 27 participated in the DAGNÄ Lip-ART study, enrolling 221 patients and reflecting the cohort as a whole. Patients receiving treatment with NNRTI(s) at any point in time were included in this sub-analysis.

Methods

– Follow-up at month 36, including detailed records of ART, AIDS-defining events, CD4 cell counts, viral loads, lipid levels, serum glucose and cardiovascular events.

– Cross-sectional assessment of the presence of HALS using standardized physician and patient questionnaires. The extent of body habitus changes in six compartments (cheeks, neck, breast, abdomen, buttocks, legs) was rated using visual analog scales.

– Circumference measurements according to WHO standards (waist, hip, right thigh).

Data analysis

Treatment-related variables were tested for an association with lipodystrophy in univariate analyses using Chi square techniques. Duration of drug intake was categorized a priori and tested as "ever taken", taken for > 6 months, > 12 months and > 18 months. Multivariate analyses were performed using multiple logistic regression models with p < 0.1 for entry into the model and p < 0.05 for remaining in the model. All analyses were performed using SAS®.

BACKGROUND

HIV-associated lipodystrophy syndrome (HALS) is a disorder consisting of changes in body fat distribution, metabolic disturbances and a number of related phenomena. HALS is reported with increasing incidence in HIV-infected individuals receiving antiretroviral therapy (ART). The DAGNÄ LipART studied the various aspects of HALS after 3 years of ART. Since antiretroviral agents do not represent a homogenous group of substances, we wanted to analyze the effects of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class on HALS in this sub-study.

OBJECTIVE

The objective of this sub-study was:

– to analyze the effect of NNRTI use on fat redistribution and lipid levels as part of LipART.

RESULTS

LIPODYSTROPHY

DAGNÄ LipART found a lipodystrophy prevalence of 34% (n = 76/221) after three years of antiretroviral treatment. NNRTI use > 12 months was found to be significantly and independently associated with a reduced risk for developing HALS. (Table 1)

Table 1.

Variable	Odds Ratio	95% CI
D4T >12 Mon.	2,52	(1.40–4.54)
CD4 Nadir < 200/µl	2,21	(1.21–4.06)
NNRTI > 12 Mon.	0.19	(0.04–0.87)

Relative risk decreased with duration of NNRTI use and reached significance after one year. An assessment of individual NNRTIs and lipodystrophy detected a non-significant associative trend between increasing duration of Nevirapine therapy and a decrease in relative risk. No associations were found with Efavirenz and Delavirdine (Table 2). However, it can be concluded that prolonged use of Efavirenz and Delavirdine contributed to the significant association between NNRTI use greater than 12 months and a decreased risk of developing lipodystrophy, since the use of Nevirapine alone does not reach significance.

Table 2. Association between therapy with NNRTI(s) and the development of lipodystrophy**

NNRTI use and lipodystrophy	Duration of use	rel. risk	p-value	95% C.I.
NNRTI use and lipodystrophy	Ever	0.880	0.527	0.592–1.309
	> 6 months	0.753	0.303	0.440–1.291
	> 12 months	0.305	0.030*	0.104–0.894
Nevirapine and lipodystrophy	Duration of use	rel. risk	p-value	
	Ever	0.875	0.601	
	> 6 months	0.558	0.156	
> 12 months	0.432	0.138		
Efavirenz and lipodystrophy	Duration of use	rel. risk		
	Ever	0.994		

* Significant = p < 0.05

** Delavirdine not included; population was too small to produce reliable results

PATIENTS

221 patients were enrolled into the DAGNÄ LipART. Of these, 33% (n = 73) received therapy with NNRTI(s) and are hence included in this sub-study.

Baseline Characteristics

Baseline characteristics of patients included in the LipART sample did not differ significantly from the "ART 96" cohort from which this sample was drawn. Further, the baseline characteristics of the subjects treated with NNRTI(s) did not significantly differ from those who were not. 84% were male, the median age was 39 years. No significant differences were found with respect to HIV-transmission route and CD4 cell count, neither in the beginning nor during the duration of the study.

Antiretroviral Therapy

Patients were evenly distributed into two treatment groups. 39 had received Nevirapine and 38 had been treated with Efavirenz. Delavirdine played only a minor role with 2 patients. The average treatment duration with Nevirapine was 9.7 months, while that of Efavirenz was significantly shorter with 5.8 months. 8% received NNRTI therapy for longer than 6 months.

HYPERLIPIDEMIA

A significant increase in relative risk for developing hypercholesterolemia was detected with NNRTI use and can be contributed to Efavirenz (Table 3). Mean cholesterol levels were significantly elevated with NNRTI-treated as compared to – naïve patients (236.2 vs. 209.0 mg/dl; p = 0.0011). No significant difference was noted with Nevirapine therapy. Efavirenz, on the other hand, was associated with a significant elevation of cholesterol levels (240.1 vs. 213.0 mg/dl; p = 0.0038).

Hypertriglyceridemia on the other hand was not associated with NNRTI treatment, though a non-significant trend of Nevirapine use with a reduced risk was detected (Table 3). This is reflected in the similar mean triglyceride levels between NNRTI-treated and – naïve patients (249.3 vs. 253.4 mg/dl; p = 0.90) and in the reduced levels seen with Nevirapine-treated vs. – naïve subjects (201.5 vs. 262.2 mg/dl; p = 0.057). Efavirenz was associated with a non-significant triglyceride elevation (290.1 vs. 244.1 mg/dl; p = 0.27).

Table 3. Association between therapy with NNRTI(s) and the development of hyperlipidemia

NNRTI use and hyperlipidemia	rel. risk	p-value
NNRTI use and hyperlipidemia	hypertriglyceridemia	0.872
	hypercholesterolemia	1.628
Nevirapine and hyperlipidemia	rel. risk	p-value
	hypertriglyceridemia	0.551
hypercholesterolemia	1.006	0.983
Efavirenz and hyperlipidemia	rel. risk	p-value
	hypertriglyceridemia	1.135
hypercholesterolemia	2.346	0.007*

* Significant = p < 0.05

** Delavirdine not included; population was too small to produce reliable results

CONCLUSIONS

- NNRTI use for > 12 months resulted in a decreased risk for developing HALS.
- NNRTI use was not associated with the occurrence of hypertriglyceridemia.
- NNRTI use was associated with the occurrence of hypercholesterolemia.

Looking at the individual agents:

- Nevirapine use was sub-significantly associated with a decreased risk for developing hypertriglyceridemia.
- Efavirenz use was associated with an increased risk for developing hypercholesterolemia.

DAGNÄ* LIPART NETWORK: PARTICIPATING CENTRES

- Adam/Weitner, Hamburg
- Becker, München
- Brust/Schuster, Mannheim
- Corzillius, Kiel
- Dupke, Berlin
- Gehring, Dortmund
- Gorriahn, München
- Gölz/Moll, Berlin
- Jäger, München
- Locher/Gute, Frankfurt a.M.
- Lichtenstein, München
- Knechten, Aachen
- Kuhlmann/von Wussow, Hannover
- Mosthaf, Karlsruhe

- Mauss und Schmutz, Düsseldorf
- Pfeil, Leipzig
- Priester, Frankfurt a. M.
- Rockstroh, Bonn
- Schnaitmann, Stuttgart
- Schwenk, London
- Staszewski, Frankfurt
- Starke, Wiesbaden
- Stellbrink, Hamburg
- Stoehr, Hamburg
- Ulmer, Stuttgart
- Wiesel, Köln

DAGNÄ = German organization representing physicians in private practice caring for HIV-infected individuals