

Changes in Androgens and Gonadotropins during HAART and Their Association with Development of Lipoatrophy in HIV infected Men

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Introduction

Disorders of the androgens are prevalent in HIV-infected men. There is a controversy about an association of changes of androgens and development of lipoatrophy.

Methods

Study aims:

1. To describe the prevalence of abnormalities of male sex hormones and gonadotropins and their change during two years of successful combination antiretroviral therapy (CART) in ART naïve HIV infected men.

2. To study the association of levels of male sex hormones and gonadotropins with the development of lipoatrophy during two years of CART on a stable nucleoside analogue backbone.

The Swiss HIV Cohort Study (www.shcs.ch) is a prospective cohort study with ongoing enrolment of adult HIV-infected patients. Patients are followed in one of seven study centres. Information is collected according to standardized criteria on structured forms at enrolment and at follow-up visits at 6 monthly intervals. We used the SHCS data-set of June 2004. There is a plasma storage every 6 months for future research questions.

Study design: Nested case control study of 99 ART-naïve HIV-infected men who started and continued a virologically successful zidovudine (AZT)/lamivudine (3TC)-based combination antiretroviral therapy (CART) for 2 years. Cases were 11 individuals who developed lipoatrophy during these two years. Of 128 patients in the Swiss HIV Cohort Study who fulfilled the eligibility criteria and did not develop lipoatrophy, we randomly chose 88 controls. Serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), free testosterone (FT), and dehydroepiandrosterone (DHEA) were measured in plasma stored before the start and 2 years later of unchanged CART.

Definition of lipoatrophy in the SHCS: Lipoatrophy is defined by the atrophy of adipose tissue. Lipoatrophy is diagnosed when fat loss occurs in one or more of the following locations: face (buccal, periorbital, temporal), arm, leg or buttocks. The presence of at least one sign of fat wasting (lipoatrophy) is considered indicative for lipoatrophy if the patient and the treating physician agree on the finding.

Statistics: Wilcoxon signed-rank test, two-sample Wilcoxon rank-sum (Mann-Whitney) test, and ChiSquare tests were used as indicated. Possible associations with the development of lipoatrophy was evaluated in a stepwise logistic regression model that included baseline hormone values, changes of hormone values, age, body mass index, CD4 count, and HIV RNA. A two sided *P* value of 0.05 or less was accepted as significant.

Descriptive statistics

The characteristics of the participants studied are shown in **Table 1**. CD4 counts at CART start were higher in cases.

Hormone levels before and after 2 years of CART are depicted in **Table 2** and the proportion of non-normal age adjusted levels at these two time-points in **Table 3**. A comparison of changes of hormone levels during treatment is shown in **Table 4**.

At CART start, age adjusted FT levels were low in 69 (70%); in those LH levels were normal 48% and low in 43%.

FSH levels were normal in 83 (84%) and low in 12 (12%). These proportions did not differ significantly in cases and controls.

All cases showed an increase in LH levels, while these consistent differences were not seen in controls.

DHEA levels were high in 26 (30%) and normal in 58 (66%) of controls and high in 1 (9%) and normal in 8 (73%) of the cases. During 2 years of CART there were no significant changes of FT and FSH levels. DHEA levels rose significantly during CART in patients who did not develop lipoatrophy but not in the case patients

Table 2: Hormone levels

	All N=99	Cases N=11	Controls N=88
FSH(IU/L)			
Before CART	2.92 (1.82-5.12)	2.79 (1.59-5.12)	2.96 (1.84-5.05)
After 2yrs of CART	3.09 (1.90-4.67)	3.67 (3.17-5.78)	2.60 (1.81-4.67)
P Value for difference before and after	0.6	0.04	0.13
LH(IU/L)			
Before CART	3.11 (1.73-5.04)	2.88 (1.93-3.59)	3.22 (1.73-5.10)
After 2yrs of CART	3.42 (1.96-5.79)	6.60 (3.73-8.63)	3.03 (1.90-5.53)
P Value for difference before and after	0.3	0.03	0.8
DHEA(ng/mL)			
Before CART	6.24 (4.32-9.14)	7.27 (4.07-9.14)	6.12 (4.36-9.25)
After 2yrs of CART	8.03 (5.04-12.80)	6.14 (4.98-10.17)	8.27 (5.13-13.08)
P Value for difference before and after	0.002	0.6	<0.0001
FT(pmol/l)			
Before CART	23.12 (17.55-29.77)	26.10 (15.30-35.07)	22.81 (17.81-28.76)
After 2yrs of CART	23.78 (17.91-31.97)	25.13 (16.07-35.76)	23.60 (17.97-31.48)
P Value for difference before and after	0.6	0.8	0.7

Table 4: Comparison of changes in hormone levels during CART

Median difference before and after 2 years of CART (IQR) in	Lipoatrophic patients (N=11)	Controls (N=88)	P value
FSH levels (IU/L)	+ 1.1 (-0.2 to 2.3)	- 0.2 (-0.7 to 0.35)	0.008
LH levels (IU/L)	+ 3.0 (1.3 to 4.6)	- 0.06 (-0.6 to 0.53)	0.0004
DHEA levels (ng/mL)	-1.2 (-2.4 to 1.8)	+ 1.3 (-0.6 to 5)	0.04
FT levels (pmol/l)	+ 0.5 (-1.6 to 1)	+ 0.2 (-0.7 to 1.1)	0.9

Results

Table 1. Patient characteristics, p-values refer to differences between cases and controls

Characteristics	All N=99	Cases N=11	Controls N=88	p-value
Med. age,yrs (IQR)	39 (35-45)	44 (41-45)	39(35-44)	
HIV transmission mode				0.3
MSM	45 (45%)	4 (36%)	41 (47%)	
Heterosexual	31 (31%)	6 (55%)	25 (28%)	
IDU	22 (22%)	1 (9%)	21 (24%)	
Unknown/other	1	0	1	
CDC-Stage (%)				0.2
A	70 (71%)	67 (64%)	63 (72%)	
B	23 (23%)	2 (18%)	21 (24%)	
C	6 (6%)	2 (18%)	4 (5%)	
CART				0.9
PI based	62 (63%)	7 (64%)	55 (63%)	
NNRTI based	37 (37%)	4 (36%)	33 (38%)	
Before CART				
Med. BMI kg/m ² (IQR)	23.4 (20.6-26.0)	23.2 (21.8-24.9)	23.5 (20.5-26.1)	0.6
Med. CD4 cells/μl (IQR)	220 (106-364)	440 (173-556)	209 (83-330.5)	0.04
Med. HIV-RNA c/ml(IQR)	4.6 (3.9-5.2)	4.44 (2.0-4.9)	4.6 (4.0-5.2)	0.14
After 2yrs of CART				
Med. BMI kg/m ² (IQR)	24.4 (21.7-26.5)	23.5 (22.6-25.3)	24.6 (21.3-26.7)	0.6
Med. CD4-cells/μl (IQR)	434 (277-674)	610 (315-752)	430 (275.5-643)	0.3

Table 3: Hormone levels above and below age adjusted norm

	All N=99	Cases N=11	Controls N=88
FSH			
Low levels before treatment	10 (10%)	1 (9%)	9 (10%)
High levels before treatment	4 (4%)	1 (9%)	3 (3%)
Low levels after two years of treatment	12 (12%)	0 (0%)	12 (14%)
High levels after two years of treatment	4 (4%)	1 (9%)	3 (3%)
LH			
Low levels before treatment	33 (33%)	4 (36%)	29 (33%)
High levels before treatment	11 (11%)	2 (18%)	9 (10%)
Low levels after two years of treatment	25 (25%)	0 (0%)	25 (28%)
High levels after two years of treatment	11 (11%)	4 (36%)	7 (8%)
DHEA			
Low levels before treatment	8 (8%)	1 (9%)	7 (8%)
High levels before treatment	13 (13%)	1 (9%)	12 (14%)
Low levels after two years of treatment	6 (6%)	2 (18%)	4 (5%)
High levels after two years of treatment	27 (27%)	1 (9%)	26 (30%)
FT			
Low levels before treatment	69 (70%)	6 (55%)	63 (72%)
High levels before treatment	1 (1%)	0 (0%)	1 (1%)
Low levels after two years of treatment	62 (63%)	5 (46%)	57 (65%)
High levels after two years of treatment	1 (1%)	0 (0%)	1 (1%)

Association of hormone levels and development of lipoatrophy

The presence of protease inhibitors in the regimen was not associated with any change.

A stepwise logistic regression model including baseline hormone values, changes of hormone values during CART, quartile of age, body mass index, baseline CD4 count, and HIV RNA was performed.

Development of lipoatrophy was associated with an increase in LH levels during HAART (*p* = 0.001) and there were associations with higher baseline DHEA levels, lower body mass index, higher baseline CD4 counts, and increasing age (Table 5).

Table 5: Logistic regression model of association with development of lipoatrophy

Parameter	Adj. OR (95% CI)	P value
Age (per quartile increase)	3.8 (1.4 – 9.9)	0.008
Baseline CD4 count (per 50 increase)	1.2 (1.02-1.5)	0.029
Body Mass Index (per unit increase)	0.69 (0.50-0.97)	0.030
Change in LH level (per IU/L increase)	2.0 (1.3-3.0)	0.001
DHEA level at CART start (per ng/ml increase)	1.2 (1.02-1.33)	0.020

Conclusions

- Hypogonadism was found in the majority in HIV-infected caucasian men and does not resolve during 2 years of CART.
- Development of lipoatrophy on a stable and uniform nucleoside-backbone was associated with particular changes in the gonadotropin-androgen axis and characterised by an increase of LH levels and lack of increase of DHEA levels during CART.
- In the studied population development of lipoatrophy was independently associated with higher baseline CD4 counts, lower BMI, higher age, higher DHEA baseline levels and increasing LH levels during CART.