Gynecomastia and potent antiretroviral therapy

Gynecomastia is defined as benign enlargement of the male mammary gland. In HIV-1-uninfected individuals, gynecomastia is found most frequently during puberty, in elderly and obese individuals as well as in individuals with liver cirrhosis [1]. The pathogenesis appears to be a hormonal imbalance such as a decreased ratio of androgens to oestrogens or an increased tissue sensitivity to oestrogens [1]. Gynecomastia has also been associated with the use of spironolacton, digitalis compounds, cimetidine, enalapril, and amiodarone as well as heroin, marijuana, amphetamine and alcohol consumption [1]. In HIV-1-infected individuals, the estimated prevalence ranges from 2 to 3%. Gynecomastia in HIV-1 infection may be associated with the use of potent antiretroviral therapy (ART) [2]. Alternatively, gynecomastia has been interpreted as a distinct form of immune reconstitution illness [2,3]. In addition, a significant relationship between the emergence of gynecomastia and the presence of the lipodystrophy syndrome was noted [4–7]. We studied the characteristics of 47 individuals in the Swiss HIV Cohort Study (SHCS) who received ART from 1996 to 2002 and were HIV-1 infected for a median time of 105 ± 52 months. They presented with an enlargement of the

breast gland, measuring on average 2.5 cm in diameter. The age of the individuals was significantly greater compared with the average age of SHCS participants (median 40 versus 35.9 years; $P = 0.001$; Table 1). Twenty-six individuals (55%) showed bilateral involvement and 27 patients (57%) suffered from breast pain. The median duration of ART was 28.5 months (interquartile range 21.7–43.7). ART consisted either of a protease inhibitor (83%; saquinavir n = 10; ritonavir n = 12; indinavir n = 9; nelfinavir n = 16; amprenavir n = 2; lopinavir n = 3) or a non-nucleoside reverse transcriptase inhibitor (36%; nevirapine n = 1; efavirenz n = 16) in combination with nucleoside analogues. Of interest is the fact that stavudine and didanosine were used more frequently in patients with gynecomastia than in other patients in the SHCS (75 versus 45% and 36.2 versus 10.6%; $P < 0.001$ for both comparisons). The median CD4 T-cell count was 384 cells/μl and the median plasma HIV-1-RNA level was 1.6 $\log_{10}$ copies/ml. The CD4 T-cell count in the SHCS after a similar duration of ART was 386 cells/μl ($P > 0.05$). Cholesterol and triglyceride levels were elevated in 38.3 and 53.2% of patients with gynecomastia, respectively. Fourteen patients (30%) suffered from concomitant lipodystrophy (fat accumulation). Twenty-two of the 47 individuals (46.8%) also showed elevated liver transaminases. The endocrinological assessment revealed that 40% (8/20) had elevated luteinizing hormone levels (range 8.9–17.1, median 12.4 U/l; male normal values 1.7–8.7 U/l). In four out of 14 patients (28.6%) testosterone concentrations were decreased (range 1.9–4.2 nmol/l, median 4.5; male normal values 9.9–28.1 nmol/l). Importantly, none of the four patients with low testosterone concentrations had increased luteinizing hormone levels. A low oestradiol level was only found in one out of 10 individuals. Prolactin (n = 13), beta-human chorionic gonadotrophin (n = 13) and thryroid-stimulating hormone (n = 14) values were in the normal range. Hepatitis C virus co-infection was detected in 42.6% of patients with gynecomastia and in 43.5% of SHCS patients without gyncecomastia ($P > 0.05$). Regular marijuana use was reported by nine out of 47 patients (19.1%), whereas heroine and cocaine use was known in five out of 47 individuals (10.6%).

In summary, our case series shows that the onset of gynecomastia in HIV-1-infected patients usually occurs more than 2 years after the initiation of ART. The large proportion of 75% of patients with gynecomastia who had received stavudine supports the hypothesis that this nucleoside analogue may play a causal role, which is in agreement with two other studies [2,8]. In addition, the percentage of patients receiving didanosine was high. However, the pathophysiology of gynecomastia may be multifactorial. We found de-

Table 1. Characteristics of HIV-infected patients with gynecomastia.

	Gynecomastia group[c] (n = 47)	Control group[d] (n = 1767)
Male sex[a]	47 (100)	1273 (72.0)
Age (years)	40 (36–48)	35.9 (31.5–42.6)
Body mass index (kg/m^2)	21.4 (19.4–23.5)	Not available
Probable route of HIV-1 transmission[a]	7 (14)	498 (28.2)
Heterosexual contact	20 (42.6)	647 (36.6)
Men who have sex with men	19 (40.4)	549 (31)
Intravenous drug use	1 (2.1)	73 (4.2)
CDC stage[a]		
A	14 (29.8)	607 (34.4)
B	17 (36.2)	619 (35.1)
C	16 (34.0)	536 (30.4)
Baseline CD4 cell count (cells/μl)	278 (179–410)	190 (72–333)
Baseline HIV-1 RNA ($\log_{10}$ copies/ml)	5.2 (4.4–5.7)	4.6 (3.9–5.2)
CD4 increase (cells/μl)	116	187
CD4 cell count[b] at diagnosis of gynecomastia or last follow-up	384	386
Hepatitis serology[a]		
HBsAg[a]	3 (6.4)	103 (8.4) (n = 1117)
HCV-Ab[a]	20 (42.6)	648 (43.5) (n = 840)
Fat accumulation[a]	14 (29.8)	Not available
Diameter of breast nodule (mean ± SD)	2.5 ± 1.5	Not applicable
Symptoms[a]		
Pain	27 (57.4)	Not applicable
Cosmetic problem	33 (70.2)	Not applicable
No symptoms	2 (4.3)	Not applicable

CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C virus antibodies.
[a]Values in parentheses indicate percentages of patients.
[b]CD4 cell count at diagnosis of gynecomastia or last follow-up for controls.
[c]All patients had at least one ART between 1996 and 2002.
[d]Controls commenced ART during the same time period, but had no signs of gynaecomastia.

creased testosterone levels in 29% of tested patients, although none of these individuals showed increased luteinizing hormone levels, indicating primary hypogonadism [9]. Similarly, Piroth *et al*. [2] noted decreased testosterone levels in three out of 10 patients, but Peyrier *et al*. [6] and Qazi *et al*. [3] did not find relevant hormonal changes. Therefore, the role of hormonal disbalance for the pathogenesis of gynecomastia remains to be determined. The hypothesis that gynecomastia may be triggered by the reconstitution of the immune system [2,3] is not supported by our results, because of the late onset of gynecomastia 28 months after the intitiation of ART. Additional factors contributing to gynecomastia in our study may have been long-term marijuana and heroin use [1].

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Sponsorship: This study was supported by the Swiss

Received: 17 November 2003; accepted: 8 December 2003.

DOI: 10.1097/01.aids.0000125974.77495.79

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treated with HAART, we analysed the incidence of SS after starting HAART. We looked at HIV-positive patients treated with HAART compared with 250 age-matched patients not treated with HAART to deter-

(spirometry, Kco and TLco). Blood was taken for a full blood count, erythrocyte sedimentation rate, liver function tests, urea and electrolytes, C-reactive protein, thyroid function tests, immunoglobulins and serum