Further events emerging during HIV infection treated with any antiretroviral therapy: the frequency and role of gynecomastia

Ulteriori eventi emergenti in corso di infezione da HIV trattata con qualunque terapia antiretrovirale: frequenza e ruolo della ginecomastia

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INTRODUCTION

The fat redistribution syndrome and the frequently associated alteration of serum lipid and glucose metabolism emerged shortly after the introduction of highly active antiretroviral therapy (HAART), and some reliable pathogenetic mechanisms were postulated to explain the potential role of protease inhibitors, as the first potent anti-HIV agents used in early HAART combinations since mid-1996 [1-3]. Within the broad range of mid- or long-term disturbances possibly related with HAART regimens, also gynecomastia emerged as an untoward effect, together with a benign breast enlargement observed in female patients immediately after HAART introduction, as a part of the so-called lipodystrophy syndrome [4-8]. All these disturbances (lipodystrophy syndrome, dyslipidemia, and gynecomastia), seemed to share some possible pathogenetic pathways, especially when a protease inhibitor-based HAART was of concern [2, 3, 7, 9-18], although anecdotal cases of female breast hypertrophy were recorded in absence of protease inhibitor, during an efavirenz-based therapy [19]. Actually, HIV-associated gynecomastia was first recognized in the pre-HAART era, in an HIV-infected untreated patient [20]. Anyway, as soon as antiretroviral compounds and associations other than protease inhibitors (non-nucleoside reverse transcriptase inhibitors, triple nucleoside analogue regimens, nucleotide analogues, fusion inhibitors) became available, a number of novel antiretroviral combinations were proposed as alternative HAART regimens, both in antiretroviral-naïve subjects, and especially in those who experienced failure or poor tolerability when on protease inhibitor-containing associations [14, 17, 18, 21-28]. As a consequence, HAART regimens sparing or excluding protease inhibitors, and based on triple nucleoside analogues, the introduction of tenofovir as the only available nucleotide analogue, and especially combinations relying on non-nucleoside reverse transcriptase inhibitor, became increasingly popular during time, according to evolving recommendations in terms of optimal antiretroviral therapeutic choices [6, 15, 22-40]. Among protease inhibitor-sparing regimens, some associations were assessed just in patients who developed metabolic abnormalities and lipodystrophy when on protease inhibitors, but most of obtained results were contradictory, probably because of the proportionally reduced patient sample (16 to 104 cases), and especially the short follow-up period of the completed literature studies (ranging from 6 to 12 months), which seemed insufficient to observe significant change in body shape and fat distribution [3, 6, 15, 24-26, 35-40]. Five of the 6 literature studies which proposed a switch from protease...
inhibitors to an efavirenz-based HAART demonstrated effects on hyperlipidemia, but a recovery of lipodystrophy occurred in only one literature experience [6, 15, 24, 28, 39, 40]. Moreover, three investigations evaluated nevirapine in the same therapeutic situation, and had a similar outcome on laboratory and clinical parameters, with only one study achieving apparent benefits on the lipodystrophy syndrome [6, 24, 35]. Three more studies assessed abacavir introduction after a previous protease inhibitor therapy [36-38]: an amelioration of serum lipid profile was obtained in all cases, contrasting with no results achieved in the field of the lipodystrophy syndrome. Furthermore, a recent pediatric study assessed the impact of protease inhibitor substitution with efavirenz in 17 children, but failed in observing cases of gynecomastia [40]. Concurrently, episodes of lipodystrophy apparently related to an initial efavirenz-related HAART are increasingly reported since the year 2000 [41].

However, after the first case report of gynecomastia apparently related to isolated nucleoside analogue therapy described by Melbourne et al. [42], other episodes of persistent gynecomastia in HIV-infected patients treated without protease inhibitors, came to the attention of clinicians [7, 9-13, 16, 43-47]. In the meantime, episodes of dyslipidemia and/or lipodystrophy appeared or worsened after abandonment of protease inhibitors towards other regimens, were increasingly reported, too [3, 6, 17, 18, 24, 28, 35-38].

Aim of our study is to identify all cases of gynecomastia occurred during HIV infection and antiretroviral therapy in a cohort of around 1,000 treated patients, with other potential risk factors for gynecomastia carefully excluded, in order to search all potential relationship between this emerging disturbance, and demographic and epidemiological variables, clinical and laboratory markers of HIV disease progression, metabolic disturbances, prior and underlying antiretroviral treatment, and subsequent evolution and outcome.

RESULTS

From year 1999 to 2003, 15 male patients out of 516 evaluable male subjects (2.9%), developed gynecomastia when aged 12 to 58 years; HIV infection was sexually-acquired in all cases but one, and was known since 19 to 183 months (Table 1). Notably, HIV-associated gynecomastia was present also in a 12-year-old child with congenital HIV disease (patient O). All patients did not suffer from a concurrent chronic hepatitis, liver cirrhosis, endocrine disorders, and kidney diseases, and those treated with drugs which potentially induce gynecomastia, including marijuana smoking [48]. The eventual fat redistribution syndrome was evaluated by clinical measurements (body weight, hip:waist ratio), appropriate patients questionnaires, impedanceometry, and dual energy X-ray absorptiometry (DEXA). A routine endocrinological workout included follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, testosterone, estradiol, and dehydroepiandrosterone assays.

PATIENTS AND METHODS

A cross-sectional survey of 1,007 HIV-infected patients treated with antiretrovirals for at least 12 months (669 males: 66.4%), was performed in mid-September 2003, in order to identify all subjects who developed true (ultrasonography-confirmed) gynecomastia (as defined by Braunstein in 1993 [48], and Qazi in 2000 [16]), and to evaluate possible risk factors, correlates of laboratory parameters and antiretroviral therapy, metabolic abnormalities, clinical evolution, and outcome. Patients with therapeutic adherence levels below 90% (as estimated by spontaneous patients declarations, specifically addressed questionnaires, and direct drug distribution and accountability carried out on monthly basis at our outpatient centre), were excluded from evaluation, as well as subjects with chronic hepatitis, liver cirrhosis, endocrine disorders, and kidney diseases, and those treated with drugs which potentially induce gynecomastia, including marijuana smoking [48].
phy was present in one patient who received only prolonged dual nucleoside analogue treatment (patient F) (Table 1). Moreover, abnormal serum triglyceride levels concurred in 11 cases, hypercholesterolemia in 6, and hyperglycemia in three patients: on the whole, only two patients out of 15 with gynecomastia did not suffer from any metabolic abnormality (patients B and P) (Table 1).

At the time of first appearance of gynecomastia, antiretroviral therapy has been taken from 23 to 142 months, and was initiated with isolated single or double nucleoside analogues in 12 out of 15 cases. The administration of protease inhibitor-containing antiretroviral regimens lasted for a mean period of 31.8±23.7 months (range 6-83 months) before the occurrence of gynecomastia, and interested only 10 patients out of 15 (66.7%): 8 subjects out of 10 received more than one protease inhibitor-based regimen, while the two remaining cases developed gynecomastia at their first protease inhibitor-containing association (lopinavir/ritonavir in patient B, and indinavir in patient C) (Table 1).

As a consequence, surprisingly even 5 episodes of gynecomastia of 15 (33.3%) occurred in patients who never received protease inhibitors. In particular, four of these last five episodes involved patients whose first HAART regimen included the non-nucleoside inhibitor efavirenz (patients A, H, M, and N), while the last case regarded a subject (patient F), who underwent very long-term (62-month) therapy with dual nucleoside analogues only (with lamivudine and 3TC).

Table 1 - Features of the 15 described patients suffering from HIV-associated gynecomastia

<table>
<thead>
<tr>
<th>Patients</th>
<th>Duration of seropositivity</th>
<th>Time from start of anti-HIV therapy</th>
<th>Time on protease inhibitors</th>
<th>HIV-RNA copies/mL</th>
<th>CD4+ lymphocyte count/µL</th>
<th>Dysmetabolism</th>
<th>Features and evolution of gynecomastia</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>37</td>
<td>23</td>
<td>-</td>
<td>2,500</td>
<td>493</td>
<td>T, C, G</td>
<td>Bilateral, stable</td>
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<tr>
<td>B</td>
<td>114</td>
<td>42</td>
<td>6</td>
<td>&lt;50</td>
<td>567</td>
<td>-</td>
<td>Monolateral, worsening</td>
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<tr>
<td>C</td>
<td>92</td>
<td>56</td>
<td>13</td>
<td>&lt;50</td>
<td>505</td>
<td>T, C</td>
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<td>D</td>
<td>107</td>
<td>67</td>
<td>27</td>
<td>&lt;50</td>
<td>611</td>
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<td>17</td>
<td>&lt;50</td>
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<td>F</td>
<td>183</td>
<td>142</td>
<td>-</td>
<td>4,200</td>
<td>524</td>
<td>T, C, G</td>
<td>Bilateral, stable</td>
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<td>G</td>
<td>41</td>
<td>29</td>
<td>29</td>
<td>&lt;50</td>
<td>434</td>
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<td>Monolateral, worsening</td>
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<td>17</td>
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<td>Bilateral, stable</td>
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<td>Bilateral, stable</td>
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<td>L</td>
<td>59</td>
<td>46</td>
<td>34</td>
<td>&lt;50</td>
<td>428</td>
<td>T</td>
<td>Bilateral, stable</td>
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<tr>
<td>M</td>
<td>124</td>
<td>101</td>
<td>-</td>
<td>&lt;50</td>
<td>505</td>
<td>T, C</td>
<td>Bilateral, stable</td>
</tr>
<tr>
<td>N</td>
<td>144</td>
<td>132</td>
<td>-</td>
<td>600</td>
<td>778</td>
<td>T, C, G</td>
<td>Monolateral, stable</td>
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<tr>
<td>O</td>
<td>131</td>
<td>121</td>
<td>83</td>
<td>&lt;50</td>
<td>432</td>
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<td>Bilateral, stable</td>
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<td>89</td>
<td>70</td>
<td>48</td>
<td>&lt;50</td>
<td>421</td>
<td>-</td>
<td>Monolateral, stable</td>
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<tr>
<td>Q</td>
<td>113</td>
<td>81</td>
<td>44</td>
<td>420</td>
<td>665</td>
<td>T</td>
<td>Bilateral, worsening</td>
</tr>
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1months; 2some form of the lipodystrophy syndrome was present in all the 15 patients; T=hypertriglyceridemia, C=hypercholesterolemia, G=hyperglycemia; 3as determined by a branched-DNA technique, with minimum detectable levels set at 50 HIV-RNA copies/mL; 4at the time of first diagnosis of gynecomastia.
and stavudine taken since 41 months, and gynecostasia developed 17 months after the introduction of this last regimen) (Table 1). On the whole, 13 out of the 15 patients who developed gynecostasia in our cohort (86.7%) were on stavudine at the time of diagnosis of this disturbance, with a treatment duration ranging from 11 to 44 months (mean 18.6±6.5 months). The remaining two patients took two nucleoside analogue other than stavudine, but experienced stavudine until 4-9 months before the occurrence of gynecostasia, for a 12-19-month period. No other nucleoside analogue has been used so extensively in our 15-patient group of HIV-infected patients who developed gynecostasia.

The evaluation of laboratory markers of HIV disease at the time of diagnosis of gynecostasia showed a complete viral suppression in 11 cases, and a residual viremia of 420 to 4,200 HIV-RNA copies/mL in the remaining four patients, while CD4+ lymphocyte count ranged from 421 to 778 cells/µL (Table 1). A prior or concurrent diagnosis of AIDS was excluded in all observed patients, but one (patient E, who experienced multiple opportunistic infections before detection of HIV infection and HAART introduction, but benefited of a successful immune recovery shortly after HAART administration). No significant correlation between the occurrence and development of gynecostasia and virological, immunological, and clinical markers of HIV disease progression was found. No significant endocrinological abnormalities were detected in the examined subjects, save an isolated, mild rise of serum FSH and LH levels, detected in patient E, with a prior AIDS diagnosis. In particular, serum prolactine levels tested normal in the entire patient series. The subsequent clinical follow-up (mean duration: 9.8±4.3 months, range 10-30 months), was characterized by a stable course of gynecostasia in 11 cases out of 15 (73.3%) even after modification of anti-HIV therapy, and a mild-to-moderate worsening and/or bilateral extension in four cases (patients B, C, G, and Q), who introduced efavirenz after interruption of the prior protease inhibitor-based regimen (Table 1). The 12-year-old child of our series (patient O), developed a bilateral painless gynecostasia after over 11 consecutive years of antiretroviral therapy, more than 7 years of protease-inhibitor containing HAART, with the last regimen containing stavudine, didanosine, and nelfinavir, taken since 31 months at the time of development of gynecostasia, a concurrent mild lipodystrophy syndrome, and a moderate increase of serum triglyceridemia (Table 1). All therapeutic changes carried out during the observation period of each patient were primarily due to lipodystrophy and/or dyslipidemia in four cases, and virological rebound in the remaining subjects. However, gynecostasia never proved so severe to discontinue HAART, and to require surgery. Paralleling the persisting course of gynecostasia, also alterations related to the lipodystrophy syndrome and the laboratory metabolic disturbances did not have a significant amelioration after modification of HAART, save a reduction of serum triglyceride and (at a lesser extent) serum cholesterol levels, prompted by a low-fat diet, increased physical exercise, and eventual concurrent administration of oral fibrates (as hypolipidemic drugs) (data not shown).

**DISCUSSION**

More than 50 cases of male gynecostasia have been described to date in correlation with HIV infection and antiretroviral therapy [7, 9-13, 16, 21, 42-47, 49-55], although some literature reports did not make a careful exclusion of all potential risk factors for gynecostasia of a different (especially pharmacological) origin [9, 10, 13, 21, 46, 54]. Most of reported episodes of HIV-associated gynecostasia referred a bilateral involvement [7, 10-13, 16, 21, 42-44, 46, 49-54], although predominantly monolateral episodes occurred, too [9, 13, 46, 54, 55]. The great majority of literature reports pointed out prior initiation of a protease inhibitor-based HAART (containing indinavir, ritonavir, nelfinavir, and lopinavir/ritonavir, as well as the less effective and usually well tolerated saquinavir, in its hard gel formulation) [12], while only three reports underlined a possible role of a prolonged nucleoside analogue use [7, 42, 43]. When evaluating carefully the composition of HAART regimens which eventually prompted the occurrence of gynecostasia, we notice that the nucleoside analogue stavudine was the most frequently used drug [7, 9-13, 16, 21, 42, 43, 46], as confirmed again in our series. In the first described case report apparently associated with stavudine use [42], gynecostasia occurred together with several sexual symptoms (increased libido, premature ejaculation, and persistent erection), and resolved just after
stavudine discontinuation [42]. Very recently, preliminary reports of efavirenz-associated gynecomastia emerged [49, 50], in absence of signs and symptoms of the lipodystrophy syndrome, so that novel pathogenetic mechanisms were postulated for this untoward effect, including the immune reconstitution syndrome [45]. In our experience, efavirenz introduction apparently prompted gynecomastia in four protease inhibitor-naïve patients, and in four more subjects who switched from a protease inhibitor-based regimen to efavirenz-containing associations. In fact, we underline the emerging of gynecomastia also in patients who never received, or abandoned protease inhibitors towards other HAART regimens, and we also focus on the first known case of pediatric gynecomastia (occurring in a 12-year-old perinatally-infected child), and point out the frequent persistence or appearance or worsening of gynecomastia under efavirenz treatment, both in HAART-naïve patients, and in those switching from protease inhibitors.

Compared with the frequency observed by Piroth et al. in 2001 [44] (0.8% of male patients treated with HAART, with increasing figures according to treatment duration), in our series a significantly greater crude frequency was observed (2.9%). In our series, as previously reported by other authors [9-11, 13, 47, 51], gynecomastia usually persists despite therapeutic changes, while the association with a syndrome of fat redistribution and/or increased serum lipid levels tested predominant, compared with literature data [9, 44, 46, 47, 49, 50]. This long-term disturbance without significant recovery during a quite prolonged follow-up (mean duration, 9.8±4.3 months), the fixed association with the lipodystrophy syndrome and the highly frequent concurrent metabolic abnormalities, may lead to suppose some common pathogenetic mechanisms. On the other hand, as already observed by other authors, no correlation was found between occurrence and features of gynecomastia, and baseline and subsequent virological and immunological markers of HIV disease progression, and HIV disease stage. The hormone profile tested normal in almost all evaluated patients, as previously noticed [9-13, 42, 47, 49, 50], so that the pathogenesis of this alteration remains unclear, with a large spectrum of postulated (but never demonstrated) hypotheses, including decreased estrogen metabolism, reduced testosterone synthesis, induced changes in the estrogen/androgen ratio, direct effect of drugs on the breast tissue, more subtle metabolic or endocrine abnormalities, or altered cytokine network (possibly characterized by increased IL-2 and reduced TNF-alpha and IL-10 production in female patients) [8, 10, 11, 13, 19, 42, 47, 49, 50], as well as the immune reconstitution syndrome [45]. On the other hand, an extensive study disclosed a 21.4% rate of hyperprolactinemia among 192 HIV-infected men, although this occurrence was not related to HAART, liver disease, metabolic disturbances, viral load, and gynecomastia, too [56]: in our 15 patients with gynecomastia, serum prolactin levels proved always normal.

Clinical and instrumental differential diagnosis of HIV-associated gynecomastia should rule out the so-called lipomastia (pseudogynecomastia), and rare malignancies [16, 53-55]. In a imaging study performed in 19 HIV-associated episodes, only one case was represented by lipomastia, and magnetic resonance imaging paralleled the outcome of sonographic studies [53]. In a series of 13 subjects followed in Boston (USA), three cases of breast lymphoma presented as an apparent gynecomastia [47, 54]. In a recently published report [55], a fine needle aspiration of breast masses showed the histopathological picture of this HIV-associated untoward disorder.

Although the great majority of literature studies focused on the relationship between occurrence of gynecomastia and therapy with protease inhibitors [7, 9-13, 44, 46, 47, 54], the elevated number of potential HAART combinations presently available, and the increasing reports of occurrence of gynecomastia even in patients who never received protease inhibitors, or abandoned these last anti-HIV compounds switching to other combinations, makes particularly intriguing the assessment of epidemiology, temporal evolution, and especially pathogenetic mechanisms which underlie the development of these untoward events in patients with HIV disease, even when multiple different antiretroviral combinations are of concern [3, 6, 14, 16-18, 21, 24, 28, 35-38, 41, 44, 46, 47, 49, 50, 55]. Gynecomastia, as well as the lipodystrophy syndrome and a broad spectrum of metabolic abnormalities, are long-term untoward events potentially related to antiretroviral therapy, possibly regardless of the extensive use of protease inhibitors. The eventual, pathogenetic pathways shared among gynecomastia, female breast hyperton-
phy [5, 7, 16, 19, 49, 50], lipodystrophy, and altered metabolism, deserve further investigation, especially after pointing out the occurrence or worsening of gynecomastia with protease inhibitor-sparing regimens, and the maintained metabolic or fat redistribution alterations, even after withdrawal of protease inhibitors, like in our experience. Switching from a protease inhibitor-based regimen to those containing efavirenz may not guarantee a significant benefit on gynecomastia, fat redistribution syndrome, and serum lipid abnormalities, since in our experience an appreciable number of patients (53.3% of cases), developed or experienced a worsening of these disturbances just after efavirenz initiation. As a result, the role of efavirenz in this field warrants particular and careful investigation, since just this drug is strongly recommended as a potent and safe alternative mainstream drug for patients abandoning a protease inhibitor-based HAART because of failure or toxicity [6, 15, 23-28, 30-34, 39], and differences with the other non-nucleoside analogue nevirapine are still under investigation [6, 29, 34, 35, 57, 58]. Pathogenetic mechanisms underlying lipodystrophy, dyslipidemia, and gynecomastia arising or persisting during treatment with non-nucleoside reverse transcriptase inhibitors are still largely unknown, especially for expected differences among the available non-nucleoside reverse transcriptase inhibitors (efavirenz, nevirapine, and delavirdine), which were repeatedly recommended as alternative agents for patients who developed lipodystrophy and/or metabolic abnormalities while on protease inhibitor-containing HAART [6, 15, 23, 27, 28, 30-35, 39].

From a therapeutic point of view, no intervention was carried out in our patients with gynecomastia, but a reductive mastoplasty proved effective in female breast enlargement [59]. Since gynecomastia is usually persisting, drug interventions other than HAART modification have been postulated [16, 46]: four patients successfully received percutaneous dihydrotestosterone gel [51], while in one case the anti-estrogen tamoxifen was administered [52]. To conclude, controlled, extensive studies are strongly warranted to evaluate both frequency and pathogenesis of gynecomastia and related untoward events under different therapeutic regimens, and to make available a reliable assessment of a still proportionally infrequent (but emerging) adverse effect of antiretroviral therapy, such as gynecomastia, which continues to pose relevant cosmetic drawbacks and psychological problems, with expected consequences on patients adherence levels to all proposed anti-HIV regimens. A careful monitoring and further investigation are strongly warranted in this field, to elucidate the etiopathogenesis of this phenomenon, its correlation with the single components of combination antiretroviral therapy, and to identify eventual preventive and/or therapeutic measures. Our experience underlines the possible occurrence of gynecomastia in absence of protease inhibitor administration, its prolonged duration and persistence despite changes in the underlying antiretroviral regimen (thus resembling some signs related to the lipodystrophy syndrome), the apparently constant association with prolonged nucleoside analogue administration (especially stavudine use), and the emerging correlation with the administration of the non-nucleoside reverse transcriptase inhibitor efavirenz. The first case of gynecomas- tia in a child with congenitally-acquired HIV disease is also reported.

Key words: Gynecomastia, lipodystrophy, HIV infection, highly active antiretroviral therapy (HAART).

To identify HIV-associated episodes of gynecomastia occurring during antiretroviral therapy in a cohort of around 1,000 patients, and to investigate potential correlations with demographic and epidemiological variables, clinical-laboratory markers of HIV disease, metabolic disturbances, and antiretroviral treatment, a cross-sectional survey of 1,007 patients treated for at least 12 months (669 males: 66.4%) identified all subjects with true (ultrasonography-confirmed) gynecomastia, after exclusion of all other predisposing conditions. Special attention was paid to eventual metabolic alterations, including lipodys-
Allo scopo di individuare i casi di ginecomastia in corso di infezione da HIV trattata con antiretrovirali in una coorte di circa 1.000 pazienti, ed esaminare le potenziali correlazioni con variabili demografiche, epidemiologiche, clinico-laboratoristiche della malattia da HIV, alterazioni metaboliche, e terapie anti-HIV, è stato condotto uno studio trasversale su 1.007 pazienti in terapia antiretrovirale da almeno 12 mesi (669 di sesso maschile: 66,4%), che ha individuato i soggetti affetti da una ginecomastia vera (confermata da indagine ultrasonografica), dopo aver escluso tutte le altre eventuali condizioni predisponenti. Particolare attenzione è stata posta alla concomitanza di alterazioni metaboliche, sindrome lipodistrofica, dislipidemia, iperglicemia, e ai farmaci antiretrovirali somministrati. Quindici pazienti su 516 evaluable male subjects (2.9%), developed gynecomastia when aged 12-58 years. In tutti i casi osservati concomitava lipodistrofia, mentre ipertrigliceridemia, ipercolesterolemia, and iperglicemia venivano rilevati rispettivamente in 11, 6, e 3 pazienti. La durata della sieropositività ed il tempo trascorso dall’inizio della terapia antiretrovirale risultavano estremamente variabili, e non si rilevava alcuna correlazione significativa anche con i markers di progressione dell’infezione da HIV. Tuttavia, 5 pazienti non erano mai stati trattati con inibitori delle proteasi, mentre combinazioni contenenti l’efavirenz erano apparentemente correlate a ginecomastia in 4 pazienti naïve per inibitori delle proteasi, e peggioravano il suo decorso in altri 4 casi che avevano sostituito gli inibitori delle proteasi con efavirenz. Un paziente sviluppava ginecomastia in corso di terapia con soli analoghi nucleosidici. In tutto il paziente gruppo, stavudine venne somministrato più frequentemente e per il periodo più lungo, e non si osservò un miglioramento della ginecomastia, nonostante eventuali modificazioni del regime antiretrovirale. Gynecomastia, as an emerging untoward event of treated HIV infection, deserves further investigation, from an epidemiological, clinical, and especially pathogenetic point of view. The frequent association with metabolic abnormalities suggests some common etiologic pathway with other HAART-related disorders.


[38] Walli RK., Michl GM., Bogner JR., Goebel FD. Improvement of HAART-associated insulin resistance and dyslipidemia after replacement of protease in-