

Immigration, HIV infection, and antiretroviral therapy in Italy. An epidemiological and clinical survey

Immigrazione, infezione da HIV, e terapia antiretrovirale in Italia. Uno studio epidemiologico e clinico

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INTRODUCTION

The ever-changing scenario of HIV infection (due to the significant variations of its natural history due to the introduction of highly active antiretroviral therapy or HAART), is broadened by other recently emerging issues, related to viral resistance, patients' adherence, and long-term unexpected toxicity [1-7]. In the meantime, also profound epidemiological modifications of HIV infection occur, because of recent migration streams which involved all Western Europe, and developed countries on the whole [8-12]. When focusing on Italy, immigration was characterized by the unexpected arrival of thousands of persons escaping from their countries of origin, fugitives, and political refugees, mostly coming from developing regions of the Mediterranean basin, Eastern Europe, Balkans, subsaharan Africa, former Soviet Union, and the far East. A particular vulnerability against HIV, as well as other infectious diseases, including sexually-transmitted infections (STIs) and tuberculosis, has been recognized as a prominent issue in these recently immigrated populations, since they come from highly endemic areas for HIV, and become at higher risk to acquire retroviral infection after they arrival in developed countries, because of the precarious socio-economic and hygienic situation, and the concurrent, significant psycho-social discomfort related to social alienation [13-17]. Immigrated female pop-

ulation appears at special risk of HIV and STIs, since it is borne by even greater difficulties in social and working possibilities, frequent resort to commercial sex, illicit drug use, an increased exposure to STIs (compared with drug or alcohol consumption), and a subsequent greater risk for mother-to-child transmission of multiple infectious diseases.

Notwithstanding this very alarming situation, anecdotal or no data are until now available to assess the specificity of HIV infection in immigrated female population, when excluding a few social-epidemiological surveys [18-23]. In a limited, recently published series, 250 Myanmar citizens immigrated to Thailand underwent serological screening for HIV infection, and their prevalence proved 4.1% among males, but only 1.2% among females [21]. A survey carried out in 7 STIs clinics in Los Angeles County, US, showed a HIV prevalence comparable between immigrated or native Americans (1.8% versus 1.6%), but a substudy disclosed a significantly greater frequency among women coming from subsaharan Africa [22]. Moreover, the local population of "immigrants" included individuals from Central America, and living in the US since over 12 years [22], so that this situation is remarkably different from that encountered in Europe and Italy during recent years, and probably involved subjects who acquired HIV infection after their arrival in the US.

Aim of our contribution is to evaluate the fre-

quency, and several demographic, epidemiological, clinical, and therapeutic features of HIV infection in women immigrated from countries outside of the European Union (EU), in a comparison which involves a matched population of consecutive male immigrants, all followed in the same time period (years 2001 and 2002), and in a single reference centre of Northern Italy.

■ PATIENTS AND METHODS

Among the 1,036 HIV-infected patients followed during the last two years (2001-2002) at our tertiary-care outpatient centre in Bologna, Italy, 82 (7.9%) came from extra-EU countries. We compared demographic, epidemiological, clinical, laboratory, and therapeutic features of 41 consecutive females, with those of 36 consecutive males followed and evaluated in the same way and in the same period (at least one year of follow-up, with at least quarterly laboratory controls), analyzing data by Student *t* test, Mantel-Haenszel chi-square test, and Fisher exact test (with significance levels fixed at $p < .05$) (Table 1). Five subjects of 82 (6.1%) were excluded from the present assessment, since they were followed for less than one year, and had adherence levels below 70% to therapeutic monitoring and drug assumption.

A triple-quadruple high-potency antiretroviral combination (HAART) including two nucleoside analogues, in association with one or two protease inhibitors, or a non-nucleoside reverse transcriptase inhibitor, was recommended to all patients. The evaluation of laboratory markers of HIV disease was performed at least every three months, through ultrasensitive virologic assays measuring up to 50 plasma HIV-RNA copies/mL, and immunological evaluation carried out by flow cytometry assays. The efficacy of HAART was assessed on the ground of updated interantional recommendations, while tolerability was monitored by monthly clinical controls, and at least quarterly laboratory workout, including hematology, basic biochemistry profile, liver and kidney function studies, plasma lipid levels, blood clotting tests, and urinalysis. The adherence to prescribed medicines was estimated by combining spontaneous patients' declarations, administration of specific, written questionnaires, and direct distribution and accountability of antiretroviral drugs, carried out every month at our dedicated outpatient ward.

■ RESULTS

When compared with the remaining 954 HIV-infected patients of our cohort, extra-EU immigrants showed a significantly increased rate of women ($p < .0001$), a higher frequency of heterosexual and perinatal transmission of HIV ($p < .0001$), and a shorter period of known seropositivity ($p < .0001$) (data not reported). While the two first features are part of the mode of HIV transmission in immigrants compared with Italian-EU citizens, the last recorded difference seems related to the shorter follow-up period since the detection of HIV disease.

When considering geographic origin, the majority of evaluable patients who came from extra-EU countries were from central, occidental, or oriental Africa (sub-Saharan Africa): 44 of 77 cases: 57.1%, followed by Northern Africa (Maghreb), with 19 patients (24.7%), Eastern Europe (7 cases), Latin America (4 patients), and Asia (three cases). However, even 26 different citizenships are represented in our 77-patient population, with a consequent broad spread of our series according to geographic origin: Eritrea (5 patients) proved the single nation with the greatest number of patients, followed by Nigeria and Zambia (4 cases each), and Morocco, Tunisia and Ethiopia (three patients each). On the whole, all extra-EU patients were infected with HIV-1, while no case of HIV-2 infection or co-infection was registered, although this last variant is endemic in several countries of origin of our immigrants.

When compared with male immigrants, female subjects were more numerous (41 *versus* 36), significantly younger ($p < .0001$), and were exposed to HIV through sexual contacts compared with drug use ($p < .02$). No difference can be observed according to country or continent of origin (data not reported), but women have their first positive HIV serology more often after their arrival in Italy ($p < .04$), since HIV infection has been more frequently acquired and/or disclosed upon arrival in our country. In particular, a negative HIV serology preceding immigration to Italy was available for five women and four males only, while HIV disease was already known before migration in 14 men *versus* 7 women ($p < .04$) (Table 1).

From a clinical point of view, the tendency to a shorter known history of HIV infection ($p < .05$ for females *versus* males), is perhaps responsible for a lower incidence of AIDS among women ($p < .02$) (Table 1).

Table 1 - Features of the 77 evaluable immigrants followed-up during the last two years (year 2001 and year 2002). Thirty-six consecutive males are compared with 41 women, on the basis of multiple epidemiological, laboratory, clinical, and therapeutic features.

<i>Patients' features</i>	<i>Males (n=36)</i>	<i>Females (n=41)</i>	<i>p value</i>
Mean patients' age (years \pm SD)	34.6 \pm 4.2	30.9 \pm 2.3	<.0001
No. patients coming from subsaharan Africa	21	23	N.S.
No. patients with sexual exposure / IVDU / vertical transmission	26 / 8 / 2	38 / 3 / 0	<.02
No. patients with a known negative serology before immigration	4	5	N.S.
No. patients with HIV infection known before immigration	14	7	<.04
Mean duration of known seropositivity (months \pm SD)	11.3 \pm 2.1	10.4 \pm 1.7	<.05
No. patients with a diagnosis of AIDS ^o	16	8	<.02
Mean duration of antiretroviral therapy (months \pm SD)	13.7 \pm 3.2	14.2 \pm 2.3	N.S.
Mean time to HAART introduction (months \pm SD)	6.1 \pm 0.4	5.9 \pm 0.6	N.S.
No. patients taking HAART since at least 12 months	26	32	N.S.
Mean Log10 plasma HIV-RNA levels (copies \pm DS)*	3.8 \pm 0.9	3.2 \pm 0.3	<.0001
No. patients with undetectable viremia (<50 copies/mL) ^o	19	29	N.S.
Mean CD4+ lymphocyte count (cells/ μ L \pm SD)*	312.4 \pm 122.2	379.2 \pm 118.4	<.02
Mean estimated adherence to HAART (%) ^o	81	95	<.0001
No. patients with therapy modified due to poor tolerability, toxicity, insufficient compliance, or personal decision ^o	14	11	N.S.

* at the last performed laboratory assay
^o during the entire follow-up period
 IVDU = i.v. drug user

The access to antiretroviral treatment, characterized by an initial time and mode absolutely comparable between female and male immigrants, the administration of drug associations of similar potency, and a statistically comparable follow-up period, makes its difference in the significantly greater compliance levels demonstrated by female immigrants compared with males ones ($p < .0001$) (Table 1). In absence of other significant differences, just this last variable could be responsible for a more elevated mean CD4+ lymphocyte count ($p < .02$), and lower mean plasma viremia ($p < .0001$), considering the last available laboratory parameters, although no difference was found when considering the rate of complete viral suppression throughout the study period (70.7% among women, *versus* 52.8% among men) (Table 1). Together with a better therapeutic adherence ($p < .0001$), female patients benefited from a significantly lower need of change of HAART reg-

imens due to poor tolerability, toxicity, or refusal (73.2% *versus* 61.1%) (Table 1): also this last variable may play favorably to ensure a better long-term HAART efficacy in females *versus* male immigrants.

A multivariate analysis of all the different demographic, epidemiological, clinical, laboratory, and therapeutic variables considered in the two study groups, did not disclose any significant association with countries or continents of origin (data not shown).

DISCUSSION

Migratory waves directed towards Italy represent a recent phenomenon in our social background, typical of the last decade. They bring to our attention either subjects coming from world regions which are endemic for HIV infection (where sexual contacts, perinatal transmission,

and internal migration play a primary role in disease spread) [18, 21], or individuals who are exposed to HIV only after coming to our country, because of their poor socio-economic and health care conditions [24]. Most of patients recently immigrated to EU are actually from regions highly endemic for HIV (i.e. subsaharan Africa) [8-12, 17], where presently the majority of cases of HIV/AIDS are concentrated, although still underdiagnosed and/or neglected, since local economic resources are insufficient to face therapeutic and prophylactic needs [15]. In these underdeveloped countries, the frequency of both heterosexual and vertical contagion led to the formation of an enormous reservoir of people infected during reproductive age, which allows an exponential spread of HIV pandemic, with expected catastrophic consequences on general population in the next future.

The immigration of persons coming from developing countries into industrialized regions is therefore responsible for a direct increase of imported diseases, and an even greater indirect increase of disorders due to poverty, socio-economic degradation, drug addiction, clandestine status, commercial sex, and consequent reduced measures of hygiene and health care assistance [10, 11, 13-16, 25]. The infectious disorder borne by the major epidemiological and social impact is perhaps represented by tuberculosis (whose frequency appears up to 7-fold increased in immigrants compared with local population) [8, 9, 12, 16, 26], but also STIs, infectious or parasitic skin disorders, and HIV infection itself [10, 11, 13, 14], are increasingly reported as illnesses directly or indirectly related to immigration from the developing world. When considering retroviral infection, a spread of HIV-1 serotypes other than B (considered not autochthonous in the EU), has been increasingly reported from a number of European countries, and seems to be linked to travel or immigration regarding subsaharan Africa, Caribbeans, and Latin America [27-30], together with an appreciable increase of HIV-2 infection or co-infection (never seen in our experience) [31].

According to the last available update, AIDS notifications in Italy at June 30 2002 were 50,271: 2,815 of them (5.6%) were represented by foreign citizens (including EU, Northern America, and other developed countries). Non-Italian citizens with AIDS came from Africa (2.4% of overall cases), followed by Southern America (1.6%), Western Europe (0.6%), East-

ern Europe and Asia (0.2% for each region), and North America (0.1%). Unfortunately, sub-analyses focusing on patient gender, and other epidemiological and clinical-therapeutic details, are lacking [32].

When considering the epidemiological trend of AIDS, developed countries significantly benefited of large-scale introduction of preventive measures [19, 33], and especially virologic and immunologic monitoring available since the introduction of combination antiretroviral therapy (HAART), demonstrated a cost-benefit ratio remarkably favorable [15, 34], notwithstanding the emerging of numerous long-term problems related to HAART itself [3-7], and increased expenses for treatment and monitoring of HIV infection for a long time [6, 34]. Unfortunately, at the present time neither retrospective nor prospective data are available regarding the epidemiology, clinical evolution, and treatment of HIV infection in patients immigrated to industrialized countries (including Italy).

In our experience, a rapid increase of absolute number and proportional incidence of extra-EU citizens was observed in our cohort of patients followed for HIV disease and related disorders. Since the year 2001, this rate is approaching a crude 8% rate, leading to remarkable differences with a survey performed in the same cohort in the year 1999 (when the cumulative rate was 2.7%; $p < .0001$) [24], and notably more elevated opposed to data coming from official AIDS notifications in Italy [32] (which are poorly comparable with local HIV prevalence figures). Although borne by limitations represented by the reduced sample size, our experience allowed us to compare a number of epidemiological, clinical, laboratory, and therapeutic features of HIV disease and its treatment, according to gender of immigrants regularly followed by us. Compared with male patients, female extra-EU immigrants are slightly more numerous, but have a comparable geographic origin (predominantly, central Africa). Women are younger, are exposed to HIV predominantly by heterosexual contacts, and check their positive serostatus when already in Italy (due to an infection acquired or disclosed in our country), sometimes when routine serological monitoring is carried out for pregnancy. Since only 21 of 77 overall patients (27.3%) were aware of their HIV infection before arrival in Italy, the majority of cases lack of elements to discriminate where and when HIV infection

was acquired (either in their country or origin, in other countries visited before reaching Italy, or after their arrival in Italy). In fact, only 9 patients (11.7%) had a negative HIV serology carried out before departure to Italy (Table 1). The continuing absence of infection or co-infection with HIV-2 [31], a frequent endemic virus in most African countries where many immigrants were born and lived, is surprising, especially since it is increasingly found in other EU countries also involved by similar immigration processes [30].

The diffuse psycho-social and economic constraints add risk for young immigrants, and especially women are poorly protected, and increasingly exposed to contract both STIs and HIV. Compared with the male extra-UE population of our cohort, women have a shorter follow-up of their HIV seropositivity, but show a lower frequency of evolution to AIDS. This situation (as well as the better virologic and immunological response of female patients), may be attributed to their different attitude towards antiretroviral therapy: in fact, although the time of start and overall duration of HAART seem comparable between our study groups, women have a significantly better adherence to prescribed medications, and a lower rate of interruption due to intolerance or refusal (Table 1). Our data confirm previous observations on the efficacy of HAART regardless the type of exposure to HIV infection, since the less favorable course of drug addicts compared with patients with sexually-acquired infection [34], may be caused by the different compliance with HAART [35]. When focusing on adherence, a multicentre Italian survey performed on 366 patients recently demonstrated that the major variable affecting compliance with recommended drug regimens is represented by drug addiction and related issues, in absence of significant differences as to gender, or type of sexual exposure [35]. In our experience, the significantly lower rate of drug abuse among immigrated women (7,3% *versus* 22.2% of males), may remarkably contribute to the greater adherence levels demonstrated by female patients, compared with matched male extra-EU immigrants, leading to a more positive therapeutic outcome.

A rapid identification and a timely treatment of HIV disease represent key points when facing recently immigrated patients, due to epidemiological reasons (nearly 8% of our over-1,000-patient single-centre cohort is represented by ex-

tra-EU immigrants), and the peculiar socio-economic and psychological-cultural features which accompany the immigration process, and the feeling of suffering from a chronic, transmissible, and potentially life-threatening infection, which requires a life-long drug therapy and unlimited periodic monitoring. Although immigrants are expected to have a clinical-laboratory course of HIV disease absolutely comparable with that of local native patients (also considering the virtual absence of HIV-2 in our population), the initial virologic response may be influenced by a shorter follow-up, counterbalanced by a more rapid tendency to treat, compared with Italian or EU citizens followed for a long time [24]. In fact, immigrated HIV-infected patients seem to show some epidemiological differences compared with Italian-EU ones, but they show a clinical and laboratory evolution, and a degree of acceptance, efficacy, and tolerability of antiretroviral therapy at least comparable, and sometimes more favorable, *versus* the same parameters monitorized in Italian-EU patients of the same cohort [24].

The most important metropolitan areas of Western Europe register a steady increase of immigration due to predominantly socio-economic or political reasons, so that it becomes more and more necessary to provide adequate strategies of health care and prevention [13, 14, 17-21, 23, 25, 26]. Among clinical and assistential programs to be implemented, a prompt screening and a timely treatment of HIV infection, and the resort to appropriate counseling and preventive measures, are strongly needed, especially when women are of concern, due to their increased exposure to sexual contagion, and potential mother-to-child transmission of infections. While some developed countries still maintain restricted access to both diagnostic and therapeutic measures when irregular immigrants are of concern [36], information and prevention campaigns focused on recently immigrated subjects at risk to acquire and transmit HIV infection and other STIs have been scheduled in all developed countries involved by heavy migration from extra-EU regions [10, 13, 23, 25, 33], in order to limit as far as possible risk behaviors, and to adequately control immigrants shortly after their arrival, through a well-defined health care program. A strict consideration of the specific cultural and social background of immigrants is the key point for successful educational and counseling pro-

grams. On the other hand, epidemiological and surveillance studies, and prospective therapeutic trials, are strongly warranted, in order to have a reliable assessment of this phenomenon in immigrated people, to check the efficacy of preventive measures, have validated data about the clinical, virologic, and immunological

evolution and outcome of HIV infection undergoing HAART, to measure drug adherence degrees, and to evaluate frequency, severity, and consequences of eventual untoward effects.

Keywords: Immigration, HIV, antiretroviral treatment, epidemiology

SUMMARY

Epidemiological, clinical, and therapeutic features of 77 consecutive HIV-infected non-European Union immigrants were compared according to gender. Immigrants (from Sub-Saharan Africa in around 60% of cases) represented 7.9% of our patient cohort at the end of 2002. Compared with male patients, females were more numerous, significantly younger ($p < .0001$), and experienced sexual exposure versus drug addiction ($p < .02$), while no difference was observed according to place of origin. A negative HIV serology preceding immigration was available for five women and four males only, while HIV disease was known before migration in 14 men versus 7 women ($p < .04$). The tendency towards a shorter known history of HIV infection ($p < .05$) of females versus males may be responsible for a lower incidence of AIDS among women ($p < .02$). The use of antiretroviral treatment was matched by time and se-

lected regimens, but compliance proved significantly greater in females versus males ($p < .0001$), and women had less need of a regimen switch due to poor tolerability or refusal (73.2% versus 61.1%); the latter could be responsible for a greater mean CD4+ count ($p < .02$), and lower mean plasma viremia ($p < .0001$), although no difference was found when considering viral suppression rate (70.7% among women, 52.8% among men). Surveillance studies and prospective therapeutic trials are strongly warranted, in order to have a reliable assessment of HIV-infected immigrated people, to check the efficacy of preventive measures, obtain validated data about the clinical, virologic, and immunological evolution and outcome of HIV infection undergoing HAART, and to evaluate the frequency and role of eventual untoward effects of pharmacologic treatment.

RIASSUNTO

Abbiamo esaminato le caratteristiche epidemiologiche, cliniche e terapeutiche di 77 pazienti consecutivi HIV-positivi immigrati in Italia da Paesi esterni all'Unione Europea, in base al sesso. I soggetti immigrati (provenienti dall'Africa subsahariana nel 60% dei casi circa), rappresentavano il 7,9% di tutti i pazienti da noi seguiti al termine dell'anno 2002. Confrontate con i soggetti di sesso maschile, le donne erano più numerose, significativamente più giovani ($p < .0001$), ed erano state contagiate prevalentemente attraverso esposizione sessuale piuttosto che tramite l'uso di droghe e.v. ($p < .02$), mentre non si rilevavano differenze riguardo i diversi Paesi di origine. Una sierologia per HIV risultata negativa in epoca antecedente l'immigrazione era disponibile per sole cinque donne e quattro uomini, mentre l'infezione da HIV era già nota prima del processo migratorio in 14 uomini, versus 7 donne ($p < .04$). La tendenza

a presentare un'anamnesi di sieropositività per HIV più breve ($p < .05$ relativo alle donne rispetto agli uomini), può essere responsabile di un'incidenza di AIDS più ridotta nel sesso femminile ($p < .02$). L'impiego di terapia antiretrovirale era comparabile tra i due sessi sulla base sia dell'epoca e delle modalità di inizio, sia della successiva conduzione, sia dei regimi e delle associazioni somministrate, ma la compliance risultava significativamente più elevata nel sesso femminile rispetto a quello maschile ($p < .0001$), e tra le donne si evidenziava una minore necessità di operare modificazioni del regime terapeutico, dettate da scarsa tollerabilità o da rifiuto del paziente (73,2% versus 61,1%). Queste condizioni erano con tutta probabilità alla base del rilievo di una conta media più elevata di linfociti CD4+ ($p < .02$), e di livelli medi di viremia più ridotti ($p < .0001$) nelle pazienti di sesso femminile, anche se non si osserva-

vano differenze significative riguardo l'indice di soppressione virale ottenuto (70,7% tra le donne, 52,8% tra gli uomini). Sulla base delle nostre osservazioni preliminari, si rendono necessari studi di sorveglianza e trial terapeutici prospettici, in grado di fornire una completa disamina del fenomeno infezione da HIV-immigrazione, di control-

lare l'efficacia delle misure di profilassi in questo specifico target di popolazione a rischio, e di disporre di dati validati relativi all'evoluzione clinica, virologica, e immunologica, e all'esito dell'infezione da HIV trattata con HAART, nonché di valutare frequenza e ruolo degli eventuali eventi avversi della terapia farmacologica.

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