

HIV+ patients and gender differences: evidence from an Italian cohort

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Summary. Introduction. Since gender differences vary across a geographical setting and are poorly reported in the extant literature, the present study aimed to investigate the presence of differences between HIV+ infected men and women, in terms of *i*) achievement of immunological/virological response, *ii*) adherence to medication, *iii*) health-related quality of life, and *iv*) absorption of resources for their management, within an HIV+ cohort of patients in Lombardy Region (Northern Italy), during a 12-month observation. **Methods.** Consecutive cases of HIV+ outpatients were enrolled in a prospective study, involving Sacco Hospital (Milan), and their demographic and clinical data were collected. Clinicians also administered to a subgroup of patients the EQ-5D questionnaire, useful to investigate the perceived quality of life. **Results.** 1,117 patients were enrolled in the study. The two populations were comparable in terms of actual CD4 and viral load, thus showing a good immunological and virological condition ($p > 0.05$). Significant differences emerged with respect to adherence to medication and quality of life measures within the subgroup of patients ($n = 302$): while women paid more attention to the administration of ART (94% vs 87% were fully adherent, $p = 0.020$), they conversely reported a worse quality of life (0.86 ± 0.025 vs 0.89 ± 0.013 , $p = 0.016$). From an economic point of view, since men patients absorbed more resources than women (€ 10,281.96 vs € 10,025.71, $p < 0.05$ for treated patients; € 1,791.95 versus € 1,359.15, $p < 0.05$ for naïve patients), male gender could be considered a determinant of higher cost for the management of HIV disease. **Discussion.** The study provides healthcare professionals with evidence-based information, useful for the identification and the personalization of the most effective and efficient clinical pathway, based on gender, in order to enhance the overall health of an HIV+ patient.

Key words: Italian patients, gender differences, resource absorption, quality of life, HIV+.

Pazienti HIV+ e differenze di genere: evidenze da una coorte italiana

Riassunto. Introduzione. Le differenze di genere possono significativamente differire in base al contesto geografico di riferimento, sia esso nazionale o internazionale, e sono raramente analizzate all'interno di evidenze empiriche e letterarie. Lo studio che qui si intende presentare si è proposto di approfondire tale complessa tematica, all'interno del percorso dell'infezione da HIV. Obiettivo principale dello studio

è investigare l'esistenza di differenze di genere in una coorte di pazienti HIV+ della Regione Lombardia, valutando tali differenze in termini di: *i*) raggiungimento di controllo immunologico e virologico, *ii*) aderenza al trattamento, *iii*) qualità di vita misurata in termini di QALY e *iv*) assorbimento di risorse correlate alla gestione quotidiana dei pazienti, all'interno di tutto il percorso diagnostico, terapeutico e assistenziale degli stessi, con un orizzonte temporale di 12 mesi. **Materiali e metodi.** Consecutive case di pazienti ambulatoriali, in carico da almeno 6 mesi e con diagnosi di HIV, sono stati arruolati all'interno di uno studio prospettico svolto presso l'Azienda Socio Sanitaria Territoriale Fatebenefratelli Sacco di Milano. Dati di natura demografica, clinica ed economica sono stati raccolti per il raggiungimento dell'obiettivo precedentemente descritto. I clinici di riferimento hanno inoltre somministrato a un sottogruppo di pazienti il questionario EQ-5D, al fine di reperire informazioni rilevanti sulla qualità di vita percepita dagli individui HIV+. **Risultati.** Nello studio sono stati arruolati 1.117 pazienti. Le due popolazioni, maschile e femminile, sono risultate essere comparabili per quanto concerne i risultati di efficacia: entrambe, infatti, mostrano una buona condizione immunologica e virologica. Dalla comparazione dei due gruppi non emergono differenze statisticamente significative ($p > 0,05$). I due sottogruppi di analisi, invece, risultano ottenere performance diverse per quanto concerne l'aderenza e la qualità di vita: nonostante le donne siano maggiormente attente al tema della compliance, con una performance migliore (94% vs 87%, $p = 0,020$), al contrario dichiarano una peggiore qualità di vita ($0,86 \pm 0,025$ vs $0,89 \pm 0,013$, $p = 0,016$). Sia nella popolazione trattata sia nella popolazione naïve si rileva come il sesso maschile sia una determinante di un maggiore assorbimento di risorse (€ 10.281,96 vs € 10.025,71, $p < 0,05$ per i pazienti trattati; € 1.791,95 vs € 1.359,15 per i pazienti naïve al trattamento $p < 0,05$). **Discussione.** Lo studio fornisce ai decision-maker e ai professionisti sanitari delle evidenze utili per l'identificazione e la personalizzazione dei percorsi diagnostici terapeutici e assistenziali maggiormente efficaci ed efficienti, rispetto al genere dei pazienti oggetto di analisi, al fine di ottimizzare le condizioni sociali e di salute dei pazienti affetti da HIV.

Parole chiave: pazienti italiani, differenze di genere, assorbimento di risorse, qualità di vita, HIV+.

Introduction and objectives of the study

The discovery of Highly Active Anti-retroviral Therapies (ARTs) and their introduction into clinical practice has transformed HIV from a fatal condition to a chronic disease, decreasing morbidity and mortality rate as well as increasing the life expectancy of HIV infected patients.

At the end of the year 2014, there were 36.9 million people living with HIV, with an equal proportion of men and women infected, with a global HIV prevalence of 0.8%¹. From an epidemiological point of view, it is important to note that the number of women diagnosed with HIV infection and AIDS has increased over the course of the epidemic, worldwide.

International literature worldwide regarding HIV gender differences could not be replicable within the specific Italian setting, because they referred to 10 years ago²⁻³, without considering the change in the epidemiological landscape. Hence, Italian evidence^{2; 5-7} declares that the proportion of female HIV+ patients has changed from 28,5 % in 1985 to 20,4% of new diagnoses in 2014.

Some authors⁴⁻⁷ reported relevant differences between HIV infected women compared with men, with regard to disease progression and the achievement of good virological and immunological status, due to biological factors such as frequent gynaecological morbidities and/or pregnancy⁸⁻⁹ as well as a higher risk of developing pre-treatment anaemia¹⁰. HIV+ women seemed to experience a progression to AIDS faster than men, because of socio-economic barriers such as family commitments, lack of support and socio-economic circumstances¹¹, self-motivation decreased, with an impact on wellbeing and treatment compliance. In this view, an association between female gender and reduced rate of adherence to ART has been reported in literature¹². This may negatively impact on the patients' reported outcomes and quality of life, thus requiring an in-depth analysis of the topic, since adult women are more likely to suffer from mental illnesses that include depression¹³.

The onset of the aforementioned gender differences occurring within the HIV+ population could also have an economic impact, reflecting on differential annual direct health costs (drugs, diagnostic exams, hospitalisations), for the clinical management of the chronic pathology. Considering the specific Italian setting, evidence concerning the costs supported by the NHS for the treatment of HIV+ individuals was growing¹⁴⁻¹⁵ while still little is known about the potential differences between women and men. Filling this knowledge gap could be relevant both from a policy-making and from a pharmaco-economic point of view, allowing an efficient and effective resources allocation and improving patients' satisfaction and reported outcomes.

Based on these arguments and since gender differences vary across geographical settings and are poorly

reported in the extant literature, the present study aimed to investigate the existence of statistically significant differences, between HIV+ infected men and women, in terms of *i*) achievement of immunological/virological response, as well as other relevant information concerning the HIV disease (HIV and/or treatment duration); *ii*) adherence to medication; *iii*) health-related quality of life and *iv*) absorption of resources for their management, within an HIV+ cohort of patients in Lombardy Region (Northern Italy).

Description of materials and methods

Study design

A prospective study, involving the Sacco Hospital (Milan), was developed within the January 2013-December 2014 period.

Consecutive cases of HIV+ patients meeting the inclusion criteria (≥ 18 years old who has had regular clinical follow-up over time for at least 6 months, both non-treated and experienced patients) were enrolled in the study, after signing a consent form, during the follow-up medical examination.

A specific case report form was completed by the clinicians of reference, for the collection of HIV+ patients' demographic and clinical data in order to investigate the differences between male and female patients.

Questions regarding adherence to antiretroviral treatment and the EQ-5D-3L questionnaire¹⁶⁻¹⁷ were administered to a subgroup of HIV+ individuals, in order to rate the patient's health information and to collect data on quality of life. Mobility information, self-care, usual daily activities, pain, discomfort, anxiety and depression were investigated. In addition, a visual analogic scale (VAS scale)¹⁸ was applied to examine the patients' overall reported perception.

In summary, the economic impact of any HIV+ male or female patient was determined utilising the following public healthcare cost components: *i*) laboratory tests; *ii*) diagnostic procedures; *iii*) outpatients exams; *iv*) hospital admissions; *v*) antiretroviral therapy (ART), and *vi*) other drugs.

The economic analysis was performed considering the 2014 Lombardy Region's outpatient and hospital admission tariffs. Drug costs derived from the officially published NHS price list.

Descriptive statistics, frequencies and distributions were applied to the data collected. In addition, inferential analyses were conducted, using the dependent variable ("gender") as "grouping variable". The Chi-square and Kruskal-Wallis tests were used to assess differences between males and females with reference to categorical and continuous variables, respectively. In this view, statistically significant differences between the two groups

of patients were investigated: the results were considered statistically significant with a level of $p < 0.05$.

Preliminary analyses were performed to ensure no violation of the assumptions of normality, linearity and homoscedasticity.

All the statistical analyses were conducted using the IBM SPSS Statistics Viewer (Version 23).

The investigated variables

Differences between groups (males *vs* females) were investigated considering the following independent variables:

- patients' personal data (such as mean age, education and risk factor for HIV);
- drug and alcohol abuse;
- anti-depressant and anxiety drugs consumption;
- sight impairment;
- Nadir CD4 cell count and current CD4 cell count, divided into: $CD4 \leq 200$ cells/mm³; $CD4 \leq 350$ cells/mm³; $CD4 \leq 500$ cells/mm³ and $CD4 \geq 501$ cells/mm³;
- viral load (VL), measured as detectable or undetectable HIV-RNA, considering a cut-off equal to 37 copies/ml;
- presence or absence, and number of comorbidities, considering the number declared by the doctor who is currently treating him;
- duration of HIV disease, considering the number of years from the HIV diagnosis;
- duration of HIV treatment, considering the number of years from the first administration of antiretroviral therapy;
- number of changes of ARTs from the first administration of antiretroviral therapy;
- adherence to HIV medication, in terms of taking at least 95% of prescribed pills over the last month;
- quality of life measures, according to both the EQ-5D-3L questionnaire and the VAS Scale.

Results

The sample population

1,117 HIV+ patients of the Sacco Hospital were enrolled into the study.

The population sample was predominately composed of males (75.65%), being on average 47.28 ± 0.31 years old.

Most of the population under investigation had a primary or secondary school diploma (34.1% and 39.1% respectively) and 18.6% of the whole population had a Master's degree.

The most frequent risk factors for HIV were represented by heterosexual contacts, drug injection abuse

Table 1. Study population characteristics.

| | |
|--|-------------------|
| Male gender [%] | 75.65 |
| Age [mean \pm SE] | 47.28 ± 0.31 |
| Heterosexual [%] | 42.1 |
| Primary school education [%] | 34.1 |
| Number of comorbidities [mean \pm SE] | 1.52 ± 0.029 |
| Number of changes of HIV treatment [mean \pm SE] | 3.72 ± 0.107 |
| Duration of HIV disease [mean \pm SE] | 12.78 ± 0.249 |
| Duration of HIV treatment [mean \pm SE] | 11.38 ± 0.255 |
| Treated patients [%] | 92.75 |

and men having sex with men, MSM (respectively affecting 42.1% and 19.8% of the overall population, the last one affecting 46.3%, of the male population only).

92.75% of the sample population consisted of treated patients (n. 1,036 subjects under treatment). Of these, 63.3% presented a good immunological status, considering CD4 cell count higher than 350 cells/mm³, and 87.5% were virologically suppressed with VL lower than 37 copies/ml.

Detailed information related to the sample population is reported in Table 1.

A random sub-group of HIV+ enrolled patients, composed of 302 male and female treated subjects, comparable to the main sample in terms of health status and individual characteristics, responded to the EQ-5D and to the treatment adherence evaluation questionnaires. 88.5% of the sub-sample population were adherent to HIV medication, thus demonstrating good compliance of the sub-sample (95% of the pills taken over the previous month). Patients declared a good perceived quality of life (0.888 ± 0.012), confirmed by a VAS score of 0.838 ± 0.011 .

Differences between groups

Grouping subjects according to the gender, Table 2 reports the existence of significant statistically differences between groups.

On average, men presented a higher level of education compared to women: in particular 20.9% (*vs* 11.2%) had a Master's degree ($p = 0.000$), consistent with recent scientific evidence available¹⁹.

Men are more prone to drug abuse ($p = 0.000$), cigarette smoking ($p = 0.003$) and alcohol abuse ($p = 0.000$); women, instead, are more frequently anti-depressant ($p < 0.05$) and anxiety drug consumers.

Table 2. Differences between groups.

| | Male n = 845 | Female n = 272 | p-value |
|--|-----------------|-------------------|-----------------|
| Demographic information | | | |
| Age [mean ± SE] | 47.44 ± 0.37 | 46.79 ± 0.57 | Not significant |
| Presence of AIDS [%] | 23.1 | 25.4 | Not significant |
| Duration of HIV disease [mean ± SE] | 11.81 ± 0.28 | 15.78 ± 0.49 | 0.000 |
| Duration of HIV treatment [mean ± SE] | 10.46 ± 0.29 | 14.24 ± 0.51 | 0.000 |
| Treated patients [%] | 92.0 | 95.2 | Not significant |
| Clinical and outcome information | | | |
| Nadir CD4 <200 [%] | 51.2 | 55.9 | Not significant |
| CD 4 >500 [%] | 63.3 | 63.6 | Not significant |
| Undetectable VL [%] | 87.5 | 87.5 | Not significant |
| Presence of comorbidities [%] | 68.9 | 50.0 | 0.000 |
| Number of comorbidities [mean ± SE] | 1.55 ± 0.034 | 1.40 ± 0.051 | 0.028 |
| Number of changes of HIV treatment [mean ± SE] | 3.47 ± 0.12 | 4.23 | 0.000 |
| Behaviours | | | |
| Years of school [mean ± SE] | 11.52 ± 0.13 | 10.81 ± 0.21 | 0.007 |
| High school diploma [%] | 38.8 | 42 | 0.004 |
| Master degree [%] | 20.9 | 11.2 | 0.004 |
| Drugs abuse [%] | 14.3 | 6.3 | 0.000 |
| Alcohol use [%] | 16.0 | 5.5 | 0.000 |
| Smoking [%] | 46.7 | 36.4 | 0.003 |
| Anti-depressants consumption [%] | 7.7 | 11.8 | 0.038 |
| Anxiety drugs consumption [%] | 17.5 | 19.1 | Not significant |
| Sight impairment [%] | 52.7 | 51.5 | Not significant |
| | Male n = 228 | Female n = 74 | p-value |
| Adherence and Quality of life measures | | | |
| Adherent patient [%] | 87.2 | 93.9 | 0.020 |
| EQ-5D value [mean ± SE] | 0.89 ± 0.013 | 0.86 ± 0.025 | 0.016 |
| VAS scale [mean ± SE] | 0.83 ± 0.012 | 0.85 ± 0.023 | Not significant |

Male and female cohorts were comparable in terms of actual CD4 and viral load, thus reporting a good immunological status and a good virological control (Figure 1).

Antiretroviral treatments are comparable in treatment frequency between men and women (92% vs 95%, $p < 0.05$), thus demonstrating gender equality in the access to care, confirmed by the number of treatment changes (every 3.21 years for female patients versus 3.01 years for male patients).

Focusing the attention on the patients' reported measures of quality of life, the EQ-5D questionnaire and the VAS scale overlapped in the measurement. However, the QoL value, analysed with the support of EQ-5D, reported that women declared a lower QoL than men (0.86 ± 0.025 versus 0.89 ± 0.013 , $p = 0.016$). In particular, HIV+ women reported problems in performing daily activities and experienced frequent depression and anxiety events.

From an economic point of view, on average, the cost of an HIV+ patient was equal to € 10,104.02 ± 292.06, assuming the Lombardy Region Health Service perspective: non-treated and treated patients show high difference in costs ($2,008.60 \pm 356.40$ versus $10,730.65 \pm 294.67$), even without considering ART costs.

Detailed information regarding the economic evaluation of HIV+ male and female, stratified by clinical history, is shown in Table 3.

Remarks and analytical discussion of the results

The results of the study reported that the two populations were super-imposable with regard to age; significant differences emerged considering risk factors, drugs abuse, duration of HIV disease and ART treatment. While HIV+ males and females were similar in the development of the most severe stages of HIV (AIDS), they significantly differ statistically if the number of comorbidities is taken

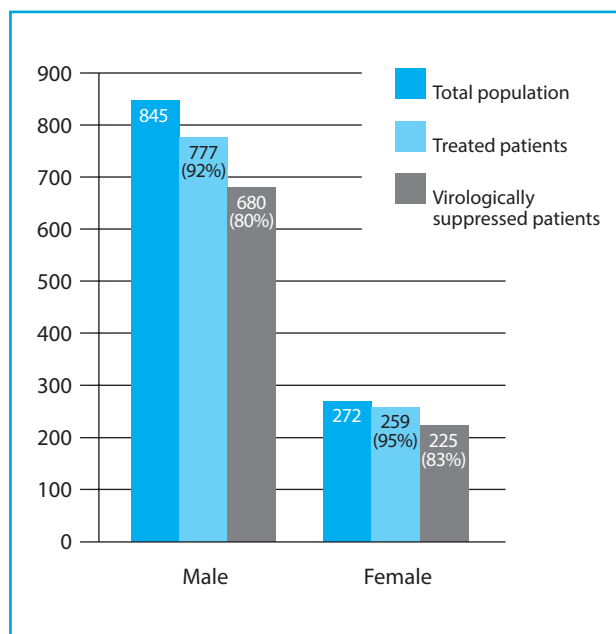


Figure 1. Male and female HIV+ population cascade, reporting total number, treated, and virologically suppressed patients.

into account: men presented a higher number of concomitant complications that have a relevant impact also on the overall cost of patient management.

On the other hand, women have suffered from HIV for a longer time, if compared with men, determining higher changes in HIV treatment regimen. In this study, women paid particular attention to adherence to medication, contrary to what is reported in literature evidence¹².

Despite a better performance of women in terms of adherence, they reported a quality of life that should be improved, thus highlighting the complexity of physical, psychological, and social factors as determinants of health-related quality of life in HIV+ female indi-

Table 3. Evaluation of treated and naïve patients, comparing male and female results.

| Mean value 2013-2014 | ART | Laboratory test, diagnostic and surgical procedures | Hospitalisation and day hospital | Other drugs consumed at home | Social and healthcare support | Total | p-value | |
|----------------------|--------|---|----------------------------------|------------------------------|-------------------------------|----------|-------------|-------|
| Treated patient | Male | € 7,501.17 | € 1,392.17 | € 942.79 | € 304.83 | € 140.99 | € 10,281.96 | <0.05 |
| | Female | € 7,464.73 | € 1,382.11 | € 883.24 | € 249.72 | € 45.91 | € 10,025.71 | |
| | % | - 0.49% | - 0.72% | - 6.32% | - 18.08% | - 67.44% | - 2.49% | |
| Non-treated patient | Male | - | € 1,437.03 | € 276.36 | € 74.76 | € 3.81 | € 1,791.95 | <0.05 |
| | Female | - | € 935.42 | € 30.61 | € 75.23 | € 3.41 | € 1,359.15 | |
| | % | - | -34.91% | -88.92% | 0.64% | -10.47% | -24.15% | |

viduals: in fact, women struggle with several social problems and cultural beliefs that may affect their perceived quality of life from a mental and social health point of view as well as cause several problems in performing usual activities²⁰. This consideration suggests that women need additional social support that has been shown to have a strong potential to influence HIV+ patients' quality of life²¹.

Focusing on the population's clinical condition, the results reported that most patients presented a good virological and immunological condition, thus demonstrating that this aspect is totally independent from the patient's gender. HIV infected patients achieve an undetectable viral load due to the good choices implemented by the clinicians following them along the clinical pathway.

In this perspective, the Regional Health Service has an excellent capability to generate good health outcomes, within the chronic setting of HIV infection. The HIV+ Italian clinical pathway can be considered as very different from other developed or developing countries (for example in the USA, ART regimens are prescribed by the general practitioner). In the Italian national setting, Hospitals specialised in infectious diseases provide HIV+ patients with a complete care and treatment that not only considers the aspects purely related to HIV disease, but also offers social and psychological aspects and deals with the management of several comorbidities.

All these considerations may be consistent with the economic data. The management cost of an HIV+ male patient was higher if compared with a female patient, presenting a statistically significant difference. Since men developed more comorbidities, the related clinical pathway should require more economic resources in terms of specialist visits, laboratory exams or additional diagnostic procedures, thus resulting in a higher absorption of resources.

The economic information here presented should be considered as an indicator of the different economic resource absorption of HIV+ men and women, thus requiring an optimization of the process of taking in charge, as well as the creation of social support activities that could improve, over the years, both the Healthcare Service's efficiency and the HIV+ patients' perceived quality of life.

Conclusions

In conclusion, the results suggested evidence of HIV+ patients gender differences. In particular, differences were reported in drug abuse, perception of depression and anxiety, and in relation to the need for social support. No differences emerged concerning effectiveness measures, such as viral load suppression. This is consis-

tent with previous literature, which suggests that men and women differ in their access to healthcare services, risk factors for HIV infection, and their use of social support networks to engage HIV+ subjects in health behaviours (this consideration could be related to the different impact of the MSM population in the male group).

The results could also be verified by analysing evidence derived from the economic resource absorption evaluation: on the one hand, males could need specific clinical pathways related to comorbidities and healthcare education in the field of adherence; on the other, females could be supported in their approach to the disease and to daily living activities. In this view, an analysis of quality of life in women with HIV could help healthcare professionals to identify social services, also including additional interventions to promote quality of life.

The Italian regional healthcare services could, therefore, consider the evidence provided by the present study as an opportunity to differentiate the two groups of patients, crystallising gender differences and offering a personalised clinical pathway, thus becoming more efficient and effective.

Key messages

- The gender of HIV+ patients is an important variable to analyse in order to personalise the clinical pathway of patients.
- Male gender could be considered a determinant of higher resource absorption and complexity of cases (higher number of comorbidities in comparison with women).
- Female gender is related to better adherence to treatment and lower perceived quality of life.
- The personalisation of the taking in charge process and the creation of social support activities could improve, over the years, both the Healthcare Service's efficiency and the HIV+ patients' perceived quality of life.
- Male individuals need specific clinical pathways related to comorbidities and healthcare education in the field of adherence; female patients need to be supported in the HIV disease acceptance process and in daily living activities.

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