RESEARCH ARTICLE

Elderly HIV-positive women: A gender-based analysis from the Multicenter Italian “GEPO” Cohort

Emanuele Focà,1*, Paola Magro1*, Giovanni Guaraldi2, Agostino Riva3, Anna Maria Cattelan4, Giuseppe Vittorio De Socio5, Cecilia Costa6, Stefania Piconi7, Benedetto Maurizio Celesia8, Silvia Nozza9, Giancarlo Orofino10, Antonella Castagna9, Giovanni Di Perri9, Francesco Castelli1, Andrea Calcagno6, on behalf of the GEPO (GEriatric Patients living with HIV/AIDS: a Prospective Multidimensional cOhort) Study Group

1 Division of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy, 2 Infectious Diseases Clinic, Department of Mother, Child and Adult Medicine and Surgical Science, University of Modena and Reggio Emilia, Modena, Italy, 3 Third Division of Infectious Diseases, University of Milan, Ospedale L. Sacco, Milano, Italy, 4 Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera-Universitaria di Padova, Padova, Italy, 5 Department of Infectious Diseases, Azienda Ospedaliero-Universitaria di Perugia, Perugia, Italy, 6 Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Turin, Italy, 7 First Division of Infectious Diseases Unit, University of Milan, Ospedale L. Sacco, Milano, Italy, 8 Division of Infectious Diseases, University of Catania, ARNAS Garibaldi, Catania, Italy, 9 Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy, 10 Unit of Infectious Diseases, Division A, Ospedale Amedeo di Savoia, Turin, Italy

* These authors contributed equally to this work.
¶ Membership is listed in the Acknowledgments
* emanuele.foca@unibs.it

Abstract

Background
HIV-positive patients are facing age-and disease-related comorbidities. Since gender differences in viro-immunological, clinical and therapeutic features have been described, aim of this analysis was to explore such differences in elderly HIV-positive females compared to males coming from the same cohort.

Design
Cross-sectional study.

Setting
Ten Infectious Diseases Center participating to a new multicenter Italian geriatric Cohort aiming at describing health transition over time in HIV-positive individuals.

Participants
HIV-positive patients aged ≥65 years old.

Measurements
We recorded clinical, viro-immunological and therapeutical data.
Results
We included 210 women (17%) out of 1237 patients. Compared to males, elderly females were less likely to present a HIV-RNA <50 copies/mL (74.3% vs. 81.8%, OR 0.64, 95%CI 0.44–0.93); they showed higher CD4+/CD8+ ratio (p = 0.016). Combined antiretroviral therapy (cART) strategies were similar between genders (p > 0.05), although women were less likely to be treated with protease Inhibitors (PIs) (p = 0.05); specifically, in triple-drug regimens females received less PIs (28% vs 38% p = 0.022) and more integrase inhibitors (30% vs. 20% p = 0.012). Bone disease was more common in females (p < 0.001) while males presented more frequently cardiovascular disease (CVD) (p < 0.001). In females with bone disease, PIs and boosted regimens (38% vs. 53.7% p = 0.026 and 30.4 vs 44.0% p = 0.048 respectively) were prescribed less frequently. Polypharmacy was common and similar in both genders (20% vs. 22.8%, p = 0.05). A higher use of lipid-lowering drugs (20.5% vs. 14.8%, p = 0.04) was observed in females and yet they were less likely to receive anti-thrombotic agents (18.6% vs. 26.3%, p = 0.019) even when CVD was recorded (57.1% vs. 83.1%, p = 0.018). In multivariate analysis, we found that female gender was independently associated with a higher CD4+/CD8+ ratio but not with virological suppression.

Conclusions
Elderly HIV-positive women display a worse virologic response despite a better immune reconstitution compared to males. The burden of comorbidities as well as the medications received (including cART) may slightly differ according to gender. Our data suggest that more efforts and focused interventions are needed in this population.

Introduction
HIV epidemic has been changing dramatically in the last decades and nowadays a growing number of people living with HIV are aged 50 years and over. According to the last estimates, this number reaches 3.6 million people worldwide [1]. In fact, thanks to combined antiretroviral therapy (cART), HIV-positive patients experienced a reduction of mortality and a consequent increase in life expectancy, which nowadays is similar to that of the general population [2]. Moreover, due to low perception of the risk of HIV acquisition and lower awareness of HIV disease, more people are contracting HIV in their middle and older ages [3]. Sexually active post-menopausal women may be less likely to use condom as long as they are not worried about becoming pregnant [4]. Moreover, the physiological thinning and increased dryness of the vaginal mucosa after menopause may expose elderly women to a higher risk of HIV transmission [5]. Smit et al estimated that by 2030, 73% of HIV infected patients will be aged 50 years or more. Therefore, these patients will be facing HIV-related together with age-related comorbidities [6–8], as well as the presence of several medications to treat them [9].

Even if still on debate [10,11], it has been generally accepted that geriatric age starts after 65 years old. Only few cohort studies assessed the clinical features of elderly HIV-positive persons, where most of them did not focus their studies on geriatric age defined as ≥65 years old and included younger patients in their studies [12–14]. To date, 51% of people living with HIV globally are women [15] and older women accounted for the 23% of new HIV diagnosis...
among people aged 50 years or older in the United States in 2014 [4]. In a recent study from Allavena et al, females represented around the 25% of the aging population of the French Dat’AIDS cohort [16]. However, females keep on being less represented than males in clinical studies [17], where very little is known about specific characteristics of elderly HIV-positive women. Some differences in HIV infection between genders have already been pointed out in some studies with regard to the risk of HIV acquisition [18], viro-immunological response [19–22] and treatment choices [23], where some of these seems to be driven by socio-economic and cultural differences between men and women, rather than by different responses to the virus itself. Therefore, aim of this study is to explore the characteristics of elderly HIV infected women from either a viro-immunological, clinical and therapeutic point of view in comparison to their male counterparts, in order to better characterize this population and its special needs for a better management of these patients in the near future.

**Methods**

We performed a cross-sectional, retrospective study, including HIV-positive patients aged ≥65 years old. We retrieved data from the GEriatric Patients living with HIV/AIDS cOhort (GEPO). This is a prospective, observational, multicenter cohort including HIV-positive geriatric patients in follow-up by 10 HIV clinics in Italy. Main cohort inclusion criteria are: age ≥65 years, confirmed HIV-positivity, being on cART for at least 6 months. Aim of this cohort is to describe health status and transition over time in HIV-positive patients aged 65 years and older, in order to better understand the process of aging with HIV infection. In this study, we wanted to explore the existence of viro-immunological, clinical and/or therapeutic differences between the female and male population. Therefore, we recorded clinical, viro-immunological and therapeutic data at initial visit, which was performed between June 2015 and May 2016. The following data were retrieved: age, ethnicity, HIV duration, CD4+ and CD8+ cells count, CD4+ nadir, HIVRNA, HCVAb, HBsAg, actual cART regimen and co-medications. Moreover, we explored the presence of the following comorbidities: cardiovascular disease (CVD), chronic kidney disease, hypertension, type 2 diabetes mellitus, bone disease, hyperlipidemia, chronic obstructive pulmonary disease and cancer, where each condition has been previously described in a more extensive way [24]. We defined polypharmacy as the prescription of ≥5 drugs not taking into account cART.

Non-parametric tests were used for all analysis. Mann-Whitney test was used for comparing continuous variables among female and male participants. Categorical variables were compared through Chi-square and Fisher exact tests (the latter when less than 5 participants fell into one of the categories of the contingency tables). Two step-wise multivariate analysis were used for estimating independent predictors of virological suppression (binary logistic regression) and CD4/CD8 ratio (linear logistic regression) including variables that showed significant p-values at bivariate analysis. All analysis were performed through SPSS version 23.0 (SPSS, IBM Corp.).

**Ethics statement**

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and the principles of Good Clinical Practice. Ethics Committee approval was obtained from Research Ethics Board of each individual centers belonging to the GEPO cohort. Ethics approval was obtained by competent Ethics Committees (protocol number 0004013, reference 135/2016, Clinica Universitaria di Malattie Infettive, P.O. Amedeo di Savoia, Torino, as coordinating center).
Because this was a retrospective and non-pharmacological study, informed consent has not been provided since in Italy ethical authorization for these studies is not needed (Italian Guidelines for classification and conduction of observational studies, established by the Italian Drug Agency, “Agenzia Italiana del Farmaco–AIFA” on March 20, 2008).

All data were fully anonymized before the statistical analysis was performed.

**Results**

We included 210 women (17%) out of 1237 patients. Overall median age was 69.8 years old (67.1–73.9). No significant differences in HIV duration has been observed between males and females [16.3 (10.3–21.5) vs. 15.6 (10.1–20.8), p = 0.436 in females and males respectively] (Table 1).

Elderly HIV-positive women were less likely to present a HIV-RNA <50 copies/mL (74.3% vs. 81.8%; OR 0.64, 95%CI 0.44–0.93; p = 0.024) while we did not find any differences in terms of plasma HIV RNA levels between females and males with detectable (>50 copies/ml) viral load (p = 0.559) (Fig 1). Female participants showed higher CD4+/CD8+ ratio [0.97 (0.58–1.29) vs. 0.78 (0.53–1.16), p = 0.007] but similar current and nadir CD4+ T-cell counts. (Fig 2A, 2B and 2C). A nadir below 200 cells/mm$^3$ was observed in 50.6% participants with no difference according to gender.

To check whether gender was independently associated the outcomes of interest we performed a binary logistic regression analysis (virological suppression) and a linear regression analysis (higher CD4/CD8 ratio) including age, current CD4+ T-cell count, nadir CD4+ t-cell count, type of treatment, multimorbidity and polypharmacy as covariates. We found that female gender was independently associated with a higher CD4/CD8 ratio (p = 0.003) but not with virological suppression.

Current antiretroviral regimens were similar between the two genders (p>0.05). Triple regimens were the most frequently used in both populations, being prescribed globally in about 70% of patients. Globally, women were less likely to be treated with protease inhibitors (PIs) (39.5% vs 46.8%, p = 0.05) (Table 2). In triple-drug regimens females received less PI (28% vs 38%, p = 0.022) and more integrase inhibitors (30% vs. 20%, p = 0.012). In females with bone disease PIs and boosted regimens (38% vs. 53.7% p = 0.026 and 30.4 vs 44.0% p = 0.048, respectively) were prescribed less frequently compared to males with bone disease.

Hyperlipidemia, hypertension and bone disease (75.3, 65.3 and 48.8%, respectively) were the most frequent comorbidities in the female population. When the two populations were compared, bone disease was more common in females (48.8% vs 22.9%, p<0.001) while males presented more frequently cardiovascular disease (22.8% vs 9.5%, p<0.001).

### Table 1. Characteristics of patients according to gender

| Variable                | Females (n = 210) | Males (n = 1027) | Total (N = 1237) | P   |
|-------------------------|-------------------|------------------|------------------|-----|
| Age—years               | 70.6 (67.3–74.8)  | 69.6 (67.1–73.8) | 69.8 (67.1–73.9) | 0.088|
| Caucasian ethnicity     | 203 (96.7%)       | 1013 (98.6%)     | 1216 (98.3%)     | 0.070|
| HIV duration—years      | 15.6 (10.1–20.8)  | 16.3 (10.4–21.5) | 16.3 (10.3–21.3) | 0.436|
| current CD4+ cell/mm$^3$| 613 (437–802)     | 619 (440–790)    | 618 (440–793)    | 0.606|
| CD4+/CD8+ ratio         | 0.97 (0.58–1.29)  | 0.78 (0.54–1.16) | 0.81 (0.54–1.19) | 0.007|
| Nadir CD4+ cell/mm$^3$  | 189 (86–286)      | 198 (82–313)     | 196 (83–308)     | 0.484|
| HIV RNA <50 copies/ml   | 136 (74.3%)       | 740 (81.8%)      | 876 (80.5%)      | 0.024|
| HCV Ab+                 | 21 (10%)          | 104 (10.2%)      | 125 (10.1%)      | 0.956|
| HBsAg +                 | 14 (6.7%)         | 77 (7.5%)        | 91 (7.3%)        | 0.674|

https://doi.org/10.1371/journal.pone.0222225.t001
Fig 1. Current plasma HIV RNA. Current plasma HIV RNA according to gender and stratified by: < 50 copies/mL; between 50 and 199 copies/mL; between 200 and 999 copies/mL; >1000 copies/mL.

https://doi.org/10.1371/journal.pone.0222225.g001
Polypharmacy was not uncommon and similarly frequent in both genders, being present in 20% of cases. A higher use of lipid-lowering drugs (20.5% vs. 14.8%, p = 0.04) was observed in female participants. Anyway, elderly women were less likely to receive anti-thrombotic agents (18.6% vs. 26.3%, p = 0.019) even when cardiovascular disease was recorded (57.1% vs. 83.1%, p = 0.018). ACE inhibitors were less commonly used in female patients (27.1% vs. 33%, p = 0.09), especially in the presence of type 2 diabetes mellitus (2.6% vs. 13.9%, p = 0.006).

Table 2. Antiretroviral therapies, co-morbidities and polypharmacy according to gender.

| Variable                   | Females (n = 210) | Males (n = 1027) | Total (n = 1237) | p     |
|----------------------------|-------------------|------------------|------------------|-------|
| ARV therapies              |                   |                  |                  |       |
| Mono-dual                  | 60 (28.6%)        | 299 (29.1%)      | 359 (29%)        |       |
| Triple                     | 147 (70%)         | 711 (69.2%)      | 858 (69.3%)      | 0.338 |
| Other                      | 3 (1.4%)          | 17 (0.3%)        | 20 (1.6%)        |       |
| Regimen including:        |                   |                  |                  |       |
| PI                         | 83 (39.5%)        | 481 (46.8%)      | 564 (45.5%)      | 0.05  |
| NNRTI                      | 86 (41%)          | 441 (42.9%)      | 527 (42.6%)      | 0.456 |
| InSTI                      | 75 (35.7%)        | 305 (29.7%)      | 380 (29.9%)      | 0.118 |
| NRTI-sparing regimens      | 52 (24.8%)        | 278 (26.9%)      | 330 (26.6%)      | 0.298 |
| TDF-sparing regimens       | 157 (74.8%)       | 742 (72.2%)      | 899 (72.6%)      | 0.314 |
| Unboosted regimens         | 143 (68.1%)       | 642 (62.5%)      | 785 (63.4%)      | 0.079 |
| Mean comorbidities (±SD)   | 2.19 (±1.42)      | 2.37 (±1.42)     | 2.34 (±1.42)     | 0.070 |
| Comorbidities              |                   |                  |                  |       |
| CVD                        | 14 (9.5%)         | 154 (22.8%)      | 168 (20.46%)     | <0.001|
| CKD                        | 34 (21.3%)        | 150 (20.8%)      | 184 (20.8%)      | 0.381 |
| Hypertension               | 113 (65.3%)       | 456 (64.5%)      | 569 (64.6%)      | 0.206 |
| T2DM                       | 38 (24.5%)        | 201 (29.1%)      | 239 (28.3%)      | 0.696 |
| Bone disease               | 79 (48.8%)        | 134 (22.9%)      | 213 (28.5%)      | <0.001|
| Hyperlipidemia             | 134 (75.3%)       | 497 (70.5%)      | 631 (71.4%)      | 0.076 |
| COPD                       | 7 (4.8%)          | 57 (8.6%)        | 64 (7.9%)        | 0.191 |
| Cancer                     | 30 (16%)          | 147 (22.3%)      | 177 (20.92%)     | 0.761 |
| Polypharmacy (≥5 drug excludécART) | 42 (20%)       | 234 (22.8%)      | 254 (20.5%)      | 0.326 |

SD = standard deviation, ARV = antiretroviral, PI = Protease Inhibitors, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitors, InSTI = Integrase Strand Transfer Inhibitors, NRTI = Nucleos(t)ide Reverse Transcriptase Inhibitors, TDF = Tenofovir Disoproxil Fumarate, CVD = Cardiovascular Disease, CKD = Chronic Kidney Disease, COPD = Chronic Obstructive Pulmonary Disease, cART = combination antiretroviral therapy.

https://doi.org/10.1371/journal.pone.0222225.t002
Discussion

To our best knowledge, this is the first study including such large sample size of geriatric women living with HIV. Some cohort studies [12,13,25] included much lower numbers of HIV-positive women, where geriatric age was not always defined as ≥65 years old.

From a virologic point of view, our results showed that women presented a lower level of virologic suppression when compared to males (74.3% vs. 81.8%, p = 0.02). This finding was unexpected, as long as lower viral loads has been described for women in comparison to men in several studies, in both naïve and cART-experienced patients [23,26,27,28]. Gender-based differences in viral load may disappear along the progression of the infection [27]. Anyway, in a cohort of naïve patients with CD4+ T cells counts <300 cell/mm3 from Grinsztejn et al [29], women showed lower values of HIVRNA also for more advanced stages of the disease. Therefore, we hypothesized that females may have a worse virologic control because of a lower adherence to cART as previously observed [23,30], or maybe a higher rate of intolerance to cART drugs or a possible presence of DDIs [23]. Unfortunately, the study design did not allow to explore such factors. Moreover, as long as we tried to explore the existence of a correlation between virological replication in females and some variables such as type of cART, comorbidities and presence of polypharmacy, no statistical significance was found.

In our study, the nadir of CD4+ T-cell count was often <200 cell/mm3 in both females and males, which is in line with the study from Tavoschi et al [31] showing that CD4+ T-cell count at diagnosis tends to be lower than 350 cell/mm3 in older patients. Despite several studies highlighted increased rates of HIV diagnosis in people aged 50 years or more [32–33], elderly individuals are more likely to present late diagnosis of HIV infection [34–36]. A delay in HIV diagnosis can be especially threatening in this population because of higher rates of mortality, especially when an AIDS-defining event is present [37–39]. Moreover, in our analysis females did not show a significant lower nadir of CD4+ T-cells when compared to males (189 vs 198 cell/mm3, p = 0.48, respectively). However, as long as more than 50% of our patients showed a CD4+ T-cell count nadir <200 cell/mm3, we can hypothesize a lack of attention from both clinicians and prevention strategies in this population, which may perceive a lower risk of sexually transmitted diseases in this population. Certainly, a low self-perception of the risk and a lack of knowledge is present in older women about HIV infection and its transmission patterns.

Nevertheless, despite worse virologic outcomes, women displayed better CD4+/CD8+ ratio in comparison to men (1.01 vs 0.9, p = 0.016). This result was confirmed in multivariate analysis, where female gender was an independent predictor of higher CD4+/CD8+ ratio.

This is in line with a recent study, which has demonstrated that female gender is a strong predictor of immune reconstitution [40], where other studies observed the same trend in the past years [41].

With regard to antiretroviral regimens, no differences between the two genders were found in relation to the use of less-drug regimens. In both cases, standard triple regimens were prescribed in about two thirds of patients. Anyway, we observed a slight lower prescription of PIs in females, in both standard and less-drug regimens. In the study from Menzaghi et al [30], women were more likely to interrupt PIs. Specifically, women on atazanavir-based regimens were more likely to discontinue or switch treatment because of grade 1–2 adverse events, low adherence and patient’s will, when compared to men. Moreover, in our cohort, females with bone disease were less likely to be prescribed with PIs and boosted regimens. Pathology of osteoporosis in HIV-positive patients is complex and has been correlated to several factors, where its correlation with different class of drugs remained controversial [42–43]. In a
previous study, we observed an overall increase of bone turnover in HIV-positive patients starting cART with tenofovir/emtricitabine plus either atazanavir/ritonavir or efavirenz, where markers of bone resorption were higher in the first group, compared to the latter [44]. On the other hand, in a study from Yin et al, which analyzed bone loss in HIV-positive post-menopausal women, the annualized rates of bone loss adjusted for baseline bone mass density (BMD) did not differ in women on PI-based in comparison to NNRTI-based ART at any site, while it was greater among those on treatment with tenofovir [45].

Whether our clinicians chose to prescribe less PIs in order to try to avoid metabolic effects and eventual drug-to-drug interactions in the female population, or whether this choice was secondary to patients adherence and/or adverse events remains uncertain, but could represent a future matter of research.

Analyzing co-morbidities, although the mean number of co-morbidities did not differ between the two genders, we found a significant higher prevalence of bone disease in females, while CVD was more prevalent in males. In HIV-positive patients, regardless of age and gender, bone disease is more frequent in comparison to the general population, in terms of either presence of osteopenia/osteoporosis and/or asymptomatic vertebral fracture [46,47].

As expected, we found a higher prevalence of CVD in males. However, among people living with HIV, CVD is frequently observed also in females and higher when compared to HIV-negative females [48]. It is important to consider that CVD is common among females overall but often underestimated due to the fact of the challenges in atypical clinical presentation and differential diagnosis.

Polypharmacy was present in one out of five patients, irrespectively of gender. Lipid-lowering drugs were more prescribed in females compared to men. These findings showed that clinicians involved in HIV care seem to pay attention to the overall risk related to hyperlipidemia in females living with HIV, although we did not perform a specific analysis on the appropriateness of prescriptions. Given that HIV per se and exposure to antiretroviral drugs have been related to deregulations in plasmatic lipids in both males and females [48], maybe the higher prescriptions of lipid-lowering drugs in the female population can be related to the awareness of clinicians about metabolic changes occurring after menopause.

As our study shows, clinicians seem not to pay the same attention for what concerns CVD in elderly females. In fact, despite previous data showed an increased risk of CV events in HIV-positive women [49], females were less likely to receive anti-thrombotic agents even though CVD had been present in the patient history [50,51]. In fact, there is a higher risk of relapse of CV event potentially related to DDIs between anti-thrombotic agents and antiretrovirals [52].

This study has some limitations: first, data of the sample of HIV-infected patients were collected within the routine clinical practice, but they were retrospectively analyzed. Therefore, some data that could have been interesting to show and report, such as previous cART regimes, the existence of any previous virological failures, duration of cART, pre-cART CD4+/CD8+ ratios, were not collected. Secondly, only seven major co-morbidities were explored, thus not allowing to draw a fully comprehensive profile of the patients we studied. Moreover, because of the cross-sectional nature of our study is that we couldn't study whether the higher viremic loads in women were due to viral load blips or to virological failure.

**Conclusions**

This study shows that a better knowledge of this special population is necessary for the years to come. Where some differences are already present in the management of elderly HIV-positive women in comparison to men, some other may be further investigated and addressed.
Especially, we believe that prevention campaigns should start to consider this population, which is actually forgotten, in order to firstly avoid HIV-infection and secondly, to diagnose it at earlier stages. Moreover, a better understanding of the characteristics and of the specific needs of these population may help for a better management and retention in care for the near, and farther, future. A gender-medicine approach should be warranted in all settings.

Supporting information
S1 Data. Anon.
(XLSX)

Acknowledgments

Other members of the GEPP Study Group:
Francesco Castelli, Eugenia Quiros Roldan from the Division of Infectious and Tropical Diseases, Department of Clinical and Experimental Sciences, University of Brescia, Italy; Giovanni Di Perri and Stefano Bonora from the Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Italy; Antonella Castagna, Andrea Poli, Nadia Galizzi from the Department of Infectious Diseases, San Raffaele Scientific Institute, Milan, Italy; Marinello Serena from the Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera-Universitaria di Padova, Italy; Andrea Marino, Bruno Cacopardo from the Division of Infectious Diseases, University of Catania, ARNAS Garibaldi, Catania, Italy; Gervasi Elena, Massimo Galli from the first Division of Infectious Diseases Unit, University of Milan, Ospedale L. Sacco, Milan, Italy; Chiara Mussi from the Infectious Diseases Clinic, Department of Mother, Child and Adult Medicine and Surgical Science, University of Modena and Reggio Emilia, Italy

Author Contributions

Conceptualization: Emanuele Focà, Giovanni Guaraldi, Giovanni Di Perri, Andrea Calcagno.

Data curation: Emanuele Focà, Paola Magro, Agostino Riva, Anna Maria Cattelan, Giuseppe Vittorio De Socio, Cecilia Costa, Stefania Piconi, Benedetto Maurizio Celesia, Silvia Nozza, Giancarlo Orofino, Andrea Calcagno.

Formal analysis: Andrea Calcagno.

Investigation: Agostino Riva, Anna Maria Cattelan.

Methodology: Andrea Calcagno.

Supervision: Emanuele Focà, Giovanni Guaraldi, Agostino Riva, Antonella Castagna, Giovanni Di Perri, Francesco Castelli, Andrea Calcagno.

Validation: Giovanni Guaraldi, Agostino Riva, Anna Maria Cattelan, Giuseppe Vittorio De Socio, Cecilia Costa, Stefania Piconi, Benedetto Maurizio Celesia, Silvia Nozza, Giancarlo Orofino, Antonella Castagna, Giovanni Di Perri, Francesco Castelli, Andrea Calcagno.

Writing – original draft: Emanuele Focà, Paola Magro, Andrea Calcagno.

Writing – review & editing: Emanuele Focà, Paola Magro, Giovanni Guaraldi.

References
1. UNAIDS. HIV and aging: A special supplement to the UNAIDS report on the global AIDS epidemic 2013. Geneva, Switzerland: UNAIDS; 2013.
2. Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. Samji H, Cescon A, Hogg RS, Modur SP, Althoff KN, et al. (2013) Closing the Gap: Increases in Life Expectancy among Treated HIV-Positive Individuals in the United States and Canada. PLOS ONE 8(12): e81355. https://doi.org/10.1371/journal.pone.0081355 PMID: 24367482

3. UNAIDS. The gap report 2014. People aged 50 years and older. Geneva, Switzerland: UNAIDS; 2014.

4. HIV among people aged 50 and over. Center for Disease Control and Prevention, 2014. Available at https://www.cdc.gov/hiv/group/age/olderamericans/index.html. Last accessed in May 2018.

5. Andany N, Kennedy VL, Aden M, Loutfy M. Perspectives on menopause and women with HIV. International Journal of Women’s Health. 2016; 8:1–22. https://doi.org/10.2147/IJWH.S62615 PMID: 26834498

6. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem Av et al; the ATHENA observational cohort. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. The Lancet Infectious Diseases. 2015; 15(7):810–818. https://doi.org/10.1016/S1473-3099(15)00056-0 PMID: 26070969

7. Balderson BH, Grothaus L, Harrison RG, McCoy K, Mahoney C, Catz S. Chronic illness burden and quality of life in an aging HIV population. AIDS Care. 2013 Apr; 25(4): 451–458. Published online 2012 Aug 15. https://doi.org/10.1080/09540121.2012.712669 PMID: 2284702

8. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis. 2011 Dec; 53 (11):1120–6. https://doi.org/10.1086/cid627 PMID: 21998278

9. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC. The Next Therapeutic Challenge in HIV: Polypharmacy. Drugs & Aging. 2013; 30(8):613–628. https://doi.org/10.1007/s40266-013-0093-9

10. Orimo, Ito H, Suzuki T, Araki A, Hosoi T, Sawabe M. Reviewing the definition of “elderly”. Geriatr Gerontol Int 2006; 6: 149–158.

11. World Health Organization. Proposed working definition of an older person in Africa for the MDS Project. 2002. Available at http://www.who.int/healthinfo/survey/ageingdefnolder/en/. Last accessed on April 2018.

12. Schouten J, Wit F, Stolte I, Kootstra N, van der Valk M, Geerlings S et al; AGENV Cohort Study Group. Cross-sectional comparison of the prevalence of age-associated comorbidities and their risk factors between HIV-infected and uninfected individuals: the AGENV cohort study. Clin Infect Dis. 2014; 59: 1787–97. https://doi.org/10.1093/cid/ciu701 PMID: 25182245

13. De Francesco D, Underwood J, Post FA, Vera JH, Williams I, Boffito M al on behalf of the POPPY study group. Defining cognitive impairment in people-living-with-HIV: the POPPY study. BMC Infectious Diseases (2016) 16:617. https://doi.org/10.1186/s12879-016-1970-8 PMID: 27793128

14. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, et al. Veterans Aging Cohort Study (VACS): Overview and Description. Medical care. 2006; 44(Suppl 2): S13–S24.

15. UNAIDS DATA 2017. Available at http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf, last accessed in May 2018.

16. Alavaina C, Hanf M, Rey D, Duvivier C, BaniSadr F, Poizot-Martin I et al; Dat’AIDS study group. Antiretroviral exposure and comorbidities in an aging HIV-infected population: The challenge of geriatric patients. PLoS One. 2018 Sep 21; 13(9):e0203895. https://doi.org/10.1371/journal.pone.0203895 PMID: 30240419

17. Curno MJ, Rossi S, Hodges-Mamelitzis I, Johnston R, Price MA, Heidari S. A Systematic Review of the Inclusion (or Exclusion) of Women in HIV Research: From Clinical Studies of Antiretrovirals and Vaccines to Cure Strategies. J Acquir Immune Defic Syndr 2016; 71: 2: 181–188.

18. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ et al. Heterosexual risk of HIV-1 infection per sexual act: a systematic review and meta-analysis of observational studies. The Lancet Infectious diseases 2009; 9(2):118–129 https://doi.org/10.1016/S1473-3099(09)70021-0 PMID: 19179227

19. Saunders P, Goodman AL, Smith CJ, Marshall N, O’Connor JL, Lampe FC et al. Does gender or mode of HIV acquisition affect virological response to modern antiretroviral therapy (ART)? HIV Med. 2016 Jan; 17(1):18–27. https://doi.org/10.1111/hiv.12272 PMID: 26140659

20. Rosin C, Elzi L, Thurnheer C, Fehr J, Cavassini M, Calmy A et al; Swiss HIV Cohort Study. Gender inequalities in the response to combination antiretroviral therapy over time: the Swiss HIV Cohort Study. HIV Med. 2015 May; 16(5):319–25. https://doi.org/10.1111/hiv.12203 PMID: 25329751

21. Welch K, Morse A, Clark R, Ogbuokiri T. Factors Associated with Incomplete Virological Response to Highly Active Antiretroviral Therapy. Clinical Infectious Diseases 2000; 30 (2): 407–408. https://doi.org/10.1086/313670 PMID: 10671360
22. Crawford KW, Wakabi S, Magala F, Kibuuka H, Liu M, Hamm TE. Evaluation of treatment outcomes for patients on first-line regimens in US President's Emergency Plan for AIDS Relief (PEPFAR) clinics in Uganda: predictors of virological and immunological response from RV288 analyses. HIV Med. 2015; Feb; 16(2):95–104. https://doi.org/10.1111/hiv.12177 PMID: 25124078

23. Floridia M, Giuliano M, Palmisano L, Vella S. Gender differences in the treatment of HIV infection. Pharmacol Res. 2008 Sep-Oct; 58(3–4):173–82. https://doi.org/10.1016/j.phrs.2008.07.007 PMID: 18708144

24. Nozza S, Malagoli A, Maia L, Calcagno A, Focà E, De Socio Get al on behalf of the GEPPO Study Group. Antiretroviral therapy in geriatric HIV patients: the GEPPO cohort study. J Antimicro b Chemother. https://doi.org/10.1093/jac/dkx169

25. Adimora AA, Ramirez C, Benning L, Greenblatt RM, Kempf MC, Tien PCet al. Cohort Profile: The Women’s Interagency HIV Study (WIHS). Int J Epidemiol. 2018 Apr 1; 47(2):393–394i. https://doi.org/10.1093/ ije/dyy021 PMID: 29688497

26. Napravnik S, Poole C, Thomas JC, Eron JJ Jr. Gender difference in HIV RNA levels: a meta-analysis of published studies. J Acquir Immune Defic Syndr. 2002 Sep 1; 31(1):11–9. https://doi.org/10.1097/ 00126334-20020901 0-00002 PMID: 12352145

27. Loupa CV, Rodriguez B, McComsey G, Gripshover B, Salata RA, Valdez H et al. Gender differences in human immunodeficiency virus (HIV) RNA and CD4 cell counts among new entrants to HIV care. Clin Microbiol Infect. 2006 Apr; 12(4):389–91. https://doi.or g/10.111 1/j.1469-0691.2006.01368.x PMID: 16524417

28. Manolescu L, Marinescu P. Sex differences in HIV-1 viral load and absolute CD4 cell count in long term survivors HIV-1 infected patients from Giurgiu, Romania. Revista Română de Medicină de Laborator 2013 (21) 2/4: 217.

29. Grinsztejn B, Smeaton L, Barnett R, Klingman K, Hakim J, Flanigan T, et al. Sex-associated Differences in Pre-Antiretroviral Therapy Plasma HIV-1 RNA in Diverse Areas of the World Vary by CD4 Cell Count. Antiviral therapy. 2011; 16(7):1057–1062. https://doi.org/10.3851/IMP1872 PMID: 22024521

30. Ellman TM, Sexton ME, Warshafsky D, Sobieszczuk ME, Morrison EAB. A forgotten population: older adults with newly diagnosed HIV. AIDS Patient Care STDs. 2014; 28(10):530 –6. https://doi.or g/10.1089/apc .2014.0152 PMID: 25211596

31. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over in 31 European countries, 2004–15: an analysis of surveillance data. Lancet HIV. 2017 Nov; 4(11):e514 –e521. https://doi.org/10.1016/S2352-3018(17)30155-8 PMID: 28967582

32. Smith RD, Delpech VC, Brown AE, Rice BD. HIV transmission and high rates of late diagnoses among adults aged 50 years and over in 31 European countries, 2004–15: an analysis of surveillance data. Lancet HIV. 2017 Nov; 4(11):e514 –e521. https://doi.org/10.1016/S2352-3018(17)30155-8 PMID: 28967582

33. Camoni L, Regine V, Raimondo M, Salfa MC, Boros S, Suligoi B. The continued ageing of people with AIDS in Italy: recent trend from the national AIDS Registry. Ann Ist Super Sanita 2014; 50: 291–97. https://doi.org/10.4415/ANN_14_03 _12 PMID: 25292277

34. Wilson KD, Dray-Spira R, Aubrière C, Hamelin C, Spire B, Lert F. Frequency and correlates of late presentation for HIV infection in France: Older adults are a risk group-results from the ANRS-VE SPA2 study, France. AIDS Care 2014; 26 (suppl 1): 83–93.

35. Davis DHJ, Smith R, Brown A, Rice B, Yin Z, Delpech V. Early diagnosis and treatment of HIV infection: magnitude of benefit on short-term mortality is greatest in older adults. Age Ageing 2013; 42: 520–26. https://doi.org/10.1097/age.0b013e32833 c7b9c PMID: 23672932

36. Lapadula G, Chatenoud L, Gori A, Castelli F, Di Giambenedetto S, Fabbiani Met al; Italian MASTER Cohort. Risk of Severe Non AIDS Events Is Increased among Patients Unable to Increase their CD4+ T-Cell Counts >200+μl Despite Effective HAART. PLoS One. 2015 May 28; 10(5):e0124741. eCollection 2015. https://doi.org/10.1371/journal.pone.0124741 PMID: 26020949
40. Calcagno A, Piconi S, Focà E, Nozza S, Carli F, Montrucchio C et al; GEPO (GEriatric Patients living with HIV/AIDS: a Prospective Multidimensional CoHort) Study Group. Role of Normalized T-Cell Subsets in Predicting Comorbidities in a Large Cohort of Geriatric HIV-Infected Patients. J Acquir Immune Defic Syndr. 2017 Nov 1; 76(3):338–342. https://doi.org/10.1097/QAI.0000000000001496 PMID: 28708610

41. Hunt PW, Deeks SG, Rodriguez B, Valdez H, Shade SB, Abrams DI et al. Continued CD4 cell count increases in HIV-infected adults experiencing 4 years of viral suppression on antiretroviral therapy. AIDS. 2003 Sep 5; 17(13):1907–15. https://doi.org/10.1097/00002030-200309050-00009 PMID: 12960824.

42. Bruera D, Luna N, David DO, Bergoglio LM, Zamudio J. Decreased bone mineral density in HIV-infected patients is independent of antiretroviral therapy. AIDS. 2003 Sep 5; 17(13):1917–23. https://doi.org/10.1097/00002030-200309050-00010 PMID: 12960824.

43. Rothman MS, Bessesen MT. HIV Infection and Osteoporosis: Pathophysiology, Diagnosis, and Treatment Options. Curr Osteoporos Rep (2012) 10: 270. https://doi.org/10.1007/s11914-012-0125-0 PMID: 23100110

44. Focà E, Motta D, Borderi M, Gottì D, Albini L, Calabresi A et al. Prospective evaluation of bone markers, parathormone and 1,25-(OH)2 vitamin D in HIV-positive patients after the initiation of tenofovir/emtricitabine with atazanavir/ritonavir or efavirenz. BMC Infectious Diseases. 2012; 12:38. https://doi.org/10.1186/1471-2334-12-38 PMID: 22333484

45. Yin MT, Zhang CA, McMahon DJ, Ferris DC, Irani D, Colon I et al. Higher rates of bone loss in postmenopausal HIV-infected women: a longitudinal study. J Clin Endocrinol Metab. 2012 Feb; 97(2):554–62. https://doi.org/10.1210/jc.2011-2197 PMID: 22090266

46. Porcelli T, Gottì D, Cristiano A, Maffezzoni F, Mazziotti G, Focà E et al. Role of bone mineral density in predicting morphometric vertebral fractures in patients with HIV infection. Osteoporos Int. 2014 Sep; 25 (9):2263–9. https://doi.org/10.1007/s00198-014-2760-z PMID: 25056799

47. Torti C, Mazziotti G, Soldini PA, Focà E, Maroldi R, Gottì D et al. High prevalence of radiological vertebral fractures in HIV-infected males. Endocrine. 2012 Jun; 41(3):312–7. https://doi.org/10.1007/s12020-011-9586-7 PMID: 22198528

48. Quiros-Roldan E, Raffetti E, Focà E, Brianese N, Ferraresi A, Parainfò G et al. Incidence of cardiovascular events in HIV-positive patients compared to general population over the last decade: a population-based study from 2000 to 2012. AIDS Care. 2016 Dec; 28(12):1551–1558. https://doi.org/10.1080/09540121.2016.1198750 PMID: 27321070

49. Womack JA, Chang CC, So-Armah KA, Alcorn C, Baker JV, Brown ST et al. HIV infection and cardiovascular disease in women. J Am Heart Assoc. 2014 Oct 16; 3(5):e001035. https://doi.org/10.1161/ JAHA.114.001035 PMID: 25324353

50. D’Ascenzo F, Cerrato E, Appleton D, Moretti C, Calcagno A, Abouzaki N et al; Percutaneous coronary intervention and surgical revascularization in HIV Database (PHD) Study Investigators. Prognostic indicators for recurrent thrombotic events in HIV-infected patients with acute coronary syndromes: use of registry data from 12 sites in Europe, South Africa and the United States. Thromb Res. 2014 Sep; 134 (3):558–64. https://doi.org/10.1016/j.thromres.2014.05.037 PMID: 25064035

51. Hauguel-Groustra M, Boccafa F, Boyd A, Salem JE, Burgier D, Curjol A et al. Platelet reactivity in human immunodeficiency virus infected patients on dual antiplatelet therapy for an acute coronary syndrome: the EVEREST-HIV study. Eur Heart J. 2017 Jun 1; 38(21):1676–1686. https://doi.org/10.1093/ eurheartj/ehw583 PMID: 28065907.

52. Bravo I, Álvarez H, Marín O, Clotet B, Molto J. Recurrent coronary disease in HIV-infected patients: role of drug-drug interactions. Br J Clin Pharmacol. 2018.