Growing old with antiretroviral therapy or elderly people in antiretroviral therapy: two different profiles of comorbidity?

Invecchiare con la terapia antiretrovirale o essere anziani in terapia antiretrovirale: due profili di comorbidità differenti?

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Abstract

In Persons Living With HIV (PLWH), the burden of non-communicable chronic diseases increased over time, because of aging linked to prolonged survival, chronic inflammation, systemic immune activation, and long-term exposure to the combination antiretroviral therapy (ART). Chronological age, age at HIV diagnosis, and exposure to ART may exert an effect on qualitative and quantitative differences.

To explore this hypothesis, we evaluated the prevalence of some selected comorbidities in patients enrolled in the SCOLTA Project, by groups of chronological age (50-59 and ≥60 years old) and ART duration.

In 1336 subjects (23.9% women), ART duration was similar between age groups, both when considered in continuous (p=0.85) and in categories (p=0.88). As expected, comorbidities and multimorbidity were less frequent in the 50-59 than in the ≥60 years class.

The age- and sex-adjusted odds ratios (ORs) showed that, in the 50-59 years group, a consistent and significant risk increase was observed through ART duration categories for CVD (ORs from 1.68 to 2.18), dyslipidemia (ORs from 3.61 to 9.08) and osteopenia/osteoporosis (ORs from 3.74 to 6.23). Consequently, the risk of multimorbidity also increased across ART duration categories (ORs from 2.04 to 4.40). In the ≥60 years group, the CVD risk was significantly increased only in those patients with ART duration ≥20 years (OR 2.61, 95% CI 1.22-5.58, reference category ≤6 months). Dyslipidemia and multimorbidity increase were consistently associated with longer ART duration.

In conclusion, age, age at HIV infection diagnosis, and ART exposure were associated to multimorbidity in PLWH.

Riassunto

Nelle persone che vivono con HIV (PLWH), il peso delle patologie corniche non trasmissibili è aumentato nel tempo, a causa dell'invecchiamento legato a una maggiore sopravvivenza, all'infiammazione cronica, all'attivazione del sistema immunitario, e all'esposizione a lungo termine alla terapia antiretrovirale (ART). L'età anagrafica, quella alla diagnosi di infezione da HIV, e l'esposizione alla ART sono fattori che possono esercitare un effetto sulle differenze sia qualitative che quantitative tra le comorbidità.

Per esplorare questa ipotesi, abbiamo valutato la prevalenza di alcune patologie selezionate nei pazienti arruolati nel progetto SCOLTA, per gruppi di età (50-59 e ≥60 anni) e durata della ART.

In 1336 soggetti (23.9% donne), la durata della ART era simile tra gruppi di età, sia considerata in continuo (p=0.85) che in categorie (p=0.88). Come atteso, le comorbidità e la multimorbidità erano meno frequenti nel gruppo 50-59 che in quello ≥60 anni.

Gli odds ratios (ORs) aggiustati per sesso ed età hanno mostrato che, nella categoria 50-59, si rilevava un aumento di rischio significativo e coerente in categorie di durata della ART, per le malattie cardiovascolari (CVD) (ORs da 1.68 a 2.18), dislipidemia (ORs da 3.61 a 9.08) e osteopenia/osteoporosi (ORs da 3.74 a 6.23). Di conseguenza, anche il rischio di multimorbidità aumentava attraverso le classi di durata della ART (ORs da 2.04 a 4.40). Nel gruppo ≥60 anni, il rischio CVD era significativamente più elevato solo nei pazienti con durata della ART ≥20 anni (OR 2.61, 95% intervallo di confidenza al 95% 1.22-5.58, categoria di riferimento ≤6 mesi). L'aumento di dislipidemia e multimorbidità era coerentemente associato con una maggiore durata della ART.

In conclusione, l'età anagrafica, quella alla diagnosi di infezione da HIV, e l'esposizione alla ART sono associate alla multi-morbidità nelle PLWH.

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Background

In recent years, the prevention and the early treatment of co-morbidities among Persons Living With HIV infection (PLWH) has become a major issue in the management of these patients. In fact, a number of non-communicable diseases (cardiovascular [5], renal [6], neurocognitive [7, 8], bone disease [9], non-AIDS related cancers [10]) are more frequently observed among PLWH with respect to the general population as a consequence of aging, chronic inflammation, systemic immune activation, and long-term exposure to the combination antiretroviral therapy (ART) [1–3]. Moreover, the presence of multiple chronic co-morbidities [10, 11], could determine further difficulties in their management.

Aimed at the purpose of defining the possible different profiles in terms of quality and quantity of non-communicable diseases among PLWH, we hypothesized that there should be qualitative and quantitative differences according to their chronological age, but also to the year of HIV diagnosis, and to the length of exposition to antiretroviral treatment.

To explore this hypothesis, we stratified our patients by groups of chronological age and by years of antiretroviral treatment (ART) and evaluated the possible differences in terms of number and types of co-morbidities in the different groups.

Methods

This was a cross-sectional analysis of baseline data from the SCOLTA project, an ongoing prospective cohort study [12]. Briefly, subjects were enrolled if they were aged 18 years or more, in need of initiating a cohort drug and gave their informed consent

to participate into the study. At enrollment, information on type and duration of previous ART were collected, as well as on diagnosed comorbidities.

Included comorbidities were cardiovascular diseases (atherosclerosis, carotid plaques, hypertensive cardiomyopathy, ischemic cardiopathy, diabetes, hypertension, atrial fibrillation, cardiac hypertrophy, metabolic syndrome, tachycardia, impaired glucose tolerance; history of brain hemorrhage, acute myocardial infarction, transitory ischemic attack, cardiac failure), dyslipidemia, central nervous system (CNS) disturbance (anxiety, depression, psychosis), osteopenia/osteoporosis and non-AIDS related cancers (current or past). Multi-morbidity was defined as the presence of two or more co-morbidities other than HIV infection. The criterion of two or more chronic conditions has been considered a cut-off score to compare multi-morbid and non multi-morbid groups.

To focus on older subjects, we selected participants enrolled since 2013 and aged 50 or more years at study entry, performing the analysis in two groups: 50-59 and ≥60 years old.

Continuous variables were described as means (and standard deviation, SD) if normally distributed, and as medians (and interquartile range, IQR) if not normally distributed. They were compared using parametric and non-parametric tests, respectively. Categorical variables were described as frequency (and percentage, %) and their distribution was compared using the chi-square test (or Fisher exact test, as appropriate).

We estimated the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for CVD, dyslipidemia, CNS disturbance, bone loss (osteopenia and osteoporosis), non-AIDS-related malignancies and multimorbidity. To account for potential confounders, we included terms for age and sex at birth. All the analyses were performed with the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Table 1. Baseline characteristics of 1336 subjects aged ≥50 years enrolled in the SCOLTA Project between 2013 and 2021

	Age class (years)				
Patients' characteristics	**50-59**		**≥60**		**p**
	N	**%**	**N**	**%**	
Sex					
M	703	74.4	314	80.3	
F	242	25.6	77	19.7	0.02
Ethnicity					
Caucasian	907	96.0	377	96.4	
Other	38	4.0	14	3.6	0.70
Risk factor for HIV acquisition					
IDU	324	34.3	48	12.3	
Heterosexual	304	32.2	193	49.4	
Homosexual	222	23.5	96	24.6	
Other/Unknown	95	10.1	54	13.8	<0.0001
HCV positive	359	38.0	65	16.6	<0.0001
CDC Stage					
A	409	43.3	183	46.8	
B	289	30.6	112	28.6	
C	247	26.1	96	24.6	0.30
Naïve	105	11.1	40	10.2	0.64
Detectable HIVRNA (exp)	119	14.2	36	10.3	0.07
CD4+ count (cell/mL)	599	386-826	524	313-816	0.01
ART duration (years)	11	4-19	13	4-19	0.85
ART duration (years)					
<6 months or naïve	115	12.2	43	11.0	
1-6	200	21.2	87	22.2	
7-14	237	25.1	91	23.3	
15-19	166	17.6	84	21.5	
≥20	227	24.0	86	22.0	0.88

Results

Out of 2916 patients enrolled since 2013, we excluded 1580 (54.2%) who were younger than 50 years at study entry. One thousand three hundred and thirty-six were eligible for this analysis, 945 (70.7%) aged 50-59 years and 391 (29.3%) aged 60 years or more. Most patients were enrolled in the dolutegravir cohort (49.0%), followed by bictegravir (17.7%), darunavir/cobicistat (10.7%), rilpivirine (9.7%), elvitegravir/cobicistat (7.5%) and doravirine (5.3%).

Mean age at enrollment was 57.4 (SD 6.5) years, and at first ART 45.3 (SD 10.7). Both were higher in men than in women (57.6 vs 56.7, p=0.02, and 45.9 vs 43.4, p=0.0003). On the contrary, ART duration was longer in women (13.3 vs 11.8 years, p=0.006).

Baseline patients' characteristics are reported in **Table 1**, by age class. In the 50-59 group, women were more represented (25.6% vs 19.7%, p=0.02), and median CD4+ count was higher (599 vs 524, p=0.01).

Risk factors for HIV acquisition were heterogeneous between age groups, with intravenous drug use more frequent (34.3% vs 12.3%) and transmission by heterosexual intercourse less frequent (32.2% vs 49.4%) in the 50-59 than in ≥60 years group (p<0.0001). Consistently, prevalence of HCV positivity was higher in the 50-59 years group (38.0% vs 16.6%, p<0.0001).

ART duration was similar between age groups, both when considered in continuous (p=0.85) and in categories (p=0.88). Classes of previous ART duration were determined as quartiles in the ≥60 years class, after exclusion of naïve subjects.

As expected, comorbidities and multimorbidity were less frequent in the 50-59 than in the ≥60 years class (**Table 2**). By age class, ART duration showed an association with CVD, dyslipidemia, and bone loss frequency, whereas the relationship was less evident with CNS disturbances and non-AIDS-related malignancies (**Table 3, Figure 1**).

To evaluate the strength of this association, we included age and sex in the logistic regression model, to account for these confounders (**Table 4**). In the 50-59 years group, CNS disturbance and presence of malignancies did not appear related to ART duration, whereas a consistent and significant risk increase for CVD, dyslipidemia and osteopenia/osteoporosis was observed. Consequently, the risk of multimorbidity also increased across ART duration categories.

In the ≥60 years group, the risk increase was less marked and inconsistently significant. For example, CVD risk was significantly increased only in those patients with ART duration ≥20 years. On the contrary, dyslipidemia and multimorbidity increase were consistently associated with longer ART duration.

Discussion

In this analysis of baseline data from a cohort study, we found that subjects aged 50-59 and ≥60 years had a risk of multimorbidity in positive relationship with years of ART exposure. As regards specific comorbidities, dyslipidemia showed the same trend in strata of age, whereas the relationship between ART duration and CVD and osteopenia/osteoporosis was more marked in the 50-59 years group with respect to the group ≥60 (29.5% vs 51.9%); this also accounts for the difference in multimorbidity among the two groups (25.8% vs 36.8%). In the 50-59 group ART duration seems to exert

Table 2. Comorbidities by age class.

Comorbidity	Age class (years)				p
	50-59		≥60		
	N	%	N	%	
CVD	279	29.5	203	51.9	<0.0001
Dyslipidemia	180	19.0	80	20.5	0.55
CNS	101	10.7	40	10.2	0.80
Osteopenia/osteoporosis	94	10.0	50	12.8	0.13
Non-AIDS-related malignancies	31	3.3	18	4.6	0.24
Multimorbidity	244	25.8	144	36.8	<0.0001

Table 3. Comorbidity (%) by ART duration and age class.

Comorbidity	ART duration					p
	<6 months	1-6 yrs	7-14 yrs	15-19 yrs	≥20 yrs	
Age class (years)			**50-59**			
CVD	19.1	28.5	30.0	32.5	33.0	0.03
Dyslipidemia	5.2	15.0	19.4	19.9	28.6	<0.0001
CNS	10.4	12.0	7.2	10.2	13.7	0.35
Osteopenia/osteoporosis	2.6	9.0	9.7	9.0	15.4	0.002
Non-AIDS-related malignancies	4.4	2.0	3.8	2.4	4.0	0.72
Multimorbidity	12.2	22.0	23.2	28.3	37.0	<0.0001
Age class (years)			**≥60 yrs**			
CVD	44.2	42.5	51.6	50.0	67.4	0.002
Dyslipidemia	4.6	14.9	26.4	17.9	30.2	0.006
CNS	9.3	9.2	7.7	11.9	12.8	0.29
Osteopenia/osteoporosis	0.0	10.3	18.9	15.5	12.3	0.17
Non-AIDS-related malignancies	2.3	4.6	5.5	3.6	5.8	0.67
Multimorbidity	23.3	27.6	40.7	36.9	48.8	0.002

Figure 1. Comorbidities in strata of age and ART exposure.

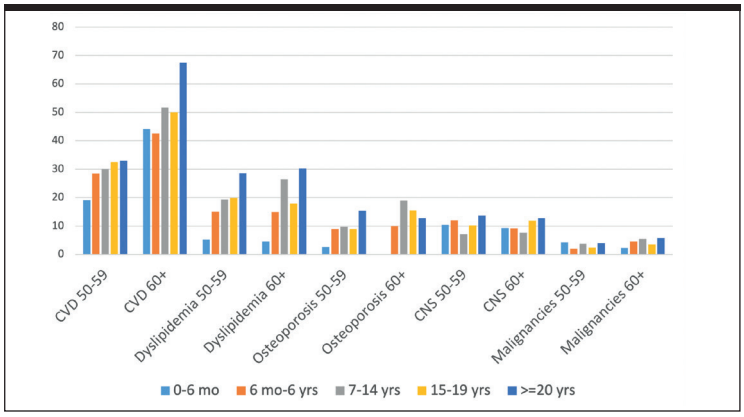

Table 4. Odds ratios and 95% confidence intervals for comorbidity by age class, age- and sex-adjusted.

Comorbidity	ART duration				
	<6 months	1-6 yrs	7-14 yrs	15-19 yrs	≥20 yrs
Age class (years)			**50-59**		
CVD	1.00	1.68 0.96-2.94	30.0	32.5	33.0
Dyslipidemia	1.00	3.20 1.29-7.95	19.4	19.9	28.6
CNS	1.00	1.17 0.56-2.45	7.2	10.2	13.7
Osteopenia/osteoporosis	1.00	3.74 1.07-13.01	9.7	9.0	15.4
Non-AIDS-related malignancies	1.00	0.45 0.12-1.71	3.8	2.4	4.0
Multimorbidity	1.00	2.04 1.06-3.90	23.2	28.3	37.0
Age class (years)			**≥60**		
CVD	1.00	0.94 0.45-1.99	1.27 0.60-2.67	1.19 0.56-2.52	2.61 1.22-5.58
Dyslipidemia	1.00	3.61 0.78-16.82	7.80 1.74-34.94	4.66 1.01-21.46	9.08 2.04-40.37
CNS	1.00	0.98 0.28-3.46	0.85 0.23-3.12	1.41 0.41-4.84	1.48 0.44-4.98
Osteopenia/osteoporosis	n.e.	1.00	1.79 0.74-4.35	1.54 0.61-3.87	1.31 0.51-3.38
Non-AIDS-related malignancies	1.00	2.01 0.22-18.59	2.30 0.26-20.56	1.50 0.15-14.89	2.55 0.29-22.57
Multimorbidity	1.00	1.25 0.54-2.93	2.20 0.96-5.04	1.90 0.82-4.39	3.14 1.38-7.15

a significant impact on CVD, dyslipidemia and osteopenia/osteoporosis and, in general, on the multimorbidity, but not on CNS disturbance and malignancy.

In the ≥60 group ART duration impacts on dyslipidemia, while an effect on CVD and multimorbidity appears only over 20 years of therapy. It is noteworthy that the effect of ART duration on the onset of comorbidities appears less marked among patients aged ≥60 years, with respect to those aged 50-59 years. We can hypothesize that this phenomenon could be due to the fact that PLWH present two profiles: those growing old with antiretroviral therapy and elderly people in antiretroviral therapy. Those who grew old with HIV and with ARV learned, over time, to perform timely controls, screening investigation and treatments for comorbidities.

The higher number of over-sixties with CVD and osteopenia/osteoporosis could be the effect of the exposition to more toxic antiretrovirals, like abacavir, protease inhibitors and tenofovir disoproxil fumarate. On the other hand, we should also consider that, among over-sixties the effect of age per se on CVD and dyslipidemia became preponderant with respect to the effect of ART and HIV infection duration.

In a recent issue of the FUNCFRAIL study [13], 801 PLWH were stratified by chronological age (50-54, 55-64 years, and > 65) and by the year of HIV diagnosis (before 1996 and after 1996).

Among patients diagnosed before 1996, the Authors found an increased burden of comorbidities and a higher prevalence of chronic obstructive pulmonary disease (COPD), history of cancer, osteoarthritis, depression, and other psychiatric disorders, but no differences regarding frailty and physical function; the prevalence of frailty and poor physical function was significantly higher among patients aged 65 years or more. Among patients aged ≥65 years, the most prevalent comorbidities were hypertension, diabetes, dyslipidemia, current cancer, and osteoarthritis.

Despite the relevant difference between the results of the two studies, in the SCOLTA cohorts the two profiles of PLWH significantly differed in terms of comorbidities, as also was observed in the FUNCFRAIL study.

Another interesting aspect was a comparison with the general Italian population, where the information was available [14]. An overall comparison was not feasible, since the age distribution of our patients was remarkably different. However, where information was provided in age class, we could compare some specific diseases (**Table 5**).

For example, in a survey conducted in 2010, an overall 1.7% of men and 12.0% of women were reported as suffering from osteoporosis. Limiting the information to age classes comparable with ours, men aged 54-59, 60-64 and 65-74 years had a prevalence of osteoporosis of 2.2%, 1.7%, and 4.5% respectively, versus 9.0%, 9.0% and 12.6% in our sample.

On the contrary, in the same age classes the presence of osteoporosis in women was 18.0%, 21.2%, and 31.9% in the general Italian population, and 17.7%, 20.0% and 29.4% among women living with HIV.

Similarly, CNS disturbance and hypertension were more frequent in men from SCOLTA study than in the general population, whereas diabetes prevalence was comparable. In women, we did not observe any remarkable differences.

In brief, comparing our data with those obtained from the general population, we can observe that, in the classes of age considered, over-fifties males are more exposed to osteopenia/osteoporosis and, if over-sixties, also to high blood pressure and CNS disturbances. On the other hand, women seem less exposed to diabetes and osteoporosis; this could be due to the success, in our outpatient facilities, of early diagnosis and treatment policy in post-menopausal HIV-positive women, a category considered at higher risk for this comorbidity.

This study has some limitations.

First, the Infectious Diseases Clinics involved in the SCOLTA study are not formally representative of the Italian Clinics (i.e., at the national level), because they were not randomly selected but participated into our observational study on a volunteer basis. Second, the subjects were not fully representative of all PLWH followed in the Infectious Diseases Clinics participating into the SCOLTA study, but only of those in need of initiating a new ART drug in the considered period.

Last, comorbidities were only reported if previously diagnosed, so an underestimate was possible.

In conclusion, PLWH over-fifties present different risk profiles for comorbidities, according to their ART exposure, and should not be considered as a uniform group. Distinguishing them according to different profiles may contribute to design different diagnostic and therapeutic approaches. ■

Table 5. Comorbidities by age class (%), comparison with the general Italian population.

	M			F		
	55-59	60-64	65-74	55-59	60-64	65-74
Diabetes						
ISTAT	7.4	9.4	12.6	5.9	7.3	13.1
SCOLTA	8.0	9.6	11.0	3.5	2.9	8.8
Hypertension						
ISTAT	-	-	43.4	-	-	48.3
SCOLTA			55.9			52.9
CNS disturbance						
ISTAT	-	-	7.3	-	-	11.6
SCOLTA			9.4			11.8
Osteoporosis						
ISTAT	2.2	1.6	4.5	18.0	21.2	31.9
SCOLTA	9.0	9.0	12.6	17.7	20.0	29.4

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