

# Premature Age-Related Comorbidities Among HIV-Infected Persons Compared With the General Population

Giovanni Guaraldi,<sup>1</sup> Gabriella Orlando,<sup>1</sup> Stefano Zona,<sup>1</sup> Marianna Menozzi,<sup>1</sup> Federica Carli,<sup>1</sup> Elisa Garlassi,<sup>1</sup> Alessandra Berti,<sup>2</sup> Elisa Rossi,<sup>2</sup> Alberto Roverato,<sup>3</sup> and Frank Palella<sup>4</sup>

<sup>1</sup>Department of Medicine and Medical Specialties, University of Modena and Reggio Emilia, <sup>2</sup>Health Care Systems Department, CINECA Consortium of Universities, <sup>3</sup>Department of Statistical Sciences, Alma Mater Studiorum, University of Bologna, Italy; and <sup>4</sup>Department of Medicine, Division of Infectious Diseases, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

**Background.** Human immunodeficiency virus (HIV)-infected patients may have a greater risk of noninfectious comorbidities (NICMs) compared with the general population. We assessed the prevalence and risk factors for NICMs in a large cohort of HIV-infected adults and compared these findings with data from matched control subjects.

**Methods.** We performed a case-control study involving antiretroviral therapy (ART)-experienced HIV-infected patients treated at Modena University, Italy, from 2002 through 2009. These patients were compared with age-, sex-, and race-matched adults (control subjects) from the general population included in the CINECA ARNO database. NICMs included cardiovascular disease, hypertension, diabetes mellitus, bone fractures, and renal failure. Polypharmacy (Pp) was defined as the concurrent presence of  $\geq 2$  NICMs. Logistic regression models were constructed to evaluate associated predictors of NICMs and Pp.

**Results.** There were 2854 patients and 8562 control subjects. The mean age was 46 years, and 37% were women. Individual NICM and Pp prevalences in each age stratum were higher among patients than among controls (all  $P < .001$ ). Pp prevalence among patients aged 41–50 years was similar to that among controls aged 51–60 years ( $P$  value was not statistically significant); diabetes mellitus, cardiovascular disease, bone fractures, and renal failure were statistically independent after adjustment for sex, age, and hypertension. Logistic regression models showed that independent predictors of Pp in the overall cohort were (all  $P < .001$ ) age (odds ratio [OR], 1.11), male sex (OR, 1.77), nadir CD4 cell count  $< 200$  cells/ $\mu\text{L}$  (OR, 4.46), and ART exposure (OR, 1.01).

**Conclusions.** Specific age-related NICMs and Pp were more common among HIV-infected patients than in the general population. The prevalence of Pp in HIV-infected persons anticipated Pp prevalence observed in the general population among persons who were 10 years older, and HIV-specific cofactors (lower nadir CD4 cell count and more prolonged ART exposure) were identified as risk factors. These data support the need for earlier screening for NICMs in HIV-infected patients.

The widespread introduction of highly effective combination antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has dramatically decreased HIV-associated morbidity and mortality

[1–4]. Despite marked increases in life expectancy, mortality rates among HIV-infected persons remain 3–15 times higher than those seen in the general population [5, 6]. Although some of the excess mortality observed among HIV-infected persons can be directly attributed to illnesses that occur as a consequence of immunodeficiency, more than half of the deaths observed in recent years among ART-experienced HIV-infected patients are attributable to noninfectious comorbidities (NICMs) [7–10]. These include cardiovascular disease (CVD), hypertension (Htn), bone fractures, renal failure, and diabetes mellitus (DM)

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Correspondence: Frank J. Palella Jr, MD, Division of Infectious Diseases, Northwestern University Feinberg School of Medicine, 645 N Michigan Ave, Ste 900, Chicago, IL 60613 (f-palella@northwestern.edu).

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[11–14], diseases that in the general population often coexist and are associated with advancing age [15–17].

It has been hypothesized that the increased prevalence of NICM observed among HIV-infected patients [2, 18], compared with the general population, is the result of premature aging in the former [11, 19]. Our objective in this report was to compare the prevalence and risk factors for several common age-related NICMs among HIV-infected persons, compared with matched controls.

## METHODS

We designed a cross-sectional retrospective case-control study. Patients were ART-experienced HIV-infected patients >18 years of age who were consecutively enrolled at the Metabolic Clinic of Modena University in Italy from 2002 through 2009. This outpatient clinic is a multidisciplinary center for the management of NICM in ART-experienced patients that is fully integrated with and operated by the same healthcare personnel employed at the Modena University HIV Clinic. Patients treated at this center include all ART-experienced patients evaluated at the Modena HIV Clinic and patients referred from neighboring HIV care centers. Control subjects were matched according to age, sex, duration of follow-up, race (all white), and geographical area and were selected from the CINECA ARNO Observational database. The ARNO Observatory is an online, multicenter observational database in which population-based data are collected and epidemiological methods [20] are used to combine and aggregate large volumes of healthcare-related data for each individual patient. These data include primary care provider-generated medication prescriptions, inpatient hospital records and discharge summaries, diagnostic laboratory tests, and radiographic examinations. This information is linked to other sources of patient data (including vital statistics and patient demographic characteristics) to provide comprehensive tracking of clinical diagnoses and healthcare use trends throughout Italy. The ARNO observatory has been active since 1986 and includes healthcare prescription data generated by 8300 general practitioners for a population of 11 million patients treated at 32 Health Units in Italy. The database is updated monthly. According to our matching criteria, controls may not have had any medical or healthcare-related data available.

### NICM Definitions

#### **Age-Related NICMs Evaluated: CVD, Htn, DM, Bone Fractures, and Renal Failure**

Prevalences of NICMs during the follow-up evaluation period were obtained by adding the prevalence of NICM at time of inclusion plus new diagnoses that occurred during the observation period. Patient self-reports and diagnostic and drug-tracing criteria obtained from metabolic clinic charts were used to identify prevalences of NICM diagnoses given to patients at

inclusion, and *International Classification of Diseases, Ninth Revision*, hospital codes for new disease and drug-tracing criteria (for medications prescribed for use for at least 30 days) during the follow-up period were used to identify NICM diagnoses given to controls. For the purpose of this report, polypathology (Pp) was defined as the simultaneous presence of  $\geq 2$  NICMs [21].

The category of CVD included the following diagnoses: myocardial infarction, stroke, angina pectoris, coronary artery bypass grafting, and angioplasty. Among patients, diagnostic criteria for Htn, DM, and renal failure included >2 consecutive measurements, respectively, of blood pressure measurements >140/90 mm Hg, fasting serum glucose levels >126 mg/dL, and Estimated Glomerular Filtration Rate <60 mL/min with use of the Modification of Diet in Renal Disease estimating equation. Drug-tracing criteria used to establish Htn and DM diagnoses in both patients and controls included current use of antihypertensive and hypoglycemic drugs. For diagnoses of CVD, Htn, DM, or renal failure, incident diagnoses that occurred during the follow-up period were analyzed. For bone fractures, patient medical history evaluation was undertaken without distinctions made between traumatic and atraumatic fractures.

### Statistical Analysis

Logistic regression models were used to evaluate the prevalence of each individual comorbidity and the prevalence of Pp, both entities as a function of chronologic age in years. For analytic purposes, age was stratified using thresholds of 40, 50, and 60 years.

To evaluate for a potential selection bias that could have resulted from our patients having been identified at the metabolic clinic, we compared the prevalence of NICM and of Pp among patients who were included from the Modena HIV Clinic with NICM prevalence among individuals referred to the Modena metabolic clinic by neighboring centers for evaluation.

The comparability of logistic regression curves evaluating patients versus controls was tested by applying the generalized likelihood ratio test on the basis of its asymptotic  $\chi^2$  distribution.

The  $\chi^2$  test was used to verify the hypothesis that the 4 NICMs (DM, CVD, bone fractures, and renal failure) were statistically independent after adjustment for sex, age, and the presence of Htn. The independence of these covariates was verified using a multivariable log-linear model and was depicted with a log-linear graphical model.

Multivariable logistic regression models were constructed using backward elimination to determine factors associated with Pp. Models were built using the following variables: sex, age, CD4 cell count, nadir CD4 cell count, and exposure to ART. Patient age was expressed in years, duration of individual ART drug class use was expressed in months, and nadir CD4 cell count <200 cells/ $\mu$ L was expressed as a binary variable. Per protocol, we assumed that, in controls, the values for ART exposure and nadir CD4 cell count <200 cells/ $\mu$ L were equal to zero.

We performed an additional stepwise logistic regression model for patients only to evaluate the association between Pp and lipodystrophy. Variables included in the model were sex, age, CD4 cell count, nadir CD4 cell count, lipodystrophy phenotypes (lipoatrophy and lipohypertrophy), and exposure to each ART drug class, including protease inhibitors, nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, fusion inhibitors, and integrase inhibitors. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

Statistical analyses were performed using the statistical software R, version 2.10.1 (<http://cran.r-project.org/>), and Stata software package, Intercooled, version 10.1 for Mac (StataCorp). The graphical model was built using MIM software (<http://www.hypergraph.dk/>) [22].

## RESULTS

There were 2854 patients and 8562 controls included in the analysis; 4244 (37%) were women. The mean age ( $\pm$  standard deviation) of the overall population was 46 ( $\pm$ 8) years.

Among patients at last visit, the median duration of HIV infection was 196 months (range, 36–248 months), median nadir CD4 cell count was 170 cells/ $\mu$ L (interquartile range [IQR], 66–263.5 cells/ $\mu$ L), and median current CD4 cell count was 520 cells/ $\text{mm}^3$  (IQR, 374–702 cells/ $\text{mm}^3$ ). Plasma HIV RNA levels were below the limit of quantification in 1825 patients (71.3%). Cumulative nucleotide reverse-transcriptase inhibitor, nonnucleotide reverse-transcriptase inhibitor, and protease inhibitor exposures were 116 months (IQR, 72–155 months), 37 months (IQR, 16–70 months), and 55 months (IQR, 29–88 months), respectively. A nadir CD4 cell count  $<200$  cells/ $\mu$ L was documented in 1525 patients (57.5%). Lipodystrophy was present in 2126 HIV-infected patients (74.34%); in particular, lipoatrophy was present in 942 (32.94%) patients, fat accumulation was present in 266 (9.30%), and a mixed-form phenotype was present in 918 individuals (32.10%).

The Table 1 shows the comparative prevalence of NICMs between HIV-infected and uninfected patients, stratified by age. Significantly higher prevalences of renal failure, bone fractures, and DM were observed among HIV-infected patients, compared with controls in all age strata. CVD and Htn prevalence were similar among patients and controls for persons  $>60$  years of age.

Among patients, a comparable prevalence of NICMs and of Pp (12.8% vs 13.5%;  $P = .288$ ) was present in patients referred to the metabolic clinic from the Modena HIV Clinic (805 patients) and from the neighboring centers (2049 patients).

Figure 1 depicts logistic regression analyses that assessed the comparative risk (OR) for renal failure, DM, bone fracture, Htn, and CVD with use of age as a continuous variable between patients and controls. We found a significantly greater likelihood of NICM risk among HIV-infected persons, compared

**Table 1. Comparative Prevalence of Selected Noninfectious Comorbidities Among Patients Versus Control Subjects, Stratified by Age**

NICM, by age	HIV-infected patients (n = 2854)	HIV-uninfected controls (n = 8562)	P value
<b>CVD</b>			
$\leq 40$ years	5 (0.91%)	4 (0.24%)	.049
41–50 years	39 (2.26%)	33 (0.64%)	$<.001$
51–60 years	27 (5.97%)	36 (2.65%)	.002
$>60$ years	22 (16.18%)	24 (5.88%)	.076
<b>Htn</b>			
$\leq 40$ years			
41–50 years	37 (6.75%)	140 (8.52%)	.206
51–60 years	340 (19.72%)	888 (17.17%)	.018
$>60$ years	176 (38.94%)	433 (31.93%)	.007
	81 (59.56%)	226 (55.39%)	.425
<b>Renal failure</b>			
$\leq 40$ years	18 (3.28%)	1 (0.06%)	$<.001$
41–50 years	90 (5.22%)	8 (0.15%)	$<.001$
51–60 years	41 (9.07%)	4 (0.29%)	$<.001$
$>60$ years	33 (24.26%)	2 (0.49%)	$<.001$
<b>Bone fracture</b>			
$\leq 40$ years	59 (10.77%)	12 (0.73%)	$<.001$
41–50 years	262 (15.20%)	48 (0.93%)	$<.001$
51–60 years	67 (14.82%)	18 (1.33%)	$<.001$
$>60$ years	17 (12.50%)	10 (2.45%)	$<.001$
<b>DM</b>			
$\leq 40$ years	18 (3.28%)	23 (1.40%)	.009
41–50 years	158 (9.16%)	151 (2.92%)	$<.001$
51–60 years	89 (19.69%)	92 (6.78%)	$<.001$
$>60$ years	53 (38.97%)	65 (15.93%)	$<.001$

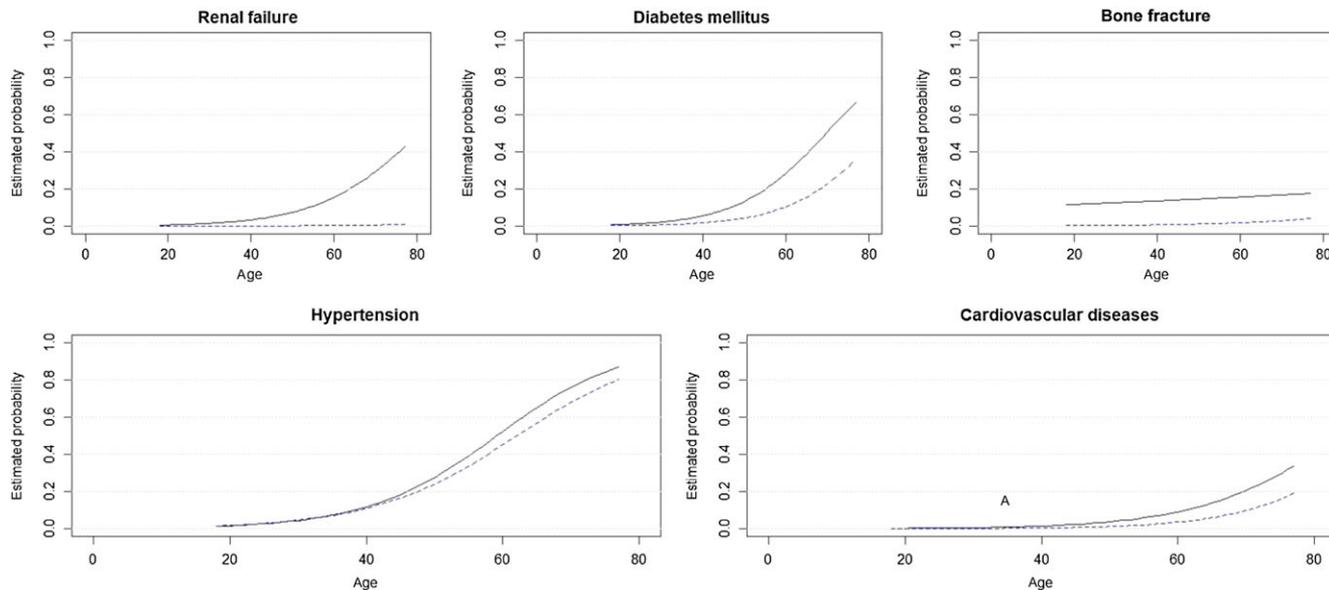
Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus; HIV, human immunodeficiency virus; Htn, hypertension; NICMs, noninfectious comorbidities.

with controls, particularly at younger ages ( $P < .001$  for all NICMs).

Figure 2 depicts the prevalence of Pp in patients versus controls, stratified by age. Across all age strata, Pp prevalence was significantly higher among patients, compared with controls (all  $P < .001$ ). Pp prevalence among patients aged 41–50 years was 9%, which was not significantly different from the prevalence observed among controls aged 51–60 years (6.6%;  $P = .282$ ).

Figure 3 shows the risk (probability) of Pp by age (as a continuous variable) for patients and controls in the whole cohort and the difference between the chronological age of patients and the age of controls with similar Pp risk. This age difference varied from 15 to 12 years for patients aged 40 or 60 years, respectively. For example, a 40-year-old HIV-infected person displayed a Pp risk similar to that seen in a 55-year-old control subject.

To explore the interactions among the various NICM diagnoses, a graphical model (Figure 4) was used. This model verified the hypothesis that DM, CVD, bone fracture, and renal



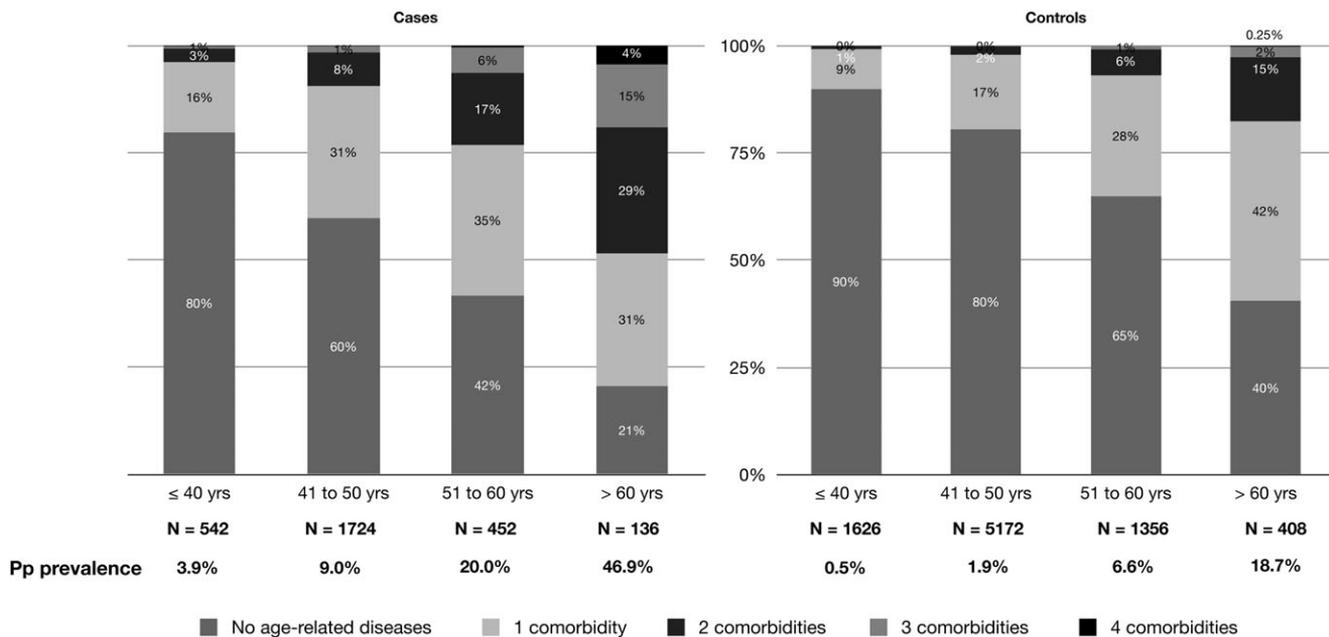
**Figure 1.** Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among patients versus control subjects.

failure were statistically independent after adjustment for sex, age, and the presence of Htn. The log-linear model evaluating this hypothesis provided a very good fit of the data ( $P = .76$ ).

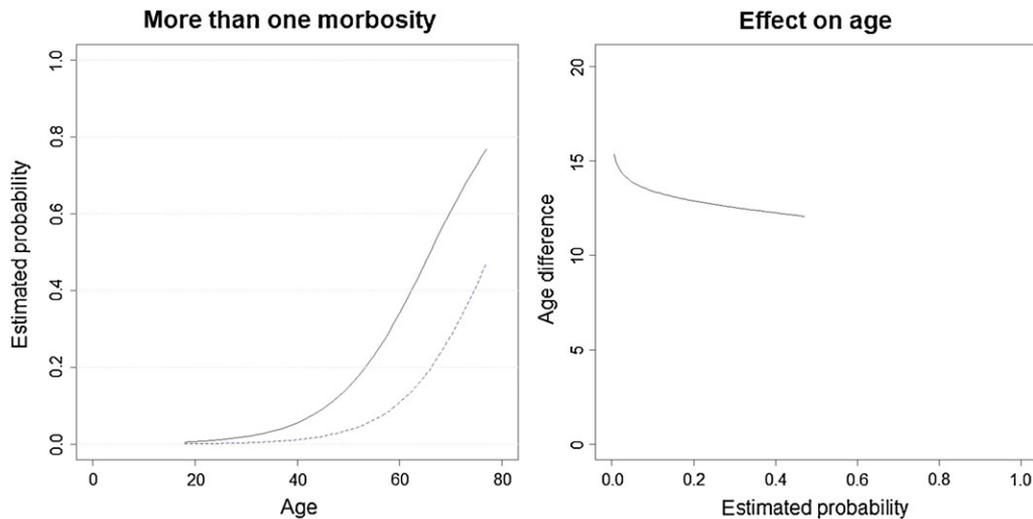
Htn was nearly always present in persons with Pp. To confirm this epidemiological link between Htn and Pp, we undertook logistic regression analyses (Figure 5) to assess the comparative risk (OR) of Pp among patients with and without Htn, with use of age as a continuous variable, in patients versus controls.

Factors significantly associated with Pp were age (per 1 year of increase: OR, 1.11; 95% CI, 1.10–1.12;  $P < .001$ ), male sex (OR, 1.77; 95% CI, 1.44–2.17;  $P < .001$ ), nadir CD4 cell count  $<200$  cells/ $\mu$ L (OR, 4.46; 95% CI, 3.73–5.34;  $P < .001$ ), and exposure to ART (per 1 month of exposure: OR, 1.01; 95% CI, 1.001–1.019;  $P = .001$ ).

In the subanalysis that included patients only, factors significantly associated with Pp were age (per 1 year of increase: OR,



**Figure 2.** Polypathology (Pp) prevalence among patients and control subjects, by age categories. The following comorbidities were included: hypertension, diabetes mellitus, hypothyroidism, cardiovascular disease, and bone fractures.



**Figure 3.** A, Risk of polyopathy (Pp), by age, among patients (continuous line) and control subjects (dotted line) in the whole cohort. B, Expected age difference between patients and control subjects at which Pp would be observed across a spectrum of odds ratios for Pp.

1.10; 95% CI, 1.08–1.12;  $P < .001$ ), male sex (OR, 1.70; 95% CI, 1.29–2.25;  $P < .001$ ), nadir CD4 cell count  $<200$  cells/ $\mu$ L (OR, 1.53; 95% CI, 1.18–1.99;  $P < .001$ ), lipoatrophy (OR, 1.56; 95% CI, 1.003–2.43;  $P = .048$ ), and lipohypertrophy (OR, 2.43; 95% CI, 1.59–3.71;  $P = .048$ ). No association with any ART drug class was found.

## DISCUSSION

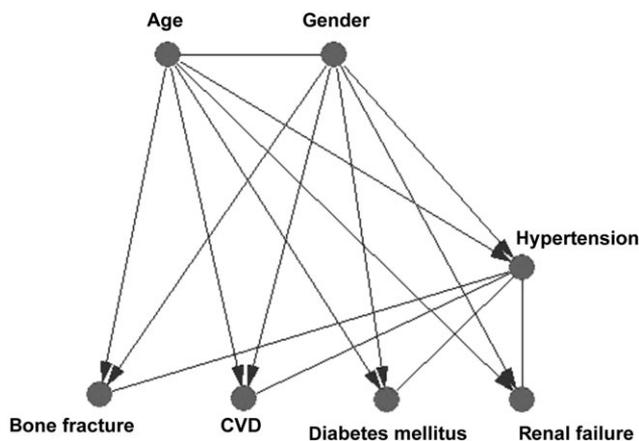
In this large case-control study that compared ART-experienced HIV-infected patients with adult control subjects from a population-based Italian national registry, we confirmed that frequently observed age-related NICMs were significantly more common in HIV-infected patients than in the general

population, in corroboration of data from other cohorts [14, 15, 23–25].

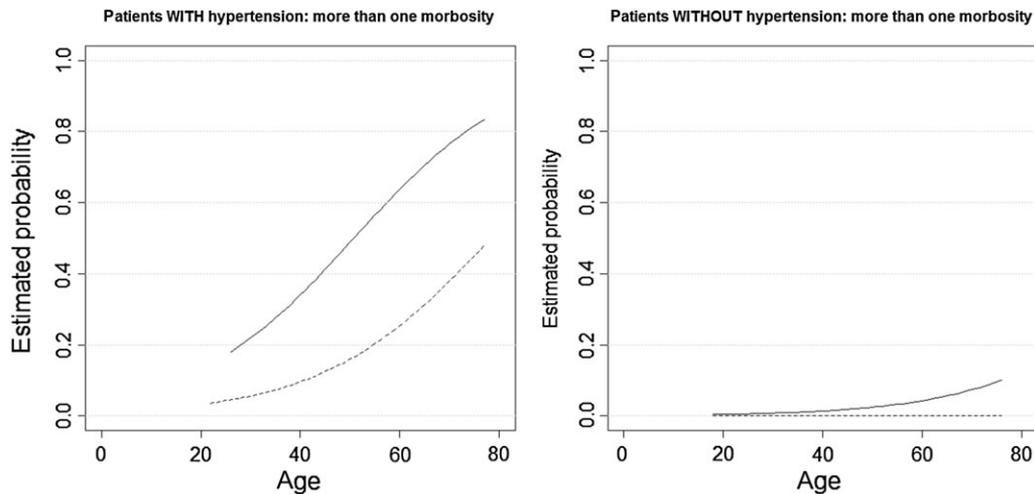
In addition, we revealed that the simultaneous presence of  $>2$  NICMs or Pp was consistently more common in HIV-infected patients than in the general population. These differences were apparent across broad age strata ranging from  $<40$  years to  $>60$  years and tended to decrease with advancing age. The prevalence of Pp among HIV-infected persons was approximately equivalent to prevalence observed in members of the general population who were 10–15 years older [26–28].

The simultaneous presence of CVD, Htn, DM, renal failure, and bone fracture can reasonably be considered to represent a frailty phenotype that has been associated with aging in the general population and is a major determinant of disability associated with geriatric syndromes [29, 30]. We believe that, in this report, by showing the premature onset of Pp among HIV-infected patients, we have contributed to the characterization of an emerging description of an HIV-specific aging phenotype.

Factors that could readily account for the occurrence of multiple traditionally age-related NICMs at significantly earlier ages among HIV-infected patients compared with HIV-uninfected persons are not immediately apparent. However, multiple hypotheses have been made to explain the premature aging that is thought to occur among HIV-infected persons, particularly those for whom ART is delayed until more advanced stages of immunodepletion and for whom more long-term chronic exposure to HIV viremia occurs [11, 31]. Pathophysiologic mechanisms that have been proposed include higher levels of chronic systemic inflammation, reduced vascular endothelial reactivity (as assessed by flow-mediated dilation), and increased endovascular hypercoagulability (as assessed by increased platelet aggregation and fibrin deposition) [2, 3, 32, 33].



**Figure 4.** Graphical model to explore the interactions among the various noninfectious comorbidity diagnoses. Abbreviation: CVD, cardiovascular diseases.



**Figure 5.** The probability of polypathology (Pp) among patients (continuous line) and control subjects (dotted line), by age, among persons with hypertension (Htn; left panel) and without Htn (right panel).

We found that HIV-specific factors (lower nadir CD4 cell count and more prolonged ART exposure) were independent predictors of Pp in multivariable regression models. Several studies have shown that both lower nadir CD4 cell count and greater cumulative exposure to ART are associated with higher prevalence of individual NICM [10]. The seeming paradox that is comprised by the apparent need for early ART to prevent NICMs that are associated with lower nadir CD4 cell count and the simultaneously apparent increased risk of NICM secondary to cumulative exposure to ART [32, 34] has been at least partially resolved by findings from the SMART (Strategies for the Management of Antiretroviral Therapy) study that have shown that HIV infection is associated with higher risk of several non-AIDS complications (including CVD and renal disease), whereas ART use reduces the risk of these events [35].

If any or all of these factors did in fact account for the excess in individual NICMs and Pp that we observed among HIV-infected persons, it is beyond the scope of this report to ascertain which of these processes were most operative. Likewise, the identification of specific ways in which these various factors and pathophysiologic processes may have interacted to result in the apparent premature aging that we observed among HIV-infected persons remains to be undertaken. Our report is a descriptive one that hopefully will be hypothesis-generating but currently highlights the differential clinical care needs of aging HIV-infected patients compared with age-matched persons in the general population (ie, HIV-infected persons may benefit from earlier screening and preemptive interventions to prevent common age-related NICMs).

We found that the diagnosis of Htn was strongly and independently associated with an increased likelihood of other NICMs being present (Pp) simultaneously, in both patients and controls, and that Pp in both groups prominently included

CVD. Although this association makes clinical and pathophysiologic sense, we nevertheless demonstrated that our observed increases in prevalence of DM, CVD, bone fracture, and renal disease occurred independently in models that adjusted for sex, age, and Htn.

Several limitations to our analysis clearly may have existed but were unavoidable. There may have been inherent differential sensitivities in our ability to detect comorbidities among patients versus controls because our methods of NICM discernment were, by necessity, different for these 2 groups. A screening bias is always present when comparing patients with chronic diseases with persons in the general population. The high prevalence of fractures observed among patients, compared with controls may have been attributable to the inclusion of self-reported diagnoses in the former. This may explain the apparent high risk of bone fractures observed in all age strata among HIV-infected patients. Moreover, we cannot fully exclude the possibility that a selection bias existed among patients who were seen at the metabolic clinic, despite the fact that we were unable to identify statistically significant differences in the prevalence of NICM and Pp between patients referred from the Modena HIV Clinic and patients referred from neighboring centers for evaluation at the metabolic clinic. In addition, factors unique to the HIV-infected population other than HIV infection itself may have existed that we could not identify but that could have resulted in increased rates of comorbid disease in this group (eg, behavioral factors). In addition, the cross-sectional nature of our study implies the possibility that a survival bias may have occurred, because patients with better prognoses were selected out, especially in the more advanced age group categories.

In conclusion, our findings suggest that an aggressive approach to the screening, diagnosis, and treatment of NICMs is warranted as part of routine healthcare for HIV-infected

patients. Furthermore, our data suggest that onset of such screening should commence at a substantially earlier age for HIV-infected persons, compared with HIV-uninfected persons, possibly at least a decade in advance. Additional studies are needed to further evaluate the impact of convergent age-related NICMs on age-related functional status, frailty, and disability among ART-experienced HIV-infected persons and to provide insights into accelerated aging processes that may be associated with chronic HIV infection.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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