Original Article

Time trend in hypertension prevalence, awareness, treatment, and control in a contemporary cohort of HIV-infected patients: the HIV and Hypertension Study

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Background: Hypertension control is often inadequate in HIV patients. In a contemporary, nationwide cohort of Italian HIV-infected adults, we assessed time trends in hypertension prevalence, awareness, treatment, and control. We also evaluated predictors of cardiovascular events and of new-onset hypertension.

Methods: Multicenter prospective cohort study, sampling 961 consecutive HIV patients (71% men, mean age 46 ± 9 years, 30% hypertensive) examined in 2010–2014 and after a median follow-up of 3.4 years.

Results: Among hypertensive patients, hypertension awareness (63% at baseline and 92% at follow-up), treatment (54 vs. 79%), and control (35 vs. 59%) all improved during follow-up. The incidence of new-onset hypertension was 50.1/1000 person-years (95% confidence interval, 41.2–60.3). Multivariable-adjusted predictors of hypertension were age, BMI, estimated cardiovascular risk, blood pressure, and advanced HIV clinical stage.
In total, 35 new cardiovascular events were reported during follow-up (11.1/1000 person-years). In a multivariate model, baseline cardiovascular risk and hypertensive status predicted incident cardiovascular events, whereas a higher $CD4^+$ cell count had a protective role. In treated hypertensive patients, the use of integrase strand transfer inhibitors at follow-up was associated with a lower SBP (average yearly change, -3.8 ± 1.6 vs. -0.9 ± 0.5 mmHg in integrase strand transfer inhibitor users vs. nonusers, respectively, $P = 0.02$).

Conclusion: Hypertension awareness, treatment, and control rates all improved in adult Italian HIV patients over the last few years, although hypertension remains highly prevalent (41%) in middle-aged HIV patients, and significantly impacts cardiovascular morbidity. Traditional risk factors and advanced HIV disease predict new-onset hypertension, whereas $CD4^+$ cell count favorably affects future cardiovascular events.

Keywords: antiretroviral therapy, blood pressure, cardiovascular disease, HIV, hypertension, integrase inhibitors, new-onset hypertension

Abbreviations: ARV, antiretroviral; BP, blood pressure; CDC, Centers for Disease Control; CI, confidence interval; CISAI, Coordinamento Italiano per lo Studio di Allergia e Infezione da HIV; HIV-HY, HIV and Hypertension Study; INSTI, integrase strand transfer inhibitors

INTRODUCTION

Hypertension is a major treatable risk factor for cardiovascular disease and a common condition in HIV-infected people, with age-related prevalence rates similar to those of the general population [1,2]. The suggestion that HIV infection and/or the use of some antiretroviral (ARV) drugs may be associated with higher blood pressure (BP) has been repeatedly raised [3–6], although conclusive evidence is missing [7]. More importantly, both elevated and borderline high BP is associated with a substantially greater relative risk of acute myocardial infarction in HIV-positive than in HIV-negative study participants [8]. Thus, identifying and appropriately managing hypertension is a clinically relevant issue in HIV-infected patients. Current clinical guidelines mandate

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preventive interventions for lifestyle modification, as well as antihypertensive drug treatment, to improve cardiovascular prognosis in HIV patients [9].

In the present study, we prospectively assessed time trends in BP and in hypertension awareness, drug treatment, and control rates in a contemporary nationwide cohort of HIV-infected patients enrolled between 2010 and 2014 and followed for a median of 3.4 years. We also investigated predictors of cardiovascular events in the whole cohort, and incidence and predictors of new-onset hypertension among those normotensive at baseline.

METHODS

The study was conducted by the Coordinamento Italiano per lo Studio di Allergia e Infezione da HIV (CISAI, Italian coordination group for the study of allergies and HIV infection). Patients were enrolled in the HIV and HYpertension (HIV-HY) study as previously reported [10], and they were followed up for an average of 3.4 years. Briefly, from May 2010 through May 2014, 1182 adult HIV patients attending scheduled or unscheduled outpatient visits at one of the centers of the CISAI group were enrolled. Anthropometric measures, smoking habits, BP, history of diabetes, lipodystrophy, chronic hepatitis, HIV stage according to the Centers for Disease Control (CDC) classification [11], use of antihypertensive drugs and lifestyle counseling were recorded using a standard data collection form. Laboratory tests included absolute $CD4^+$ T lymphocyte count, fasting total, low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, blood glucose, and creatinine levels. The combination of hypertriglyceridemia and an elevated waist circumference ('hypertriglyceridemic waist') was used as a simple clinical phenotype to identify individuals with excess visceral adipose tissue [12]. Scheduled parameters were collected by a physician at baseline and every year. All study participants provided informed consent to participate in the study, which was approved by the institutional ethics committee of the coordinating center (Ethics Committee of the Umbria Region, no. 992/07) and of each of the participating centers.

Hypertension was defined as an office SBP of at least 140 mmHg and/or a DBP of at least 90 mmHg, or those who were receiving antihypertensive therapy at the time of the index examination [13]. The diagnosis of diabetes was based on standard international criteria [14]. Office BP was measured by a physician in the outpatient clinic and measurement procedures were standardized before starting enrollment as previously reported [10]. BP was measured in both arms at first visit, and the arm with the higher value was used as the reference if significant differences were found [13]. The 10-year risk for coronary heart disease and atherosclerotic cardiovascular disease were estimated using the Framingham equation [15]. Patients were followed up by their general practitioners, and received regular clinical control of HIV infection at least every 6 months at the outpatient infectious diseases clinic. Treatment choices and BP goals were at the discretion of treating physicians and took into account current clinical guidelines. Data collection including BP measurement, cardiovascular risk assessment, and information on therapeutic and lifestyle interventions was required every year.

Awareness and treatment of hypertension were defined by self-report. Hypertension control was defined as a BP less than 140/90 mmHg. We also evaluated optimal BP control, defined as a SBP less than 120 mmHg, as well as the distance to optimal SBP in hypertensive-treated patients. The following fatal or nonfatal cardiovascular endpoints were ascertained: myocardial infarction, hospitalized heart failure, revascularized angina, coronary revascularization procedures, sudden cardiac death, stroke, peripheral arterial disease. A secondary outcome of the study was to evaluate the association between hypertension and HIV-related parameters, such as HIV disease stage, low $CD4^+$ nadir, and ARV treatment.

Statistical analysis

Categorical and discrete variables were described as frequency and percentage, continuous variables as mean and SD if normally distributed, median and interquartile range if not normally distributed.

In the crude analysis, we used the Mantel–Haenszel χ^2 test to assess the association between categorical variables. Means were compared using the analysis of variance and medians by means of Mann–Whitney U test.

The variables considered for the analysis of risk factors were the following: sex, age, family history of cardiovascular disease and hypertension, previous cardiovascular events, BMI, diabetes, presence of hepatitis, mode of HIV transmission, CDC stage, $CD4^+$ T-lymphocyte count at enrollment, nadir $CD4^+$ cell count, ARV treatment drug class used at baseline and follow-up, cumulative time on ARV treatment. Hypertension incidence rate was calculated as the number of newly diagnosed hypertensive patients, in relation to the person/years of observation forming the risk period. Cardiovascular disease rate was calculated as the number of cardiovascular events occurring during the observation period, in relation to the person/years of overall observation. Confidence intervals (CI) at 95% were calculated based on mid-P value [16].

Hazard ratios were calculated, and logistic regression was used to adjust simultaneously for the potentially confounding effects of selected variables, according to the Cox model [17]. Variables significant at univariate were subsequently included in the model equation as appropriate (i.e., scores were adjusted only for variables not included in their calculation and correlated variables were included in turn). Statistical analysis was performed using the SAS/STAT statistical package (version 9.4; SAS Institute Inc., Cary, North Carolina, USA).

RESULTS

Overall, 961 patients out of 1182 (81.3%) had at least 1 follow-up visit with BP determination and information about cardiovascular events after enrollment. Table 1 shows patients' characteristics. Mean age at enrolment was 46.4 years (range 18–78, SD 9.5). In total, 92% of patients were Caucasian; 6.1 and 1.6% were ARV-treatment naïve at enrollment and at the last visit, respectively. The median follow-up time was 3.4 years (interquartile range 2.9–3.9).

TABLE 1. Patients' characteristics at baseline and last visit ($n = 961$)

Variable	Baseline *n* (%) or mean (SD) or median (IQR)	Follow-up *n* (%) or mean (SD) or median (IQR)
Age, mean (SD)	46.4 (9.5)	49.8 (9.4)
Time on study (years), mean (SD)	NA	3.4 (0.8)
Men (%)	681 (70.9)	
Caucasian ethnicity, *n* (%)	884 (92.0)	NA
Family history of CV disease, *n* (%)	277 (28.8)	277 (28.8)
BMI ($kg \times m^{-2}$)	24.4 (3.9)	24.6 (4.1)
HIV risk factor, *n* (%)		
Intravenous drug users	214 (22.3)	
Sexual transmission	703 (73.2)	
Other	38 (4.0)	
Missing	6 (0.6)	
Smokers, *n* (%)		
No	364 (37.9)	333 (34.6)
Current	449 (46.7)	449 (46.7)
Former	148 (15.4)	179 (18.6)
CDC stage, *n* (%)		
A	433 (45.1)	434 (45.2)
B	237 (24.7)	234 (24.4)
C	273 (28.4)	273 (28.4)
Missing	18 (1.9)	20 (2.1)
Antiretroviral-naïve, *n* (%)	59 (6.1)	15 (1.6)
HIV-RNA detectable, *n* (%)	187 (19.5)	122 (12.7)
$CD4^+$ cell count, mean (SD)	620 (313)	688 (335)
Metabolic syndrome, *n* (%)	303 (31.5)	266 (27.7)
Diabetes, *n* (%)	42 (4.4)	53 (5.5)
Hypertension, *n* (%)	293 (30.5)	399 (41.5)
SBP (mmHg), mean (SD)	124 (14)	123 (14)
DBP (mmHg), mean (SD)	79 (10)	78 (9)
Glucose (mg/dl), mean (SD)	91.2 (20.4)	92.8 (20.9)
Total cholesterol (mg/dl), mean (SD)	198 (45)	197 (43.6)
HDL-cholesterol (mg/dl), mean (SD)	47 (15)	49 (16.3)
Triglycerides (mg/dl), median (IQR)	131 (91–191)	126 (90–186)
10-year Framingham Risk, median (IQR)	7.0 (3.9–12.3)	8.0 (4.3–14.7)
eGFR (ml/min per 1.73 m^2), mean (SD)	95 (80–112)	93 (78–112)
Chronic hepatitis, *n* (%)	275 (28.6)	252 (26.2)

BP, blood pressure; CDC, Center for Disease Control; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein.

Hypertension awareness, treatment, and control rates

In total, 293 (30.5%) patients were hypertensive at baseline. Among them, 62.8% ($n = 184$) were aware of their hypertensive condition, and 37.2% ($n = 109$) were unaware of their condition. Among hypertensive patients, 54.6% were on treatment at baseline. Hypertension control had been achieved in 35.2% of the patients, whereas 19.4% had high BP despite treatment, and 8.2% were aware but untreated.

Overall, 399 study participants were hypertensive at last follow-up visit; 316 (79.2%) were receiving lifestyle and/or drug treatment. Hypertension control was achieved in 58.6%, whereas 20.6% had high BP despite treatment, 13.3% were aware but untreated, and 7.5% were unaware of their hypertensive condition.

In the whole sample, awareness, treatment, and control rates of hypertension increased over time (Fig. 1). During the follow-up period, hypertension awareness increased substantially from 62.8 to 92.5%. Treatment rate also increased from 54.6 to 79.2%. Control rate was 35.2% at baseline and 58.6% at follow-up.

The 'optimal' target of SBP 120 mmHg or less was reached in 14% and in 27% of the patients with treated hypertension at baseline and at last follow-up visit. The individual distance from 'optimal' target of SBP was 17.3 (SD 13.8) mmHg and 11.7 (SD 14.2) mmHg at baseline and at last follow-up, respectively.

At follow-up, BP control rate was similar in ARV-treatment compliant and noncompliant patients (64.8 and 62.5%, respectively). Among hypertensive patients, the use of integrase strand transfer inhibitors (INSTI) at follow-up ($n = 78$) was associated with a significant reduction in SBP (average yearly SBP change, -3.1 ± 1.3 vs. -0.5 ± 0.4 mmHg in 321 patients not on INSTI, $P = 0.01$), but not in DBP. The above difference was also significant in the subgroup ($n = 61$) of patients under antihypertensive treatment (average yearly SBP change, -3.8 ± 1.6 vs. -0.9 ± 0.5 mmHg in patients not on INSTI, $P = 0.02$). Age-adjusted changes held significant in patients under BP-lowering treatment, but not in untreated patients (-0.6 ± 1.9 vs. $+0.1 \pm 0.6$ mmHg, $P = 0.68$).

As shown in Fig. 2, the proportion of hypertensive study participants taking combination BP-lowering treatment did not change from baseline to follow-up (44 vs. 43%, respectively). At follow-up, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were the most frequently used drugs (78%). Calcium-channel blockers were used in 19% of patients, diuretics in 25%, and β-blockers in 26%.

New-onset hypertension

Among the 668 patients who were normotensive at baseline, a total of 106 (16%) developed hypertension. The incidence of new-onset hypertension was 50.1/1000 person-years (95% CI, 41.2–60.3). Predictors of new-onset hypertension are reported in Table 2. At the univariate analyses, new-onset hypertension was predicted by age, BMI, current smoking, SBP and DBP, total cholesterol, hypertriglyceridemic waist, low estimated glomerular filtration rate, and CDC stage.

At multivariate analysis, these findings were confirmed for age, BMI, estimated cardiovascular risk, SBP and DBP, whereas hypertriglyceridemic waist and total cholesterol had borderline statistical significance. Among HIV-related variables, CDC stage B and C at study entry (Fig. 3) was strongly predictive of hypertension onset compared with CDC stage A, even after taking into account all the other significantly associated variables.

Cardiovascular events

Overall, 35 cardiovascular morbid events were reported during follow-up (rate 11.1/1000 person-years, 95% CI 7.9–15.3). Patients with incident cardiovascular events were older and had a higher Framingham Risk Score; they also had more frequently hypertension, a family history of

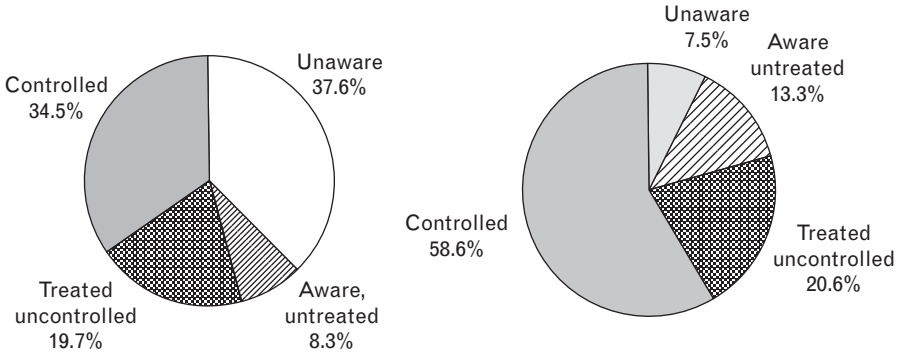

FIGURE 1 Hypertension awareness, treatment and control rates in HIV-positive hypertensive study participants at baseline (left panel) and at the last follow-up visit (right panel).

cardiovascular events, a CDC stage C disease, and a lower $CD4^+$ cell count (Table 3). In a multivariate model, after adjusting for sex, age, previous cardiovascular events, hypertension diagnosis (or estimated cardiovascular disease risk), we found that a higher $CD4^+$ cell count significantly predicted a lower cardiovascular event rate ($P = 0.017$ for trend). Duration of HIV infection, ARV treatment, and nadir $CD4^+$ cell count less than 50/ml were not related to incident cardiovascular event rate in the multivariate model.

DISCUSSION

In the general population, 45% of coronary deaths and 51% of stroke deaths have been attributed to high BP [18], and hypertension is reported to be the single most important contributor to disease burden under a worldwide perspective [19]. With longer life expectancy because of better ARV treatment, hypertension has emerged as a frequent comorbid condition in HIV patients. There are only limited prospective data on how well HIV-infected patients are treated for hypertension [10,20].

In the present observational study, carried out in a large, unselected cohort of Italian HIV-infected patients, mostly on ARV treatment, in routine outpatient clinical care, we observed a significant improvement over a median 3.4-year period in hypertension awareness (63% at baseline and 92% at follow-up), treatment (54 vs. 79%), and control (35 vs. 59%). Patients were followed in their routine outpatient care, and no specific interventional measures were attempted within the study. Our findings suggest that there is an important need to implement programs to provide all HIV professionals with the knowledge base to navigate the increasingly complex demands of comprehensive HIV care, particularly in light of the rising importance of HIV-associated non-AIDS conditions in the aging HIV population. Understanding and optimizing preventive care in HIV patients is essential in maintaining the substantial advances in prognosis for those study participants. Although HIV patients are considered at high cardiovascular risk, they still tend to be undertreated in terms of drugs for cardiovascular prevention [21].

Adequate BP control is considered the mainstay in reducing cardiovascular risk in hypertension [22]. Although a SBP/DBP goal below 140/90 mmHg is currently suggested for most hypertensive patients [13], the recent Systolic Blood Pressure Intervention Trial (SPRINT) showed that lowering SBP to a goal of less than 120 mmHg, as compared with the standard goal of less than 140 mmHg, may result in lower rates of fatal and nonfatal cardiovascular events and death from any cause [23]. In our cohort study, a SBP less than 120 mmHg was obtained only in 27% of hypertensive-treated patient at the last visit, and the average distance from optimal control was 11.7 (SD 14.2) mmHg.

In our study, angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers were the preferred antihypertensive drugs in about 80% of cases, probably because of a combination of good tolerability and lowest risk of drug interactions with ARV. In addition, these treatments may show anti-inflammatory benefit for HIV-infected persons [24,25].

The potential effect of ARV treatment on hypertension was raised by previous reports [3,4]; specifically, ritonavir-boosted protease inhibitors may induce the activation of the renin-angiotensin system, thus contributing to the development of hypertension [26]. A recent meta-analysis of 39 cross-sectional and cohort studies confirmed that ARV treatment exposure is significantly associated with increases in BP and the risk of developing hypertension [27], although in that review, most studies did not include treatment with INSTI. Interestingly, in our analysis, patients on INSTI had a significant reduction of SBP during follow-up. Although the impact of INSTI on hypertension had received little

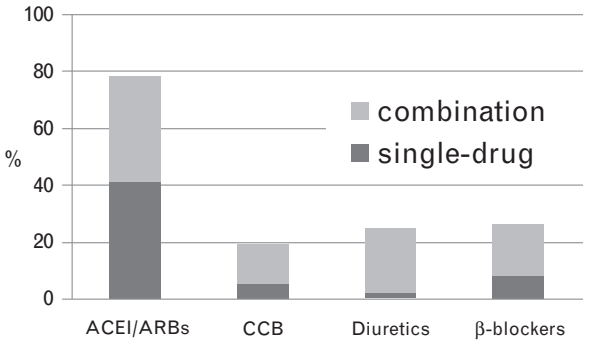

FIGURE 2 Proportion of study participants with treated hypertension under different antihypertensive drug classes (as single-drug or combination treatment) at the last follow-up visit. ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin-receptor blockers; CCB, calcium-channel blockers.

TABLE 2. Baseline characteristics and predictors of hypertension in 668 HIV-infected patients with normal blood pressure at study entry, who did or did not develop hypertension during follow-up

Variable	No hypertension ($n = 562$)	Hypertension ($n = 106$)	Crude HR (95% CI)	Adjusted[a] HR (95% CI)	*P*
Female sex (%)	33.3	29.2	0.76 (0.49–1.16)		
Age (years), mean (SD)	44.2 (8.7)	48.6 (9.3)	1.05 (1.03–1.07)	1.04 (1.02–1.06)	0.0006
BMI ($kg \times m^{-2}$), mean (SD)	23.6 (3.5)	24.7 (4.1)	1.06 (1.01–1.11)	1.06 (1.01–1.12)	0.03
Smoking, *n* (%)					
No	210 (37.4)	37 (34.9)	1	1	
Current	281 (50.0)	47 (44.3)	1.88 (1.11–3.19)	1.22 (0.70–2.14)	0.48
Former	71 (12.6)	22 (20.8)	0.91 (0.59–1.41)	0.83 (0.52–1.30)	0.41
Family history of hypertension, *n* (%)	108 (26.0)	25 (31.2)	1.17 (0.72–1.89)		
Previous cardiovascular events, *n* (%)	10 (1.8)	6 (5.7)	3.48 (1.52–7.95)	2.35 (0.98–5.63)	0.05
10-year Framingham risk, *n* (%)					
<10	432 (76.9)	62 (58.5)	1	1	
10–20	88 (15.7)	25 (23.6)	1.84 (1.15–2.93)	1.72 (1.06–2.80)	0.03
>20	22 (3.9)	13 (12.3)	3.80 (2.08–6.94)	3.20 (1.69–6.06)	0.0004
Not available	20 (3.6)	6 (5.7)	2.84 (1.21–6.63)	2.50 (1.06–5.91)	0.04
CDC stage, *n* (%)					
A	277 (50.1)	38 (36.9)	1	1	
B	130 (23.5)	28 (27.2)	1.78 (1.08.2.92)	1.99 (1.18–3.35)	0.009
C	146 (26.4)	37 (35.9)	1.99 (1.26–3.16)	1.90 (1.18–3.03)	0.007
CD4 nadir (cells/μl), *n* (%)					
≥50	439 (80.7)	81 (79.4)	1		
<50	105 (19.3)	21 (20.6)	1.13 (0.70–1.83)		
CD4 cell count (cell/ml), *n* (%)					
<200	29 (5.2)	7 (6.6)	1		
200–349	66 (11.9)	16 (5.1)	0.91 (0.38–2.21)		
≥350	461 (82.9)	83 (78.3)	0.66 (0.30–1.42)		
Hypertriglyceridemic waist, *n* (%)	76 (13.5)	29 (27.4)	2.00 (1.29–3.11)	1.58 (0.97–2.55)	0.06
Total cholesterol (mg/dl), mean (SD)	194.6 (43.8)	210 (58.1)	1.05 (1.01–1.08)[b]	1.04 (1.00–1.08)[b]	0.05
SBP (mmHg), mean (SD)	116.4 (9.9)	124.0 (8.9)	1.07 (1.05–1.09)	1.06 (1.04–1.09)	<0.0001
DBP (mmHg), mean (SD)	74.5 (6.8)	78.0 (5.8)	1.08 (1.04–1.11)	1.06 (1.03–1.10)	0.0005
eGFR (ml/min per 1.73 m^2), *n* (%)					
>90	364 (64.9)	55 (52.4)	1	1	
60–90	182 (32.4)	47 (44.8)	1.52 (1.02–2.25)	1.38 (0.92–2.07)	0.12
<60	15 (2.7)	3 (2.9)	1.30 (0.41–4.16)	0.65 (0.16–2.74)	0.56

BP, blood pressure; CDC, Center for Disease Control; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
[a]Adjustment was allowed, in turn for: age, BMI, and CDC stage at baseline. Scores were adjusted only for variables not included in their calculation.
[b]by 10 mg/dl.

attention so far, our data suggest a potentially favorable role on BP control. Potential explanation for this finding, which needs to be confirmed in properly designed studies, is the improvement in plasma biomarkers associated with atherosclerosis, observed in switch from boosted protease inhibitors to raltegravir in the switching from protease inhibitor to raltegravir (SPIRAL) study [28], and the lower drug–drug interaction between INSTI and antihypertensive

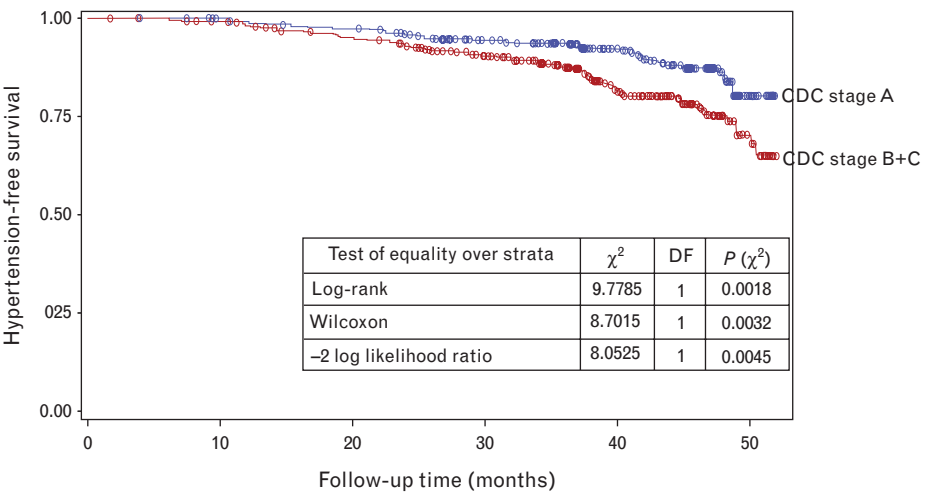

FIGURE 3 Hypertension-free Kaplan–Meier survival curves in HIV patients and CDC stage A (blue line), or CDC stage B or C (red line). CDC, Center for Disease Control.

TABLE 3. Selected characteristics of study participants with or without incident cardiovascular events. Crude and adjusted hazard ratios for cardiovascular events are also reported

Variable	No CV events[a] ($n=926$)	CV events[a] ($n=35$)	Crude HR (95% CI)	Adjusted[b] HR (95% CI)	P
Sex					
Male	653	28	1		
Female	273	7	0.58 (0.26–1.34)		
Age (years)					
≤50	529	13	1	1	
>50	397	22	2.18 (1.10–4.33)	1.71 (0.84–3.47)	0.14
Family history of CV events					
No	642	23	1		
Yes	265	12	1.30 (0.65–2.62)		
Previous CV events					
No	888	31	1	1	
Yes	38	4	3.07 (1.08–8.71)	2.38 (0.59–5.18)	0.31
10-year Framingham risk					
<10%	597	11	1	1	
10–20%	196	12	3.28 (1.44–7.43)	2.68 (1.03–7.00)	0.04
>20%	98	11	6.22 (2.69–14.38)	4.24 (1.24–14.45)	
Hypertension diagnosis					
No	552	10	1	1	
At baseline	278	15	3.14 (1.41–7.00)	2.42 (1.08–5.42)	0.007
At follow-up	96	10	5.30 (2.21–12.74)	4.27 (1.69–10.81)	
CDC stage					
A-B	651	19	1	1	
C	258	15	2.02 (1.02–3.97)	1.67 (0.84–3.32)	0.15
Years of HIV infection, quartile					
≤5.0	229	8	1		
5.1–11.0	234	6	0.77 (0.27–2.21)		
11.1–18.0	242	12	1.36 (0.54–3.46)		
≥18.0	205	6	1.06 (0.40–2.83)		
Years of ARV treatment, quartile					
≤3.2	222	10	1		
3.2–8.4	225	6	0.63 (0.23–1.73)		
8.5–13.3	224	7	0.70 (0.26–1.83)		
≥13.4	220	11	1.34 (0.57–3.17)		
$CD4^+$ nadir (cells/μl)					
≥50	730	25	1		
<50	167	8	1.38 (0.62–3.06)		
$CD4^+$ cell count, quartile (cells/μl)					
≤415	224	15	1	1	
416–569	229	12	0.77 (0.36–1.64)	0.82 (0.38–1.80)	0.048
570–775	235	2	0.14 (0.03–0.59)	0.16 (0.04–0.69)	
≥776	231	6	0.41 (0.16–1.05)	0.40 (0.14–1.14)	0.017
Trend			0.62 (0.45–0.87)	0.66 (0.47–0.92)	

ARV, antiretroviral; CDC, Center for Disease Control; CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
[a]The sum may occasionally not add up to the total because of missing values.
[b]Adjustment was allowed, in turn, for age, sex, previous CV events, CDC stage C, hypertension diagnosis. Scores were adjusted only for variables not included in their calculation.

drugs [9]. Polypharmacy in HIV patients may increase the rate of drug–drug interactions and facilitate drug toxicity and low treatment compliance. The lower rate of interaction between INSTI and antihypertensive drugs may theoretically facilitate the achievement of an adequate BP control. In this contemporary cohort with a relatively high rate of HIV-viral control and good $CD4^+$ cell recovery, we could not confirm the association reported by others [29] between suboptimal control of HIV viremia and insufficient control of hypertension.

In this study, carried out in HIV-infected patients with an average age around 50 years, the overall prevalence of hypertension at last follow-up was as high as 41%. In previous studies on HIV-infected patients, the prevalence ranged from 13 to 49% [1,2,4,6,7,30], thus hypertension is a common event in the course of HIV infection, at least as important as in the general population. In addition, we observed a rate of new-onset hypertension of 50.1/1000 person-years. The crude hypertension incidence observed in the present study is intermediate between previous reports from HIV people. Indeed, new onset of hypertension per 1000 person-years occurred with an incidence of 72.1 from patients enrolled in Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study (mean age 39 years, follow-up 2.3 years) [31], 34.4 from the University of North Carolina HIV Clinical Cohort (UCHCC; median age 36 years, follow-up 5.5 years) [32], and 29.8 in HIV individuals in a Norwegian cohort aged 43 years with a 3.4-year follow-up [33]. The incidence of hypertension was higher in a study carried out in African patients (111.5/1000 person-year) [34].

In previous studies, hypertension had been associated mainly with traditional risk factors such as aging and the metabolic syndrome [31]. Although we confirmed these previous findings, we also found that a more advanced HIV disease, defined as a CDC stages B and C, was a significant independent predictor of new-onset hypertension. This observation is in line with the recent report by Okeke *et al.* [32], who found that a low nadir $CD4^+$ cell count is associated with incident hypertension. More interesting, we also found that a high $CD4^+$ cell count is associated with a lower rate of future cardiovascular complications. This suggests that an adequate treatment of HIV infection may play a role in cardiovascular risk management in these patients.

The present study has a number of strengths. We examined a well characterized, unselected multicenter sample of Italian HIV-infected outpatients, followed at current infectious diseases clinics, which likely represents the general assisted population at the same sites. We adopted a validated and standardized procedure for BP measurements for all observed patients.

The most relevant limitations in our present work include the relatively high rate of dropouts, and the lack of a parallel control group of uninfected individuals. Although standardized, BP was measured only in the physician's office following current guidelines, and no systematic home or 24-h ambulatory BP monitoring was performed. Even if no specific intervention was attempted to improve cardiovascular risk management in this study, the investigators at sites participating in the HIV-HY study are likely to be particularly interested in cardiovascular risk; thus, changes in risk factors in this cohort may not necessarily mirror those reported elsewhere. Finally, the relatively small sample size, the short follow-up and the limited number of events precluded an extensive multivariate analysis of morbidity and mortality, although assessment of cardiovascular events was not a primary objective of the study.

In conclusion, we showed that clinical management of hypertension improved over the last few years in an Italian HIV-infected cohort, although it remains inadequate in many HIV patients. Traditional risk factors and advanced HIV disease both predict new-onset hypertension, and a high $CD4^+$ cell count may have a protective role on future cardiovascular events. A higher level of attention to traditional risk factors is warranted in the clinical setting of HIV infection.

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The authors had full access to the data and take responsibility for their integrity. All authors have read and agreed to the manuscript as written.

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The HIV-HY group

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Conflicts of interest

There are no conflicts of interest.

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