Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003

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Objective: To examine the impact of HIV infection and highly active antiretroviral therapy on systolic and diastolic hypertension.

Design: Cohort study with semi-annual assessment of the outcome.

Methods: We studied 5578 participants of the Multicenter AIDS Cohort Study with blood pressure measurements obtained between 1984 and 2003. The primary outcomes were systolic hypertension (SH; systolic blood pressure > 140 mmHg) and diastolic hypertension (DH; diastolic blood pressure > 90 mmHg). Statistical analyses were performed using multiple logistic regression with robust variance estimation.

Results: Of the 84 813 person-visits available for analysis, 7.3 and 8.0% showed SH and DH, respectively. Controlling for age, race, body mass index, and smoking, HIV positive men not taking antiretroviral therapy were significantly less likely than HIV negative men to have SH [odds ratio (OR), 0.79; 95% confidence interval (CI), 0.70–0.89], as were men taking mono/combination therapy (OR, 0.69; 95% CI, 0.59–0.80). The prevalence of SH among men taking highly active antiretroviral therapy (HAART) for less than 2 years was similar to that among HIV negative men (OR, 1.06; 95% CI, 0.87–1.30), but was significantly higher thereafter; for 2 to 5 years of HAART (OR, 1.51; 95% CI, 1.25–1.82) and for more than 5 years of HAART (OR, 1.70; 95% CI, 1.34–2.16). In contrast, DH was not significantly higher among men with prolonged HAART use compared to that among HIV negative controls.

Conclusions: Prolonged HAART use was significantly associated with a higher prevalence of SH. This finding suggests that individuals taking HAART may be at increased risk of developing hypertension-related conditions and underscores the importance of blood pressure monitoring among these individuals.

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Introduction

Since the introduction of highly active antiretroviral therapy (HAART) in the mid 1990s, AIDS-related morbidity and mortality rates dropped markedly [1,2] whereas concerns of a link between HAART and coronary heart disease (CHD) have increased. An elevated risk of myocardial infarction (MI) among people taking HAART has been found in some [3–5] but not all [6,7] studies. Carotid intima–media thickness (IMT), a marker of atherosclerotic disease, may increase more rapidly with age in HIV-infected persons than in HIV-uninfected controls [8], but neither the duration of the use of protease inhibitors (PI) [8] nor the use of HAART [9] were found to be associated with carotid IMT in cross-sectional studies that adjusted for traditional cardiovascular disease risk factors [9]. Additionally, PI use has been linked to an increased prevalence of carotid artery atherosclerotic lesions [10], but HIV infection, rather than PI use, was found to be associated with carotid plaques [11] and with hospitalizations related to CHD [12].

Investigators have also assessed the relationship between the use of antiretroviral therapy and components of the metabolic syndrome [13] including dyslipidemia [14–16], insulin resistance [14,15], and abnormal body fat distribution [15]. HAART, and especially PIs, seem to be associated with metabolic dysfunction and may lead to an increased risk of cardiovascular events [17], yet the events, pathways, and mechanisms remain to be clarified.

The relationship between HAART and hypertension, another component of the metabolic syndrome, has not been well studied [18]. Conflicting results have been reported for the association between anti-HIV therapy and blood pressure (BP) [19,20] and for the association between HAART and the prevalence of hypertension [21,22]. Interestingly, increased BP has been found to be associated with lipodystrophy [23], providing additional evidence that HAART and hypertension may be linked via pathways involving lipodystrophy or other metabolic disorders [24].

The aim of our study, conducted using data from a large HIV cohort study, the Multicenter AIDS Cohort Study (MACS), with nearly 20 years of accrued follow-up, was to examine the association of hypertension with HIV infection and HAART while adjusting for age, race, smoking, and body mass index (BMI). An important strength of our study is the availability of a comparison group of HIV-negative individuals from the same source population who were followed under the same protocol.

Methods

Study cohort

We analyzed data from the MACS, an ongoing observational study of men in four metropolitan areas of the United States (Baltimore, MD/Washington DC; Chicago, IL; Pittsburgh, PA; and Los Angeles CA) who reported having had sex with men. Recruitment and follow-up procedures for the MACS have been described previously [25,26]. Briefly, during semi-annual visits, HIV clinical markers were assessed, interviewer-administered questionnaires were completed, physical examinations were performed, and biological specimens were obtained to measure markers of HIV/AIDS disease and for repository storage. Longitudinal HIV serology testing was performed using an enzyme-linked immunosorbent assay with western blot confirmation. All 5622 participants enrolled in 1984–1985 ($n = 4954$) and in 1987–1995 ($n = 668$) were eligible to contribute data to our study. We analyzed data collected up to 31 March 2003. The MACS protocol and forms were approved by the institutional review board at each site, and all study participants provided written informed consent.

Study outcomes

Blood pressure was measured during physical examinations conducted at the semi-annual visits. These BP measurements were taken by clinically trained study personnel according to their own practice and, thus, correspond to the clinical BP values obtained from this large cohort of individuals followed for nearly 20 years. The intra-class correlation coefficients (ICC) assessing the within-patient agreement of the BP measurements at consecutive visits during 1985, 1993, and 2002 ranged from 0.37 to 0.57 for SBP and from 0.28 to 0.56 for DBP reflecting fair to moderate agreement for pairs of clinical BP measurements obtained approximately 6 months apart. The ICCs did not differ across the study sites or calendar time.

The primary outcomes for this study were systolic hypertension (SH), defined as systolic BP greater than 140 mm Hg, and diastolic hypertension (DH), defined as diastolic BP greater than 90 mmHg. We also conducted a second set of analyses that incorporated anti-hypertension therapy (AHT) into the study design where the outcomes were defined to be the combined outcomes of SH or taking AHT (SH/AHT) and DH or taking AHT (DH/AHT). The results from these secondary analyses with correlated outcomes (i.e., both outcomes included AHT) are not detailed in this report because our primary objective was to investigate the differential effects of antiretroviral therapies on SH and DH.

Primary exposure

Antiretroviral therapy (ART) was determined by self-report on an interviewer-administered questionnaire. Participants listed each medication that they were taking at the time of the visit and all medications they had taken since the previous visit. We classified the ART reported since the previous visit into one of three broad categories: no therapy, mono/combination therapy, or HAART. Based on guidelines from a panel of the Department of

Health and Human Services and the Henry J. Kaiser Family Foundation [27], HAART was defined as: (a) two or more nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor (PI) or one non-nucleoside reverse transcriptase inhibitor (NNRTI); (b) one NRTI in combination with at least one PI and at least one NNRTI; (c) a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTIs; and (d) an abacavir- or tenofovir-containing regimen of three or more NRTIs in the absence of both PIs and NNRTIs. Combinations of zidovudine (ZDV) and stavudine (d4T) with either a PI or NNRTI were not considered HAART, but were classified as combination therapy.

Follow-up time was classified according to HIV serostatus and ART. Prior to HAART initiation, person-visits were stratified by HIV status and ART category. For men taking HAART, the duration of HAART exposure was estimated as the time since HAART initiation. We further stratified the HAART group to investigate the impact of the duration of HAART exposure (categorized as less than 2 years, 2 to 5 years, and more than 5 years since HAART initiation), whether or not HAART included a PI, and HAART discontinuation on the study outcomes. Person-visits occurring after HAART discontinuation were grouped into a single category regardless of whether or not any individual ART medications were taken. However, for the men who later resumed HAART, the person-visits that occurred following HAART resumption were classified into one of the three HAART exposure categories defined above based on the total cumulative duration of HAART exposure. Thus, a participant could contribute data to all groups: HIV negative, HIV positive without any therapy, HIV positive on mono or combination therapy, taking HAART for 0–2 years, taking HAART for 2–5 years, taking HAART for more than 5 years, and having discontinued HAART.

Statistical analysis

Because the measurement error resulting from clinical BP measurements would probably result in the overestimation of the true incidence of hypertension, we conducted this analysis of the factors associated with prevalent rather than incident hypertension to minimize the potential impact of this form of measurement error on our study. The basic unit of analysis was the person-visit, with each participant contributing data for up to 38 visits (19 years). Descriptive statistics were used to characterize the study population at enrollment and to summarize the cohort characteristics across all person-visits. We determined the average prevalence of SH and of DH by calculating the percentage of person-visits at which each outcome was documented. Multiple logistic regression with robust variance estimation [28] was used to assess the association between ART use and the prevalence of hypertension while adjusting for potential confounding factors and simultaneously accounting for within-subject correlation. Except for race, all other potential confounders (age, BMI, smoking status, and HIV status) were treated as time-dependent covariates. We quantified the magnitudes of the associations using the odds ratio (OR) and the corresponding statistical strengths using 95% confidence intervals (CI) and *P*-values. Statistical significance was defined as a *P*-value less than 0.05. All statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, North Carolina, USA).

Results

The study population included 5578 (99.2%) of the 5622 eligible men enrolled in the MACS. A total of 84 813 person-visits were included in this analysis, and the median number of person-visits per participant was 14 (inter quartile range: 6 to 22).

The characteristics of the study cohort at enrollment and across all visits are summarized in Table 1. At enrollment, the median age was 32.6 years, the median BMI was 23.1 kg/m^2, 83.3% were Caucasian, 58.9% had a history of smoking, 39.9% were HIV positive, and the median systolic and diastolic blood pressure levels were 120 and 80 mmHg, respectively. During follow-up the median BMI increased to 25.8 kg/m^2 in 2003, and the prevalence of active smoking declined from 39.2% at enrollment to 18.5% at the end of follow-up. Of the 3351 men who were HIV negative at baseline, 520 (15.5%) became HIV positive during follow-up. Overall, ART use was reported at 12 215 (35.0%) of the 34 929 person-visits from the HIV-positive participants, and HAART was reported at 4535 (37.1%) visits. However, therapy use varied over time with 30% of MACS participants taking ART in 1990 whereas 80% were taking ART and 65% were taking HAART in 1998 [29].

The prevalence of SH and of DH stratified by the participant characteristics are summarized in Table 2. Both SH and DH were present in 5.9% of the men at enrollment, but across all person-visits these percentages increased to 7.3 and 8.0%, respectively. The prevalence of hypertension was higher among African-Americans and former smokers, and increased with age and BMI. We also observed a higher prevalence of hypertension, especially SH, among HIV-positive men taking HAART in comparison with the HIV-positive men not taking HAART.

The prevalence of hypertension stratified by HIV serostatus and therapy is displayed in Fig. 1. Among the 49 884 person-visits from HIV-negative men, SH and DH were present in 8.3 and 9.0%, respectively, but were distinctly lower among HIV-positive men not taking any ART (5.0% with SH and 6.1% with DH) and among men taking ART but not HAART (5.4% with SH and 6.2% with DH). The prevalence of both SH and DH were

Table 1. Participant characteristics and blood pressure outcomes at baseline and across follow-up.

Characteristics	Baseline		All visits	
	No. participants	Percentage	No. visits	Percentage
All	5578	100.0	84813	100.0
Age (years)				
< 30	1981	35.5	10874	12.8
30–39	2568	46.0	35421	41.8
40–49	845	15.2	27717	32.7
≥ 50	184	3.3	10801	12.7
Race/ethnicity				
Caucasian	4647	83.3	73954	87.2
African-American	562	10.1	6120	7.2
All others	369	6.6	4739	5.6
Body mass index (kg/m^2)				
< 20	451	8.1	4767	5.6
20–24.9	3794	68.0	48178	56.8
25–29.9	1079	19.3	25004	29.5
≥ 30	254	4.6	6864	8.1
Smoking history				
Never	2274	41.1	30719	36.4
Former	1094	19.8	28844	34.2
Current	2168	39.2	24858	29.4
Missing	42	–	392	–
HIV sero-status				
Negative	3351	60.1	49884	58.8
Positive	2227	39.9	34929	41.2
Taking antiretrovial therapy[a]				
No	2213	99.4	22714	65.0
Yes	14	0.6	12215	35.0
Taking HAART[b]				
No	14	100.0	7680	62.9
Yes	0	–	4535	37.1
Calendar period				
1984–1987	5198	93.2	28456	33.6
1988–1991	365	6.5	25748	30.4
1992–1995	15	0.3	17399	20.5
1996–2003	0	–	13210	15.6
Blood pressure outcomes				
Systolic BP > 140 mmHg	327	5.9	6222	7.3
Diastolic BP > 90 mmHg	330	5.9	6757	8.0
Taking anti-hypertension medications[c]	–	–	2984	7.3

[a]Percentages are based on HIV-positive men.
[b]Percentages are based on HIV-positive men taking antiretroviral therapy.
[c]Documentation of anti-hypertension (AH) medications began in April 1990 and, thus, AH medications were not recorded at baseline; percentage is based on the 40 775 person-visits at which AH medications were documented. HAART, highly active antiretroviral therapy. BP, blood pressure.

markedly higher among the 4535 person-visits from men taking HAART: 12.0% with SH and 9.2% with DH.

Figure 1 also depicts the temporal relationship between the prevalence of hypertension and the duration of HAART exposure. The percentage of men with DH remained relatively constant for the 5 years following HAART initiation, similar to the prevalence rate observed among HIV-negative men. In contrast, the prevalence of SH was stable at 8 to 9% during the first 2 years following HAART initiation and then increased sharply to approximately 13% where it remained for several years. With more than 5 years of HAART exposure, the prevalence of both SH and DH appeared to increase although these estimates are based on comparatively little information and, thus, are subject to greater uncertainty.

The results from the multiple logistic regression analyses are shown in Table 3. Higher age, African-American race, and higher BMI were independently associated with higher prevalence rates of SH. We also observed a modest but statistically significant ($P < 0.05$) increase in the prevalence of SH among smokers. In comparison with HIV-negative men, a significantly lower prevalence of SH was shown among HIV-positive men who either were not taking any ART or were taking mono or combination therapy. Among the men taking HAART for less than 2 years, the prevalence of SH was statistically indistinguishable from the prevalence among HIV-negative men. However, among the men taking HAART for more than 2 years, the prevalence of SH was significantly higher than among HIV-negative men. These results are consistent with the unadjusted results depicted in Fig. 1.

Table 2. Prevalence of systolic hypertension (SH) and diastolic hypertension (DH) at baseline and across follow-up stratified by participant characteristics.

	Percentage with SH		Percentage with DH	
Characteristics	Baseline	All visits	Baseline	All visits
All	5.9	7.3	5.9	8.0
Age (years)				
< 30	4.3	3.6	3.0	3.3
30–39	5.8	5.2	6.0	6.4
40–49	6.9	8.0	10.1	9.7
≥ 50	19.6	16.6	17.9	13.4
Race/ethnicity				
Caucasian	5.9	7.2	5.8	7.7
African-American	7.5	10.1	8.2	11.8
All others	3.5	5.4	4.3	6.7
Body mass index (kg/m^2)				
< 20	1.8	2.5	3.3	2.9
20–24.9	4.3	4.7	4.4	5.0
25–29.9	9.5	10.0	8.3	10.9
≥ 30	20.9	19.3	23.2	21.5
Smoking history				
Never	5.8	6.4	6.4	7.9
Former	6.9	8.6	6.3	9.0
Current	5.4	7.0	5.3	6.9
HIV sero-status				
Negative	6.8	8.3	7.0	9.0
Positive	4.4	6.0	4.3	6.5
Taking antiretrovial therapy[a]				
No	4.4	5.0	4.3	6.1
Yes	0.0	7.8	0.0	7.3
Taking HAART[b]				
No	0.0	5.4	0.0	6.2
Yes	n/a	12.0	n/a	9.2

[a]Prevalence rates are based on HIV-positive men.
[b]Prevalence rates are based on HIV-positive men taking antiretroviral therapy. HAART, highly active antiretroviral therapy. n/a, not applicable.

Interestingly, the adjusted odds of SH among men who had discontinued HAART was lower than among those who had taken HAART for 2 or more years and was not significantly different from that among the HIV negative controls.

We extended this analysis in two different ways to assess whether the observed association between HAART and SH might be due to PIs. First, we added an indicator variable for PI use (yes versus no) to the model shown in Table 3. The OR for PI use was 0.97 ($P = 0.83$) indicating that PI use did not contribute to the prevalence of SH over and above the characteristics already reported above. We also assessed individual PIs and found that none of them were independently associated with SH when adjusted for the characteristics listed in Table 3 (data not shown). Our second approach was to stratify HAART into two groups: PI-containing HAART ($n = 3584$ person-visits) and PI-sparing HAART ($n = 951$ person-visits). Adjusted for age, race, BMI, smoking history, and HIV status, the ORs for these two HAART groups were the same: OR = 1.37 ($P < 0.001$) for PI-containing HAART and OR = 1.37 ($P = 0.03$) for PI-sparing HAART. Therefore, PI use was neither independently associated with SH nor explains the observed association between HAART and SH.

The results of the multiple regression analysis for DH were largely consistent with those for SH among HIV-positive men not taking HAART, but differed according to the duration of HAART (Table 3). The most striking difference between the SH and DH models was among the men who had been taking HAART for 2 to 5 years. In this subgroup, the prevalence of SH was significantly

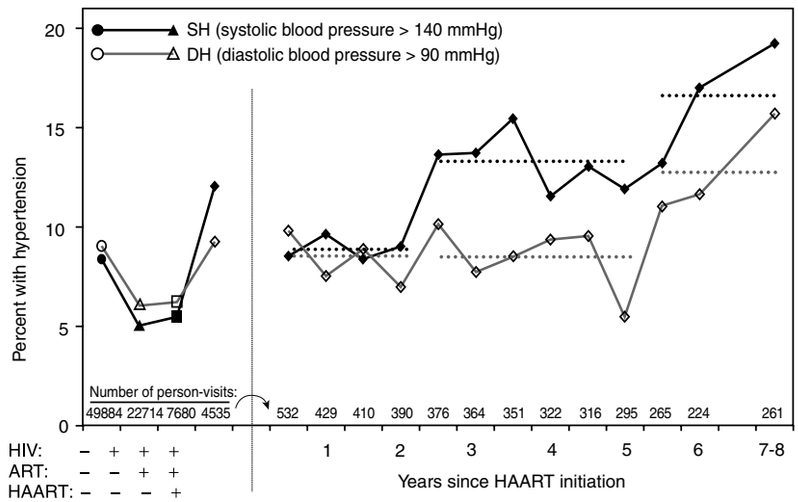

Fig. 1. Prevalence of systolic hypertension (SH) and diastolic hypertension (DH) by HIV sero-status and therapy, and relative to the time of highly active antiretroviral therapy (HAART) initiation. The dotted lines represent the mean prevalence of SH and DH for the three categories of the duration of HAART exposure included in the multiple regression analyses: less than 2 years, 2 to 5 years, and more than 5 years. ART, antiretroviral therapy.

Table 3. Multiple regression analyses: systolic hypertension and diastolic hypertension.

	Systolic hypertension		Diastolic hypertension	
Characteristics	OR	95% CI	OR	95% CI
Age (years)				
< 30	1		1	
30–39	**1.21**	**1.06, 1.37**	**1.67**	**1.47, 1.90**
40–49	**1.69**	**1.46, 1.96**	**2.36**	**2.05, 2.73**
≥ 50	**3.23**	**2.73, 3.82**	**3.05**	**2.58, 3.62**
Race/ethnicity				
Caucasian	1		1	
African-American	**1.42**	**1.16, 1.72**	**1.67**	**1.40, 1.99**
All others	0.90	0.68, 1.18	1.01	0.79, 1.29
Body mass index (kg/m^2)				
< 20	1		1	
20–24.9	**1.66**	**1.36, 2.01**	**1.46**	**1.23, 1.74**
25–29.9	**2.83**	**2.31, 3.47**	**2.46**	**2.05, 2.96**
≥ 30	**5.20**	**4.15, 6.51**	**4.43**	**3.62, 5.43**
Cigarette smoking history				
Never	1		1	
Former	**1.21**	**1.08, 1.35**	1.04	0.93, 1.15
Current	**1.17**	**1.03, 1.33**	0.93	0.82, 1.05
HIV / ART / HAART (years since HAART initiation)				
− no	1		1	
+ no naive	**0.79**	**0.70, 0.89**	**0.84**	**0.76, 0.94**
+ yes naive	**0.69**	**0.59, 0.80**	**0.73**	**0.63, 0.84**
+ yes yes (<2 years)	1.06	0.87, 1.30	0.84	0.68, 1.03
+ yes yes (2-5 years)	**1.51**	**1.25, 1.82**	**0.78**	**0.63, 0.96**
+ yes yes (>5 years)	**1.70**	**1.34, 2.16**	1.21	0.94, 1.56
+ discontinued HAART	1.32	0.91, 1.90	1.02	0.69, 1.49

Bold indicates $P < 0.05$. OR, odds ratio; CI, confidence interval; ART, antiretroviral therapy; HAART, highly-active antiretroviral therapy.

higher (OR, 1.51; 95% CI, 1.25–1.82) than among the HIV-negative control group while the prevalence of DH remained significantly lower (OR, 0.78; 95% CI, 0.63–0.96) compared with the same control group. In contrast to the SH model, the prevalence of DH among men taking HAART for more than 5 years was not significantly higher than that among the HIV-negative control group. The only other difference between the two models was that a positive smoking history was significantly associated with an increased prevalence of SH but not DH. Regarding protease inhibitors, PI use was not independently associated with the prevalence of DH (OR, 0.88; 95% CI, 0.66–1.17), and similarly non-significant differences were observed for HAART whether or not it included a PI (OR, 0.98; 95% CI, 0.76–1.26 for PI-sparing HAART and OR, 0.84; 95% CI, 0.70–1.01 for PI-containing HAART).

Finally, we conducted a series of additional analyses to assess the sensitivity of our results to the SBP and DBP thresholds used in this study (data not shown). Results very similar to those reported in Table 3 were obtained when we set the DBP threshold at 85, 95, and 100 mmHg, and when we set the SBP threshold at 135 and 150 mmHg. However, when we set the SBP threshold at 160 mmHg (stage II hypertension), none of the ORs for the HAART duration categories were significantly different from 1, but this finding might be due to a lack of statistical power since only 79 person-visits with SBP greater than or equal to 160 mmHg were observed among HIV-positive men.

Discussion

Our study showed that HAART was associated with an increase in the prevalence of hypertension. Importantly, the effect of the duration of HAART use was different for SH versus DH. Whereas the prevalence of DH was stable over the first 5 years following HAART initiation, the prevalence of SH increased after only 2 years of HAART use. Among the men who had initiated HAART between 2 and 5 years earlier, the odds of SH was 51% higher than among comparable HIV negative men (Table 3). Our estimate of the increased risk of SH with prolonged HAART use is likely to be conservative because this analysis did not distinguish men with therapeutically controlled SH from men without SH. Indeed, when we extended our analysis using the combined endpoints SH/AHT and DH/AHT, the odds ratios for the prolonged HAART exposure categories were higher than those in the SH model reported in Table 3 whereas the inferences for both combined outcomes, SH/AHT and DH/AHT, were largely consistent with those from the SH model. In many respects this last observation is not surprising because incorporating a common measure, AHT, into the two outcomes induces a correlation and diminishes the differences between them. Because our primary objective

was to investigate the differential effects of antiretroviral therapies on SH and DH rather than on a more general hypertension outcome, we decided to focus this report on these outcomes defined only by the actual blood pressure measurements.

The finding that HAART use for 2 to 5 years carried a significantly increased odds of SH, but not DH, suggests that HAART may directly lead to changes in arterial walls producing a syndrome similar to isolated systolic hypertension (ISH), which is most commonly observed among the elderly [30]. In ISH, atherosclerosis and loss of aortic distensibility results in decreased arterial compliance, which in turn leads to SH because the large vessels are less able to reduce the pressure resulting from left ventricular contraction [31]. The risks associated with SH and ISH have been investigated in the Framingham Study [32] and the Multiple Risk Factor Intervention Trial (MRFIT) [33] and summarized by others [30,34–37]. Although both systolic and diastolic BP are associated with cardiovascular morbidity and mortality, systolic BP has often been found to be a better predictor of coronary heart disease, stroke, and all-cause mortality, with ISH being independently associated with an increased risk of these cardiovascular events [30,32–37]. These risks can be reduced through the treatment of ISH [38,39]. An alternative explanation is that HAART may be indirectly linked to SH by a mechanism involving metabolic disorders. We were unable to examine this hypothesis because glucose, lipids, and lipodystrophy data have only been collected in the MACS since the middle of 1999.

The interpretation of our results regarding the association of SH and DH with prolonged HAART use (i.e., $>$ 5 years) is less clear. The odds ratios for both SH and DH were highest among men taking HAART for more than 5 years suggesting that additional pathogenic mechanisms may be important. For instance, men who take HAART for more than 5 years may be the subset of those who thrive and are subject to other etiologic mechanisms for essential hypertension such as weight gain. However, we must caution against the over interpretation of our results because we observed a relatively small number of person-visits from men who had taken HAART for more than 5 years.

This study has several strengths. First of all, we analyzed a large number of person-visits ($n = 84\,813$) over a long follow-up period (19 years). More importantly, when investigating possible adverse events of therapies (e.g., SH due to HAART), it is essential not only to control for known risk factors of the event (e.g., age, race, and BMI for SH), but also to compare the rates of the events among individuals exposed to the therapies to the corresponding rates among individuals who have the condition for which the therapy is indicated (i.e., HIV positive HAART-naive) as well as to the rates among individuals for whom the therapy is not pertinent (i.e., HIV negative). Cohort studies such as the MACS that follow HIV-negative, HIV-positive HAART-naive, and HAART-exposed persons under a standard protocol provide invaluable data to comprehensively characterize the epidemiology of adverse events due to antiretroviral therapies.

This study also has several limitations. First, BP was not measured according to a standardized protocol, which could have led to the non-differential misclassification of hypertension status and underestimation of the magnitude of the association between HAART duration and hypertension. Even if such a bias had affected our study, it did not preclude us from finding a significant association between HAART and SH. Second, we used a statistical model that described the changes over time within the cohort rather than within individuals. Further studies are required to confirm whether or not the increased prevalence of SH that we observed is due to SBP increases within individuals. Finally, this study was restricted to relatively affluent and educated gay men, so we cannot generalize our results to women or other populations of HIV-infected persons such as injection drug users, some minority groups, and hemophiliacs. For instance, the very high ART adherence rates observed in the MACS [40] may have helped to illuminate the association between duration of HAART use and SH, whereas in cohorts with lower ART adherence rates this association might be more difficult to detect.

In summary, we found that HAART was associated with SH and that the prevalence of SH increased as the duration of HAART exposure increased, raising the possibility that men taking HAART have an increased risk for hypertensive heart disease and the attendant complications such as progressive ischemic heart disease, renal damage, and stroke. Our findings underscore the importance of monitoring blood pressure and for signs and symptoms of hypertension-related complications among HIV positive men taking HAART.

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References

1. Detels R, Munoz A, McFarlane G, Kingsley LA, Margolick JB, Giorgi J, *et al*. **Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. Multicenter AIDS Cohort Study Investigators.** *JAMA* 1998; **280**:1497–1503.
2. Pallela FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, *et al*. **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.** *N Eng J Med* 1998; **338**:853–860.
3. Duong M, Cottin Y, Piroth L, Fargeot A, Lhuiller I, Bobillier M, *et al*. **Exercise stress testing for detection of silent myocardial ischemia in human immunodeficiency virus-infected patients receiving antiviral therapy.** *Clin Infect Dis* 2002; **34**:523–528.
4. Rickerts V, Brodt H, Staszewski S, Stille W. **Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-cohort study.** *Eur J Med Res* 2000; **18**:329–333.
5. The DAD Study Group. **Combination antiretroviral therapy and the risk of myocardial infarction.** *N Engl J Med* 2003; **349**:1993–2003.
6. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. **Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection.** *N Engl J Med* 2003; **348**:702–710.
7. Pugliese A, Isnardi D, Saina A, Sdcarabelli T, Raddino R, Torre D. **Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement.** *J Infect Dis* 2000; **40**:282–284.
8. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, *et al*. **Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection.** *Circulation* 2004; **109**:1603–1608.
9. Mercie P, Thiebaut R, Lavignolle V, Pellegrin JL, Yvorra-Vives MC, Morlat P, *et al*. **Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement.** *Ann Med* 2002; **34**:55–63.
10. Maggi P, Serio G, Epifani G, Fiorentino G, Saracino A, Fico C, *et al*. **Premature lesions of the carotid vessels in HIV-1-infected patients treated with protease inhibitors.** *AIDS* 2000; **14**:123–128.
11. Depairon M, Chessex S, Sudre P, Rodondi N, Doser N, Chave JP, *et al*. **Premature atherosclerosis in HIV-infected individuals–focus on protease inhibitor therapy.** *AIDS* 2001; **15**:329–334.
12. Klein D, Hurley LB, Quesenberry CP, Sidney S. **Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-2 infection?** *J Acquir Immune Defic Syndr* 2002; **30**:471–477.
13. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. **Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** *JAMA* 2001; **285**:2486–2497.
14. Mulligan K, Grunfeld C, Tai VW, Algren H, Pang M, Chernoff DN, *et al*. **Hyperlipidemia and insulin are induced by protease inhibitors independent of changes in body composition in patients with HIV infection.** *J Acquir Immune Defic Syndr* 2000; **23**:35–43.
15. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. **Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study.** *Lancet* 1999; **353**:2093–2099.
16. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, *et al*. **Impact of HIV infection and HAART on serum lipids in men.** *JAMA* 2003; **289**:2978–2982.
17. Currier JS. **Cardiovascular risk associated with HIV therapy.** *J Acquir Immune Defic Syndr* 2002; **31**:S16–S23.
18. Falusi OM, Aberg JA. **HIV and cardiovascular risk factors.** *AIDS Reader* 2001; **11**:263–268.
19. Thiebaut R, El-Sadr W, Chenuc G, Friis-Moller N, Rickenbach M, Reiss P, *et al*. **Predictors of hypertension and changes in blood pressure in HIV-infected patients in the D:A:D Study.** *11th Conference on Retroviruses and Opportunistic Infections*, San Francisco, February 2004 [abstract #75].
20. Chow D, Souza S, Richmond-Crum S, Shikuma C. **Epidemiological evidence of increasing blood pressure in HIV-1-infected individuals in the era of HAART.** *Antiviral Ther (Lond)* 2000; **5(suppl 5)**:31–32.
21. Gazzaruso C, Bruno R, Garzaniti A, Giordanetti S, Fratino P, Sacchi P, *et al*. **Hypertension among HIV patients: prevalence and relationships to insulin resistance and metabolic syndrome.** *J Hypertens* 2003; **21**:1377–1382.
22. Bergersen BM, Sandvik L, Dunlop O, Birkeland K, Bruun JN. **Prevalence of hypertension in HIV-positive patients on highly active retroviral therapy (HAART) compared with HAART-naive and HIV-negative controls: results from a Norwegian study of 721 patients.** *Eur J Clin Microbiol Infect Dis* 2003; **22**:731–736.
23. Sattler FR, Qian D, Louie S, Johnson D, Briggs W, DeQuattro V, *et al*. **Elevated blood pressure in subjects with lipodystrophy.** *AIDS* 2001; **15**:2001–2010.
24. Barbaro B, Klatt EC. **HIV Infection and the cardiovascular system.** *Aids Rev* 2002; **4**:93–103.
25. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR. **The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants.** *Am J Epidemiol* 1987; **126**:310–318.
26. Detels R, Phair JP, Saah AJ, Rinaldo CR, Muñoz A, Kaslow RA, *et al*. **Recent scientific contributions to understanding HIV/AIDS from the Multicenter AIDS Cohort Study.** *J Epidemiol (Japan)* 1992; **2**:S11–S19.
27. Department of Health and Human Services/Henry J. Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. February 04, 2002. revision. Available at: http://www.aidsinfo.nih.gov/guidelines/archive.asp. Accessed: June 10, 2004.
28. Zeger SL, Liang KY. **Longitudinal data analysis for discrete and continuous outcomes.** *Biometrics* 1986; **42**:121–130.
29. Detels R, Tarwater P, Phair JP, Margolick J, Riddler SA, Munoz A. **Multicenter AIDS Cohort Study. Effectiveness of potent antiretroviral therapies on the incidence of opportunistic infections before and after AIDS diagnosis.** *AIDS* 2001; **15**:347–355.
30. Silagy CA, McNeil JJ. **Epidemiologic aspects of isolated systolic hypertension and implications for future research.** *Am J Cardiol* 1992; **69**:213–218.
31. Simon AC, Safar MA, Levenson JA, Kheder AM, Levy BI. **Systolic hypertension: hemodynamic mechanism and choice of antihypertensive treatment.** *Am J Cardiol* 1979; **44**:505–511.
32. Kannel WB. **Risk stratification in hypertension: New insights from the Framingham Study.** *Am J Hypertens* 2000; **13**:3S–10S.
33. Rutan GH, Kuller LH, Neaton JD, Wentworth DN, McDonald RH, Smith WM. **Mortality associated with diastolic hypertension and isolated systolic hypertension among men screened for the Multiple Risk Factor Intervention Trial.** *Circulation* 1988; **77**:504–514.
34. Lichtenstein MJ. **Isolated systolic hypertension: how common? how risky?** *South Med J* 1985; **78**:972–978.
35. Stamler J, Stamler R, Neaton JD. **Blood pressure, systolic and diastolic, and cardiovascular risks. US population data.** *Arch Intern Med* 1993; **153**:598–615.
36. Mancia G, Seravalle G, Grassi G. **Systolic blood pressure: an underestimated cardiovascular risk factor.** *J Hypertens* 2002; **20(suppl 5)**:S21–S27.
37. Kannel WB. **Elevated systolic blood pressure as a cardiovascular risk factor.** *Am J Cardiol* 2000; **85**:251–255.
38. SHEP Cooperative Research Group. **Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension.** *JAMA* 1991; **265**:3255–3264.
39. Staessen JA, Fagard R, Thijs L, Celis H, Arabidze GG, Birkenhäger WH, *et al*. **Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension.** *Lancet* 1997; **350**:757–764.
40. Kleeberger CA, Phair JP, Strathdee SA, Detels R, Kingsley L, Jacobson LP. **Determinants of heterogeneous adherence to HIV-antiretroviral therapies in the Multicenter AIDS Cohort Study.** *J Acquir Immune Defic Syndr* 2001; **26**:82–92.