

# Risk of Cardiovascular Events and Blood Pressure Control in Hypertensive HIV-Infected Patients: Swiss HIV Cohort Study (SHCS)

Reto Nüesch, MD,\* Qing Wang, PhD,† Luigia Elzi, MD,‡ Enos Bernasconi, MD, MSc,§ Rainer Weber, MD,|| Matthias Cavassini, MD,¶ Pietro Vernazza, MD,# Maria C. Thurnheer, MD,\*\* Alexandra Calmy, MD, PhD,†† Manuel Battegay, MD,‡ and Heiner C. Bucher, MD, MPH,†‡, for the Swiss HIV Cohort Study

**Background:** Prevalence of hypertension in HIV infection is high, and information on blood pressure control in HIV-infected individuals is insufficient. We modeled blood pressure over time and the risk of cardiovascular events in hypertensive HIV-infected individuals.

**Methods:** All patients from the Swiss HIV Cohort Study with confirmed hypertension (systolic or diastolic blood pressure above 139 or 89 mm Hg on 2 consecutive visits and presence of at least 1 additional cardiovascular risk factor) between April 1, 2000 and March 31, 2011 were included. Patients with previous cardiovascular events, already on antihypertensive drugs, and pregnant women were excluded. Change in blood pressure over time was modeled using linear mixed models with repeated measurement.

**Results:** Hypertension was diagnosed in 2595 of 10,361 eligible patients. Of those, 869 initiated antihypertensive treatment. For patients treated for hypertension, we found a mean (95% confidence interval) decrease in systolic and diastolic blood pressure of  $-0.82$  ( $-1.06$  to  $-0.58$ ) mm Hg and  $-0.89$  ( $-1.05$  to  $-0.73$ ) mm Hg/yr, respectively. Factors associated with a decline in systolic blood pressure were baseline blood pressure, presence of chronic kidney disease, cardiovascular events, and the typical risk factors for cardiovascular disease. In patients with hypertension, increase in systolic blood pressure [(hazard ratio 1.18 (1.06 to 1.32) per 10 mm Hg increase), total cholesterol, smoking, age, and cumulative exposure to protease inhibitor-based and triple nucleoside regimens were associated with cardiovascular events.

**Conclusions:** Insufficient control of hypertension was associated with increased risk of cardiovascular events indicating the need for improved management of hypertension in HIV-infected individuals.

**Key Words:** HIV infection, antiretroviral therapy, hypertension, cardiovascular event, risk factor

(*J Acquir Immune Defic Syndr* 2013;62:396–404)

Received for publication August 20, 2012; accepted December 21, 2012.

From the \*Division of Infectious Diseases, Hirslanden Klinik St. Anna, Lucerne, Switzerland; †Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Basel, Switzerland; ‡Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland; §Division of Infectious Diseases, Regional Hospital of Lugano, Lugano, Switzerland; ||Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; ¶Division of Infectious Diseases, University Hospital Lausanne, Lausanne, Switzerland; #Division of Infectious Diseases and Hospital Epidemiology, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland; \*\*Division of Infectious Diseases, University Hospital Bern and University of Bern, Bern, Switzerland; and ††Division of Infectious Diseases, University Hospital of Geneva, Geneva, Switzerland.

R. Nüesch has received travel grants, honoraria, and unrestricted research grants from Abbott, Bristol-Myers-Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme-Chibret, Janssen-Cilag, and Pfizer. H. C. Bucher and Q. Wang are funded by unrestricted grants by santésuisse and the Gottfried and Julia Bangerter-Rhyner-Foundation. H. C. Bucher has received travel grants, honoraria, and unrestricted research grants from Abbott, Bristol-Myers-Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme-Chibret, Janssen-Cilag, Pfizer, and ViiV Healthcare. M. Battegay has received unrestricted research or educational grants from Abbott, Bristol-Myers-Squibb, Gilead Sciences, Merck Sharp & Dohme-Chibret, Janssen-Cilag, Pfizer, and ViiV Healthcare. He has served on advisory boards of Abbott, Boehringer-Ingelheim, Gilead Sciences, Janssen-Cilag, Pfizer, and ViiV Healthcare. A. Calmy has received educational grants from Abbott, Gilead Sciences, and Janssen-Cilag and travel grants from Janssen-Cilag.

Supported by the framework of the Swiss HIV Cohort Study and the Swiss National Science Foundation (grant # 33CS30\_134277).

Correspondence to: Heiner C. Bucher, MD, MPH, Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel, Hebelstrasse 10, CH-4031 Basel, Switzerland (e-mail: Heiner.Bucher@usb.ch).

Copyright © 2013 by Lippincott Williams & Wilkins

## INTRODUCTION

With the success of modern combination antiretroviral therapy (cART), HIV-infected patients have much longer life expectancy and are therefore increasingly at risk of non-AIDS-related morbidity and deaths.<sup>1–4</sup> Individuals with chronic HIV infection present high levels of risk factors for cardiovascular diseases, such as smoking, hypertension, diabetes, and dyslipidemia.

Hypertension is among the leading risk factors for cardiovascular diseases and accounts for 6% of adult deaths worldwide. The incidence of hypertension in HIV-infected populations is growing and only partly related to improved survival and the aging effect in HIV cohorts.<sup>5,6</sup> Older HIV-infected patients develop more hypertension and other cardiovascular comorbidities than what would be expected with aging in HIV-negative individuals.<sup>7,8</sup> The reasons for this remain unclear and may be partially related to HIV-dependent endothelial inflammatory processes or antiretroviral drugs.<sup>9–23</sup> Some antiretroviral drugs may increase the risk of cardiovascular events independently from antiretroviral drug-induced dyslipidemia and insulin resistance, and some studies have

found an association between cART and hypertension.<sup>24–28</sup> Protease inhibitors (PIs) against HIV may induce the activation of the renin–angiotensin system.<sup>29</sup> There are also potential pharmacokinetic and metabolic interactions between antihypertensive drugs and cART.<sup>30</sup> However, the beneficial effects of cART by far outweigh these side effects.

Effective treatment of hypertension in HIV-infected patients independently of the cART regimen is thus very important to prevent cardiovascular morbidity and mortality. Studies from the international DAD study and the Swiss HIV Cohort Study (SHCS) show that the prevalence of hypertension in HIV-infected individuals is high with little change over time.<sup>25,31</sup> This raises questions on the extent of hypertension control. Surprisingly only limited data are available on how well HIV-infected patients are treated for hypertension and to what extent blood pressure reduction can be achieved. We therefore investigated changes in blood pressure over time and the risk of cardiovascular events in patients with hypertension in the SHCS.

## METHODS

### Study Population

The SHCS is a multicenter, prospective cohort study with continuing enrollment of HIV-infected adults (aged  $\geq$  18 years).<sup>32</sup> Enrollment in the SHCS is independent of the stage of disease, the degree of immunosuppression, or whether the individual is receiving cART. Over 15,000 HIV-infected individuals have been included in the SHCS so far, corresponding to approximately 70% of all HIV-infected individuals in Switzerland. Informed consent is obtained from all participants. Participants are followed up every 6 months at outpatient clinics and private practices and asked to provide information on sociodemographics, comorbidities, and concomitant medications. Laboratory data, including CD4 cell counts and HIV viral load, are collected at each visit.

Since April 2000, systolic and diastolic blood pressure measurements together with other cardiovascular risk factors are recorded every 6 months in the SHCS. Based on the guidelines from the European Society of Hypertension and the European Society of Cardiology,<sup>33–35</sup> we define hypertension as systolic or diastolic blood pressure measurements above 139 or 89 mm Hg on 2 consecutive cohort visits and the presence of at least 1 cardiovascular risk factor. Cardiovascular risk factors include smoking ( $>1$  cigarette per day), dyslipidemia (defined as a total cholesterol  $>6.5$  mmol/L or high-density lipoprotein (HDL) cholesterol  $<1.0$  mmol/L), family history of cardiovascular disease, diabetes (defined as a clinical diagnosis, any plasma glucose measurement  $>11.1$  mmol/L or  $>7.0$  mmol/L in fasting state, or taking antidiabetic drugs or insulin), and chronic kidney disease (defined as a glomerular filtration rate  $<50$  mL/min/1.73 m<sup>2</sup> measured by the Cockcroft–Gault equation). We define a cardiovascular event to be myocardial infarction, coronary angioplasty, bypass surgery, or stroke.

This longitudinal study includes all patients in the SHCS diagnosed with hypertension between April 1, 2000 and March 31, 2011. These patients are monitored to September 30, 2011

to ensure at least 6 months of follow-up. Patients with previous cardiovascular events, already on antihypertensive treatment, and pregnant women were excluded.

### Statistical Analyses

The primary outcome for this study is changes in blood pressure since starting antihypertensive treatment in treated patients. Changes in blood pressure over time are modeled using linear mixed models with repeated measurements. Separated models are fitted for systolic and diastolic blood pressure. We follow individuals from the start of antihypertensive treatment until their last recorded measurement to date or censoring (because of loss of follow-up or death).

We evaluate the impact of multiple variables on blood pressure change; these include age, gender, ethnicity, time since HIV diagnosis, total and HDL cholesterol, body mass index (BMI), waist-to-hip ratio, diabetes, cardiovascular events, chronic kidney disease, smoking, intravenous drug use (IDU) or being in a drug maintenance program, psychiatric problems (defined as being either diagnosed or treated by a psychiatrist or taking antidepressant drugs), AIDS, HIV RNA viral load, CD4 cell count, and cumulative exposure to antiretroviral drug classes. For the 92 patients with a missing date of HIV diagnosis, we use the SHCS registration date to calculate an approximate time since HIV diagnosis. We further adjust the models by baseline blood pressures to better control for the regression to the mean phenomenon<sup>36</sup> and center effect (1 of the 7 HIV centers).

For the secondary end point analysis, we estimate the risk of a cardiovascular event and sudden cardiac death from the time of diagnosis in all patients with hypertension using time-dependent Cox proportional hazards models. The models are stratified by centers and adjusted by the same covariates as above. Blood pressures are also included as time-dependent covariates. Likewise, we explore the predictors of initiating antihypertensive treatment in this population of hypertensive HIV-infected patients, with cumulative exposure to antiretroviral drug classes being replaced by the current exposure. For each analysis, hazard ratios (HRs) and 95% confidence intervals (CIs) are presented.

All analyses and graphics are done with SAS version 9.2 (SAS Institute Inc., Cary, NC) and R version 2.15.0 (R Foundation for Statistical Computing, www.r-project.org).

## RESULTS

During the study period, hypertension was diagnosed in 2659 of 10,361 eligible patients with at least 2 consecutive blood pressure measurements, 28 patients were excluded due to pregnancy and 36 were excluded due to past cardiovascular events. Data on blood pressure were not available in 87 patients who had at least 1-year follow-up; these patients were more likely to be IDUs, off cART, and had longer time since HIV diagnosis. Of the 2595 patients included in the study, 869 initiated antihypertensive treatment (79 patients per 1000 patient-year), of which 317 discontinued antihypertensive treatment later in the study. The median (interquartile range) systolic and diastolic blood pressure in those starting

**TABLE 1.** Baseline Characteristics of HIV-Infected Patients With Confirmed Hypertension in the SHCS

| Baseline Variable                        | All Patients at the Time of Confirmed Hypertension, n = 2595 | Treated Patients at the Time of Starting Treatment, n = 869 |
|--|--|---|
| Age, yrs*                                | 43 (38–50)   | 49 (43–56)  |
| Male gender, %                           | 84   | 84  |
| Caucasian ethnicity, %                   | 90   | 91  |
| Education <9 yrs, %                      | 22   | 21  |
| Time since HIV diagnosis, yrs*           | 7.6 (2.5–13.6)   | 11.0 (6.3–16.6)   |
| Transmission risk category, %            |  |   |
| Homosexual                               | 44   | 42  |
| Heterosexual                             | 32   | 36  |
| IDU                                      | 20   | 18  |
| Other                                    | 4  | 4   |
| Systolic hypertension, %                 | 27   | 19  |
| Diastolic hypertension, %                | 31   | 11  |
| Systolic and diastolic hypertension, %   | 42   | 39  |
| Systolic blood pressure, mm Hg*          | 140 (135–149)  | 145 (135–157)   |
| Diastolic blood pressure, mm Hg*         | 90 (88–95)   | 92 (82–100)   |
| Total cholesterol, mmol/L*               | 5.2 (4.3–6.3)  | 5.4 (4.5–6.2)   |
| HDL cholesterol, mmol/L*                 | 1.1 (0.9–1.4)  | 1.2 (0.9–1.5)   |
| BMI, kg/m <sup>2</sup> *                 | 24.2 (21.9–26.6)   | 24.8 (22.5–27.7)  |
| Waist-to-hip ratio*                      | 0.93 (0.88–0.98)   | 0.96 (0.91–1.00)  |
| Diabetes, %                              | 8  | 19  |
| Cardiovascular events, %                 | —  | 5   |
| GFR < 50 mL/min/1.73 m <sup>2</sup> , %  | 0.7  | 3   |
| Smoker, %                                | 60   | 48  |
| IDU or in drug maintenance program, %    | 13   | 17  |
| Psychiatric problems, %                  | 12   | 24  |
| CDC stage, %                             |  |   |
| A  | 49   | 41  |
| B  | 27   | 29  |
| C  | 24   | 29  |
| HIV RNA viral load, %                    |  |   |
| <50 copies/mL                            | 56   | 71  |
| 50 to <400 copies/mL                     | 10   | 10  |
| ≥400 copies/mL                           | 34   | 19  |
| CD4 <sup>+</sup> T-cell count            |  |   |
| CD4 <sup>+</sup> T-cell count, cells/μL* | 446 (292–636)  | 467 (305–676)   |
| <200 cells/μL, %                         | 12   | 11  |
| 200 to <350 cells/μL, %                  | 23   | 21  |
| ≥350 cells/μL, %                         | 65   | 68  |
| ART regimen, %                           |  |   |
| NNRTIs                                   | 23   | 31  |
| Pis                                      | 43   | 45  |
| Triple NRTI and others                   | 8  | 10  |
| Off treatment                            | 26   | 14  |
| Median time on ART, yrs (IQR)            | 3.5 (0.6–6.8)  | 6.7 (3.3–9.9)   |

**TABLE 1.** (Continued) Baseline Characteristics of HIV-Infected Patients With Confirmed Hypertension in the SHCS

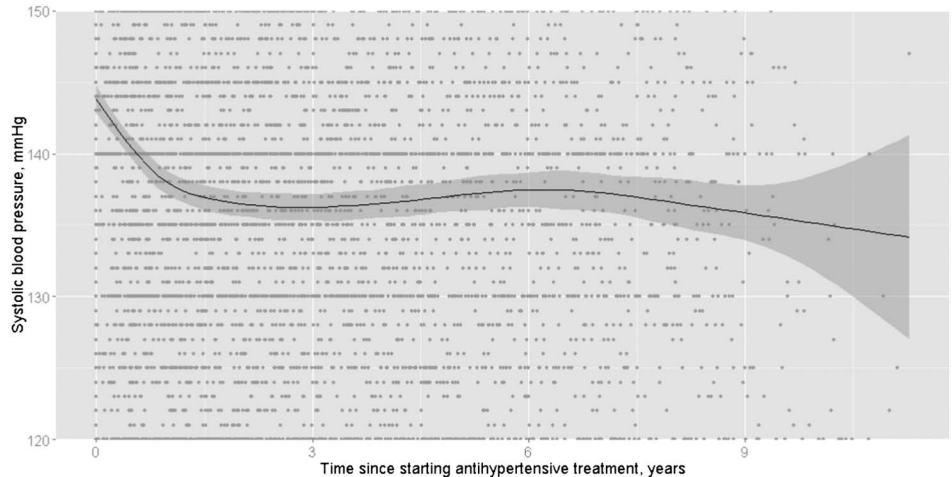
| Baseline Variable                        | All Patients at the Time of Confirmed Hypertension, n = 2595 | Treated Patients at the Time of Starting Treatment, n = 869 |
|--|--|---|
| Number of cardiovascular risk factors, % |  |   |
| 1  | 65   | 62  |
| 2  | 30   | 32  |
| 3  | 5  | 6   |
| 4  | 0.2  | 0.1   |

\*Median (interquartile range).  
GFR, glomerular filtration rate; NNRTI, non-nucleoside reverse transcriptase inhibitor.

antihypertensive treatment was 145 (134–157) mm Hg and 92 (82–100) mm Hg, respectively, the follow-up was 3.7 (1.7–6.3) years, age was 49 (43–56) years, and 84% of patients were men. At the time of antihypertensive treatment initiation, 19% of patients had diabetes, 5% had experienced a cardiovascular event, and 48% were smokers; the median CD4 cell count was 467 cells per microliter (305–676); and 71% of patients had a HIV viral load <50 copies per milliliter (Table 1). Figure 1 illustrates the evolution of systolic blood pressure over time in patients initiating antihypertensive treatment. These patients had a higher mean blood pressure at baseline, and the mean change in blood pressure tended to level off after 2 years.

In multivariate models adjusted for HIV centers, patients treated for hypertension were found to have a mean decrease in systolic blood pressure of  $-0.82$  (95% CI:  $-1.06$  to  $-0.58$ ) mm Hg per year and in diastolic blood pressure of  $-0.89$  ( $-1.05$  to  $-0.73$ ) millimeter of mercury per year (Table 2). Systolic blood pressure increased in older patients [ $1.53$  (0.95–2.11) millimeter of mercury per 10-year increase], men [ $3.32$  (1.71–4.93) mm Hg compared with women], IDU or those in a drug maintenance program [ $1.98$  (0.41–3.55) mm Hg compared with non-IDU], patients with higher total cholesterol [ $0.90$  (0.57–1.23) mm Hg/1 mmol/L increase], higher HDL cholesterol [ $3.281$  (2.24–4.32) mm Hg/1 mmol/L increase], higher BMI [ $0.46$  (0.33–0.59) millimeter of mercury per 1 index increase], higher waist-to-hip ratio [ $0.77$  (0.11–1.43) millimeter of mercury per 0.1 index increase], and viral load  $\geq 400$  copies per milliliter [ $2.00$  (0.62–3.38) mm Hg compared with viral suppression (<50 copies per milliliter)]. Systolic blood pressure decreased in patients with longer time since HIV diagnosis [ $-1.37$  ( $-2.50$  to  $-0.25$ ) millimeter of mercury per 10-year increase], cardiovascular events [ $-2.42$  ( $-4.29$  to  $-0.55$ ) mm Hg], and glomerular filtration rate  $< 50$  mL/min/1.73 m<sup>2</sup> [ $-3.10$  ( $-5.19$  to  $-1.00$ ) mm Hg]. Similar patterns in risk factors were found for diastolic blood pressure, except that diastolic blood pressure decreased with increasing age [ $-1.17$  ( $-1.57$  to  $-0.77$ ) millimeter of mercury per 10-year increase].

In all patients diagnosed with hypertension, 118 experienced cardiovascular events: 54 acute myocardial infarctions, 18 coronary angioplasties, 4 coronary bypass surgeries, 32



**FIGURE 1.** Population changes in systolic blood pressure after starting antihypertensive treatment.

strokes, and 10 sudden cardiac deaths. In a multivariate model stratified by centers, systolic blood pressure increased the risk of cardiovascular events by a HR (95% CI) of 1.18 (1.06 to 1.32) per 10 mm Hg increase (Table 3). The risk of a cardiovascular event was also increased for older age [HR: 1.71 (95% CI: 1.39 to 2.10) per 10-year increase), higher total cholesterol [HR: 1.16 (95% CI: 1.07 to 1.26) per 1 mmol/L increase], smoking [HR: 1.95 (95% CI: 1.28 to 2.96)], longer cumulative exposure to PI [HR: 1.11 (95% CI: 1.02 to 1.21) per 1-year increase], and triple nucleoside reverse transcriptase inhibitor (NRTI) regimen [HR: 1.28 (95% CI: 1.09 to 1.49) per 1-year increase].

For all patients with confirmed hypertension, those with a cardiovascular event [HR: 7.03 (95% CI: 4.89 to 10.1)], chronic kidney disease [HR: 2.42 (95% CI: 1.54 to 3.80)], and diabetes [HR: 1.54 (95% CI: 1.28 to 1.84)] were more likely to initiate antihypertensive treatment (Table 3). Additional predictors for the initiation of antihypertensive treatment were older age, non-Caucasian ethnicity, higher BMI, advanced HIV infection, and less suppressed viral load. Patients who were off antiretroviral treatment were less likely to receive antihypertensive treatment.

### DISCUSSION

In this study of HIV-infected patients with confirmed hypertension, we found a decline of systolic blood pressure over time after patients initiated antihypertensive treatment. Factors associated with a decline in systolic blood pressure for those initiating antihypertensive treatment were baseline blood pressure, the presence of established cardiovascular and chronic kidney disease, and the typical risk factors for cardiovascular disease. However, only 79 patients per 1000 patient-year initiated antihypertensive treatment after confirmed hypertension. In addition, increase in systolic blood pressure and total cholesterol, besides age, smoking, and cumulative exposure to PI and abacavir-containing triple NRTI regimens were associated with risk of a cardiovascular event.

Only few studies have investigated blood pressure control in hypertensive HIV-infected patients despite the fact that HIV itself may increase the risk of cardiovascular diseases. In the US Veterans Aging Cohort Study, the HR

for acute myocardial infarction of uncontrolled systolic blood pressure above 139 mm Hg was 2.80 (95% CI: 1.57 to 4.86) and basically the same as in patients on antihypertensive drugs with a blood pressure below 140 mm Hg.<sup>37</sup> In this study, the adjusted hazards for acute myocardial infarction were higher in HIV-infected compared with uninfected men. In a demographics-matched study from a US health care system in Boston, the adjusted hazards of ischemic stroke were higher for HIV-infected compared to HIV-negative patients. For HIV-infected patients, a higher risk of stroke was found according to HIV viral load.<sup>38</sup> In our study, we could not confirm any association between unsuppressed viral load and the risk of a cardiovascular event. In contrast, *in vitro* studies indicate that HIV is a strong inducer of endothelial inflammation promoting endothelial damage, atherosclerosis, and hypertension. Injury of endothelial cell may occur by direct infection<sup>13,15,17,21–23</sup> or activation of endothelial cell proliferation through HIV proteins and cytokines.<sup>9,11</sup> The interruption of cART leads to an increase of hsCRP, IL-6, D-Dimers, s-VICAM-1, P-selectin, and leptin, biomarkers that are associated with endothelial inflammation and may lead to a higher risk of cardiovascular events.<sup>12,16,20</sup> HIV-induced endothelial inflammation has been found to be associated with increased vascular stiffness<sup>10,14,19</sup> and impaired flow mediated dilatation in arteries,<sup>18</sup> factors known to be associated with hypertension.

However, we observed that hypertensive HIV-infected patients who had less suppressed viral load were more frequently treated and that those off antiretroviral treatment seemed to be less likely to initiate antihypertensive treatment. We may interpret this as indirect evidence that better adherence to cART may lead to better overall drug adherence. Indeed, a recent study showed that suboptimal control of HIV viremia correlates with suboptimal control of diabetes and hypertension.<sup>39</sup>

As expected, systolic blood pressure increased with older age, higher BMI, higher waist-to-hip ratio, and was higher in men than in women. Diastolic blood pressure seemed to decrease with older age, which may be related to increased arterial stiffness. This phenomenon has also been observed by the Framingham Heart Study investigators.<sup>40</sup>

For our definition of hypertension, we requested 2 consecutive blood pressure measurements above 139 mm Hg for

**TABLE 2.** Mean Change in Blood Pressure in HIV-Infected Patients on Antihypertensive Treatment

| Parameter   | Systolic Blood Pressure (mm Hg)                                  |                                |       | Diastolic Blood Pressure (mm Hg)                                 |                                |       |
|---|--|--------------------------------|-------|--|--------------------------------|-------|
|   | Estimate Adjusted by Baseline Blood Pressure and Center (95% CI) | Multivariate Estimate (95% CI) | P     | Estimate Adjusted by Baseline Blood Pressure and Center (95% CI) | Multivariate Estimate (95% CI) | P     |
| Time since starting treatment per year                    | -0.96 (-1.17 to -0.74)   | -0.82 (-1.06 to -0.58)         | <0.01 | -0.99 (-1.13 to -0.85)   | -0.89 (-1.05 to -0.73)         | <0.01 |
| Age per 10-year increase                                  | 1.30 (0.75 to 1.84)  | 1.53 (0.95 to 2.11)            | <0.01 | -1.18 (-1.56 to -0.80)   | -1.17 (-1.57 to -0.77)         | <0.01 |
| Male gender   | 1.76 (0.23 to 3.29)  | 3.32 (1.71 to 4.93)            | <0.01 | 0.69 (-0.34 to 1.72)   | 1.25 (0.18 to 2.32)            | 0.02  |
| Caucasian ethnicity                                       | -0.64 (-2.50 to 1.23)  | -0.32 (-2.27 to 1.63)          | 0.75  | -0.51 (-1.77 to 0.75)  | 0.73 (-0.56 to 2.03)           | 0.27  |
| Time since HIV diagnosis per 10-year increase             | -2.42 (-3.31 to -1.54)   | -1.37 (-2.50 to -0.25)         | 0.02  | -0.77 (-1.37 to -0.17)   | 0.10 (-0.65 to 0.84)           | 0.80  |
| Total cholesterol per 1 mmol/L increase                   | 1.23 (0.92 to 1.55)  | 0.90 (0.57 to 1.23)            | <0.01 | 0.82 (0.62 to 1.03)  | 0.78 (0.57 to 0.99)            | <0.01 |
| HDL cholesterol per 1 mmol/L increase                     | 2.76 (1.78 to 3.74)  | 3.28 (2.24 to 4.32)            | <0.01 | 1.31 (0.67 to 1.95)  | 1.37 (0.69 to 2.04)            | <0.01 |
| BMI per 1 kg/m <sup>2</sup> increase                      | 0.49 (0.37 to 0.60)  | 0.46 (0.33 to 0.59)            | <0.01 | 0.29 (0.21 to 0.36)  | 0.28 (0.19 to 0.36)            | <0.01 |
| Waist-to-hip ratio per 0.1 increase                       | 1.66 (1.07 to 2.26)  | 0.77 (0.11 to 1.43)            | 0.02  | 0.84 (0.45 to 1.22)  | 0.64 (0.22 to 1.07)            | <0.01 |
| Diabetes  | -0.23 (-1.47 to 1.00)  | -0.69 (-1.90 to 0.52)          | 0.27  | -1.55 (-2.37 to -0.73)   | -1.49 (-2.29 to -0.69)         | <0.01 |
| Cardiovascular events                                     | -3.24 (-5.11 to -1.36)   | -2.42 (-4.29 to -0.55)         | 0.01  | -2.16 (-3.41 to -0.90)   | -1.11 (-2.35 to 0.12)          | 0.08  |
| GFR < 50 mL/min/1.73 m <sup>2</sup>                       | -3.83 (-5.94 to -1.73)   | -3.10 (-5.19 to -1.00)         | <0.01 | -3.09 (-4.49 to -1.69)   | -1.63 (-3.00 to -0.25)         | 0.02  |
| Smoker  | -1.37 (-2.37 to -0.37)   | -0.03 (-1.08 to 1.01)          | 0.95  | 0.41 (-0.25 to 1.07)   | 0.31 (-0.37 to 0.99)           | 0.37  |
| IDU or in drug maintenance program                        | -0.31 (-1.81 to 1.19)  | 1.98 (0.41 to 3.55)            | 0.01  | 0.58 (-0.39 to 1.54)   | 0.81 (-0.19 to 1.82)           | 0.11  |
| Psychiatric problems                                      | -1.11 (-2.00 to -0.21)   | -0.98 (-1.88 to -0.09)         | 0.03  | 0.14 (-0.42 to 0.70)   | 0.04 (-0.53 to 0.60)           | 0.90  |
| AIDS  | -0.65 (-1.79 to 0.50)  | 0.07 (-1.07 to 1.20)           | 0.91  | -0.01 (-0.78 to 0.77)  | 0.50 (-0.26 to 1.26)           | 0.20  |
| HIV RNA viral load (copies/mL)                            |  |                                |       |  |                                |       |
| <50   | Reference  | Reference                      | —     | Reference  | Reference                      | —     |
| 50 to <400  | 1.58 (0.31 to 2.86)  | 1.77 (0.51 to 3.04)            | <0.01 | 0.60 (-0.20 to 1.39)   | 0.65 (-0.14 to 1.44)           | 0.11  |
| ≥400  | 1.54 (0.23 to 2.85)  | 2.00 (0.62 to 3.38)            | <0.01 | 0.85 (0.01 to 1.69)  | 1.05 (0.17 to 1.93)            | 0.02  |
| CD4 <sup>+</sup> T-cell count (cells/μL)                  |  |                                |       |  |                                |       |
| <200  | Reference  | Reference                      | —     | Reference  | Reference                      | —     |
| 200 to <350   | 1.31 (-0.40 to 3.01)   | 0.92 (-0.76 to 2.61)           | 0.28  | 0.35 (-0.73 to 1.43)   | 0.14 (-0.93 to 1.21)           | 0.80  |
| ≥350  | 0.62 (-1.06 to 2.30)   | 0.04 (-1.65 to 1.74)           | 0.96  | 0.22 (-0.87 to 1.30)   | -0.21 (-1.30 to 0.88)          | 0.70  |
| Cumulative time on NNRTI per 1-year increase              | 0.16 (-0.03 to 0.36)   | 0.12 (-0.12 to 0.36)           | 0.31  | 0.10 (-0.03 to 0.23)   | 0.06 (-0.10 to 0.22)           | 0.45  |
| Cumulative time on PI per 1-year increase                 | -0.36 (-0.50 to -0.22)   | -0.18 (-0.37 to 0.01)          | 0.06  | -0.28 (-0.37 to 0.19)  | -0.22 (-0.34 to -0.09)         | <0.01 |
| Cumulative time on triple NRTI per 1-year increase        | 0.03 (-0.28 to 0.34)   | 0.11 (-0.22 to 0.45)           | 0.50  | -0.01 (-0.22 to 0.20)  | 0.12 (-0.11 to 0.34)           | 0.31  |
| Cumulative time on other ART regimens per 1-year increase | -0.05 (-0.32 to 0.22)  | 0.22 (-0.07 to 0.50)           | 0.14  | 0.02 (-0.16 to 0.20)   | 0.15 (-0.04 to 0.34)           | 0.13  |

GFR, glomerular filtration rate; NNRTI, non-nucleoside reverse transcriptase inhibitor.

**TABLE 3.** HR for Cardiovascular Events and Starting Antihypertensive Treatment in All Patients With Confirmed Hypertension

| Parameter   | Cardiovascular Events            |                          |       | Starting Antihypertensive Treatment |                          |       |
|---|----------------------------------|--------------------------|-------|-------------------------------------|--------------------------|-------|
|   | HR Stratified by Center (95% CI) | Multivariate HR (95% CI) | P     | HR Stratified by Center (95% CI)    | Multivariate HR (95% CI) | P     |
| Systolic blood pressure per 10 mm Hg increase             | 1.25 (1.12 to 1.38)              | 1.18 (1.06 to 1.32)      | <0.01 | 1.63 (1.57 to 1.69)                 | 1.59 (1.53 to 1.66)      | <0.01 |
| Age per 10-year increase                                  | 1.76 (1.49 to 2.07)              | 1.71 (1.39 to 2.10)      | <0.01 | 1.44 (1.35 to 1.54)                 | 1.20 (1.12 to 1.29)      | <0.01 |
| Male gender   | 1.05 (0.62 to 1.79)              | 0.99 (0.55 to 1.78)      | 0.97  | 0.91 (0.76 to 1.09)                 | 0.90 (0.73 to 1.10)      | 0.29  |
| Caucasian ethnicity                                       | 1.70 (0.74 to 3.90)              | 0.95 (0.40 to 2.26)      | 0.90  | 0.86 (0.68 to 1.09)                 | 0.73 (0.57 to 0.93)      | 0.01  |
| Time since HIV diagnosis per 10-year increase             | 1.62 (1.19 to 2.20)              | 1.33 (0.85 to 2.07)      | 0.21  | 1.04 (0.93 to 1.16)                 | 1.15 (1.02 to 1.30)      | 0.02  |
| Total cholesterol per 1 mmol/L increase                   | 1.17 (1.08 to 1.26)              | 1.16 (1.07 to 1.26)      | <0.01 | 1.11 (1.07 to 1.16)                 | 1.04 (0.98 to 1.09)      | 0.19  |
| HDL cholesterol per 1 mmol/L increase                     | 0.88 (0.58 to 1.34)              | 0.62 (0.39 to 1.00)      | 0.05  | 1.20 (1.04 to 1.39)                 | 1.13 (0.96 to 1.32)      | 0.15  |
| BMI per 1 kg/m <sup>2</sup> increase                      | 0.97 (0.93 to 1.02)              | 1.00 (0.95 to 1.05)      | 0.95  | 1.05 (1.04 to 1.07)                 | 1.04 (1.02 to 1.05)      | <0.01 |
| Waist-to-hip ratio per 0.1 increase                       | 1.05 (0.96 to 1.15)              | 0.87 (0.65 to 1.16)      | 0.35  | 1.07 (1.05 to 1.10)                 | 1.07 (1.02 to 1.12)      | <0.01 |
| Diabetes  | 1.58 (1.00 to 2.50)              | 1.41 (0.87 to 2.27)      | 0.16  | 1.80 (1.51 to 2.14)                 | 1.54 (1.28 to 1.84)      | <0.01 |
| Cardiovascular events                                     | —                                | —                        | —     | 6.48 (4.57 to 9.18)                 | 7.03 (4.89 to 10.1)      | <0.01 |
| GFR < 50 mL/min/1.73 m <sup>2</sup>                       | 3.45 (1.65 to 7.22)              | 2.10 (0.97 to 4.57)      | 0.06  | 2.88 (1.86 to 4.45)                 | 2.42 (1.54 to 3.80)      | <0.01 |
| Smoker  | 1.14 (0.79 to 1.64)              | 1.95 (1.28 to 2.96)      | <0.01 | 0.82 (0.71 to 0.93)                 | 1.16 (1.00 to 1.35)      | 0.05  |
| IDU or in drug maintenance program                        | 0.85 (0.47 to 1.56)              | 0.83 (0.42 to 1.65)      | 0.59  | 0.72 (0.58 to 0.90)                 | 0.81 (0.63 to 1.04)      | 0.09  |
| Psychiatric problems                                      | 0.73 (0.40 to 1.34)              | 0.79 (0.42 to 1.46)      | 0.45  | 0.80 (0.65 to 1.00)                 | 0.92 (0.73 to 1.15)      | 0.46  |
| AIDS  | 1.58 (1.09 to 2.30)              | 1.35 (0.91 to 2.00)      | 0.13  | 1.28 (1.10 to 1.48)                 | 1.18 (1.02 to 1.38)      | 0.03  |
| HIV RNA viral load (copies/mL)                            |                                  |                          |       |                                     |                          |       |
| <50   | Reference                        | Reference                | —     | Reference                           | Reference                | —     |
| 50 to <400  | 1.20 (0.63 to 2.26)              | 1.25 (0.66 to 2.39)      | 0.49  | 1.08 (0.85 to 1.36)                 | 1.11 (0.88 to 1.43)      | 0.36  |
| ≥400  | 0.98 (0.59 to 1.63)              | 1.26 (0.72 to 2.20)      | 0.43  | 0.94 (0.79 to 1.12)                 | 1.29 (1.02 to 1.62)      | 0.03  |
| CD4 <sup>+</sup> T-cell count (cells/μL)                  |                                  |                          |       |                                     |                          |       |
| <200  | Reference                        | Reference                | —     | Reference                           | Reference                | —     |
| 200 to <350   | 0.77 (0.39 to 1.49)              | 0.84 (0.42 to 1.70)      | 0.63  | 0.82 (0.63 to 1.06)                 | 0.91 (0.70 to 1.19)      | 0.48  |
| ≥350  | 0.55 (0.30 to 1.00)              | 0.72 (0.38 to 1.38)      | 0.32  | 0.72 (0.58 to 0.91)                 | 0.90 (0.70 to 1.14)      | 0.38  |
| Cumulative time on NNRTI per 1-year increase              | 0.97 (0.82 to 1.15)              | 1.01 (0.84 to 1.21)      | 0.92  |                                     |                          |       |
| Cumulative time on PI per 1-year increase                 | 1.16 (1.08 to 1.24)              | 1.11 (1.02 to 1.21)      | 0.02  |                                     |                          |       |
| Cumulative time on triple NRTI per 1-year increase        | 1.25 (1.08 to 1.44)              | 1.28 (1.09 to 1.49)      | <0.01 |                                     |                          |       |
| Cumulative time on other ART regimens per 1-year increase | 1.12 (1.03 to 1.22)              | 1.02 (0.92 to 1.14)      | 0.65  |                                     |                          |       |
| Current exposure to ART regimen                           |                                  |                          |       |                                     |                          |       |
| NNRTI based   |                                  |                          |       | Reference                           | Reference                | —     |
| PI based  |                                  |                          |       | 1.03 (0.88 to 1.20)                 | 1.03 (0.88 to 1.21)      | 0.72  |
| Triple NRTI   |                                  |                          |       | 1.00 (0.76 to 1.33)                 | 1.00 (0.75 to 1.33)      | 0.99  |
| Other   |                                  |                          |       | 1.01 (0.69 to 1.48)                 | 1.00 (0.68 to 1.48)      | 0.99  |
| Off treatment   |                                  |                          |       | 0.75 (0.60 to 0.93)                 | 0.70 (0.53 to 0.93)      | 0.01  |

GFR, glomerular filtration rate; NNRTI, non-nucleoside reverse transcriptase inhibitor.

systolic and 89 mm Hg for diastolic blood pressure. Because blood pressure is only measured biannually in the SHCS, the time between measurements is quite long. Therefore, individuals falling under our definition of hypertension are likely to have had increased blood pressure over extended periods. With this conservative definition, the incidence of individuals initiating antihypertensive treatment is surprisingly low, given the regular follow-up within the SHCS. According to the 2007 Swiss National Health Survey done by phone contact, a third of interviewees who were told to be hyperten-

sive remained untreated.<sup>41</sup> In a study based on repetitive random samples from the Canton Geneva, hypertension unawareness decreased from 35.9% to 17.7% but was not paralleled by a concomitant increase in hypertension treatment, which remained low (38.2%).<sup>42</sup> Similar rates for treated hypertension have been reported in HIV-negative individuals from other settings.<sup>43–45</sup> But recent population data from different countries all indicate increased treatment and control rates of hypertension.<sup>46–51</sup> In our study, patients with established cardiovascular and renal disease, those of older age, advanced HIV infection,

and less suppressed viral load were more likely to initiate antihypertensive treatment. Thus, clinicians caring for HIV-infected patients seem to be more inclined to treat hypertensive patients at very high cardiovascular risk of preventing relapsing cardiovascular events. Surveillance data from HIV-negative hypertensive patients indicate similar trends of higher treatment rates in individuals at higher cardiovascular risk.<sup>46,47,52–54</sup> The mean decrease of systolic blood pressure per year in patients treated for hypertension was low but clinically relevant and would correspond to a mean decrease of  $-2.5$  mm Hg over a median observation period of 3.7 years. In a prospective study with high-risk patients, a blood pressure reduction in this magnitude could significantly reduce cardiovascular end points.<sup>55</sup> Extrapolation from observational and clinical trial data indicates that a long-term reduction of the mean population blood pressure of  $-7$  mm Hg by treating all individuals at low absolute risk would reduce the occurrence of major cardiovascular events by 26% in the following 10 years.<sup>56,57</sup>

Increased systolic blood pressure in our cohort was associated with an increased risk of cardiovascular events. We also confirmed in this population an association between cumulative exposure to PI and triple NRTI and increased risk of a cardiovascular event as previously shown in case-control study from the SHCS and the large DAD cohort study.<sup>58–60</sup>

There are several limitations of this study. The SHCS does not collect specific information of the type and combination of used antihypertensive drugs. Hypothetically, metabolic side effects might be amplified by the use of antihypertensive drugs such as diuretics and beta-blockers and lessen the cardiovascular benefits of lowering blood pressure.<sup>61–65</sup> Nevertheless, the main goal of antihypertensive treatment is to lower blood pressure, as this has clearly been associated with lower morbidity and mortality.<sup>35</sup> Blood pressure measurements in the SHCS are not standardized, and for example, information on 24-hour blood pressure measurements for the exclusion of white coat hypertension is missing. There was a center effect in blood pressure measurement with end digit preferences that may be related to imprecise reading, rounding documentation of blood pressure, or the use of different blood pressure measuring devices such as manual sphygmomanometers or digital devices. Over the years with the more widespread use of electronic devices, we noted less end digit preferences. For these reasons, we decide to model blood pressure change over time and not to report rates of individuals achieving blood pressure target values. In addition, many HIV-infected patients in the SHCS are also treated by general practitioners, and other specialists and infectious disease specialists may delegate or consider the treatment of cardiovascular risk factor management as not their domain. Although listing of antihypertensive drugs for SHCS patients at biannual visits is mandatory, underreporting may still occur. We lack data on HIV-infected patients that are mainly managed by HIV specialists.

This study has several strengths. The SHCS is not focused on specific risk groups and includes a fairly high proportion of female patients and patients from non-European ethnic background. The cohort has an excellent follow-up and continued repetitive measurement of blood pressure allowed to model blood pressure over time using a time-updated

model. To better control for the regression to the mean phenomenon, we based our inclusion criteria for patient selection on 2 consecutive measurements that were taken 6 months apart; hence, the measurement variability is reduced. End point assessment for cardiovascular events was done according to the DAD protocol, which is a further strength of this investigation.

In conclusion, in HIV-infected hypertensive patients treated for hypertension in the SHCS, we find a decline in systolic blood pressure over time. Risk factors for hypertension and insufficient control of blood pressure for individuals in this cohort are not different from those of HIV-negative hypertensive individuals. Indirect evidence suggests that HIV-infected individuals in Switzerland are not a neglected population in regard with the management of hypertension compared with HIV-negative individuals. However, clinicians caring for HIV-infected patients should consider that HIV-infected patients may be at increased risk of the development of chronic kidney disease and cardiovascular events compared with HIV-negative individuals.<sup>25</sup> Although HIV-infected patients at high cardiovascular risk were more likely to receive antihypertensive treatment, our study shows that many patients remain untreated or insufficiently treated for hypertension and at increased risk of a cardiovascular event. Recent evidence from the NHANES surveys from the United States underlines that better control of cardiovascular risk factors may be achieved and is associated with decreased cardiovascular mortality.<sup>66</sup> Therefore, more aggressive treatment and better management of hypertension are urgently needed in HIV-infected patients.

## ACKNOWLEDGMENTS

*The members of the Swiss HIV Cohort Study are J. Barth, M. Battegay, E. Bernasconi, J. Böni, H. C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, C. Cellera, M. Egger, L. Elzi, J. Fehr, J. Fellay, M. Flepp, P. Francioli (President of the SHCS), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. A. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), D. Haerry (deputy of "Positive Council"), B. Hasse, H. H. Hirsch, B. Hirschel, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, C. Kind, T. Klimkait, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, F. Schöni-Affolter, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.*

## REFERENCES

1. Collaboration ATC. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet*. 2008;372:293–299.
2. d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *Arch Intern Med*. 2005;165:416–423.
3. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Ann Intern Med*. 2007; 146:87–95.

4. Palella FJ Jr, Baker RK, Moorman AC, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr*. 2006;43:27–34.
5. Manner IW, Baekken M, Oektedalen O, et al. Effect of HIV duration on ambulatory blood pressure in HIV-infected individuals with high office blood pressure. *Blood Press*. 2010;19:188–195.
6. Vance DE, Mugavero M, Willig J, et al. Aging with HIV: a cross-sectional study of comorbidity prevalence and clinical characteristics across decades of life. *J Assoc Nurses AIDS Care*. 2011;22:17–25.
7. Onen NF, Overton ET, Seyfried W, et al. Aging and HIV infection: a comparison between older HIV-infected persons and the general population. *HIV Clin Trials*. 2010;11:100–109.
8. Hsue PY, Lo JC, Franklin A, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation*. 2004;109:1603–1608.
9. Albin A, Soldi R, Giunciuglio D, et al. The angiogenesis induced by HIV-1 tat protein is mediated by the Flk-1/KDR receptor on vascular endothelial cells. *Nat Med*. 1996;2:1371–1375.
10. Baker JV, Henry WK, Patel P, et al. Progression of carotid intima-media thickness in a contemporary human immunodeficiency virus cohort. *Clin Infect Dis*. 2011;53:826–835.
11. Bragardo M, Buonfiglio D, Feito MJ, et al. Modulation of lymphocyte interaction with endothelium and homing by HIV-1 gp120. *J Immunol*. 1997;159:1619–1627.
12. Calmy A, Gayet-Ageron A, Montecucco F, et al. HIV increases markers of cardiovascular risk: results from a randomized, treatment interruption trial. *AIDS*. 2009;23:929–939.
13. Canque B, Marandin A, Rosenzweig M, et al. Susceptibility of human bone marrow stromal cells to human immunodeficiency virus (HIV). *Virology*. 1995;208:779–783.
14. Charakida M, Loukogeorgakis SP, Okorie MI, et al. Increased arterial stiffness in HIV-infected children: risk factors and antiretroviral therapy. *Antivir Ther*. 2009;14:1075–1079.
15. Cornali E, Zietz C, Benelli R, et al. Vascular endothelial growth factor regulates angiogenesis and vascular permeability in Kaposi's sarcoma. *Am J Pathol*. 1996;149:1851–1869.
16. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006;355:2283–2296.
17. Gujulova C, Burns AR, Pushkarsky T, et al. HIV-1 penetrates coronary artery endothelial cells by transcytosis. *Mol Med*. 2001;7:169–176.
18. Ho JE, Scherzer R, Hecht FM, et al. The association of CD4+ T-cell count on cardiovascular risk in treated HIV disease. *AIDS*. 2012;26:1115–1120.
19. Kaplan RC, Sinclair E, Landay AL, et al. T cell activation predicts carotid artery stiffness among HIV-infected women. *Atherosclerosis*. 2011;217:207–213.
20. Kuller LH, Tracy R, Belloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008;5:e203.
21. Lafon ME, Steffan AM, Royer C, et al. HIV-1 infection induces functional alterations in human liver endothelial cells in primary culture. *AIDS*. 1994;8:747–752.
22. Nakamura S, Endo H, Higashi Y, et al. Human immunodeficiency virus type 1 gp120-mediated disruption of tight junction proteins by induction of proteasome-mediated degradation of zonula occludens-1 and -2 in human brain microvascular endothelial cells. *J Neurovirol*. 2008;14:186–195.
23. Wolf K, Tsakiris DA, Weber R, et al. Antiretroviral therapy reduces markers of endothelial and coagulation activation in patients infected with human immunodeficiency virus type 1. *J Infect Dis*. 2002;185:456–462.
24. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349:1993–2003.
25. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS*. 2003;17:1179–1193.
26. Baekken M, Os I, Sandvik L, et al. Hypertension in an urban HIV-positive population compared with the general population: influence of combination antiretroviral therapy. *J Hypertens*. 2008;26:2126–2133.
27. Crane HM, Grunfeld C, Harrington RD, et al. Lipatrophy and lipohypertrophy are independently associated with hypertension. *HIV Med*. 2009;10:496–503.
28. Crane HM, Van Rompaey SE, Kitahata MM. Antiretroviral medications associated with elevated blood pressure among patients receiving highly active antiretroviral therapy. *AIDS*. 2006;20:1019–1026.
29. Boccaro F, Auclair M, Cohen A, et al. HIV protease inhibitors activate the adipocyte renin angiotensin system. *Antivir Ther*. 2010;15:363–375.
30. Peyriere H, Eiden C, Macia JC, et al. Antihypertensive drugs in patients treated with antiretrovirals. *Ann Pharmacother*. 2012;46:703–709.
31. Glass TR, Ungsedhapand C, Wolbers M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time: the Swiss HIV Cohort Study. *HIV Med*. 2006;7:404–410.
32. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: the Swiss HIV Cohort study. *Int J Epidemiol*. 2009;39:1179–1189.
33. Mancia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. *J Hypertens*. 2007;25:1751–1762.
34. Mancia G, De Backer G, Dominiczak A, et al. 2007 guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2007;25:1105–1187.
35. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *Blood Press*. 2009;18:308–347.
36. Chuang-Stein C, Tong DM. The impact and implication of regression to the mean on the design and analysis of medical investigations. *Stat Methods Med Res*. 1997;6:115–128.
37. Armah K, Justice A, Oursler K, et al. The impact of elevated and prehypertensive systolic blood pressure and the risk of acute myocardial infarction in HIV+ and HIV- veterans. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections CROI, March 5–8, 2012; Seattle, Washington, DC.
38. Chow F, Regan S, Foske S, et al. HIV is an independent risk factor for ischemic stroke: US health care system. Paper presented at: 19th Conference on Retroviruses and Opportunistic Infections CROI, March 5–8, 2012; Seattle, Washington, DC.
39. Monroe AK, Chander G, Moore RD. Control of medical comorbidities in individuals with HIV. *J Acquir Immune Defic Syndr*. 2011;58:458–462.
40. Franklin SS, Wt Gustin, Wong ND, et al. Hemodynamic patterns of age-related changes in blood pressure. The Framingham Heart Study. *Circulation*. 1997;96:308–315.
41. Marques-Vidal P, Paccaud F. Regional differences in self-reported screening, prevalence and management of cardiovascular risk factors in Switzerland. *BMC Public Health*. 2012;12:246.
42. Guessous I, Bochud M, Theler JM, et al. 1999–2009 trends in prevalence, unawareness, treatment and control of hypertension in Geneva, Switzerland. *PLoS One*. 2012;7:e39877.
43. Glynn LG, Murphy AW, Smith SM, et al. Interventions used to improve control of blood pressure in patients with hypertension. *Cochrane Database Syst Rev*. 2010;CD005182.
44. Spranger CB, Ries AJ, Berge CA, et al. Identifying gaps between guidelines and clinical practice in the evaluation and treatment of patients with hypertension. *Am J Med*. 2004;117:14–18.
45. Yokokawa H, Goto A, Sanada H, et al. Achievement status toward goal blood pressure levels and healthy lifestyles among Japanese hypertensive patients; cross-sectional survey results from Fukushima Research of Hypertension (FRESH). *Intern Med*. 2011;50:1149–1156.
46. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000. *JAMA*. 2003;290:199–206.
47. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988–2008. *JAMA*. 2010;303:2043–2050.
48. Estoppey D, Paccaud F, Vollenweider P, et al. Trends in self-reported prevalence and management of hypertension, hypercholesterolemia and diabetes in Swiss adults, 1997–2007. *BMC Public Health*. 2011;11:114.
49. Andersen UO, Jensen GB. Trends and determinant factors in hypertension control in a population study with 25 years of follow-up. *J Hypertens*. 2010;28:1091–1096.
50. Nilsson PM, Cederholm J, Zethelius BR, et al. Trends in blood pressure control in patients with type 2 diabetes: data from the Swedish National Diabetes Register (NDR). *Blood Press*. 2011;20:348–354.



51. McAlister FA, Wilkins K, Joffres M, et al. Changes in the rates of awareness, treatment and control of hypertension in Canada over the past two decades. *CMAJ*. 2011;183:1007–1013.
52. Gu D, Reynolds K, Wu X, et al. Prevalence, awareness, treatment, and control of hypertension in china. *Hypertension*. 2002;40:920–927.
53. Setaro JF, Black HR. Refractory hypertension. *N Engl J Med*. 1992;327:543–547.
54. Lavery AA, Bottle A, Majeed A, et al. Blood pressure monitoring and control by cardiovascular disease status in UK primary care: 10 year retrospective cohort study 1998–2007. *J Public Health (Oxf)*. 2011;33:302–309.
55. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153.
56. Emberson J, Whincup P, Morris R, et al. Evaluating the impact of population and high-risk strategies for the primary prevention of cardiovascular disease. *Eur Heart J*. 2004;25:484–491.
57. Psaty BM, Furberg CD, Kuller LH, et al. Association between blood pressure level and the risk of myocardial infarction, stroke, and total mortality: the cardiovascular health study. *Arch Intern Med*. 2001;161:1183–1192.
58. Sabin CA, d'Arminio Monforte A, Friis-Moller N, et al. Changes over time in risk factors for cardiovascular disease and use of lipid-lowering drugs in HIV-infected individuals and impact on myocardial infarction. *Clin Infect Dis*. 2008;46:1101–1110.
59. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. 2008;371:1417–1426.
60. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2009;201:318–330.
61. Bradley HA, Wiysonge CS, Volmink JA, et al. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. *J Hypertens*. 2006;24:2131–2141.
62. Collins R, Peto R, MacMahon S, et al. Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context. *Lancet*. 1990;335:827–838.
63. Lindholm LH, Persson M, Alaupovic P, et al. Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation (ALPINE study). *J Hypertens*. 2003;21:1563–1574.
64. Stas S, Appesh L, Sowers J. Metabolic safety of antihypertensive drugs: myth versus reality. *Curr Hypertens Rep*. 2006;8:403–408.
65. Vecchiet J, Ucciferri C, Falasca K, et al. Antihypertensive and metabolic effects of telmisartan in hypertensive HIV-positive patients. *Antivir Ther*. 2011;16:639–645.
66. Yang Q, Cogswell ME, Flanders WD, et al. Trends in cardiovascular health metrics and associations with all-cause and CVD mortality among US adults. *JAMA*. 2012;307:1273–1283.