High Prevalence of Peripheral Arterial Disease in HIV-Infected Persons

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Background. Atherosclerosis has been assessed in human immunodeficiency virus (HIV)–infected persons by using various methods. Peripheral arterial disease (PAD) has not been evaluated, however. We studied the cross-sectional prevalence of lower limb PAD in an HIV-infected population.

Methods. PAD was assessed using the Edinburgh Claudication Questionnaire and by measuring the systolic ankle-brachial blood pressure index (ABI) at rest and after exercise. Patients with PAD were further evaluated by duplex scan of lower limb arteries.

Results. Ninety-two consecutive HIV-infected patients were evaluated (23.9% women; mean age, 49.5 years; 61.9% current smokers). Claudication was reported by 15.2% of the patients. PAD was found in 20.7% of the patients: 9.8% had an abnormal ABI (<0.90) at rest, and 10.9% had normal ABI at rest but a >25% decrease after exercise. Of the patients with PAD, 84.2% were investigated with duplex scan, all of whom had atherosclerotic occlusions or stenoses of the iliac or femoral arteries. Age, diabetes, smoking, and low $CD4^+$ T lymphocyte counts were identified as independent predictors of PAD.

Conclusions. The prevalence of symptomatic and asymptomatic PAD is high in the HIV-infected population and is much higher than expected (prevalence in the general population, ~3% at 60 years). This study suggests the presence of an epidemic of PAD ~20 years earlier in the HIV-infected than in the general population. Larger epidemiological studies are needed to better define risk factors and to evaluate whether PAD is associated with increased mortality, as it is in the general population.

Combination antiretroviral therapy has dramatically decreased the mortality and illnesses related to HIV infection. However, a variety of atherogenic metabolic abnormalities, including dyslipidemia, lipodystrophy, and insulin resistance [1, 2], have been observed soon after the introduction of combination antiretroviral therapy. Concern about increased cardiovascular mortality was raised by the detection of subclinical atherosclerosis by measuring the carotid intima-media thickness [3–5], endothelial dysfunction [6, 7], and coronary calcifications [8]. An association between premature coronary events and use of protease inhibitors (PIs) is now well established in the HIV-infected population [9, 10].

The prevalence of peripheral arterial disease (PAD) has not been assessed in HIV-infected patients. In the general population, PAD is associated with traditional cardiovascular risk factors, particularly smoking, diabetes, hypertension, and hypercholesterolemia [11]. These factors may have an increased prevalence among HIV-infected patients [10, 12]. PAD of the lower limbs can be assessed by a marker validated in numerous studies, the ankle-brachial index (ABI) [11]. A decreased ABI is associated with a shorter survival in the general population, which is mainly due to an increase in coronary and cerebrovascular events [13, 14]. The aim of our study was to assess the cross-sectional prevalence of PAD in an HIV-infected population and to evaluate the feasibility of measuring the ABI in the routine HIV care setting.

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METHODS

Patients. From 1 July through 30 September 2006, all consecutive HIV-infected patients aged ⩾40 years who were observed in the Infectious Disease Outpatient Clinic at the University Hospital in Lausanne, Switzerland, were invited to take part to the study. The only exclusion criteria were active injection drug use or known arterial complications from previous use. Informed consent was obtained from all patients, and the study was approved by the institutional ethics committee. Symptoms potentially related to PAD (claudication, rest pain, and nonhealing leg wounds) were recorded using the Edinburgh Claudication Questionnaire [15].

Cardiovascular risk factors. Abnormal plasma lipid levels were defined using the third adult treatment panel guidelines of the National Education Cholesterol Program [16]. To take into account the longitudinal variability in lipid levels due to changes of combination antiretroviral therapy, lipid-lowering medication, and fasting status, we considered, in addition to the point prevalence of dyslipidemia at the most recent blood draw, the longitudinal prevalence of sustained dyslipidemia, as previously reported [17], by including all lipid levels determined during the 5-year period preceding the ABI measurement. Sustained non–high-density lipoprotein (HDL) hypercholesterolemia, low HDL cholesterol levels, and hypertriglyceridemia were defined as more than two-thirds of an individual patient's respective measurements in plasma being >4.9 mmol/L (190 mg/L), <1.03 mmol/L (40 mg/L), and >2.26 mmol/L (200 mg/L), respectively. Hypertension was defined as a brachial blood pressure of >140/90 mm Hg, as measured after 5 min of rest, or by the current use of any antihypertensive drug. Metabolic syndrome was defined by the International Diabetes Federation criteria [18].

Rest and postexercise ABI measurement. Patients rested for 5 min lying on a bed, after which blood pressure was mea-

Table 1. Clinical characteristics of the 92 study participants, compared with the 511 patients aged ⩾40 years observed in the outpatient HIV clinic of the University Hospital of Lausanne in 2006 who were not included in the study.

Characteristic	Study participants (n = 92)	Patients not included in the study (n = 511)
Male	70 (76.1)	357 (69.9)
Age, mean years ± SD	49.5 ± 7.4	49.7 ± 7.9
Ethnicity		
White	81 (88.0)	448 (87.7)
Black	7 (7.6)	44 (8.6)
Other	4 (4.3)	19 (3.7)
Presumed mode of HIV transmission		
Heterosexual sex	27 (29.3)	224 (43.8)
Homosexual sex	37 (40.2)	182 (35.6)
Injection drug use	26 (28.3)	88 (17.2)
Other	2 (2.2)	17 (3.3)
HIV load <400 copies/mL	73 (79.3)	387 (75.7)
$CD4^+$ T cell count, cells/μL		
<200	5 (5.4)	46 (9.0)
200–500	35 (38.0)	218 (42.7)
>500	51 (55.4)	246 (48.1)
Family history of cardiovascular disease	21 (22.8)	93 (18.2)
Hypertension	25 (27.2)	153 (29.9)
Diabetes mellitus	4 (4.3)	33 (6.5)
Increased plasma non-HDL cholesterol level[a]	12 (13.0)	62 (12.1)
Low plasma HDL cholesterol level[b]	16 (17.4)	109 (21.3)
Elevated plasma triglyceride level[c]	33 (35.9)	134 (26.2)
Metabolic syndrome	25 (27.2)	NA
Current smoking	57 (62.0)	197 (38.6)

NOTE. Data are no. (%) of patients, unless otherwise indicated. HDL, high-density lipoprotein; NA, not available.

[a] Defined as a level >4.9 mmol/L.
[b] Defined as a level <1.03 mmol/L.
[c] Defined as a level >2.26 mmol/L.

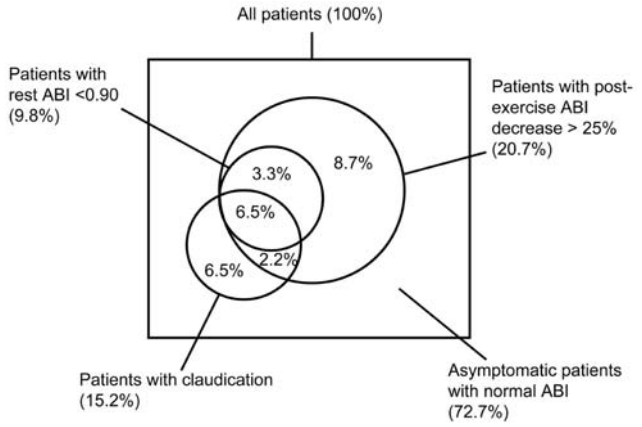

Figure 1. Distribution of abnormal ankle-brachial blood pressure index (ABI) values at rest and after exercise according to symptoms.

sured at the posterior tibialis and dorsalis pedis arteries of both ankles with a 5.0 MHz vascular Nicolet Elite Doppler probe (Viasys) and a sphygmomanometer. Brachial pressure was simultaneously measured at both arms by 2 HEM-907 automated manometers (Omron), with cuff size adapted to the arm circumference. For each leg, the ABI was calculated by dividing the higher systolic ankle pressure by the higher brachial systolic pressure. The ABI threshold of 0.90, measured at rest, has 79% sensitivity and 96% specificity to detect stenoses of ⩾50% reduction in arterial luminal diameter [19]. To evaluate the presence of presumably less severe arterial stenoses that were not detected at rest, the same ABI measurement was repeated immediately after the patient slowly performed 20 squats, under supervision. Among the different exercise protocols used to confirm or quantify PAD [20], we chose squatting because it is simple to perform and does not require a mechanical treadmill. PAD was investigated by the same ABI measures in a control group of HIV-uninfected subjects. These subjects were recruited among hospital coworkers if they were current smokers and were aged ⩾40 years.

Definition of PAD. According to the American Heart Association and American College of Cardiology guidelines, PAD was diagnosed when the ABI was <0.90 at rest or when the ABI significantly decreased after exercise [11]. Different thresholds to define an exercise-related ABI decrease have been used in different studies [21–23]. Considering the intra-observer variability of ABI measurement (estimated to be 0.06–0.08) [24], an absolute decrease in ABI of >0.15 (2 SDs) is usually considered to be significant [11]. To increase specificity, we defined a postexercise decrease of >25% as significant.

Duplex scan. To confirm and localize vascular lesions, patients with abnormal rest or postexercise ABI were invited to undergo arterial duplex scanning (En Visor HD; Philips Ultrasounds). The wall and lumen of the main arteries from the abdominal aorta to the ankles were evaluated. Plaque was defined as >1.2-mm thickening of the intima-media of the arterial wall, with or without calcifications. The percentage of stenosis was estimated by the peak systolic velocity ratio [25]. All ABI measurements and duplex scans were performed by 1 of 3 vascular specialists (D.P., M.C., or D.H.).

Statistical analysis. The contribution of clinical characteristics, cardiovascular risk factors (hypertension, smoking, diabetes, plasma lipid levels, and metabolic syndrome), and infectious parameters (most recent $CD4^+$ T cell count, most recent HIV load, duration of seropositivity, and cumulative exposure to PIs and nonnucleoside reverse-transcriptase inhibitors) to prevalence of PAD were analyzed using multivariable logistic regression analysis. Factors were first analyzed individually in bivariate analysis and then selected for multivariable analysis on the basis of a P value <.2 or a confounding effect. Linearity on the logit scale was assessed with the fractional polynomial method. Because of the limited sample size, no more than 4 factors were assessed at any time. Goodness of fit was determined using the Hosmer Lemeshow test and area under the receiver operating curve. All statistical analyses were performed using Stata software, version 9.2 (Stata).

RESULTS

Patients. Ninety-two patients (23.9% women) were included in the study. Their clinical characteristics were compared with those of the remaining 511 HIV-infected patients aged ⩾40 years who were observed in our clinic in 2006 but did not participate in the study (table 1). Claudication (grade 1 and 2 of Edinburgh Questionnaire) was reported by 15.2% of the patients. No patient reported leg pain at rest or nonhealing leg ulcers.

ABI results are shown in figure 1. PAD was found in 20.7% (95% CI, 12.2%–29.1%) of the patients: 9.8% (95% CI, 3.6%–16.0%) had an abnormal ABI at rest, and 10.9% (95% CI, 4.4%–17.4%) had a normal rest ABI but a >25% decrease after exercise. All 9 patients with rest ABI of <0.90 also had a postexercise ABI decrease of >25% (mean decrease ± SD, 34.1% ± 20.0%). Among the 15.2% of patients reporting claudication of the lower limbs, 6.5% had normal ABI results, 6.5% had decreased ABI at rest, and 2.2% had a normal rest ABI but an abnormal ABI after exercise.

Duplex scan revealed classical atherosclerotic occlusive disease of the iliac and femoral arteries in all 9 patients with rest ABI of <0.90 (table 2). Among the 10 patients with rest ABI of ⩾0.90 and >25% decrease after exercise, 7 agreed to duplex scanning. Atherosclerotic plaques or stenoses were found in all 7 patients (table 3).

Among the 9 patients with rest ABI of <0.90, 2 had known coronary disease, 1 had a previous stroke due to carotid dissection, and 5 had no known history of cerebral or coronary vascular disease. One patient gave a history of exercise-related

Table 2. Clinical characteristics and duplex scan findings of the 9 patients with ankle-brachial blood pressure index (ABI) of <0.90 at rest.

Patient	Sex	Age, years	Claudication[a]	Risk factor(s)	ABI at rest	ABI after exercise	Duplex scan findings
1	M	77	After 200 m	None	0.77	0.55	Femoropopliteal and calf atherosclerosis
2	M	68	After 50 m	Diabetes, cholesterol	0.71	0.48	Diffuse aorto-iliac, femoropopliteal and calf atherosclerosis
3	M	66	None	Diabetes	0.81	0.63	Diffuse aorto-iliac, femoropopliteal, and calf atherosclerosis
4	M	56	After 150 m	Hypertension, cholesterol, smoking	0.82	0.42	Diffuse aorto-iliac, femoropopliteal, and calf atherosclerosis
5	M	56	After 50 m	Smoking, hypertension, cholesterol	0.79	0.48	95% Stenosis of the left common iliac artery
6	M	46	After 150 m	Smoking	0.65	0.45	Bilateral occlusion of the popliteal arteries
7	M	45	After 100 m	Smoking, cholesterol	0.70	0.32	90% Stenosis of the left and occlusion of the right common iliac arteries
8	F	42	After 80 m	Smoking	0.74	0.44	Diffuse aorto-iliac atherosclerosis with 95% stenosis of the left common iliac artery
9	F	40	After 200 m	Smoking	0.55	0.20	Diffuse aorto-iliac atherosclerosis with occlusion of the left extern iliac artery

[a] Distance of walk after which symptoms appear in the lower limbs.

chest pain, which occurred at the time of preanesthesia evaluation before peripheral artery bypass surgery. Among the 10 patients with rest ABI of ⩾0.90 and >25% decrease after exercise, one had known coronary artery disease.

Controls. Thirty-two HIV-uninfected, currently smoking control subjects (mean age, 47 years; range, 41–56 years) were included. Four (12.5%) had hypertension. None had a rest ABI of <0.90, and 2 (6.3%) had a >25% decrease after exercise.

Predictors of PAD. Results of logistic regression analysis are shown in table 4. In bivariate analysis, a correlation was found between PAD and age, smoking, hyperlipidemia, diabetes mellitus, hypertension, metabolic syndrome, family history of cardiovascular disease, and $CD4^+$ T cell count of <200 cells/μL. Other factors related to HIV infection (duration of seropositivity, clinical stage, and cumulative exposure to PIs) had ORs that suggested a correlation with PAD but that did not reach statistical significance. Multivariate analysis identified age, smoking, diabetes, and $CD4^+$ T cell of <200 cells/μL as important and significant predictors of PAD (table 4). The fit of this model was satisfactory (area under receiver operating curve, 0.78; sensitivity, 67%; specificity, 62%; $P = .58$, by Hosmer Lemeshow test). Dyslipidemia, metabolic syndrome, and familial history had ORs that were ⩾2.0 but did not reach significance in multivariable analysis.

DISCUSSION

The major finding of this pilot study is a high cross-sectional prevalence of PAD in a population representative of HIV-infected persons in western Europe. PAD was evaluated using widely accepted definitions and screening tools, and duplex scan confirmed atherosclerotic disease of the main limb arteries in all patients with an abnormal ABI either at rest or after exercise. Atherosclerotic lesions were localized in the iliac and femoral arteries, as generally seen in nondiabetic patients with PAD. Most patients with PAD had symptoms limited to exertion, and no study participant had ischemic rest pain or critical limb ischemia, consistent with the relatively young age of participants. Duplex scan identified more-severe atherosclerotic disease in patients with abnormal rest ABI than in those with decreased ABI after exercise only. Only 5 of the 19 patients with PAD were previously known to have cerebral or coronary vascular disease, potentially allowing the 14 newly identified patients with PAD to receive interventions to correct modifiable cardiovascular risk factors.

Large epidemiological studies have reported a prevalence of PAD of ~1% at 50 years and 3% at 60 years of age in the general population [26, 27]. The 20.7% prevalence of PAD in our study, evaluating a relatively young population of HIV-infected patients (median age, 49.5 years), is therefore strikingly higher than expected. This difference with historical control subjects may be attributed in part to technical differences in the method used to screen for PAD. Most large population studies have used rest ABI of <0.90 as the definition of PAD. In our study, the systematic performance of a second ABI after exercise raised the sensitivity of screening and doubled the proportion of patients with PAD. The utility of this exercise was demonstrated by duplex scan confirmation of PAD in all patients (including those whose ABI decreased only after exercise). However, even if we consider only the proportion of patients who had rest ABI of <0.90 in our study (9.8%), this proportion remains considerably higher than that for historical control subjects aged <50 years.

A high proportion of patients included in the study were smokers, which may have contributed to the high proportion

Table 3. Clinical characteristics and duplex scan findings of 7 patients with ABI of ⩾0.90 at rest and a >25% decrease after exercise.

Patient	Sex	Age, years	Claudication[a]	Risk factor(s)	ABI at rest	ABI after exercise	Duplex scan findings
1	M	55	None	Smoking, cholesterol	1.08	0.79	Common femoral and superficial femoral atherosclerotic plaque
2	M	54	After 300 m	Smoking	0.92	0.69	Bilateral stenosis of the superficial femoral arteries
3	M	49	None	Smoking, cholesterol	1.25	0.87	Common femoral and superficial femoral atherosclerotic plaque
4	M	44	None	Smoking	1.12	0.84	Common femoral and superficial femoral atherosclerotic plaque
5	M	44	None	Smoking, cholesterol	1.19	0.89	Atherosclerotic plaques in the iliac and femoral arteries
6	M	40	After 150 m	Smoking, diabetes	1.16	0.72	Common femoral and superficial femoral atherosclerotic plaque
7	F	40	None	Smoking	1.23	0.87	Superficial femoral atherosclerotic plaque

[a] Distance of walk after which symptoms appear in the lower limbs.

of PAD detected. However, smoking alone cannot fully explain the high PAD prevalence, because 3 of the 9 HIV-infected patients with rest ABI of <0.9 were nonsmokers and because only 2 (6.3%) of the 32 HIV-uninfected control subjects, all of whom were smokers, had PAD. This is consistent with the results of a study of HIV-seronegative men aged 45–50 years, 72.3% of whom were current or past smokers, which found a prevalence of PAD of 1% [26].

Considerable attention has been paid in the literature to the effect of combination antiretroviral therapy on premature atherosclerosis of the coronary or carotid arteries [3–9]. Nevertheless, to our knowledge, the incidence of PAD of the lower limbs has not been investigated in the HIV-infected population. Subclinical atherosclerosis was found in several studies using by B-mode ultrasound on the carotid or femoral arteries, indicated by either an increase in intima-media thickness or the presence of plaques [3, 4, 28–31]. Depairon et al. [4] found that 55% of HIV-infected patients had at least 1 carotid or femoral plaque, compared with 38% of healthy control subjects. Maggi et al. [3] found an increased proportion of carotid plaques or thickened intima-media thickness in HIV-infected patients treated with PIs, compared with the proportion among PI-naive patients and healthy control subjects. They also found a more rapid onset of new lesions and a more rapid thickening of previous lesions in patients treated with PIs than in patients treated with nonnucleoside reverse-transcriptase inhibitors [28]. Sevastianova et al. [32] found that prolonged PI exposure was associated with increased peripheral arterial stiffness measured by pulse wave velocity. Van Wijk et al. [7] found that HIV-infected patients had decreased flow-mediated vasodilation but a normal pulse wave velocity. All of these findings are considered to be the first measurable manifestations of atherosclerosis at various stages in a process leading to peripheral arteriopathy. Most of these markers of atherosclerosis are associated with an increased cardiovascular mortality or are putative markers of concomitant coronary disease in the general population.

Several possible mechanisms might be responsible for premature development of PAD in the HIV-infected population. First, HIV-infected patients tend to have lifestyle-related cardiovascular risk factors, including a high prevalence of smoking, as identified in our study. Second, combination antiretroviral therapy–related dyslipidemia, lipodystrophy, and impaired glucose tolerance may be associated with the development of premature atherosclerosis, as previously shown [3, 4, 28, 29, 32–35], even though an association between PI exposure and vascular disease was not consistently identified [30, 31]. This discrepancy might be explained by the mechanisms by which PIs are supposed to be atherogenic. PIs are associated with usually reversible dyslipidemia, and long-term exposure to PIs is probably necessary for atherosclerosis to develop, whereas a short duration of PI exposure may temporarily modify lipid levels without substantial development of atherosclerosis. Moreover, not all patients develop dyslipidemia on exposure to PIs. This may have been illustrated in our study by the weak association between PAD and PI use, whereas the association with dyslipidemia was stronger. In our study, PI use was associated with a slight increase (OR, 1.03; $P = .6$) in PAD risk, per additional year of exposure. Nevertheless, sustained dyslipidemia, which is attributable predominantly to PI use in this young patient population, was associated with larger ORs for PAD (for non-HDL hypercholesterolemia: OR, 2.94; $P = .15$; for hypertriglyceridemia: OR, 2.98; $P = .20$). This suggests the presence of an association between PIs and PAD that needs further clarification. Larger studies with many more patients will be necessary to confirm the role of PIs and to evaluate potential associations of other antiviral agents with PAD.

A third hypothetical mechanism could be a direct HIV injury to the arterial wall, resulting in inflammatory lesions, as recently suggested by Maggi et al. [36]. This is illustrated by the ectatic or aneurysmal dilation of large arteries observed in HIV-infected children. Lai et al. [37] reported aortic root dilations in children aged 2–9 years with vertically transmitted HIV infection. The aortic root size was associated with left ventricular dilation, increased viral load, and lower $CD4^+$ T cell count. Dubrovsky et al. [38] reported the cases of 13 HIV-infected children with cerebral artery aneurysms. The etiology of these aneurisms remains unknown, but vasculitis, either infectious

Table 4. Bivariate and multivariable logistic regression analysis of variables associated with the presence of peripheral arterial disease.

	Bivariate logistic regression		Multivariable logistic regression	
Variable	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex (male vs. female)	3.20 (0.67–15.5)	.14	1.24 (0.22–6.85)	.81
Age (per additional year)	1.07 (1.00–1.15)	.04	1.09 (1.00–1.18)	.04
Smoking (per additional 10 pack-year)	1.30 (0.99–1.70)	.05	1.70 (1.17–2.46)	.005
Diabetes mellitus	13.5 (1.32–138.34)	.03	Predicts perfectly[a]	
Plasma non-HDL cholesterol level >4.9 mmol/L[b]	5.50 (1.52–19.94)	.009	2.94 (0.67–12.89)	.15
Plasma triglyceride level >2.26 mmol/L[b]	3.49 (0.83–14.72)	.09	2.98 (0.56–15.75)[c]	.20
Hypertension	2.39 (0.83–6.91)	.10	1.56 (0.44–5.50)[c]	.69
Metabolic syndrome	2.58 (0.88–7.60)	.08	2.12 (0.59–7.60)[c]	.25
Exposure to PI (per additional year)	1.03 (0.91–1.17)	.63	…	
Family history of cardiovascular disease	2.55 (0.84–7.75)	.10	3.19 (0.87–11.69)[c]	.08
HIV load <400 copies/mL	1.50 (0.39–5.79)	.56	…	
$CD4^+$ T cell count <200 cells/μL	7.1 (1.09–46.24)	.04	27.2 (2.55–286.01)[c]	.006
Presumed duration of HIV infection (per additional year)	1.01 (0.91–1.12)	.84	…	
HIV clinical stage B	1.25 (0.34–4.64)	.74	…	
HIV clinical stage C	1.67 (0.48–5.82)	.43	…	

NOTE. PAD, peripheral arterial disease; PI, protease inhibitor.

[a] Because of 1 missing value, all diabetic patients included in the multivariable analysis had PAD, providing a perfect prediction.

[b] Sustained lipid levels (see Methods).

[c] Factors individually analyzed in models including 4 variables (with sex, age, and smoking).

or inflammatory, may be the causative mechanism. These aneurysms may have preferentially affected children in the era before combination antiretroviral therapy was available, because of their presumable exposure to prolonged viremia, resulting in large vessel vasculitis. More recently, Solages et al. [39] also found a correlation between high HIV load and endothelial dysfunction, supporting this hypothesis. However, in many survivors from the era before combination antiretroviral therapy, the HIV load is now controlled by HAART. This may explain why the most recent HIV load did not correlate with PAD in our study. However, low $CD4^+$ T cell counts were strongly associated with PAD in our study (OR, 27.2; $P = .006$). Such an association has previously been reported by Mercié et al. [30], but the underlying mechanism is not clear. Low $CD4^+$ T cell counts may reflect the duration and severity of uncontrolled HIV infection and be a surrogate marker of potential endothelial toxicity of HIV. The association of PAD with low $CD4^+$ T cell count may also be partially confounded by patient age, because older age is a predictor of a less robust increase in $CD4^+$ T cell counts after the introduction of antiretroviral therapy.

This study evaluated the feasibility of identifying patients with PAD using a reliable test, the ABI. Although the ABI measurements were performed by 3 vascular specialists in this study, we previously demonstrated that ABI testing can be easily performed by primary care physicians after minimal training [40]. Because large-scale studies of ABI testing in the general population have shown increased vascular and nonvascular mortality for patients with an ABI of <0.90 [13–15, 28], this is a call for widespread use of ABI testing in the HIV–infected middle-aged population. Identification of persons with PAD by ABI testing could serve to promote aggressive efforts at cardiovascular risk reduction, particularly smoking cessation.

This study identified a high prevalence of symptomatic and asymptomatic PAD in HIV-infected patients and suggests the presence of an epidemic of PAD ~20 years earlier in this population than in the general population. Patients can be easily and reliably identified by ABI testing, and they presumably are at increased cardiovascular risk, assuming that ABI mortality correlations from the general population can be extrapolated to HIV-infected persons. However, this pilot study is limited by its small sample size, and larger studies are required to better characterize risk factors for PAD and its prognosis in this population.

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