



# HIV-1 INFECTION IS ASSOCIATED WITH ACCELERATED VASCULAR AGING

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## ABSTRACT

Background: Cardiovascular disease (CVD) and acute vascular events often occur in HIV-1-infected adults younger than 50 years of age, suggesting an accelerated rate of atherosclerosis in this population. The mechanisms responsible for the heightened cardiovascular risk in individuals infected with HIV-1 under the age of 50 years are not clear. Impairments in vascular endothelial function, particularly endothelium-dependent vasodilation, play an important role in the pathogenesis of cardiovascular disease and increase with advancing age. The aim of this study was to determine whether endothelium-dependent vasodilation is impaired in untreated HIV-1-seropositive men compared with healthy men of similar age and, if so, whether the degree of impairment in untreated HIV-1 seropositive men is similar to that of older healthy men. Methods: To address this aim we studied: 10 healthy young (age: 36±3 yr), 10 healthy older (62±1 yr) men and 10 young HIV-1-seropositive treatment naive (34±2 yr) men. All subjects were non-obese and free of overt cardiometabolic disease. Forearm blood flow (FBF) responses to intrabrachial infusions of acetylcholine (an endothelium-dependent vasodilator; ACh: 8.0-32.0 mcg/min) and sodium nitroprusside (an endothelium-independent vasodilator; SNP: 2.0-8.0 mcg/min) were measured by venous occlusion plethysmography. Group differences in FBF responses to each vasoactive agent were determined by repeated measures ANOVA. Results: FBF responses to ACh were ~25% lower (P<0.01) in the HIV-1 seropositive (from 4.4±0.3 to 13.5±1.2 mL/100 mL tissue/min) compared with healthy (5.0±0.4 to 17.8±0.9 mL/100 mL tissue/min) men of similar age. Of note, the FBF responses to ACh between the HIV-1 seropositive men and healthy older (4.9±0.3 to 13.1±0.9 mL/100 mL tissue/min) men were not different (P=0.89). There were no significant differences amongst the groups in FBF responses to SNP, indicating that the observed differences in ACh-mediated vasodilation between the young healthy and untreated HIV-1-seropositive men were endothelium-dependent. Conclusion: Endothelium-dependent vasodilation in young untreated HIV-1 infected men is markedly lower than their healthy peers and similar to that of healthy men 25 years older. These data indicate that untreated HIV-1 infection is associated with accelerated vascular aging. Impaired endothelial function may contribute to the increased risk of vascular events in HIV-1-seropositive adults under the age of 50 years. Support: NIH HL088911, HL076434, HL076434, RR00051, AHA 0840167N, and T32AI007447

## BACKGROUND

- HIV-1 infection is associated with increased cardiovascular disease morbidity resulting from atherosclerotic coronary artery disease and elevated rates of acute vascular events compared with the general population.
- The onset of vascular complications in HIV-1 infected adults often occurs before 50 years of age, suggesting accelerated progression of atherosclerosis in this population.
- Impaired endothelium-dependent vasodilation, a hallmark characteristic of endothelial dysfunction, is recognized to be an underlying event in the pathogenesis of atherosclerotic vascular disease and increases with advancing age.
- A potential mechanism contributing to the early onset of cardiovascular disease in HIV-1 infected individuals may be accelerated endothelial vasodilator dysfunction.

## EXPERIMENTAL AIM

To determine whether endothelium-dependent vasodilation is impaired in HIV-1-seropositive men compared with healthy men of similar age and, if so, whether the degree of impairment in HIV-1-seropositive men is similar to that of older healthy men.

## METHODS

### Subjects

- 30 adult non-obese men
  - 10 Healthy [age: 22-42 years]
  - 10 HIV-1-Seropositive [age: 28-44 years]
  - 10 Healthy Older [age: 59-68 years]

### Inclusion Criteria

- normotensive
- non-diabetic
- non-medicated
- sedentary
- normolipidemic
- free of overt cardiovascular disease

### HIV-1 infected adults:

- Seropositive for the HIV-1 virus for a minimum of one year. Mean duration of infection: 26.0±4.5 months.
- CD4<sup>+</sup> T cell counts >350 cells/μL. Mean cell number: 653±98 cells/μL.
- No history of antiretroviral therapy.

### Screening and Testing Procedures

- Medical history with physical examination and graded exercise testing
- Fasting blood chemistries
- Body composition (dual energy X-ray absorptiometry)

### Intra-arterial Assessment of Forearm Blood Flow

- Brachial artery of the non-dominant arm was catheterized.
- Forearm blood flow (FBF) was assessed by strain-gauge venous occlusion plethysmography in response to:
  - Acetylcholine (ACh: 4-16 μg/100 mL tissue/min)
  - Sodium Nitroprusside (SNP: 1.0-4.0 μg/100 mL tissue/min)
- Sequence of drug administration was randomized.
- The total amount of FBF in response to each vasoactive agonist was calculated as the area under the curve above baseline using a trapezoidal model.

## STATISTICAL ANALYSIS

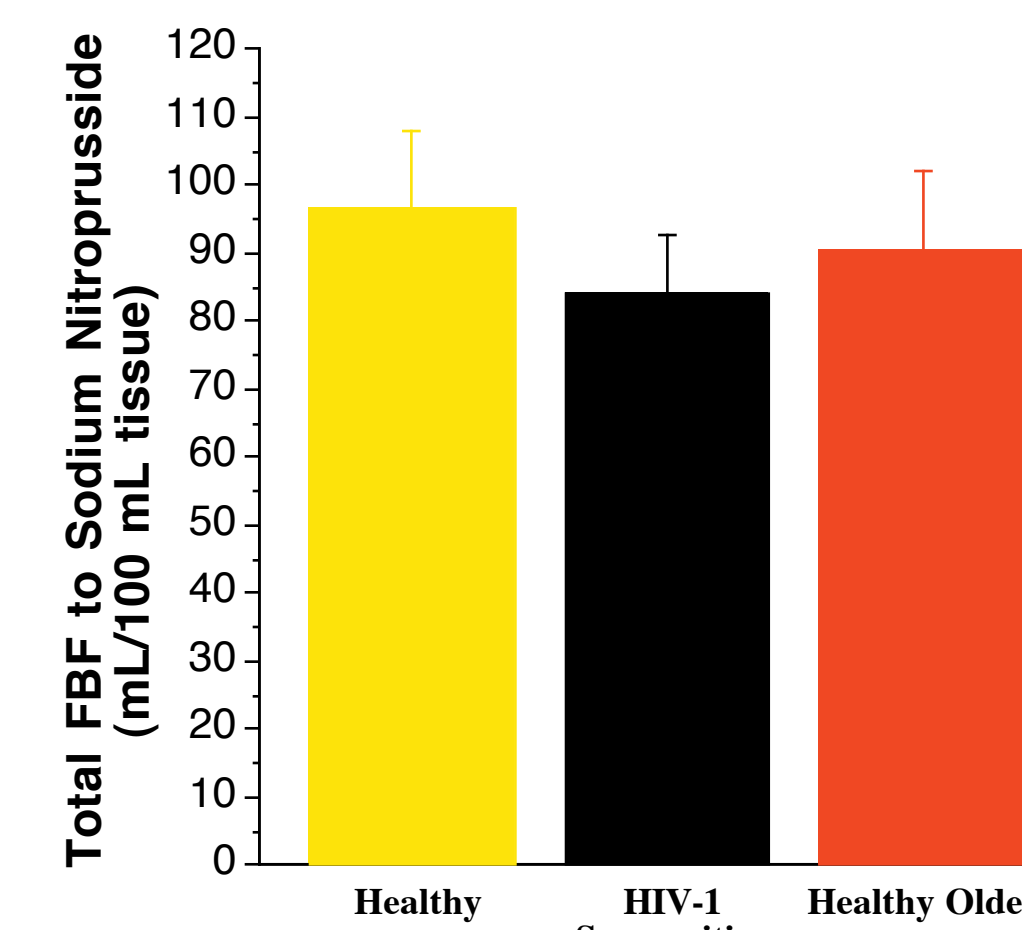
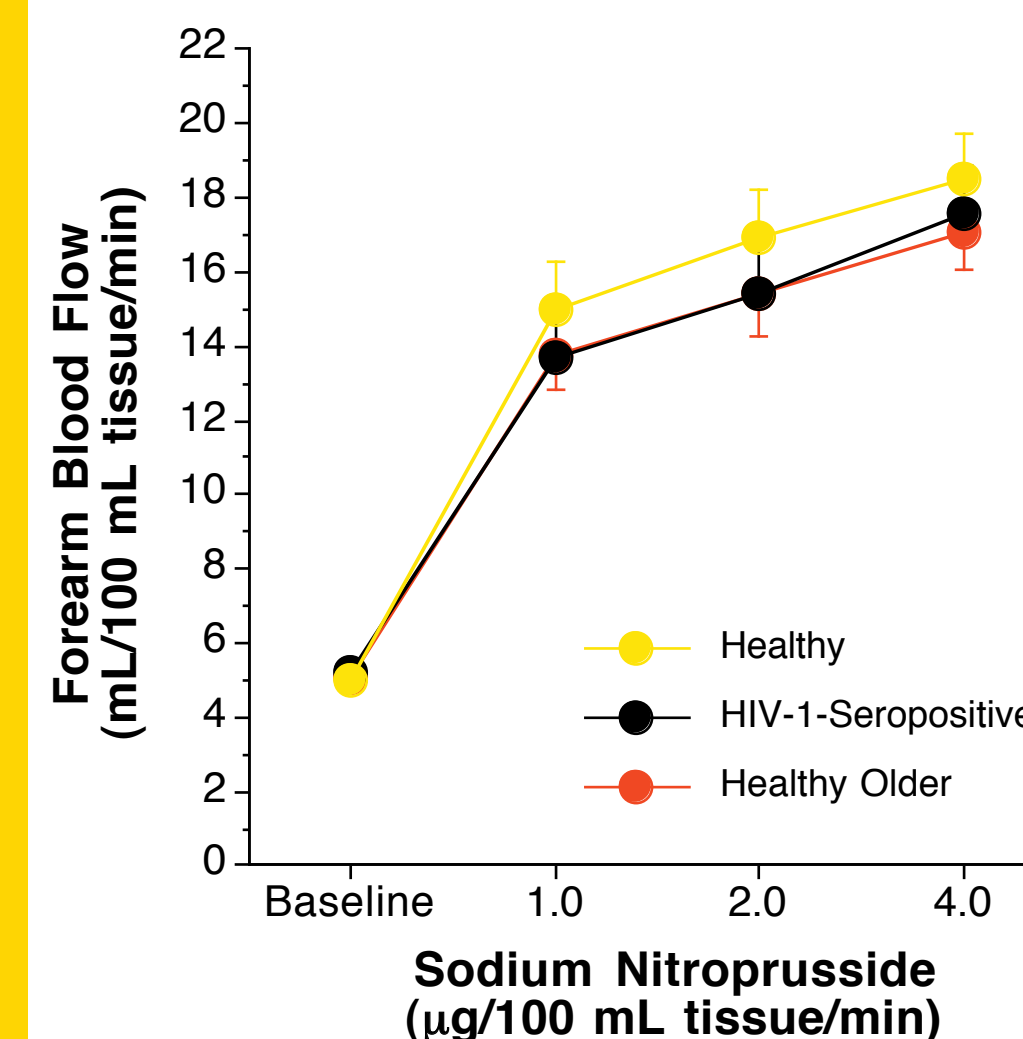
Group differences in subject characteristics and area under the curve data were determined by one-way analysis of variance (ANOVA). Group differences in FBF in response to the vasoactive agents were determined by repeated measures ANOVA. When indicated by a significant main effect, a post-hoc test using the Newman-Keuls method was performed to identify specific group differences. All data are presented as mean ± SEM. Statistical significance was set *a priori* at P < 0.05.

### I. Subject characteristics

Variable	Healthy (n=10)	HIV-1-Seropositive (n=10)	Healthy Older (n=10)
Age, yr	37±3	36±2	62±1*†
BMI, kg/m <sup>2</sup>	24.9±0.9	25.9±1.4	25.3±0.6
Body mass, kg	79.2±4.7	78.6±4.5	80.3±2.9
Body fat, %	18.6±1.8	25.6±3.1*	25.3±1.3*
Waist circumference, cm	85.3±2.6	89.0±2.1	93.2±2.2
Systolic BP, mmHg	116±3	121±3	125±3
Diastolic BP, mmHg	74±3	79±2	78±2
Total cholesterol, mmol/L	4.2±0.3	4.6±0.4	5.2±0.1*
LDL-cholesterol, mmol/L	2.6±0.2	2.9±0.3	3.3±0.1
HDL-cholesterol, mmol/L	1.1±0.1	1.0±0.1	1.2±0.1†
Triglycerides, mmol/L	1.0±0.1	1.6±0.3	1.5±0.1
Glucose, mmol/L	4.6±0.1	5.0±0.2*	5.3±0.1*
Insulin, pmol/L	30.0±4.8	44.0±7.5	38.4±5.9
HOMA-IR	1.1±0.2	2.0±0.5	1.5±0.3

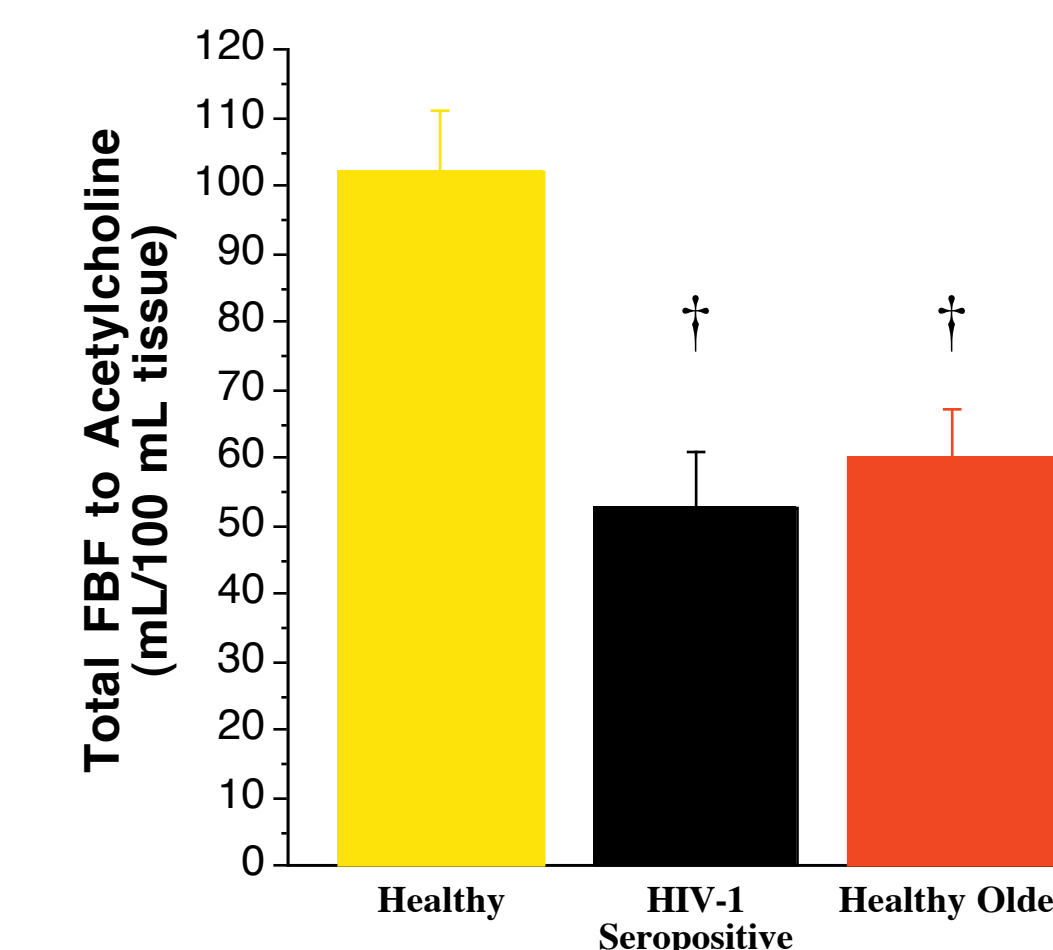
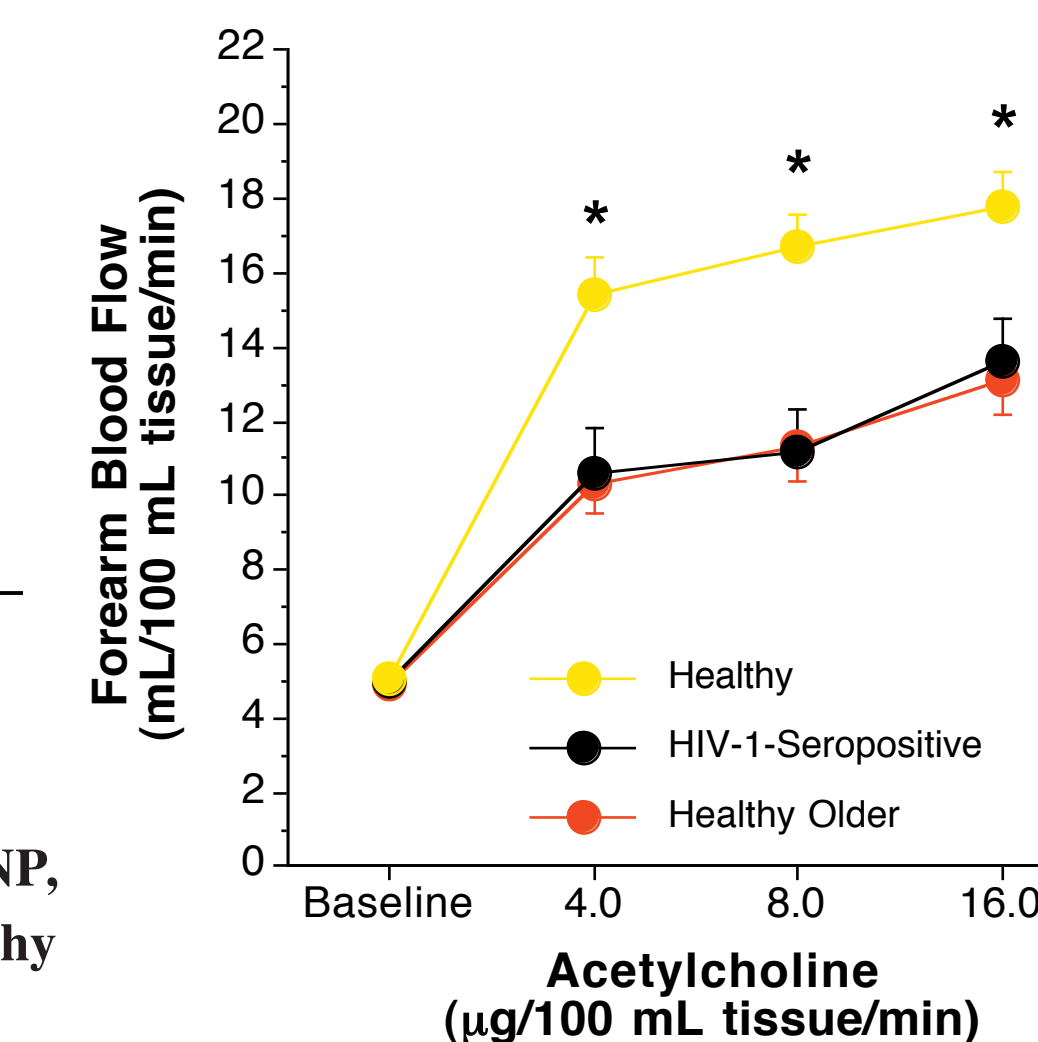
Values are mean ± SEM; \*P < 0.05 vs. Healthy; †P < 0.05 vs. HIV-1-Seropositive

III. There were no differences amongst the groups in the vasodilator response to SNP, indicating that the differences observed in ACh-stimulated vasodilation between the healthy and HIV-1-seropositive men were endothelium-dependent.



## RESULTS

II. FBF responses to ACh were significantly blunted (~25%) in the HIV-1-seropositive compared with healthy men of similar age. Notably, the vasodilator response to ACh between the HIV-1-seropositive and healthy older men was not different. Total FBF (area under the ACh curve) was also markedly lower (~50%) in both the HIV-1-seropositive and healthy older men compared with the healthy younger men. \*P < 0.05 vs. HIV-1-seropositive and healthy older; †P < 0.05 vs. healthy



## CONCLUSIONS

- The results of the present study demonstrate that endothelium-dependent vasodilation is impaired in HIV-1-seropositive treatment naive men compared with healthy men of similar age.
- The degree of impairment in endothelial vasodilation in the HIV-1-seropositive men was similar to that of healthy men 25 years older, suggesting that HIV-1 infection is associated with accelerated vascular aging.
- Diminished endothelial-dependent vasodilator function may contribute to the greater risk of cardiovascular disease and adverse vascular events in HIV-1-seropositive adults under the age of 50 years.