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### **HIV, pressure wave reflections, and arterial stiffness: It's a matter of time**

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## INVITED COMMENTARY

## HIV, pressure wave reflections, and arterial stiffness: It's a matter of time

Since early reports in 1981, millions of people have died from acquired immunodeficiency syndrome and in 2007, an estimated 33 millions of adults are living with human immunodeficiency virus (HIV) infection worldwide.<sup>1</sup> The rate of new cases of HIV infection has stabilized in some parts of the developed world, but in other areas of the world, especially in Sub-Saharan Africa, south-east Asia and eastern Europe, the number of newly infected individuals continues to rise alarmingly.<sup>2</sup> With the advent of combined antiretroviral treatment, which impressively prolonged survival of HIV-infected people, cardiovascular disease is a growing concern, and the goals of therapy have shifted from simply increasing life expectancy to achieving and maintaining a satisfactory quality of life, while effectively treating comorbidities. Emerging data indicate that, even after adjusting for traditional risk factors, HIV-infected persons exposed to long-term combination antiretroviral treatment have higher cardiovascular event rates.<sup>3</sup>

Despite the increased relative risk when compared with uninfected subjects, absolute cardiovascular risk remains low in HIV-positive individuals due to their relatively young age, and this limits the statistical power of event-based prognostic studies examining the long-term predictors of cardiovascular disease in HIV patients. As a result, there has been a growing interest in surrogate measures of atherosclerosis as tools for estimating cardiovascular risk in HIV-infected individuals. Arterial stiffness and wave reflection, two parameters based on the mechanical behaviour of the arterial system, have recently gained wide popularity as simple, noninvasive, reproducible, pathophysiologically relevant and prognostically significant surrogate measures of atherosclerosis. Table 1 summarizes the studies exploring arterial stiffness and wave reflection in antiretroviral-treated subjects. With a few exceptions,<sup>7</sup> most studies show that regional or systemic arterial stiffness is increased in treated HIV-infected patients than in healthy controls.<sup>4–6,8–10</sup> There is also limited evidence of enhanced wave reflection, as expressed by a higher aortic augmentation index.<sup>5,11</sup>

Besides the effects of antiretroviral drugs, there is also evidence that HIV infection itself may promote atherogenesis. Premature atherosclerosis had been reported in

young adults with HIV infection in the pre-antiretroviral treatment era,<sup>12,13</sup> and recent data support the hypothesis that HIV infection *per se* can increase cardiovascular risk.<sup>14–16</sup> New developments in the understanding of the complex relation between HIV infection and arterial functional properties appear in the present issue of *Artery Research*. Vlachopoulos et al.<sup>18</sup> compared markers of arterial stiffness and wave reflection in 51 adult subjects with a recent, untreated HIV infection and in 35 healthy control subjects. HIV subjects had a lower aortic augmentation index and a shorter timing of the reflected wave, although carotid-femoral pulse wave velocity did not differ in the two groups.

A list of studies examining arterial stiffness and wave reflection in untreated HIV subjects is reported in Table 2. As reported in Table 2, an impairment of large-artery functional properties had been already described in HIV treatment-naïve patients. The paper by Vlachopoulos et al. brings about two appreciable elements of novelty in this regard. First, the study is carried out in subjects with a recent HIV infection (<2 years, with a mean of 0.67 years), while previous studies had been conducted in individuals with a longer duration of HIV infection. Secondly, the present study is the first to provide data on aortic augmentation in subjects with untreated HIV infection. Aortic augmentation index, defined as the difference between the second and first systolic peaks (augmented pressure) expressed as a percentage of the pulse pressure, is a composite measure which depends on timing and amplitude of the reflected wave. As aortic stiffness increases, PWV increases, which causes the reflected wave to arrive earlier in the central aorta and augments pressure in late systole. Augmentation index should not be regarded simply as a measure of aortic stiffness, however – it is also determined by wave reflection amplitude, which depends on stiffness of the muscular arteries, the number and branching pattern of arterioles, vasomotor tone, and the ratio of distal to proximal arterial diameters.<sup>19,20</sup>

Given that augmentation index and aortic PWV reflect in part the same physiological phenomenon, one might expect that their change occur in parallel. This is not the case with the paper by Vlachopoulos et al.,<sup>18</sup> in which the lower augmentation index observed in HIV-infected patients

**Table 1** Studies investigating arterial stiffness and pulse wave reflection in HIV-infected subjects receiving antiretroviral treatment.

Authors	Patients (n)	Main findings	Comments
<i>Arterial stiffness</i>			
Bonnet, 2004 <sup>4</sup>	49 cases, 24 controls	Carotid stiffness higher than in controls	Children; mixed population (treated + untreated), no formal comparison between treated patients and controls
Schillaci, 2005 <sup>5</sup>	32 cases, 32 controls	Aortic PWV higher than in controls	
Boccarda, 2006 <sup>6</sup>	84 cases	Duration of HIV infection and of cART exposure predicts carotid stiffness	No HIV-uninfected control group
van Wijk, 2006 <sup>7</sup>	37 cases, 14 controls	Aortic PWV similar to controls	
van Vonderen, 2009 <sup>8</sup>	77 cases, 52 controls	Carotid stiffness higher than in controls, aortic PWV similar to controls	HIV patients younger than controls, no age-adjustment
van Vonderen, 2009 <sup>9</sup>	37 cases	Femoral stiffness increases after starting cART	
Lekakis, 2009 <sup>10</sup>	34 cases, 28 controls	Aortic PWV higher than in controls	
<i>Aortic augmentation</i>			
Schillaci, 2005 <sup>5</sup>	32 cases, 32 controls	Aortic Alx higher than in controls	
Sevastianova, 2005 <sup>11</sup>	59 cases	Duration of cART predicts aortic Alx	No HIV-uninfected control group

Alx, augmentation index; PWV, pulse wave velocity; cART, combination antiretroviral therapy.

compared with healthy subjects is at variance with the unchanged levels of aortic PWV. A discordance between aortic stiffness and wave reflections had already been reported in other pathological conditions. The acute systemic inflammation induced by *Salmonella typhi*

vaccination increases aortic stiffness and decreases wave reflections and augmentation index.<sup>21</sup> Also, the acute inflammatory phase of Behçet's disease, a relapsing inflammatory vasculitis, is characterized by a reduced Alx and an increased aortic stiffness when compared with healthy

**Table 2** Studies investigating arterial stiffness and pulse wave reflection in patients with untreated HIV infection.

Authors	Patients (n)	Main findings	Comments
<i>Arterial stiffness</i>			
Bonnet, 2004 <sup>4</sup>	49 cases, 24 controls	Carotid stiffness higher than in controls	Children; mixed population (treated + untreated), no formal comparison between untreated patients and controls
Schillaci, 2008 <sup>16</sup>	39 cases, 78 controls	Aortic PWV higher than in controls	
Baker, 2009 <sup>17</sup>	32 cases, 30 controls	Systemic stiffness higher than in controls	
Lekakis, 2009 <sup>10</sup>	22 cases, 28 controls	Aortic PWV higher than in controls	
Vlachopoulos, 2009 <sup>18</sup>	51 cases, 35 controls	Aortic PWV similar to controls	
<i>Aortic augmentation</i>			
Vlachopoulos, 2009 <sup>18</sup>	51 cases, 35 controls	Aortic Alx lower than in controls	No significant difference after controlling for heart rate

Alx, augmentation index; PWV, pulse wave velocity.

controls.<sup>22</sup> In the setting of acute inflammation, lower wave reflections in the face of unchanged aortic stiffness could be due to an increased peripheral vasodilatation. In chronic inflammatory disorders such as antineutrophil cytoplasmic antibody-associated systemic vasculitis and rheumatoid arthritis, some studies suggest that both Alx and aortic PWV are increased<sup>23,24</sup> and correlate with the degree of active inflammation.<sup>23</sup> The above similarities between HIV infection and inflammatory disease are underlined in a recent study by Maggi et al.,<sup>25</sup> who reported that the ultrasonographic structure of carotid plaques in HIV-positive patients substantially differs from those in atherosclerotic patients, and resembles those found in patients with arteritis.

Based on the findings of this and other studies, the hypothesis can be made that the effects of HIV on the vascular wall might depend on the duration of the infection.<sup>18</sup> In the early stage, inflammation-driven peripheral vasodilatation might cause decreased wave reflections and augmentation index, without major changes in aortic stiffness.<sup>18</sup> Later, the complex interplay between long-term infection, viral load, immunodeficiency, and chronic subclinical inflammation leads to a progressive increase in arterial stiffness.<sup>4,10,16,17</sup> In this context, initiation of combination antiretroviral treatment is accompanied by a further increase in arterial stiffness<sup>9,26</sup> and an increase in augmentation index,<sup>5</sup> while markers of endothelial function tend to improve.<sup>9</sup>

The findings of the study by Vlachopoulos et al<sup>18</sup> should be interpreted in the context of their limitations. First, augmentation index was lower in patients than in controls, but controls also had a significantly lower heart rate, which could artificially increase augmentation index. Indeed, augmentation index standardized to a heart rate of 75 beats per minute did not differ significantly between cases and controls ( $p = 0.21$ ). Thus, the findings of the present study should be taken as hypothesis-generating rather than as a positive proof. Secondly, the shorter timing of the reflected wave in HIV patients in the face of similar aortic PWV does not support the view of an increased aortic stiffness, but could be due to a more proximal reflection site in HIV patients. No potential explanation is offered by the Authors for this potentially intriguing finding, which could be related to the peripheral vasodilatation secondary to inflammation.

As a chronic, decade-long infection, HIV-related disease is an attractive model for investigating the relation between infection and cardiovascular disease. In this setting, investigation of arterial stiffness and wave reflections may prove promising not only for identifying those HIV patients at increased risk for future cardiovascular disease, but also for understanding the complex chain of events leading to atherosclerotic disease in HIV-infected people.

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