HIV infection and aortic stiffness

Infection par le VIH et rigidité artérielle

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KEYWORDS
Aortic stiffness; Vascular aging; Pulse wave velocity; HIV; Cardiovascular risk

Summary People living with human immunodeficiency virus (HIV) infection and receiving antiretroviral therapy now have the same life expectancy as the general population. However, they have a higher risk of atherosclerotic cardiovascular events because of a complex and polyfactorial vasculopathy, combining the effects of antiretroviral therapy, the HIV virus itself, immune activation, chronic inflammation and metabolic disturbances. Whether people living with HIV infection experience increased vascular aging compared with the general population remains controversial. To summarize current knowledge of the association between HIV infection and aortic stiffness as a marker of vascular aging. This review included 18 clinical studies in adult populations, published between 2009 and 2016, and identified on PubMed/MEDLINE or other databases. Search terms were aortic stiffness, arterial stiffness, vascular aging, pulse wave velocity and HIV. All 18 studies were observational, and compared groups infected (HIV+) and not infected (HIV−) with HIV. Ten studies (55%) reported no significant differences in aortic stiffness between HIV+ groups and age-matched HIV− control groups. The main reported

Abbreviations: ART, antiretroviral therapy; ART+, receiving antiretroviral therapy; ART−, not receiving antiretroviral therapy; cf-PWV, carotid-femoral pulse wave velocity; HIV, human immunodeficiency virus; HIV+, infected with HIV; HIV−, not infected with HIV; MetS+, with metabolic syndrome; MetS−, without metabolic syndrome; PWV, pulse wave velocity.

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Background

Cardiovascular disease is an increasing cause of morbidity and mortality in people infected with the human immunodeficiency virus (HIV+) and receiving antiretroviral therapy (ART). Cardiovascular risk among people living with HIV infection is multifactorial, and involves the HIV infection itself, duration of infection, immune activation, chronic low-grade inflammation and ART-related metabolic disturbances. Identifying HIV+ patients at higher cardiovascular risk is of great clinical importance [1].

Arterial stiffness is a powerful predictor of cardiovascular mortality. Modern non-invasive techniques such as applanation tonometry are widely available to measure aortic stiffness and thus evaluate vascular health. Carotid-femoral pulse wave velocity (cf-PWV) is the gold standard, as it is non-invasive, relatively easy to perform and reliable after repeated measurements. Reference values by age were established by Bossuyt et al. in 2010 [2].

A growing body of evidence has demonstrated that structural and functional changes occur in the large arteries following HIV infection. Leading the way in 2008, Schillaci et al. [3] reported higher aortic stiffness in the group of HIV+ patients than in the uninfected control group (HIV−) (7.6 vs 6.8 m/s; P = 0.02). The authors observed that aortic stiffness was associated with age, HIV infection and duration of ART.

Other more recent cross-sectional studies have examined the impact of HIV infection [4–6] or ART [7–9] on aortic stiffness using different evaluation methods, including cf-PWV, radial PWV and cardiac magnetic resonance. Results were discordant, as certain studies observed increased aortic stiffness in the HIV+ group compared with the HIV− control group [3,6], while other studies did not [4,5]. Discordant results were also reported concerning the impact of ART on aortic stiffness, as certain studies observed that ART is associated with deleterious effects [7,8], whereas others observed no significant associations [9]. However, it is important to note that all these studies were observational and small in size, so their reported results may reflect the effects of chance, bias (notably in the recruitment of participants) or confounding factors. Differences in study populations, design or methodology across studies may also explain such discordant study results.

In this review, we aimed to summarize current knowledge about the impact of HIV-related conditions on aortic stiffness measurements.
HIV infection and aortic stiffness

Methods

Literature search and study selection

For this literature review, we searched and retrieved scientific articles listed on PubMed/MEDLINE and additional databases. The literature search was conducted in English between 1 and 30 August 2016, and included the following key words: aortic stiffness, arterial stiffness, vascular aging, pulse wave velocity and HIV. The search was limited to clinical trials in human adults published in English between 2009 and 2016. The study aim had to be evaluation of the association between HIV and aortic stiffness.

Statistical results of the studies are presented as percentages, means ± standard deviations, medians (interquartile ranges), risk ratios and/or odds ratios with 95% confidence intervals.

Included studies

Our literature review identified 36 studies, and retained 18 relevant studies comparing PWV measurements between HIV+ and HIV− groups [4–7,9–22]; nine of these studies went on to describe PWV determinant factors [4–7,11,13,14,17,21]. The main reasons for excluding studies were the absence of an HIV− control group, studies in children, pregnant women or experimental studies. A flow diagram of the included studies is shown in Fig. 1.

All studies were observational, with varying designs, including: 15 cross-sectional studies (83%); two retrospective case–control studies (11%); and one prospective case–control study (5%). Aortic stiffness was evaluated by cf-PWV in 11 studies (61%), carotid-dorsalis pedis PWV in one study (5%), ultrasound in two studies (11%), cardiac magnetic resonance in one study (5%), the tibial arteries in one study (5%), the radial artery in one study (5%) and arteriography in one study (5%). Seventeen studies (94%) reported PWV values, eight studies (44%) also reported PWV determinants and one study reported neither, but presented the authors’ conclusions based on study findings.

Studies were conducted across Africa, Asia, Europe, Latin America and North America. All included studies were relatively small: only six (33%) had more than 200 participants and none had more than 350. Numbers in the 23 HIV+ groups ranged from 17 to 261; in total, 1656 HIV+ participants were included. Numbers in the 18 HIV− groups ranged from 30 to 135; in total, 1147 HIV− participants were included.

All 18 studies had at least one HIV+ group and one HIV− group. Three studies only included HIV+ participants who were not receiving ART. Seven studies separated HIV+ participants into two groups by ART status (treated [ART+]untreated [ART−]). One study separated both HIV+ and HIV− groups by metabolic syndrome status (yes [MetS+]no [MetS−]). One study separated the HIV− group by diabetes status (yes/no).

Results

Participant characteristics

Overall, the participants in all 18 studies were relatively young; the mean or median age of the groups ranged from 33 to 52 years. Little age variation was observed within studies, as all HIV− participants were age matched (±5 years) to HIV+ participants. The participants were predominantly...
male. The cited variation for the prevalence of cardiovascular risk factors was hypertension (4–48%), current smoking (22–54%), diabetes mellitus (1.0–10.8%) and dyslipidemia (9.0–46.6%). For the HIV variables, the cited variation in duration of HIV infection was 33 months to 14 years, in T CD4+ count was 285–648 cells/mm³ and in time of exposure to ART was 33 months to 14 years. A summary of the studies is provided in Table 1.

PWV

The range of reported mean or median PWVs was 5.6–9.7 m/s for all the HIV+ groups and 5.1–8.5 m/s for all the HIV− groups. Ten studies (55%) reported no statistically significant difference in PWV between all HIV+ and HIV− groups, seven studies (38%) found statistically significant PWV differences between the groups and one study (5%) reported that the “arterial elasticity of small and large arteries was impaired in HIV+ individuals versus controls”, but did not report PWV values.

Seven studies (38%) separated HIV+ participants into two groups based on their ART treatment status (ART+/ART−), and then compared PWV between the two HIV+ groups. Three of these studies observed no statistically significant difference in PWV between HIV+ ART+ and HIV+ ART− groups. However, two of these three studies reported a slight trend toward the HIV+ ART+ group having a higher PWV than the HIV+ ART− group (8.86 vs 8.48 m/s and 7.6 vs 7.4 m/s). One of these three studies observed the same PWV for the HIV+ ART+ group and the HIV+ ART− group (7.0 vs 7.0 m/s). Two studies reported that the HIV+ ART+ group had a higher PWV than the HIV+ ART− group (9.7 vs 8.8 m/s and 8.4 vs 7.5 m/s). In contrast to these studies, in 2010, Zeng et al. [22] observed a higher PWV in the HIV+ ART− group compared with the HIV+ ART+ group (1358 vs 1283 cm/s; P = 0.01).

These same seven studies also evaluated PWV in HIV+ ART+ and HIV+ ART− groups in comparison with HIV− groups. Three of these studies observed no statistically significant PWV difference between the HIV+ ART+, HIV+ ART− and HIV− groups. However, all three of these studies observed a slight trend toward both the HIV+ ART+ and HIV+ ART− groups having a higher PWV than the HIV− group: 8.86 vs 8.48 vs 8.40 m/s (P > 0.05); 7.6 vs 7.4 vs 7.4 m/s (P > 0.05); and 7.0 vs 7.0 vs 6.7 m/s (P > 0.05). Two of these two studies reported that the HIV+ ART+ and HIV+ ART− groups had higher PWVs than the HIV− group: 9.7 vs 8.8 vs 8.5 m/s (P < 0.001); and 8.4 vs 7.5 vs 6.7 m/s (P < 0.001). Again, divergent from the other authors’ findings, Zeng et al. [22] observed higher a PWV in the HIV+ ART− group compared with both the HIV+ ART+ group and the HIV− group (1358 vs 1283 vs 1270 cm/s, respectively). However, the HIV+ ART− group had higher systolic blood pressure levels compared with the HIV− group (134 vs 117 mmHg; P < 0.001) and a higher prevalence of hypertension (data not shown by the authors).

In 2014, Rider et al. [6] separated HIV+ and HIV− participants into four groups by metabolic syndrome status (MetS+/MetS−), and then compared PWV between them: PWV was highest in the HIV+ MetS+ group, second highest in the HIV+ MetS− group and lowest in the HIV− group (7.4 vs 6.2 vs 5.6 m/s; P < 0.001). Along with observing higher PWV values in the HIV+ group compared with the HIV− group, Lemogoum et al. [16] also reported that the proportion of participants presenting with metabolic syndrome was significantly higher in the HIV+ group (41% vs 21%; P = 0.001).

In 2012, Eira et al. [7] separated HIV+ participants by ART status (ART+/ART−) and separated HIV− participants by diabetes status (yes/no), and then compared PWV between groups. The authors showed higher PWV values in the HIV+ ART+ and HIV+ ART− groups compared with the HIV− group (9.7 vs 8.8 vs 8.5 m/s; P < 0.001), and similar PWV values among participants with type 2 diabetes and HIV+ ART− participants (9.7 and 9.8 m/s, respectively; P > 0.05).

Determinant factors for PWV

Eight of the 18 included studies reported determinant factors for PWV (Table 1). Traditional PWV determinant factors included age, systolic and diastolic blood pressure, smoking, body mass index and metabolic syndrome. Biological determinant factors included white blood cell count and concentrations of triglycerides, low-density lipoprotein cholesterol and glucose. Determinant factors related to HIV included T-CD4 cell count < 200/mm³, nadir T-CD4 cell count < 200/mm³, current use of efavirenz and current use of ritonavir-boosted lopinavir.

Discussion

This literature review presents conflicting conclusions regarding the impact on vascular health of HIV infection and the deleterious metabolic effects of ART reported in current scientific articles. HIV-related determinant factors for PWV include traditional, biological and HIV-related variables, particularly: T-CD4 cell count < 200/mm³; nadir T-CD4 cell count < 200/mm³; current use of efavirenz; and current use of ritonavir-boosted lopinavir. Because of the conflicting conclusions presented for the PWV results, these findings should not be generalized. The results concerning the role of ART in aortic stiffness may be generalized, with great caution, to HIV-infected populations treated with ART worldwide, particularly in Europe. The determinant factors of PWV may be generalized to middle-aged men living with HIV infection.

Regarding the role of HIV infection “per se” on accelerated vascular stiffening in an HIV-infected population, Vlachopoulos et al. [21], examined 51 adults (mean age 33 years,) in the early stages of HIV infection (<1 year) and free of ART. This study observed that the HIV+ group had similar PWV values compared with HIV− controls. An accumulating number of cross-sectional studies also investigated the impact of long-term HIV infection on aortic stiffness through comparison with HIV− controls. Eight studies reported increased aortic stiffness in the HIV+ group, and support an association between accelerated vascular aging and HIV [6,7,10,14–16,18,22]. In contrast, 10 studies reported no difference in vascular stiffness between the groups [4,5,9,11–13,17,19,20]. These results may reinforce the dual effect of HIV infection, with a neutral impact during the acute phase of HIV course (no immune activation, no immune depression) then an increased vascular aging link to immunodepression during the chronic phase. Several reasons
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<td>Maia-Leite, 2016 [17]; France</td>
<td>Prospective; 7 years</td>
<td>133 HIV+; 135 HIV−; 47 years</td>
<td>Aortic stiffness (cf-PWV); Complior&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Kooij, 2016 [14]; The Netherlands</td>
<td>Cross-sectional</td>
<td>556 HIV+; 507 HIV−; 52 years</td>
<td>Aortic stiffness (PWV); arteriography</td>
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<td>Fourie, 2015 [12]; South Africa</td>
<td>Cross-sectional</td>
<td>66 HIV+ ART+; 78 HIV+ ART−; 165 HIV−; 48–50 years</td>
<td>Aortic stiffness (cd-PWV); Complior</td>
<td>PWV does not differ between all groups; HIV+ ART+ vs HIV+ ART− vs HIV− (8.86 vs 8.48 vs 8.40 m/s; P&gt;0.05)</td>
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<td>Gleason, 2015 [13]; Ethiopia</td>
<td>Cross-sectional</td>
<td>51 HIV+ ART−; 36 HIV−; 38–39 years</td>
<td>PWV (Cf-PWV); SphygmoCor&lt;sup&gt;b&lt;/sup&gt;</td>
<td>PWV does not differ between HIV+ ART− vs HIV− (7.0 vs 7.1 m/s; P&gt;0.05); determinant factors = age, current EFV, LPV/r, BP, TG, LDL</td>
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<td>Maloberti, 2015 [9]; Italy</td>
<td>Cross-sectional</td>
<td>94 HIV+ (63 ART+, 31 ART−); 37 HIV−; 44 years</td>
<td>Aortic stiffness (cf-PWV); SphygmoCor</td>
<td>PWV does not differ between HIV+ ART+ vs HIV+ ART− vs HIV− (7.6 vs 7.4 vs 7.4 m/s; P&gt;0.05)</td>
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<td>Lemogoum, 2014 [16]; Cameroon</td>
<td>Cross-sectional</td>
<td>238 HIV+; 96 HIV−; 40–41 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>PWV higher in HIV+ vs HIV− (7.3 vs 6.8 m/s; P=0.0369)</td>
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<td>Escheverria, 2014 [4]; Spain</td>
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<td>174 HIV+; 80 HIV−; 46 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>Median PWV does not differ between HIV+ vs HIV− (8.0 [7.0–9.2] vs 7.1 [6.4–7.7] m/s; P&gt;0.05); determinant factors = DBP and TG</td>
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<td>Rider, 2014 [6]; England</td>
<td>Cross-sectional</td>
<td>17 HIV+ MetS+; 73 HIV+ MetS−; 44 HIV− MetS+; 92 HIV− MetS−; 44–49 years</td>
<td>Aortic PWV; magnetic resonance</td>
<td>PWV was higher in HIV+ MetS+ vs HIV+ MetS− vs HIV− (7.4 vs 6.2 vs 5.6 m/s; P&lt;0.001); determinant factors = age, BP, glucose, WC, BMI, smoking</td>
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<tr>
<td>Maloberti, 2013 [18]; Italy</td>
<td>Cross-sectional</td>
<td>108 HIV+ (72 HIV+ ART+, 36 HIV+ ART−); 224 HIV−; 40–46 years</td>
<td>Aortic stiffness (cf-PWV); SphygmoCor</td>
<td>PWV was higher in HIV+ ART+ vs HIV− (10.8 vs 9.3 m/s; P&gt;0.02); PWV was higher in HIV+ MetS+ vs HIV+ MetS− (10.5 vs 9.7 m/s; P=0.04)</td>
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<td>Eira, 2012 [7]; Brazil</td>
<td>Cross-sectional</td>
<td>28 HIV+ ART+; 28 HIV+ ART−; 44 HIV− Diabetes+; 30 HIV− Diabetes−; 41–44 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>Median PWV HIV+ ART+ vs HIV+ ART− vs HIV− (9.7 [9.1–10.2] vs 8.8 [8.2–9.3] vs 8.5 [8.0–9.1] m/s; P&lt;0.001); determinant factors = age, SBP, WC and glucose</td>
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Table 1 (Continued)

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<tr>
<td>Monteiro, 2012 [5]; Brazil</td>
<td>Cross-sectional</td>
<td>261 HIV+; 82 HIV−; 42 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>PWV does not differ between HIV+ vs HIV− (7.85 vs 7.75 m/s; P &gt; 0.05); determinant factors = age, BP, CD4 &lt; 200 and MetS</td>
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<td>Papita, 2011 [19]; Romania</td>
<td>Cross-sectional</td>
<td>63 HIV+; 36 HIV−; 37 years</td>
<td>Ultrasound system (carotid-brachial PWV)</td>
<td>PWV does not differ between HIV+ vs HIV− (5.6 vs 5.10 m/s; P = 0.060) Median PWV does not differ between HIV+ vs HIV− (5.7 [5.0–6.5] vs 5.8 [5.3–6.4] m/s; P = 0.885); determinant factor = age</td>
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<td>Ferraioli, 2011 [11]; Italy</td>
<td>Cross-sectional</td>
<td>54 HIV+; 54 HIV−; 46–48 years</td>
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<td>Zeng, 2010 [22]; China</td>
<td>Cross-sectional</td>
<td>41 HIV+ ART−; 41 HIV+ ART+; 43 HIV−; 37–39 years</td>
<td>Pulse pressure analyser; PWV (tibial arteries)</td>
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<td>Lekakis, 2009 [15]; Greece</td>
<td>Case-control</td>
<td>56 HIV+ (34 ART+, 22 ART−); 56 HIV−; 40 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>PWV was higher in HIV+ ART+ vs HIV+ ART− vs HIV− (8.4 vs 7.5 vs 6.7 m/s; P &lt; 0.001)</td>
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<td>Baker, 2009 [10]; USA</td>
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<td>Radial pulse waveform analysis; PWV</td>
<td>The arterial elasticity of small and large arteries was impaired in HIV+ group vs healthy controls (values not shown)</td>
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<tr>
<td>Van Voderen, 2009 [20]; The Netherlands</td>
<td>Case-control</td>
<td>77 HIV+ (55 ART+ 22 ART−); 52 HIV−; 38–49 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>PWV does not differ between HIV+ ART+ vs HIV− ART− vs HIV− (7.0 vs 7.0 vs 6.7 m/s; P &gt; 0.05)</td>
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<tr>
<td>Vlachopoulos, 2009 [21]; Greece</td>
<td>Cross-sectional</td>
<td>51 HIV+ ART−; 35 HIV−; 33 years</td>
<td>Aortic stiffness (cf-PWV); Complior</td>
<td>PWV does not differ between HIV+ vs HIV− (6.4 vs 6.3 m/s; P = 0.740); determinant factors = age, BMI, BP</td>
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ART: antiretroviral therapy; BP: blood pressure; BMI: body mass index; cd-PWV: carotid-dorsalis pedis pulse wave velocity; cf-PWV: carotid-femoral pulse wave velocity; DBP: diastolic blood pressure; EFV: efavirenz; HDL: high-density lipoprotein; HIV: human immunodeficiency virus; LDL: low density lipoprotein; LPV/r: lopinavir/ritonavir; MetS: metabolic syndrome; PWV: pulse wave velocity; SBP: systolic blood pressure; TG: triglycerides; WC: waist circumference.

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may account for these conflicting conclusions, including the variable techniques used to measure PWV and the presence of confounding factors (because of poor baseline matching by only age), such as blood pressure, which have been shown to be associated with higher PWV [2].

The impact of ART on aortic stiffness in HIV+ populations has been studied, and the results reported were also controversial, with no differences seen between ART+ and ART− groups [23,24] or associations observed between aortic stiffness and HIV conditions related to ART, particularly metabolic disturbances provoked by certain drugs. The protease inhibitor class of antiretroviral drugs is most widely associated with atherosclerosis and increases in PWV [7]. In 2012, Lopez-Sublet et al. [8] reported a higher PWV in the HIV+ group who received protease inhibitors compared with the HIV+ group who did not receive protease inhibitors (9.0 vs 8.1 m/s; \( P = 0.016 \)). Earlier, Papita et al. had reported similar results [19]. More recently, Gleason et al. [13] described significantly higher PWV values in the HIV+ group who received efavirenz and lopinavir/ritonavir compared with nevirapine treatment. These findings were confirmed in a longitudinal study. After 12 months of follow-up, greater progression of PWV was observed in the HIV+ group who received protease inhibitor treatment [25]. Taken together, these results show that the metabolic complications and arterial hypertension associated with ART may be more important than HIV infection ‘per se’ for the vascular aging consequences reported in some studies. However, definitive conclusions should not be made because of the differences in these studies, with various HIV populations included, leading to difficulties in comparing these studies.

The most frequent determinants associated with increased aortic stiffness in the HIV+ population reported in the literature were traditional cardiovascular risk factors, e.g. age, blood pressure, metabolic complications, smoking, waist circumference and body mass index [4–7,13,14,17,21]. On the other hand, several cross-sectional studies pointed out the importance of factors related to HIV, particularly a low CD4:CD8 ratio [26] and current T-CD4+ < 200/mm³ [8,25], suggesting an impact of HIV severity or dysimmunity on vascular health.

Only a limited number of prospective studies in the HIV population have been published so far [25]. Recently, in a prospective study, our group evaluated the impact of HIV infection and ART on vascular aging after 7 years of follow-up. We showed an association between vascular aging and nadir T-CD4+ count < 200/mm³, blood pressure and age [17].

The true underlying mechanisms linking profound immunodepression with arterial stiffness remain unknown. Findings from several epidemiological studies support a highly plausible relationship between profound immunodepression and the development of hypertension among HIV+ individuals [27,28]. Along with the incontestable role of inflammation in the pathophysiology of hypertension, recent reviews have implicated both the innate and adaptive immune systems in the development of arterial hypertension [29]. ART use could also affect vascular aging, either directly or indirectly, via metabolic disturbances, including dyslipidemia, insulin resistance and lipodystrophy, and also via hyperactivation of the renin–angiotensin system and vascular smooth muscle cell senescence and calcifications [30,31].

Study strengths and limitations

The original studies included in our review have several limitations that must be addressed. First, all included studies, except one, were cross-sectional, and consequently do not enable conclusions to be made about causality. Second, many included studies had small sample sizes, and therefore lacked statistical power. Third, attempts to minimize selection bias, particularly concerning the HIV+ controls, were not well described in all studies. As a result, the two populations may be non-comparable, as the HIV+ and HIV− groups may not have been drawn from the same populations. Last, although statistical adjustments were used in most studies, a multivariable analysis should have been done to avoid variables with possible collinearity with aortic stiffness measurements.

The present literature review has two key limitations. Only PubMed/MEDLINE and one additional database was searched; hence, all published literature not indexed on this site and all ‘grey’ and unpublished literature were not included. Also, there was considerable variability across several study elements. PWV ascertainment methods and determinant factors varied across the included studies and, consequently, results are less comparable. Discrepancies across study findings may be the result of variation in study population characteristics, notably ART use, immunological status and cardiovascular risk level (see Table 1). The original studies had several noteworthy strengths. First, in most the studies (61%) aortic stiffness was measured by the same methodology (cf-PWV). Second, all studies had an uninfected control group matched by age and sex.

To establish the true role of HIV-related factors in vascular aging, further prospective studies are needed with long-term follow-up, as the impact of HIV and ART may differ in terms of time (acute versus chronic), given that in developed countries more and more HIV+ subjects will be treated as soon as they get infected and for a very long period of life. Further studies should investigate the impact of new antiretroviral drugs, particularly integrase inhibitors, on vascular aging in these specific populations at high cardiovascular risk.

Conclusions

Our review found discordant results regarding whether HIV+ participants had increased aortic stiffness compared with controls. However, there is emerging evidence that HIV affects vascular health and large arteries. In fact, HIV-related conditions — particularly past profound immunodepression determined by nadir CD4-T cell count < 200/mm³ and CD4:CD8 ratio — were associated with vascular health in most studies, reinforcing the need for earlier initiation of ART in HIV+ patients, but this needs to be proven in large clinical trials.

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Disclosure of interest

The authors declare that they have no competing interest.

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