Infezione da HIV e invecchiamento vascolare.
HIV infection and vascular aging.

Elisa Mattachini, Federica Sofia, Angelo Scuteri
School of Geriatrics - Department of Medical, Surgical, and Experimental Sciences - University of Sassari - Sassari (Italy)

Autore per la corrispondenza:

Elisa Mattachini
School of Geriatrics
Department of Medical, Surgical, and Experimental Sciences
University of Sassari
Sassari (Italy)

elisa.mattachini@gmail.com

Keywords:
HIV; vascular aging; arterial stiffness; anti-retroviral therapy; pulse wave velocity; cardiovascular risk.

Potenziali conflitti di interesse:
nessuno.

JHA 2019; 4(3): 58 - 61

DOI: 10.19198/JHA31479

Riassunto

L'avvento della terapia antiretrovirale altamente attiva (HAART) ha significativamente migliorato l'aspettativa di vita degli individui affetti da HIV, rendendola una malattia cronica e trattabile.
L'infezione da HIV ha un legame ben documentato con le malattie cardiovascolari, con evidenza non solo di una maggiore aterosclerosi, ma anche di un'aumentata rigidità vascolare. Infatti, la rigidità arteriosa, un indice di invecchiamento vascolare valutabile clinicamente in modo non invasivo attraverso la velocità dell'onda pressoria carotido-femorale (cf-PWV), è risultata essere associata all'insorgenza di eventi cardiovascolari e declino cognitivo. La letteratura concorda sul fatto che i pazienti con HIV mostrano un rischio maggiore di eventi cardiovascolari aterosclerotici a causa di una vasculopatia complessa e ad eziologia polifattoriale, che combina gli effetti della terapia antiretrovirale, l'azione del virus da HIV stesso, l'infiammazione cronica e i disturbi metabolici. Per questo motivo, in questa popolazione è di fondamentale importanza l'applicazione di misure preventive, al fine di ridurre non solo il rischio cardiovascolare, ma anche il prematuro declino cognitivo.

Abstract

Highly active antiretroviral therapy (HAART) has significantly improved life expectancy among individuals with HIV infection, turning it into a chronic and manageable disease.
HIV infection has a well-documented link to cardiovascular disease, with evidence not only of greater atherosclerosis but also of increased vascular stiffness. Indeed, arterial stiffness and aging, clinically evaluated noninvasively as carotid-femoral pulse wave velocity (cf-PWV), has emerged as a risky condition for cardiovascular events and cognitive decline. Literature agrees that HIV+ patients show higher risk of atherosclerotic cardiovascular events because of a complex and polyfactorial vasculopathy, combining the effects of antiretroviral therapy and HIV virus itself, chronic inflammation and metabolic disturbances. For this reason, preventive interventions in this population are important to lessen not only cardiovascular risk, but also premature cognitive decline.

Global situation and trends

Since the beginning of the epidemic, more than 70 million people have been infected with the HIV virus and about 35 million people have died of HIV. Globally, 37.9 million (32.7-44 million) people were living with HIV at the end of 2018. An estimated 0.8% (0.6-0.9%) of adults aged 15-49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. The WHO African region remains most severely affected, with nearly 1 in every 25 adults (4.1%) living with HIV and accounting for nearly two-thirds of the people living with HIV worldwide (1).
Gains continue to be made against HIV, especially in testing and treatment. An estimated 23.3 million of the 37.9 million people living with HIV globally were on treatment, more than three times as many as in 2010 (2).
Effective use of highly activated antiretroviral therapy (HAART) has improved life expectancy among people living with HIV infection. Treatment scale-up contributed to a decrease in the mortality rate from a peak of 1.7 million (1.3-2.4 million) in 2004 to 770 000 (570 000-1 100 000) in 2018 (3).

Changing paradigm of care

The advent of HAART has prolonged the survival of HIV+ individuals, turning acquired immunodeficiency syndrome (AIDS) into a chronic and manageable disease.
In 1986, the median survival for a person with HIV infection was 10 years; currently, more than 85% of patients with HIV infection survive more than 10 years (4).
As a result of advances in treatment of HIV infection, traditional risk factors and chronic debilitating illnesses have become more important proportionally as major causes of morbidity and mortality for many patients.

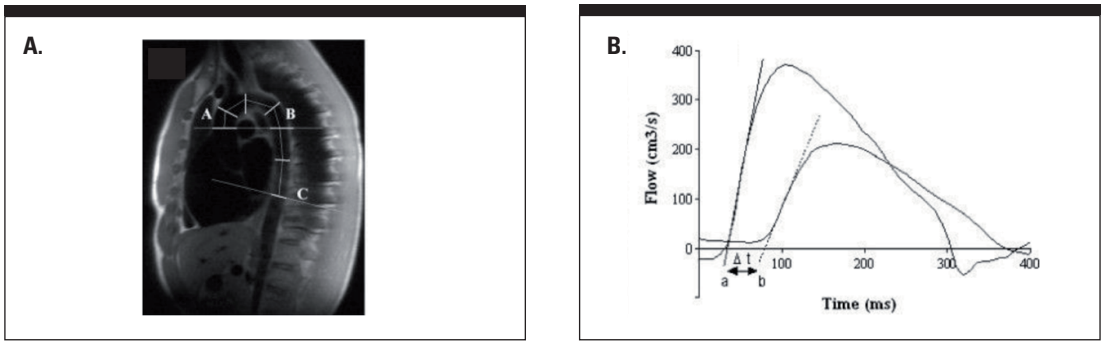

Figure 1. Calculating pulse wave velocity. A. Distance Δx was taken as the total distance between
A. (ascending aorta) and C (abdominal aorta). This was calculated using the sum of the distances between the centre points of lines drawn at 45°, 90° and 135° to the scan level.
B. Aortic flow/time curves used to calculate the arrival times of aortic pulse waveform. Δt represents the time (m/s) between the intercepts (b-a) of the tangents to the curve at the half maximal point of flow in the ascending aorta (a) and the abdominal aorta (b). (28)

Consequently, in the HAART era, the goals of therapy have shifted from simply keeping patients alive to maintaining good quality of life and effectively treating comorbidities. Management of HIV-infected patients must now include the prevention and treatment of concomitant diseases such as chronic kidney disease, diabetes, HCV coinfection and cardiovascular (CV) complications (5).

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 HAART-related metabolic disturbances. Identifying HIV+ patients at higher cardiovascular risk is of great clinical importance (6).

The role of antiretroviral therapy

HAART includes a combination of protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs) and integrase strand transfer inhibitors (InSTIs).

The benefit of HAART on mortality in HIV+ patients is undeniable. However, the appearance of metabolic alterations at the basis of the increased risk of cardiovascular events was described a few years after its introduction (7).

Adverse metabolic effects attributed to HAART include dyslipidemia, increased blood pressure, and insulin resistance (8). The incidence of diabetes in HIV-positive men under HAART has been reported as over four times higher than in HIV-negative individuals (9). The drugs most often associated with diabetes are PIs and some NRTIs (10). Furthermore, certain PIs have been also associated with a dyslipidemic profile. NNRTIs, instead, generally result in a more favorable lipid profile than PIs (11).

Some studies suggest that the prevalence of hypertension is increased in HIV-positive individuals on HAART (12), even though the role of HIV and HAART in the pathogenesis of hypertension is not clear. To confirm this, in 2016 Dimala et al. observed that HIV patients on HAART were twice more likely to suffer from hypertension than patient HAART-naïve (13).

In conclusion, various cardiovascular risk factors can be induced or strengthened by HAART, leading to an increased risk for myocardial infarction (14). The detrimental effect of HAART on arterial wall properties (15) and atherosclerotic plaque formation was proposed as a potential mechanism for the above finding. In addition to atherosclerotic disease, arterial stiffness may affect arterial function and increase the risk of cardiovascular events.

Relationship among arterial stiffness, HIV infection and HAART

Modern non-invasive techniques are widely available to estimate 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 (16). Other methods, such as measuring central systolic blood pressure (BP) and augmentation index ***(Figure 1)***, are more affected by pathophysiological conditions, medications, heart rate and age, which make them less reliable (17).

In recent years, great emphasis has been placed on the role of arterial stiffness, indexed as cf-PWV, in the development of cardiovascular diseases. Indeed, the measure of arterial stiffness has been found to better stratify individual risk of multiple organ damage (18) and to be a powerful predictor of cardiovascular mortality (19).

A growing body of evidence has demonstrated that structural and functional changes occur in the large arteries following HIV infection. Schillaci et al. reported higher aortic stiffness in the group of HIV+ patients than in the uninfected control group (HIV-) (20) and a significant association between aortic stiffness and HIV infection and its severity (21).

Conversely, the impact of HIV infection treatment on aortic stiffness is still controversial: some recent cross-sectional studies observed that antiretroviral therapy is associated with deleterious vascular effects, while others reported no significant associations (22).

Notably, several factors observed in HAART and described above have been reported as independent determinants of greater cf-PWV, such as metabolic syndrome (23), BP levels and variability (24,25), chronic inflammation (26).

Therefore, the association between PWV and HAART is influenced by several factors: from duration of treatment to the prescribed class of antiretroviral drug, from changes in cardiovascular risk factors to chronic inflammation (27).

Arterial stiffness and cognitive decline among HIV+ patients

Assessment of arterial elasticity is clinically important as it correlates with the pathogenesis of a large spectrum of cardiovascular and non-cardiovascular outcomes, such as kidney disfunction and several types of cognitive deficits. As HIV+ patients are aging, they are at greater risk of cognitive decline and dementia (29).

Despite the proven relationship between HIV serostatus and cf-PWV, only few studies were conducted evaluating the effects of vascular stiffness on the cognitive decline among HIV+ patients.

HAART has greatly reduced medical morbidity and mortality with HIV infection, but high rates of HIV-associated neurocognitive disorders (HAND) continue to be reported (30).

In 2018, Huck et al. confirmed that HIV-infected patients with high-risk features including AIDS history and longer PIs use had faster decline in neuropsychological performance compared with HIV+ patients without these features (31). Notably, studies identified different patterns of neurocognitive impairment (NCI): patients HAART-naïve had more impairment in motor skills, cognitive speed, and verbal fluency, whereas HIV patients undergoing HAART therapy showed memory and executive function impairment (30).

A link between persistent viral suppression and greater slope of decline in neuropsychological test performance runs counter to expectation, but it could be explained by deleterious effects of long-term potent HAART use on central and cerebral vasculature, including greater arterial stiffness (28).

Interestingly, greater arterial stiffness has been linked to cognitive decline (32). Independent or synergistic pathophysiological pathways linking cf-PWV and risk of dementia concerns cerebral microcirculation damage (32), endothelial damage (33), left ventricular hypertrophy (34), and greater susceptibility to hypotensive episodes (35), supporting the notion that increased pulsatile load is deleterious for cerebral vasculature (17,36). To confirm this, Scuteri et al. recently confirmed that cf-PWV is a strong predictor of loss in cognitive function, independent of age, sex and education, remarking the importance of prevention as a critical goal (32).

Conclusion

HAART has dramatically prolonged life-expectancy in HIV+ patients. Although its benefits are undeniable, HAART adverse effects on arterial aging, clinically measurable as described above with cf-PWV, may not be innocent features. In fact, arterial aging is associated with greater risk of cardiovascular morbidity and cognitive decline. For this reason, given the increase in cardiovascular related mortality and decline in neurophysiological performance in HIV-infected patients treated with HAART, identifying those at higher risk is of great clinical importance. All considered, the data collected confirmed the positive risk-benefit ratio of HAART, that significantly improved the prognosis for many individuals with HIV infection in the last decades. ■

REFERENCES

1. WHO - *World Health Organization web site on HIV/AIDS, Global Health Observatory data GHO,* 2019 update.

2. UNAIDS Global Report 2019.

3. Aberg J. *Cardiovascular complications in HIV management: past, present, and future.* J Acquir Immune Defic Syndr. 2009; 50: 54-64.

4. Palella FJ Jr, Delaney KM, Moorman AC, et al. *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.* HIV Outpatient Study Investigators. N Engl J Med 1998; 338: 853-60. [PubMed: 9516219].

5. Manfredi R, Sabbatani S, Agostini D. *Trend of mortality observed in a cohort of drug addicts of the metropolitan area of Bologna, North-Eastern Italy, during a 25-year-period.* Coll Antropol 2006; 30: 479-88. [PubMed: 17058511].

6. Boccara F, Lang S, Meuleman C, et al. *HIV and coronary heart disease: time for a better understanding.* J Am Coll Cardiol 2013; 61: 511-23.

7. Friis-Møller N, Sabin CA, Weber R, et al. *Data Collection On Adverse Events Of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction.* N Engl J Med. 2003; 349: 1993-2003 [correction published in N Engl J Med. 2004; 350: 955].

8. Vigouroux C, Gharakhanian S, Salhi Y, Nguyen TH, Chevenne D, Capeau J, Rozenbaum W. *Diabetes, insulin resistance and dyslipidaemia in lipodystrophic HIV infected patients on highly active antiretroviral therapy (HAART).* Diabetes Metab 1999; 25: 225–32.

9. Brown TT, Cole SR, Li X, et al. *Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS Cohort Study. Arch Intern Med.* 2005; 165: 1179-84.

10. Petoumenos K, Worm SW, Fontas E, et al. *Predicting the short-term risk of diabetes in HIV-positive patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) study.* J Int AIDS Soc. 2012; 15: 17426.

11. Anastos K, Lu D, Shi Q, et al. *Association of serum lipid levels with HIV serostatus, specific antiretroviral agents, and treatment regimens.* J Acquir Immune Defic Syndr. 2007; 45: 34-42.

12. Palacios R, Santos J, Garcia A, et al. *Impact of highly active antiretroviral therapy on blood pressure in HIV-infected patients. A prospective study in a cohort of naive patients.* HIV Med. 2006; 7: 10-5.

13. Dimala CA, Atashili J, Mbuagbaw JC, Wilfred A, Monekosso GL. *Prevalence of Hypertension in HIV/AIDS Patients on Highly Active Antiretroviral Therapy (HAART) Compared with HAART-Naive Patients at the Limbe Regional Hospital, Cameroon. PLoS One.* 2016; 11: e0148100.

14. Study Group. *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.* JID 2010; 201: 318-30.

15. Barbaro G, Di Lorenzo G, Grisorio B, et al. *Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV positive patients.* N Engl J Med. 1998; 339: 1093-9 [retraction published in N Engl J Med. 2002; 347: 140].

16. Laurent S., Cockcroft J., Van Bortel L. *Expert consensus document on arterial stiffness: methodological issues and clinical applications.* Eur Heart J. 2006; 27: 2588–605.

17. Townsend RR, Wilkinson IB, Schiffrin EL, et al. *American Heart Association Council on Hypertension Recommendations for improving and standardizing vascular research on arterial stiffness: a scientific statement from the American Heart Association.* Hypertension. 2015; 66: 698–722.

18. Scuteri A, Rovella V, Alunni Fegatelli D, Tesauro M, Gabriele M, Di Daniele N. *An operational definition of SHATS (Systemic Hemodynamic Atherosclerotic Syndrome): Role of arterial stiffness and blood pressure variability in elderly hypertensive subjects. Int J Cardiol.* 2018; 263: 132-7.

19. Scuteri A, Lakatta, EG. *Bringing prevention in geriatrics: Evidences from cardiovascular medicine supporting the new challenge.* Exp. Gerontol. 2013; 48: 64-8.

20. Schillaci G, De Socio GV, Pucci G, et al. *Aortic stiffness in untreated adult patients with human immunodeficiency virus infection.* Hypertension 2008; 52: 308-13.

21. Luisa Helena Maia Leite, Ariel Cohenb, Franck Boccara. *HIV infection and aortic stiffness, Arch Cardiovasc Dis.* 2017; 110: 495-502.

22. Eira M, Bensenor IM, Dorea EL, Cunha RS, Mill JG, Lotufo PA. *Potent antiretroviral therapy for human immunodeficiency virus infection increases aortic stiffness.* Arq Bras Cardiol 2012; 99: 1100-7.

23. Scuteri A, Najjar SS, Orrù M, et al. *The central arterial burden of the metabolic syndrome is similar in men and women: the SardiNIA Study.* Eur Heart J. 2010; 31: 602-13.

24. Scuteri A, Morrell CH, Orrù M, et al. *Gender specific profiles of white coat and masked hypertension impacts on arterial structure and function in the SardiNIA study.* Int J Cardiol. 2016; 217: 92-8.

25. Nilsson PN, Laurent S, Cunha PG, et al. *Characteristics of healthy vascular ageing in pooled population-based cohort studies: the global Metabolic syndrome and Artery REsearch (MARE) Consortium.* Journal of Hypertension 2018, 36: 2340-49.

26. Scuteri A, Orru M, Morrell C, Piras MG, Taub D, Schlessinger D, Uda M, Lakatta EG. *Independent and additive effects of cytokine patterns and the metabolic syndrome on arterial aging in the SardiNIA Study.* Atherosclerosis. 2011; 215: 459-64.

27. Lopez-Sublet M, Honore P, Bentata M, et al. *Protease inhibitor treatment effect on aortic stiffness in normotensive patients with human immunodeficiency virus infection.* J Mal Vasc 2012; 37: 179-85.

28. Rider et al. *HIV is an independent predictor of aortic stiffness.* Journal of Cardiovascular Magnetic Resonance 2014 16: 57.

29. Scuteri A, Palmieri L, Lo Noce C, Giampaoli S. *Age-related changes in brain functions: cognition, executive process, and motor speed. A population-based study.* Aging Clin Exp Res 2005; 17: 367-73.

30. Heaton RK, Franklin DR, Ellis RJ, et al. *HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors.* J Neurovirol. 2011; 17.

31. Huck DM, Hanna DB, Rubin LH, et al. *Carotid artery stiffness and cognitive decline among women with or at risk for HIV infection.* J Acquir Immune Defic Syndr 2018: 78: 338-47.

32. Scuteri A, Wang H. *Pulse wave velocity as a marker of cognitive impairment in the elderly.* J Alzheimers Dis. 2014; 42 Suppl 4: S401-10.

33. Scuteri A, Stuehlinger MC, Cooke JP, Wright JG, Lakatta EG, Anderson DE, Fleg JL.*Nitric oxide inhibition as a mechanism for blood pressure increase during salt loading in normotensive postmenopausal women.* J Hypertens. 2003; 21: 1339-46.

34. Scuteri A, Coluccia R, Castello L, Nevola E, Brancati AM, Volpe M. *Left ventricular mass increase is associated with cognitive decline and dementia in the elderly independently of blood pressure.* Eur Heart J. 2009; 30: 1525-9.

35. Scuteri A, Tesauro M, Guglini L, Lauro D, Fini M, Di Daniele N. *Aortic stiffness and hypotension episodes are associated with impaired cognitive function in older subjects with subjective complaints of memory loss.* Int J Cardiol. 2013; 169: 371-7.

36. Zeki Al Hazzouri A, Newman AB, Simonsick E, et al. *Pulse wave velocity and cognitive decline in elders: the Health, Aging, and Body Composition Study. Stroke.* 2013; 44: 388–93.