Epigenetics, HIV, and Cardiovascular Disease Risk

Bertrand Fabien Ebner, MD, Teresa Chueng, MD, and Claudia A. Martinez, MD

Abstract: Human immunodeficiency virus (HIV) is currently considered a risk factor for cardiovascular disease (CVD). With the advent of antiretroviral treatment and prevention, HIV-related morbidity and mortality rates have decreased significantly. Prolonged life expectancy heralded higher prevalence of diseases of aging, including CVD-associated morbidity and mortality, having an earlier onset in people living with HIV (PLHIV) compared to their noninfected counterparts. Several epigenetic biomarkers are now available as predictors of health and disease, with DNA methylation being one of the most widely studied. Epigenetic biomarkers are changes in gene expression without alterations to the intrinsic DNA sequence, with the potential to predict risk of future CVD, as well as the outcome and response to therapy among PLHIV. We sought to review the available literature referencing epigenetic markers to determine underlying biomechanism predisposing high-risk PLHIV to CVD, elucidating areas of possible intervention. (Curr Probl Cardiol 2021;46:100615.)

Introduction

In 2018, the World Health Organization (WHO) declared that 37.9 million people globally were living with HIV/AIDS, 3.5 million of whom live in the Americas.[1] Most recent CDC report from 2018 disclosed that HIV prevalence in the United States was

The authors have no conflicts of interest to disclose.
Curr Probl Cardiol 2021;46:100615
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100615

near 1.1 million.[2] Since 2010, AIDS-associated mortality worldwide decreased by 33%.[3] This significant decline in mortality, likely related to a reduction in opportunistic infections and acquired immunodeficiency syndrome(AIDS)-defining cancer, is correlated with increased accessibility to antiretroviral therapy (ART), earlier diagnosis, and improvement in medication profiles.[3-5] However, age-related comorbidities, including cardiovascular disease (CVD), have also been attributed to these trends.[6-8] Although genetic factors attribute to CVD risk, a large proportion may be accounted for by an interaction of genomic and nongenomic processes.

In the recent decade, evidence has emerged on the potential role of epigenetic changes and its association with CVD risk. Epigenetics is defined as the study of chemical modifications of intrinsic and extrinsic factors of the genetic code regulating gene expression.[9] Epigenetic markers can also predict chronological age. Among people living with HIV (PLHIV), the predicted epigenetic age is greater than chronological age, suggesting accelerated aging within this population, and correlating to a collectively heightened CVD risk group.[6] We posit that a basic understanding of epigenetics is vital among cardiologists, as the 3 types of epigenetic markers: DNAm, post-translational histone modifications, and non-coding RNA (ncRNA) function are mediators of CVD pathogenesis and progression.

Epigenetic Modifications

One of the most studied epigenetic markers is DNA methylation (DNAm), which involves changes in the DNA that are influenced by environmental factors. This process is mainly cause by enzymes called DNA methyltransferases (DNMTs). Most DNAm is essential for regulation of key processes, including genomic imprinting and suppression of transcription. Recently, global DNAm is regarded as a new marker of "biological age" correlating with telomere length.[10] The principle of DNA hypermethylation is related to a loss of gene expression and subsequent dysregulation accounting for various diseases, such as CVD.[11-14] Therefore, DNAm is not only an indicator of accelerated aging, but may serve as a potential mediator of factors on subclinical CVD pathophysiology. For example, multiple studies reviewed the relationship between aging and CVD, and found, age causes an increase in DNAm, as well as an increase of cardiac disorders.[6,15-17] DNA hypermethylation is independently associated with other CVD pathophysiology promoting inflammation, adiposity, and glycemic dysregulation. This includes atherosclerosis, hypertension (HTN), and diabetes mellitus.[12,18-20]

Another epigenetic change is post-translational histone modifications (PTHM) that alter histone interactions with DNA and other nuclear proteins, thus, repressing or activating gene transcription.[21] Increased histone acetylation is linked to atherosclerosis pathogenesis as well as chronic inflammatory states observed in obese patients.[22] Similarly, to DNAm, PTHM are also associated with HTN and DM.[21,23] Circulating histone in serum could be used for evaluation of CVD.[24,25]

Lastly, ncRNA are a heterogenous group of functional RNA that is transcribed from non−protein-coding DNA.[26] Different subtypes of ncRNA were associated with different CVD. Among others conditions, microRNAs are associated with atherosclerosis and HTN.[27,28] Long ncRNAs were found to be related with aging and hypertrophic cardiomyopathy.[29,30] Due to the very low level of these molecules in the body fluids, quantitative polymerase chain reaction would allow amplification to detectable levels and serve as a novel biomarker to identify biomechanisms of aging predisposing PLHIV to CVD.[31]

Epigenetic Markers and HIV

HIV is one of the most studied viruses over the last two decades.[32] The pathogenesis of HIV infection is mainly related to dysregulation of the immune system affecting CD4+ and CD8+ T cells, and it can be divided into 3 chronological phases: primary or acute HIV infection, chronic asymptomatic HIV infection, and late stage or symptomatic HIV infection.[33,34]

During early phases of HIV-infection, more specifically HIV-1, the host cells recognize viral particles, adapting with epigenetic pattern changes to avoid potential invasion.[35] However, the virus itself may also change its epigenetic structures to facilitate integration and further replication.[36] An example of epigenetic changes in the early phase (first 36 hours, time for HIV-1 to replicate once) of infection, is the increase of DNMTs shortly after HIV-1 infects a cell. This increase of methylation causes silencing of different genes at an early stage in the disease of the host cells, suggesting that even with recent contact among the host cells, HIV-1 changes the defense mechanisms of the host to attempt viral latency.[37] Other genes are related to transcriptional silencing, so HIV-1 infection may cause epigenetic modulations in host cells that may lead these cells to transcriptional repression with important functional consequences.[38]

After the acute infection of HIV, the virus integrates into the host cells via epigenetic processes, including DNAm, to establish a period of latency. Epigenetic suppression of the genomic sequence plays a role in mitigating detection of HIV by the immune system.[39,40]

In addition, chronic infection and progression to AIDS are linked with abnormal gene expression of proinflammatory cytokines, whether on ART or not.[41] Studies suggest a decrease of expression of cytokines in this stage, more specifically IL-2 and INF-γ, 2 very important molecules helping to combat against infections, including HIV-1.[42] Furthermore, the degree of DNAm from patient infected with HIV-1, on treatment or not, during more than 4 years, showed an increase in DNAm due to upregulation of DNMTs, causing gene silencing, and affecting transcriptional process. This increase in methylation is also associated with aging of lymphocyte T, and impacts the T-cell-mediated immune response.[43] These alterations of the immune system cause an immunosuppressed state that lead to development of AIDS as well as non AIDS-related comorbidities.

Epigenetic Markers and Cardiovascular Implications

CVD is the number one killer worldwide with aging as an important risk factor.[7,8] During the last decade, there is an increase of nonrelated HIV/AIDS deaths, with CVD accounting for most cases.[44] Furthermore, HIV infection is considered as an independent risk factor for CVD.[45] Existing evidence shows that PLHIV display an increase in DNAm since the early stages of infection, yet exhibit longer life expectancies with the advent of ART.[46] Though the exact change in biological age among PLHIV differs among studies, however, DNAm changes are still present in this population. A cross-sectional study taking sample of 2 age-different groups with one inclusion criteria of ART naive, determined an increase of 14 years in PLHIV by using a model as prediction.[47] However, another cross-sectional study taking sample of individuals with HIV on ART found an increase of 4.9 years with their model.[48] Variability in years most likely related to the use of ART in the latter study compared with the former. These findings suggest that extrinsic factors, including medication compliance, have the potential to modify onset of age-related conditions. Another prospective study compared DNAm biological age between ART-naive HIV-positive and HIV-negative patients. After 7-11 years of follow-up, 80% of PLHIV who started ART demonstrated an improvement in the DNAm biological age. However, the study sample was very small, and it is uncertain if generalizations can be achieved.[49]

In search of an explanation of the progression and relationship between HIV status and epigenetic age acceleration, multiple models posit HIV infection as linked to senescent or exhausted T cell and age acceleration.[50] HIV alters T-lymphocyte function, but it is unclear yet whether or not the virus itself also augments aging process. Therefore, an increase of

aging by HIV in conjunction with the process of aging itself interfere with the genome of the cells by affecting the methylation of the DNA, suggesting a higher risk of cardiac disorders in this population.[6,15,16] With each year of "epigenetic age," there is an associated elevation in CVD risk by 4%, despite adjusting for risk factors of blood pressure, dyslipidemia, tobacco use, and body mass index.[51] PLHIV in general exhibit accelerated aging of approximately 5 years by epigenetic age, correlated by an increase in mortality risk by 19%.[48]

Another association between HIV-infection, aging, and CVD is chronic inflammatory state.[52] The mechanism of inflammation is multifactorial; however, one important factor is DNA hypermethylation causing cell dysfunction and decreased cytokines, perpetuating the proinflammatory state.[53] These changes suggest that PWLH who start treatment early can alter their risk of AIDS-related death, ultimately linked back to the aging process. PLHIV have a prolonged exposure to inflammation over their lifetime, elevating their risk of CVD.[54]

Conclusion

HIV infection not only causes a dysregulation of the immune system but also epigenetic changes that predispose to other comorbidities such as CVD. PLHIV are now living longer due to the decrease of HIV-related conditions however, the increase of DNAm, and thus, biological age, exacerbate the chronic inflammatory state within this population, significantly elevating the risk of CVD. Additionally, the increase of the process of DNAm in the host cells by HIV, insinuates a higher risk of earlier CVD in PLHIV. Therefore, further studies should examine the association between epigenetic markers of CVD in the context of HIV.

Future Perspectives

The search for a method to detect HIV even before seroconversion is underway, with multiple molecules currently under study such as the SETDB2 protein. If able to leverage this protein, it can serve as a potential early marker of HIV even before HIV-antigen is detectable in body fluids and have significant clinical implications.[55] Early treatment could potentially decrease the rise of age-related conditions in HIV patients by decreasing the effect of DNAm caused by the virus.[56]

Other studies are assessing prevention of early DNAm secondary to HIV in the host.[57,58] As potential targets for treatment, DNAm can act as a biomarker during reactivation of latent HIV in the host cells, so it could be recognized and eliminated by the immune system.[59] ART cannot

affect the cells where HIV-genome was integrated, due to changes in the expression of DNA, caused by the virus.[60] Some pharmacological agents with action on DNAm attempted to reactivate the virus; however, results were equivocal with only partial reactivation of the virus.[61-63] If full reactivation can be achieved, ART could lead to total eradication of the virus.

Lastly, the HIV virus causes an increase in DNAm, leading to a decrease expression of cytokines, more specifically IL-2 and INF-γ. These findings have led investigators to work with these molecules for a possible vaccine against HIV.[42]

REFERENCES

1. Organization WH. HIV/AIDS[Available from: https://www.who.int/hiv/data/en/.
2. Prevention CfDCa. HIV Surveillance Report, 2018 (Preliminary) 2018 updated November 2019. Available from: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html.
3. UNAIDS. 2017 GLOBAL HIV STATISTICS2018 Available from: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
4. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One* 2013;8:e81355.
5. Baril JG, Angel JB, Gill MJ, et al. Dual therapy treatment strategies for the management of patients infected with HIV: a systematic review of current evidence in ARV-naive or ARV-experienced, virologically suppressed patients. *PLoS One* 2016;11:e0148231.
6. Zhang W, Song M, Qu J, Liu GH. Epigenetic modifications in cardiovascular aging and diseases. *Circ Res* 2018;123:773–86.
7. Melonie Heron PD. Division of vital statistics. deaths: leading causes for 2016. *Natl Vital Stat Rep* 2018;67.
8. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. *Circ Res* 2012;110:1097–108.
9. García-Giménez JL, Sanchis-Gomar F, Lippi G, Mena S, Ivars D, Gomez-Cabrera MC, et al. Epigenetic biomarkers: A new perspective in laboratory diagnostics. *Clin Chim Acta* 2012;413:1576–82.
10. Jacob JA. Men with HIV age faster according to DNAm study. *JAMA* 2016;316:135–6.
11. Jin B, Li Y, Robertson KD. DNAm: superior or subordinate in the epigenetic hierarchy? *Genes Cancer* 2011;2:607–17.
12. Xu S, Pelisek J, Jin ZG. Atherosclerosis Is an Epigenetic Disease. *Trends Endocrinol-Metab* 2018;29:739–42.
13. Virzi GM, Clementi A, Brocca A, de Cal M, Ronco C. Epigenetics: a potential key mechanism involved in the pathogenesis of cardiorenal syndromes. *J Nephrol* 2018;31:333–41.
14. Rosa-Garrido M, Chapski DJ, Vondriska TM. Epigenomes in cardiovascular disease. *Circ Res* 2018;122:1586–607.

15. Roetker NS, Pankow JS, Bressler J, Morrison AC, Boerwinkle E. Prospective study of epigenetic age acceleration and incidence of cardiovascular disease outcomes in the ARIC Study (Atherosclerosis Risk in Communities). *Circ Genom Precis Med* 2018;11:e001937.
16. Costantino S, Camici GG, Mohammed SA, Volpe M, Luscher TF, Paneni F. Epigenetics and cardiovascular regenerative medicine in the elderly. *Int J Cardiol* 2018;250:207–14.
17. Spolnicka M, Pospiech E, Adamczyk JG, et al. Modified aging of elite athletes revealed by analysis of epigenetic age markers. *Aging (Albany N Y)* 2018;10:241–52.
18. Tibaut M, Caprnda M, Kubatka P, et al. Markers of atherosclerosis: Part 2-Genetic and imaging markers. *Heart Lung Circ* 2019;28:678–89.
19. Kato N, Loh M, Takeuchi F, et al. Trans-ancestry genome-wide association study identifies 12 genetic loci influencing blood pressure and implicates a role for DNAm. *Nat Genet* 2015;47:1282–93.
20. Ortiz R, Joseph JJ, Lee R, Wand GS, Golden SH. Type 2 diabetes and cardiometabolic risk may be associated with increase in DNAm of FKBP5. *Clin Epigenetics* 2018;10:82.
21. Costantino S, Ambrosini S, Paneni F. The epigenetic landscape in the cardiovascular complications of diabetes. *J Endocrinol Invest* 2019;42:505–11.
22. Davis FM, Gallagher KA. Epigenetic mechanisms in monocytes/macrophages regulate inflammation in cardiometabolic and vascular disease. *ArterioscIerThrombVasc Biol* 2019;39:623–34.
23. Arif M, Sadayappan S, Becker RC, Martin LJ, Urbina EM. Epigenetic modification: a regulatory mechanism in essential hypertension. *Hypertens Res* 2019;42:1099–113.
24. Borissoff JI, Joosen IA, Versteylen MO, et al. Elevated levels of circulating DNA and chromatin are independently associated with severe coronary atherosclerosis and a prothrombotic state. *Arterioscler Thromb Vasc Biol* 2013;33:2032–40.
25. Gao H, Zhang N, Lu F, et al. Circulating histones for predicting prognosis after cardiac surgery: a prospective study. *Interact Cardiovasc Thorac Surg* 2016;23:681–7.
26. Gangwar RS, Rajagopalan S, Natarajan R, Deiuliis JA. Noncoding RNAs in cardiovascular disease: pathological relevance and emerging role as biomarkers and therapeutics. *Am J Hypertens* 2017;31:150–65.
27. Nandakumar P, Tin A, Grove ML, et al. MicroRNAs in the miR-17 and miR-15 families are downregulated in chronic kidney disease with hypertension. *PLoS One* 2017;12:e0176734.
28. Xu S, Kamato D, Little PJ, Nakagawa S, Pelisek J, Jin ZG. Targeting epigenetics and non-coding RNAs in atherosclerosis: from mechanisms to therapeutics. *Pharmacol Ther* 2019;196:15–43.
29. Lozano-Vidal N, Bink DI, Boon RA. Long non-coding RNA in cardiac aging and disease. *J Mol Cell Biol* 2019;11:860–7.
30. Liu X, Ma Y, Yin K, et al. Long non-coding and coding RNA profiling using strand-specific RNA-seq in human hypertrophic cardiomyopathy. *Sci Data* 2019;6:90.
31. Santer L, Bar C, Thum T. Circular RNAs: a novel class of functional RNA molecules with a therapeutic perspective. *Mol Ther* 2019;27:1350–63.

32. UNAIDS. Miles To Go: Closing gaps, breaking barriers, righting injustices. *Global AIDS Update* 2018.
33. Metzner KJ. [Pathogenesis of HIV-1]. *TherUmsch* 2014;71:443–50.
34. Weber J. The pathogenesis of HIV-1 infection. *Br Med Bull* 2001;58:61–72.
35. Cohen MS, Shaw GM, McMichael AJ, Haynes BF. Acute HIV-1 infection. *New Engl J Med* 2011;364:1943–54.
36. Maricato JT, Furtado MN, Takenaka MC, et al. Epigenetic modulations in activated cells early after HIV-1 infection and their possible functional consequences. *PLoS One* 2015;10:e0119234.
37. Nunes JM, Furtado MN, de MoraisNunes ER, Sucupira MCA, Diaz RS, Janini LMR. Modulation of epigenetic factors during the early stages of HIV-1 infection in CD4 (+) T cells in vitro. *Virology* 2018;523:41–51.
38. Maricato JT, Furtado MN, Takenaka MC, et al. Epigenetic modulations in activated cells early after HIV-1 infection and their possible functional consequences. *PLoS One* 2015;10:e0119234.
39. Siddiqui S, Perez S, Gao Y, et al. Persistent viral reservoirs in lymphoid tissues in SIV-infected rhesus macaques of Chinese-origin on suppressive antiretroviral therapy. *Viruses* 2019;11:105.
40. Kumar A, Darcis G, Van Lint C, Herbein G. Epigenetic control of HIV-1 post integration latency: implications for therapy. *Clin Epigenetics* 2015;7:103.
41. Verma M. Epigenetic regulation of HIV, AIDS, and AIDS-related malignancies. *Methods Mol Biol* 2015;1238:381–403.
42. Jost S, Tomezsko PJ, Rands K, et al. CD4+ T-cell help enhances NK cell function following therapeutic HIV-1 vaccination. *J Virol* 2014;88:8349–54.
43. Bogoi RN, de Pablo A, Valencia E, et al. Expression profiling of chromatin-modifying enzymes and global DNAm in CD4+ T cells from patients with chronic HIV infection at different HIV control and progression states. *Clin Epigenetics* 2018;10:20.
44. Croxford S, Kitching A, Desai S, et al. Mortality and causes of death in people diagnosed with HIV in the era of highly active antiretroviral therapy compared with the general population: an analysis of a national observational cohort. *Lancet Public Health* 2017;2:e35–46.
45. Cerrato E, Calcagno A, D'Ascenzo F, et al. Cardiovascular disease in HIV patients: from bench to bedside and backwards. *Open Heart* 2015;2:e000174.
46. Weber R, Ruppik M, Rickenbach M, et al. Decreasing mortality and changing patterns of causes of death in the Swiss HIV Cohort Study. *HIV Med* 2013;14:195–207.
47. Rickabaugh TM, Baxter RM, Sehl M, et al. Acceleration of age-associated methylation patterns in HIV-1-infected adults. *PLoS One* 2015;10:e0119201.
48. Gross AM, Jaeger PA, Kreisberg JF, et al. Methylome-wide analysis of chronic HIV infection reveals five-year increase in biological age and epigenetic targeting of HLA. *Mol Cell* 2016;62:157–68.
49. Nelson KN, Hui Q, Rimland D, et al. Identification of HIV infection-related DNAm sites and advanced epigenetic aging in HIV-positive, treatment-naive U.S. veterans. *AIDS* 2017;31:571–5.

50. Horvath S, Levine AJ. HIV-1 infection accelerates age according to the epigenetic clock. *J Infect Dis* 2015;212:1563–73.
51. Huang R-C, Lillycrop KA, Beilin LJ, et al. Epigenetic age acceleration in adolescence associates with BMI, inflammation, and risk score for middle age cardiovascular disease. *J Clin Endocrinol Metab* 2019;104:3012–24.
52. Lagathu C, Cossarizza A, Bereziat V, Nasi M, Capeau J, Pinti M. Basic science and pathogenesis of ageing with HIV: potential mechanisms and biomarkers. *AIDS* 2017;31(Suppl 2):S105–s19.
53. Sundermann EE, Hussain MA, Moore DJ, et al. Inflammation-related genes are associated with epigenetic aging in HIV. *J Neurovirol* 2019;25:853–65.
54. Fioranelli M, Bottaccioli AG, Bottaccioli F, Bianchi M, Rovesti M, Roccia MG. Stress and inflammation in coronary artery disease: a review psychoneuroendocrineimmunology-based. *Front Immunol* 2018;9:2031.
55. Chan RK, Ali K, Thoe SY. Human immunodeficiency virus (HIV) antigen testing to detect HIV infection in female sex workers in Singapore. *Ann Acad Med Singapore* 1995;24:534–6.
56. Leung JM, Fishbane N, Jones M, Morin A, et al. Longitudinal study of surrogate aging measures during human immunodeficiency virus seroconversion. *Aging (Albany N Y)* 2017;9:687–705.
57. Aldawsari FS, Aguayo-Ortiz R, Kapilashrami K, et al. Resveratrol-salicylate derivatives as selective DNMT3 inhibitors and anticancer agents. *J Enzyme Inhib Med Chem* 2016;31:695–703.
58. Cicenas J. The Aurora kinase inhibitors in cancer research and therapy. *J Cancer Res Clin Oncol* 2016;142:1995–2012.
59. Dahabieh MS, Battivelli E, Verdin E. Understanding HIV latency: the road to an HIV cure. *Annu Rev Med* 2015;66:407–21.
60. Datta PK, Kaminski R, Hu W, et al. HIV-1 latency and eradication: past, present and future. *Curr HIV Res* 2016;14:431–41.
61. Crosby B, Deas CM. Repurposing medications for use in treating HIV infection: a focus on valproic acid as a latency-reversing agent. *J Clin Pharm Ther* 2018;43:740–5.
62. Archin NM, Kirchherr JL, Sung JA, et al. Interval dosing with the HDAC inhibitor vorinostat effectively reverses HIV latency. *J Clin Invest* 2017;127:3126–35.
63. Zhao M, De Crignis E, Rokx C, et al. T cell toxicity of HIV latency reversing agents. *Pharmacol Res* 2019;139:524–34.