Opinion Piece

Poor Adherence: The Conceivable Cause of Cardiovascular Diseases in People on Antiretroviral Therapy

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Abstract

Apart from the deterrence of human immunodeficiency virus (HIV) progression, antiretroviral therapy (ART) has been associated with the development of cardiovascular diseases (CVD), as with HIV itself. With both HIV and ART being linked to CVDs in similar mechanisms, there is not yet an established relationship between ART and CVDs using adherence in people living with HIV (PLWH). The use of adherence may help shed light on understanding whether the CVDs are a result of ART or HIV due to poor adherence. Henceforth, the aim of this paper was to explore the possible relationship between ART adherence and CVDs. Based on evidence from the literature, there is convincing evidence to suggest that CVDs in people on ART are from HIV itself as a result of uncontrolled viremia due to poor adherence to ART.

Keywords: adherence; antiretrovirals; antiretroviral therapy; cardiovascular diseases; human immunodeficiency virus (HIV)

Introduction

Human immunodeficiency virus (HIV) is an infectious pathogen that results in the reduction of the immune system's potential to detect and consequently fight infections (Vidya Vijayan et al. 2017). The development of antiretroviral (ARV) drugs in the early 1990s, coupled with aggressive public health campaigns, led to efficient control of HIV progression and transformed it into a chronic disease (Tseng, Seet, and Phillips 2015). The initial viremia results in gut-associated lymphoid tissue (GALT) destruction, compromising the gastrointestinal barrier and enabling pathological microbial translocation (Mak et al. 2021) and subsequent gut dysbiosis. Gut microbial

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translocation then triggers systemic immune activation, stimulating the release of pro-inflammatory and pro-fibrotic cytokines, predisposing patients to cardiovascular diseases (CVDs) (Dillon, Frank, and Wilson 2016).

Interestingly, ARVs have also been reported to be a CVD risk through similar mechanisms to that of HIV (Ruamtawee et al. 2023), further reducing the possibility of complete positive health outcomes for people living with HIV (PLWH). Although antiretroviral therapy (ART) is essential in the management of the disease, it must be taken lifelong in order to achieve continuous suppression of the virus, and this requires consistency, patience, and adherence from PLWH (Nyambuya et al. 2020). It is understood that an average adherence ≥95% is sufficient for HIV viral suppression, and this might be higher or lower depending on the ART regimen (Byrd et al. 2019).

Even though newer ART regimens have been made simple and user-friendly to PLWH, long-term adherence itself remains a challenge for many reasons. Social perspectives, economic status, and occurrence of side effects not discussed prior to the treatment of patients by healthcare providers are among the causes of poor adherence (Nyambuya et al. 2020). The results of poor adherence include the risk of drug resistance, further destruction of the immune system, and uncontrolled HIV viremia, which are all linked to CVDs (Byrd et al. 2019).

How does Human Immunodeficiency Virus Lead to Cardiovascular Diseases?

The gastrointestinal tract (GIT), which is an indirect target of HIV, plays a role in structural and immunological defence against exposure from the external environment (Moszak, Szulińska, and Bogdański 2020). Not only does it come in contact with food and antigens from the environment, but it also comes in contact with microorganisms that reside in it, such as bacteria, archaea, and fungi, collectively named the gut microbiota (Saxena and Sharma 2016). This makes the GIT an essential immunological site for the maintenance of the delicate balance between reactivity and tolerance (Moszak et al. 2020). With the main immunological defence mechanism to the gut barrier being the development of the GALT that forms part of the GIT epithelium, it functions to detect and react to pathogens. The GALT is tolerant to the gut microbiota, but not to other microorganisms (Saxena and Sharma 2016).

The protective function of the GALT against microorganisms is altered during HIV infection due to the virus attacking and destroying the tissue through the CD4+ cells, which make up most of the structure (Vidya Vijayan et al. 2017). HIV-Tat protein directly induces apoptosis to enterocytes by a redox-dependent mechanism, which subsequently leads to the translocation of the gut microbiota (Sarnelli et al. 2018), making the GALT the major site of transmission, replication, and seeding, which leads to CD4+ T cell depletion.

The consistent loss of CD4+ T cells is persistent through the chronic stage of HIV infection, in which most apoptosis is motivated by the killing of CD4+ T cells that were not actively infected (Vidya Vijayan et al. 2017). The alteration of CD4+Th17 cells, which is a subgroup of CD4+ T cells, is consistent with the disruption of the intestinal barrier function in which the tightly packed enterocytes become unstable and lose their adherence to adjacent cells (Sarnelli et al. 2018).

The imbalance of CD4+ Th17 cells coincides with the increase in Regulatory T cells, leading to suppression of viral clearance on HIV and inappropriate tolerance of other microbes (Crakes and Jiang 2019). This results in the translocation of the gut microbial products and harmful microorganisms to move from the gut lumen to the systemic circulation, moving to other organs such as the brain and liver, inducing immune activation (Yoon, Lee, and Sang 2014). The microbes that cross the GIT barrier then interfere with the pattern recognition receptor expression in the gut mucosa, which inhibits the appropriate cellular response to oppose viral infection and influence gut inflammation (Glavan et al. 2016).

The presence of an anti-inflammatory cytokine IL-10, which has been found to be linked to gut inflammation, is used as evidence to confirm the effect that HIV has towards causing the destruction of the intestinal barrier, which subsequently leads to gut inflammation due to the movement of gut microbiota and other microbes from the gut lumen into the systemic circulation. The subsequent mechanisms lead to the release of pro-inflammatory and pro-fibrotic cytokines, all leading to CVDs (Azzoni, Metzger, and Montaner 2020).

Association of Antiretroviral Therapy with Cardiovascular Diseases

Gut dysbiosis as a result of the destruction of the GALT due to HIV infection remains compromised even during ART (Nowak et al. 2015), although there is evidence that the long-term use of ART for chronic HIV infection can partially restore the gut microbiota, even though it does not normalise it completely (Ling et al. 2016). Recent studies went further to differentiate ART combinations on the gut microbiome to understand the effects of different ARVs on gut microbiota, inflammation and CVDs. ART regimens that are protease inhibitor (PI)-based were found to increase endothelial damage and exhibit higher levels of soluble CD4+ in plasma compared to the non-nucleoside reverse transcriptase inhibitor (NNRTI)-base ART and HIV-uninfected controls. Furthermore, a comparison of PI, NNRTI, and integrase inhibitor (II)-based ART regimens showed that II-based ARVs had the lowest levels of systemic inflammation and CVDs (Villanueva-Millan et al. 2017).

On top of its relation to incomplete recovery of gut microbiota, ARVs have also been associated with unfavourable changes in the lipid profile. Drugs like ritonavir, lopinavir and indinavir have been linked with persistent elevations in total serum cholesterol, low-density lipoprotein and triglycerides (Da Cunha et al. 2015), like effects of its counterpart, which is HIV.

Moreover, studies were done to further investigate the relationship of ARVs with CVDs, and these studies have reported that the use of PI-based ARVs, specifically ritonavir and indinavir, is associated with an increased risk of myocardial infarction (MI) and heart disease (Eyawo et al. 2019; Feinstein et al. 2019). However, some alternative measures have been exerted to assess the most likely pathophysiologic mechanisms that the use of abacavir could influence the occurrence of CVD, and it is speculated that abacavir is related to an increase in systemic inflammation, which itself may possibly lead to CVD (Dirajlal-Fargo and Funderburg 2022).

Adherence to Antiretroviral Therapy

Although ART access continues to expand since the implementation of the universal test-and-treat (UTT) policy in South Africa, there is still evidence of poor adherence from several studies (Azia, Mukumbang, and Van Wyk 2016; Moosa et al. 2019; UNAIDS Joint United Nations Programme 2017). Adherence rate ≥95% has been reported to be adequate for the suppression of viral progression. Properly adherent ART patients are expected to have an undetectable viral load, which is lower than 50 copies per millilitre, and this is expected to be the case after six months from initiation of ART (Byrd et al. 2019). During this period, the patient is said to have reached viral suppression, although the virus continues to reside dormant in the viral reservoirs. As the viral load continues to be suppressed, the CD4+ cells begin to recover, steadily restoring immune function (Bishop et al. 2016).

Poor adherence to ART leads to uncontrolled HIV viremia, and hence continues to put the immune system under pressure, continuing to lose CD4 cells in the process. In addition to a lower CD4 cell count, uncontrolled HIV viremia persists in inducing systemic inflammation in those on ART (Collins, Gaiha, and Walker 2020). This leads to elevated levels of c-reactive protein (CRP), characterised by the presence of detectable viral load due to poor ART adherence (Castillo-Mancilla et al. 2020). Inflammation, characterised by the presence of CRP, downregulates nitric oxide synthetase activity, causing overproduction of reactive oxygen species, which both contribute to endothelial dysfunction and oxidative stress, leading to the development of hypertension (Dinh et al. 2014). As with pure HIV infection, uncontrolled viremia during ART as a result of poor adherence continues to cause unfavourable lipid disturbances. This is due to persistent inflammation, contributing to modifications of lipid compositions and critically mitigating CVDs (Funderburg and Mehta 2016).

Conclusion and Future Directions

HIV viral progression due to poor ART adherence continues to predispose ART patients to CVDs as if they were not on therapy. This suggests that poor adherence to ART may be a contributing factor of CVDs in PLWH due to uncontrolled HIV viremia. Despite the huge prevalence of HIV in Southern Africa, the impact of adherence to ART remains understudied. Therefore, nursing researchers are encouraged to conduct additional scientific research to fill this gap.

References

Azia, I. N., F. C. Mukumbang, and B. van Wyk. 2016. “Barriers to Adherence to Antiretroviral Treatment in a Regional Hospital in Vredenburg, Western Cape, South Africa.” *Southern African Journal of HIV Medicine* 17 (1): 476. https://doi.org/10.4102/sajhivmed.v17i1.476.

Azzoni, L., D. Metzger, and L. Montaner. 2020. “Effect of Opioid Use on Immune Activation and HIV Persistence on ART.” *Journal of Neuroimmune Pharmacology: The Official Journal of the Society on NeuroImmune Pharmacology*: 15. https://doi.org/10.1007/s11481-020-09959-y.

Bishop, J. D., S. DeShields, T. Cunningham, and S. B. Troy. 2016. “CD4 Count Recovery after Initiation of Antiretroviral Therapy in Patients Infected with Human Immunodeficiency Virus.” *The American Journal of the Medical Sciences* 352 (3): 239–244. https://doi.org/10.1016/j.amjms.2016.05.032.

Byrd, K. K., J. G. Hou, R. Hazen, H. Kirkham, S. Suzuki, and P. G. Clay. 2019. “Antiretroviral Adherence Level Necessary for HIV Viral Suppression Using Real-world Data.” *Journal of Acquired Immune Deficiency Syndromes* 82 (3): 245–51. https://doi.org/10.1097/QAI.0000000000002142.

Castillo-Mancilla, J. R., T. T. Brown, F. J. Palella, B. J. C. Macatangay, E. C. Breen, L. P. Jacobson, and N. I. Wada. 2020. “Partial Normalisation of Biomarkers of Inflammation and Immune Activation among Virally Suppressed Men with HIV Infection and High ART Adherence.” *Open Forum Infect Dis*.7 (4): ofaa099. https://doi.org/10.1093/ofid/ofaa099.

Collins, D. R., G. D. Gaiha, and B. D. Walker. 2020. “CD8+ T Cells in HIV Control, Cure and Prevention.” *Nat Rev Immunol* 20: 471–482. https://doi.org/10.1038/s41577-020-0274-9.

Crakes, K. R., and G. Jiang. 2019. “Gut Microbiome Alterations during HIV/SIV Infection: Implications for HIV Cure.” *Frontiers in Microbiology*, 10. https://doi.org/10.3389/fmicb.2019.01104.

Da Cunha, J., L. M. Maselli, A. C. Stern, C. Spada, and S. P. Bydlowski. 2015. “Impact of Antiretroviral Therapy on Lipid Metabolism of Human Immunodeficiency Virus-infected Patients: Old and New Drugs.” *World Journal of Virology* 4 (2): 56–77. https://doi.org/10.5501/wjv.v4.i2.56.

Dillon, S. M., D. N. Frank, and C. C. Wilson. 2016. “The Gut Microbiome and HIV-1 Pathogenesis: A Two-way Street.” *AIDS (London, England)* 30 (18): 2737–2751. https://doi.org/10.1097/QAD.0000000000001289.

Dinh, Q. N., G. R. Drummond, C. G. Sobey, and S. Chrissobolis. 2014. “Roles of Inflammation, Oxidative Stress, and Vascular Dysfunction in Hypertension.” *Biomed Res Int*. 2014: 406960. https://doi.org/10.1155/2014/406960.

Dirajlal-Fargo, S., and N. Funderburg. 2022. “HIV and Cardiovascular Disease: The Role of Inflammation.” *Current Opinion in HIV and AIDS* 17 (5): 286–292. https://doi.org/10.1097/COH.0000000000000755.

Eyawo, O., G. Brockman, C. H. Goldsmith, M. W. Hull, S. A. Lear, M. Bennett, S. Guillemi, C. Franco-Villalobos, A. Adam, E. J. Mills, J. S. G. Montaner, and R. S. Hogg. 2019. “Risk of Myocardial Infarction among People Living with HIV: An Updated Systematic Review and Meta-analysis.” *BMJ Open* 9 (9): e025874. https://doi.org/10.1136/bmjopen-2018-025874.

Feinstein, M. J., P. Y. Hsue, L. A. Benjamin, G. S. Bloomfield, J. S. Currier, M. S. Freiberg, S. K. Grinspoon, J. Levin, C. T. Longenecker, and W. S. Post. 2019. “Characteristics, Prevention, and Management of Cardiovascular Disease in People Living with HIV: A Scientific Statement from the American Heart Association.” *Circulation* 140 (2): e98-e124. https://doi.org/10.1161/CIR.0000000000000695.

Funderburg, N. T., and N. N. Mehta. 2016. “Lipid Abnormalities and Inflammation in HIV Infection.” *Curr HIV/AIDS Rep*. 13 (4): 218–25. https://doi.org/10.1007/s11904-016-0321-0.

Glavan, T. W., C. A. Gaulke, C. Santos Rocha, S. Sankaran-Walters, L. A. Hirao, and M. Raffatellu. 2016. “Gut Immune Dysfunction through Impaired Innate Pattern Recognition Receptor Expression and Gut Microbiota Dysbiosis in Chronic SIV Infection.” *Mucosal Immunology* 9: 677–688. https://doi.org/10.1038/mi.2015.92.

Ling, Z., C. Jin, T. Xie, Y. Cheng, L. Li, and N. Wu. 2016. “Alterations in the Fecal Microbiota of Patients with HIV-1 Infection: An Observational Study in a Chinese Population.” *Sci. Rep*. 6: 30673. https://doi.org/10.1038/srep30673.

Mak, G., J. J. Zaunders, M. Bailey, N. Seddiki, G. Rogers, L. Leong, T. G. Phan, A. D. Kelleher, K. K. Koelsch, M. A. Boyd, and M. Danta. 2021. “Preservation of Gastrointestinal Mucosal Barrier Function and Microbiome in Patients with Controlled HIV Infection.” *Frontiers in Immunology* 12: 688886. https://doi.org/10.3389/fimmu.2021.688886.

Moosa, A., T. N. Gengiah, L. Lewis, and K. Naidoo. 2019. “Long-term Adherence to Antiretroviral Therapy in a South African Adult Patient Cohort: A Retrospective Study.” *BMC Infectious Diseases* 19: 775. https://doi.org/10.1186/s12879-019-4410-8.

Moszak, M., M. Szulińska, and P. Bogdański. 2020. “You Are What You Eat: The Relationship between Diet, Microbiota, and Metabolic Disorders: A Review.” *Nutrients* 12 (4): 1096. https://doi.org/10.3390/nu12041096.

Nowak, P., M. Troseid, E. Avershina, B. Barqasho, U. Neogi, and K. Holm. 2015. “Gut Microbiota Diversity Predicts Immune Status in HIV-1 Infection.” *AIDS* 29: 2409–2418. https://doi.org/10.1097/QAD.0000000000000869.

Nyambuya, T. M., P. V. Dludla, V. Mxinwa, and B. B. Nkambule. 2020. “The Effect of Successful Antiretroviral Therapy on Immune Activation and Reconstitution in HIV Infected Adults: A Systematic Review and Meta-analysis.” *AIDS Reviews* 23 (3). https://doi.org/10.24875/AIDSRev.20000039.

Ruamtawee, W., M. Tipayamongkholgul, N. Aimyong, and W. Manosuthi. 2023. “Prevalence and Risk Factors of Cardiovascular Disease among People Living with HIV in the Asia-Pacific Region: A Systematic Review.” *BMC Public Health* (23): 4777. https://doi.org/10.1186/s12889-023-15321-7.

Sarnelli, G., L. Seguella, M. Pesce, J. Jie Lu, S. Gigli, E. Bruzzese, R. Lattanzi, A. D’Alessandro, R. Cuomo, L. Steardo, and G. Esposito. 2018. “HIV-1 Tat-induced Diarrhea Is Improved by the PPAR Alpha Agonist, Palmitoylethanolamide, by Suppressing the Activation of Enteric Glia.” *J Neuroinflammation* 15: 94. https://doi.org/10.1186/s12974-018-1126-4.

Saxena, R., and V. K. Sharma. 2016. “A Metagenomic Insight Into the Human Microbiome: Its Implications in Health and Disease.” *Medical and Health Genomics*, 107–119. https://doi.org/10.1016/B978-0-12-420196-5.00009-5.

Tseng, A., J. Seet, and E. J. Phillips. 2015. “The Evolution of Three Decades of Antiretroviral Therapy: Challenges, Triumphs and the Promise of the Future.” *British Journal of Clinical Pharmacology* 79 (2): 182–194. https://doi.org/10.1111/bcp.12403.

UNAIDS, Joint UN Programme, Country Factsheets South Africa. 2017. Accessed April 30, 2023. http://www.unaids.org/en/regionscountries/countries/southafrica.

Vidya Vijayan, K. K., K. P. Karthigeyan, S. P. Tripathi, and L. E. Hanna. 2017. “Pathophysiology of CD4+ T-cell Depletion in HIV-1 and HIV-2 Infections.” *Frontiers in Immunology* 8: 580. https://doi.org/10.3389/fimmu.2017.00580.

Villanueva-Millan, M. J., P. Perez-Matute, E. Recio-Fernandez, J. M. Lezana Rosales, and J. A. Oteo. 2017. “Differential Effects of Antiretrovirals on Microbial Translocation and Gut Microbiota Composition of HIV-infected Patients.” *Journal of International AIDS Society* 20: 21526. https://doi.org/10.7448/IAS.20.1.21526.

Yoon, M. Y., K. Y. Lee, and S. Sang. 2014. “Protective Role of Gut Commensal Microbes against Intestinal Infections.” *Journal of Microbiology*, 52. https://doi.org/10.1007/s12275-014-4655-2.