 doi:10.20944/preprints202205.0051.v1

A reality we have to face in the era of tenofovir-derived pre-exposure prophylaxis and antiretroviral therapy: A paradigm shift from the reduction of HIV risk to the increased risk of cardiovascular disease?

Jason Kar-Sheng Lew[1,2], Ph.D., Ilias Yee[3], MBBCh BAO

[1]Department of Physiology, University of Otago, Dunedin, New Zealand

[2]Radcliffe Department of Medicine, Division of Cardiovascular Medicine, University of Oxford, United Kingdom

[3]Centre of Excellence for Research in AIDS (CERiA), University of Malaya, Kuala Lumpur, Malaysia

Running head: Risk of cardiovascular disease in PrEP and ART users among the LGBT adults

Keywords: Tenofovir, Pre-exposure prophylaxis, anti-retroviral therapy, cardiovascular disease, LGBT

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 May 2022 doi:10.20944/preprints202205.0051.v1

Abstract

The introduction of tenofovir-derived prodrugs has revolutionised the prevention and management of HIV, which has coincided with 23% reduction in new HIV incidences globally. To date, there are two formulations of tenofovir-derived nucleoside reverse transcriptase inhibitor (NRTI): tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and tenofovir alafenamide fumarate/emtricitabine (TAF/FTC). Although these prodrugs have shown favourable safety profile, their effects on cardiovascular health are differ from one another: TDF/FTC exhibits potential lipid-lowering effect, TAF/FTC demonstrates potential lipid-inducing effect, which is a major risk factor for cardiovascular diseases. However, this issue has not been previously elucidated, especially among the marginalised populations [lesbian, gay, bisexual and transgender (LGBT) and men who have sex with men (MSM)] who are likely be the main users of these prodrugs. This is of clinically significance as the cardiovascular health in these populations is often overlooked, in addition to a lack of appropriate cardiovascular risk prediction algorithm. Therefore, this review aims to (1) highlight the cardiovascular risks of tenofovir-derived prodrugs in the marginalized populations, and also to (2) establish the importance of having a cardiovascular risk prediction model that is specific to this particular populations so that their health management could be more comprehensive.

Introduction

The administration of tenofovir-derived prodrugs in the forms of pre-exposure prophylaxis and antiretroviral therapy (ART) has demonstrated significant effectiveness in reducing HIV transmission, particularly among the marginalised populations such as sexually active LGBT individuals, men who have sex with men (MSM), and people who inject drug[1]. This has coincided with 23% reduction in new HIV incidence globally[2].

Currently, there are two formulations of tenofovir-derived nucleoside reverse transcriptase inhibitor (NRTI), tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) and tenofovir alafenamide fumarate/emtricitabine (TAF/FTC). Although these tenofovir-derived prodrugs have shown favourable safety profile, evidence of nausea, headache, renal and bone toxicity have been reported. [3,4].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 5 May 2022 doi:10.20944/preprints202205.0051.v1

Particularly, TAF/FTC could minimize the renal- and bone-related side effects due to its improved pharmacokinetics, its indication does not widely cover the LGBT spectrum and cisgender-women[4].

Cardiovascular diseases include, but are not limited to, coronary artery disease, heart failure (HF), cerebrovascular disease and peripheral artery disease, have contributed to 17.9 million of death globally each year, making CVD as the top leading cause of death[5]. Emerging evidence shows a higher tendency of CVD mortality and morbidity among the marginalised population[6,7], which likely attributed to a significant mental distress acquired from the psychosocial aspects such as stigma, discrimination and mistreatment[8,9], as well as the higher prevalence of smoking rate[10], all of which are major risk factors of CVD. Whether these risk factors, when compounded with the chronic use of tenofovir-derived PrEP or ART, would accelerate the development or progression of CVD remain to be elucidated.

Tenofovir disoproxil fumarate/emtricitabine and risk of cardiovascular diseases

1. **Seronegative population**

Compelling evidence shows a low cardiovascular risk of TDF/FTC on seronegative individuals and PLHIV[11,12]. In the landmark Pre-exposure Prophylaxis Initiative (iPrEx) trial, which included 2174 cisgender men and 325 transgender women who have sex with men in 6 countries were followed for nearly 2 years[12]. Noteworthy, the TDF/FTC arm had no significant change in lean body mass in addition to a lower fat accumulation compared to the placebo arm. This is also linked to a modest decline in CVD risk factors such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein (HDL-C) and total cholesterol relative to their baseline. Although TDF/FTC has no substantial effect on insulin sensitivity and energy metabolism regulation[13], TDF/FTC has been reported to have a more favorable lipid profile in comparison to other NRTIs such as stavudine and zidovudine[12]. Both of these NRTIs have been associated with increased risk of myocardial infarction[14].

2. **Seropositive population**

Given that chronic HIV infection could disturb one's metabolism, this could make PLHIV more vulnerable to CVDs[15]. Hence, selecting an appropriate ART that could match to patient's metabolic profile is crucial in minimising the risk of CVDs.

Interestingly, Santos et al. demonstrated the possible intrinsic lipid-lowering effect of TDF/FTC in PLHIV with underlying hypercholesterolemia who were on a stable protease inhibitor (PI)

monotherapy[11], an ART that is known to cause dyslipidemia and increased risk of myocardial infarction[16]. In this randomised controlled trial, alternating treatment of TDF/FTC or placebo were given over 9 months, in addition to their backbone PI treatment[11]. The outcomes were intriguing because the authors not only reported the absence of treatment failure, TDF/FTC exposure alone statistically reduced triglycerides, LDL-C and HDL-C by an average of 10%.

Collectively, the findings on the minimal CVD risk of TDF/FTC for both populations of seronegative individuals and PLHIV suggest its favorable safety profile on long-term usage.

To support this notion, a large cohort study that involved 21435 veterans living with HIV showed a significant 30-50% reduction of HF risk for the current and past users of TDF/FTC, in comparison to those who have never been exposed to TDF/FTC[17]. Concomitantly, TDF/FTC even lowered HF risk by 21% among those current users with each additional year exposure. Intriguingly, this favouable outcome was conflicted with the authors' initial hypothesis, whereby they expected TDF/FTC to increase HF risk due to its kidney complications (a strong predictor of CVD)[17].

Ultimately, if TDF/FTC is administered according to guidelines with the exclusion of pre-existing kidney complications, the low CVD risk of TDF/FTC would warrant a sustainable regimen among the seronegative and seropositive populations.

Tenofovir alafenamide fumarate/emtricitabine and risk of cardiovascular diseases

1. **Seronegative population**

Studies on the effect of TAF/FTC on CVD risks are limited as it is just recently approved by the U.S. Food and Drug Administration (FDA) for the use as PrEP. However, in a head-to-head DISCOVER trial over 96 weeks, TAF/FTC is non-inferior to TDF/FTC for HIV prevention among the cisgender MSM and transgender women who have sex with men[4]. While the exposure to TAF/FTC shows favourable effects on bone mineral density and renal safety, TAF/FTC had less influence in lowering total cholesterol (-0.03 vs. -0.28 mmol/L) and HDL-C (-0.05 vs. -0.13 mmol/L) compared to TDF/FTC therapy[4]. In their analyses, the risk factors of CVD such as body weight, LDL-C and triglycerides were markedly increased at week 48, in comparison to TDF/FTC group. Noteworthy, in the highly cited Framingham Heart Study, every 1kg/m^2 BMI increment may elevate the risk of HF by 5% in men and 7% in women[18]. This figure could be even higher, if the individuals are compounded with other

underlying metabolic diseases. Therefore, whether long term administration of TAF/FTC would contribute to increased risk of CVDs among the LGBT adults with seronegative status remains to be verified.

2. Seropositive population

In a real-world setting that involved PLHIV, the lipid profile was even significantly exaggerated when exposed to TAF/FTC[19,20]. In particular, a study that included 490 seropositive patients has demonstrated higher total cholesterol, LDL-C, and >20% increase in the number of patients who experienced severe dyslipidemia after switching treatment from TDF/FTC to TAF/FTC for 2 months[19]. In line with this observation, Lagoutte-Renosi et al. reported a significant elevation of the same CVD risk factors among 103 seropositive patients[20]. Of which, 4 patients required lipid-lowering therapy after switching. Thus far, it remains uncertain as to whether TAF/FTC therapy with evidence of disturbed lipid profile may clinically contribute to a higher risk of CVD, because two recent studies that used the 10-year atherosclerotic cardiovascular disease (ASCVD) risk algorithm on PLHIV showed conflicting outcomes[21,22]. According to the current clinical guidelines, lipid profile monitoring was not recommended for PrEP users. Perhaps, the inclusion of this parameter would help better managing patient prognosis in a more comprehensive approach.

Predicting cardiovascular risks in marginalised populations

Traditionally, predicting the risks of CVD in the general population has been performed using different algorithm models such as Framingham Risk Score, ASCVD Risk Score and Systematic Coronary Risk Evaluation (SCORE)[23]. These prediction models included CVD risk factors such as age, gender, lipid profile, family history of CVDs, blood pressure and smoking status, have been relatively reliable in estimating 10-year risk of CVD and stroke, specifically in the age group of 40-79 within the European and American populations. However, this may not be the most reliable models to predict CVD risks in the marginalised populations for several critical reasons.

Firstly, the psychosocial factors such as quality of life, stigma and discrimination among the LGBT members and PLHIV have been inevitably linked to lifetime depression and mental distress, all of which could lead to increased CVD risks[8,9]. Secondly, since the access to PrEP is increasing and some PrEP may influence lipid profile, it is sensible to include this variable into the algorithm because

similar parameter (i.e. ART) has been added in the Data-Collection on Adverse effects of Anti-HIV Drug (D:A:D) Full Risk Score to predict CVD risk in PLHIV[24], but not for the seronegative PrEP users. Thirdly, as the smoking rate among the LGBT adults is 2.5-fold higher than the heterosexual adults[10], this would likely accelerate the onset of CVD but it has not been considered. Furthermore, a study shows that the use of hormone therapy could increase the risk of myocardial infarction in transgender men >2-fold, after adjusting for the conventional risk factors mentioned above[6], but this has been considered in the transgender population who are on PrEP. Finally, since there is an increasing trend of premature CVD (<45 years old)[25], these models have not considered a younger age group especially those who are on PrEP.

Conclusion

The use of tenofovir-derived PrEP and ART has increased over the years. Although it shows good safety profile and low incidence of CVD risks, growing body of evidence suggests that the disparities in psychosocial and the acquired negative health behaviors among the LGBT population and PLHIV may even make them more susceptible to the development of CVD. Importantly, the conventional algorithm described earlier may potentially underestimate the CVD prognosis in the marginalised population, thereby delaying comprehensive health management. Hence, research to formulating a more reliable and robust algorithm specially cater for the marginalised population should be considered, especially when the newly approved tenofovir-derived prodrug tends to increase CVD risks.

Acknowledgement

The author thanks Dr Ilias Yee for his contribution relating to current clinical practices.

Authors' contributions

JK-SL conceived, performed literature review and wrote the manuscript.

Author disclosure statement

The author declares no competing interests.

Funding information

The article did not receive support from any funding sources.

References

1. Wilton J, Senn H, Sharma M, Tan DH. Pre-exposure prophylaxis for sexually-acquired HIV risk management: a review. *HIV AIDS (Auckl).* 2015;7:125-136.
2. U.S. Department of Health & Human Services. The Global HIV/AIDS Epidemic. 2020; https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics. Accessed September 28, 2020.
3. Wassner C, Bradley N, Lee Y. A Review and Clinical Understanding of Tenofovir: Tenofovir Disoproxil Fumarate versus Tenofovir Alafenamide. *J Int Assoc Provid AIDS Care.* Jan-Dec 2020;19:2325958220919231.
4. Mayer KH, Molina JM, Thompson MA, et al. Emtricitabine and tenofovir alafenamide vs emtricitabine and tenofovir disoproxil fumarate for HIV pre-exposure prophylaxis (DISCOVER): primary results from a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial. *Lancet.* Jul 25 2020;396(10246):239-254.
5. World Health Organization. Cardiovascular Diseases. 2020; https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1. Accessed September 28, 2020.
6. Alzahrani T, Nguyen T, Ryan A, et al. Cardiovascular Disease Risk Factors and Myocardial Infarction in the Transgender Population. *Circ Cardiovasc Qual Outcomes.* Apr 2019;12(4):e005597.
7. Farmer GW, Jabson JM, Bucholz KK, Bowen DJ. A population-based study of cardiovascular disease risk in sexual-minority women. *Am J Public Health.* Oct 2013;103(10):1845-1850.
8. Caceres BA, Makarem N, Hickey KT, Hughes TL. Cardiovascular Disease Disparities in Sexual Minority Adults: An Examination of the Behavioral Risk Factor Surveillance System (2014-2016). *Am J Health Promot.* May 2019;33(4):576-585.
9. Bialer PAM, C. A. Discrimination, stigma, and hate: The impact on the mental health and well-being of LGBT people. *Journal of Gay & Lesbian Mental Health.* 13 July 2016 2016;20(4):297-298.
10. Lee JG, Griffin GK, Melvin CL. Tobacco use among sexual minorities in the USA, 1987 to May 2007: a systematic review. *Tob Control.* Aug 2009;18(4):275-282.
11. Santos JR, Saumoy M, Curran A, et al. The lipid-lowering effect of tenofovir/emtricitabine: a randomized, crossover, double-blind, placebo-controlled trial. *Clin Infect Dis.* Aug 1 2015;61(3):403-408.
12. Glidden DV, Mulligan K, McMahan V, et al. Metabolic Effects of Preexposure Prophylaxis With Coformulated Tenofovir Disoproxil Fumarate and Emtricitabine. *Clin Infect Dis.* Jul 18 2018;67(3):411-419.
13. Randell PA, Jackson AG, Zhong L, Yale K, Moyle GJ. The effect of tenofovir disoproxil fumarate on whole-body insulin sensitivity, lipids and adipokines in healthy volunteers. *Antivir Ther.* 2010;15(2):227-233.
14. Lang S, Mary-Krause M, Cotte L, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med.* Jul 26 2010;170(14):1228-1238.
15. Feinstein MJ, Hsue PY, Benjamin LA, et al. Characteristics, Prevention, and Management of Cardiovascular Disease in People Living With HIV: A Scientific Statement From the American Heart Association. *Circulation.* Jul 9 2019;140(2):e98-e124.
16. Group DADS, Friis-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med.* Apr 26 2007;356(17):1723-1735.
17. Chen R, Scherzer R, Hsue PY, et al. Association of Tenofovir Use With Risk of Incident Heart Failure in HIV-Infected Patients. *J Am Heart Assoc.* Apr 24 2017;6(4).
18. Kenchaiah S, Evans JC, Levy D, et al. Obesity and the risk of heart failure. *N Engl J Med.* Aug 1 2002;347(5):305-313.
19. Kauppinen KJ, Kivela P, Sutinen J. Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide Significantly Worsens the Lipid Profile in a Real-World Setting. *AIDS Patient Care STDS.* Dec 2019;33(12):500-506.

 doi:10.20944/preprints202205.0051.v1

20. Lagoutte-Renosi J, Flammang M, Chirouze C, et al. Real-Life Impact on Lipid Profile of a Switch from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in HIV-Infected Patients. *Curr HIV Res.* Aug 23 2020.
21. Huhn GD, Shamblaw DJ, Baril JG, et al. Atherosclerotic Cardiovascular Disease Risk Profile of Tenofovir Alafenamide Versus Tenofovir Disoproxil Fumarate. *Open Forum Infect Dis.* Jan 2020;7(1):ofz472.
22. Schafer JJ, Sassa KN, O'Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in Body Mass Index and Atherosclerotic Disease Risk Score After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide. *Open Forum Infect Dis.* Oct 2019;6(10):ofz414.
23. Studzinski K, Tomasik T, Krzyszton J, Jozwiak J, Windak A. Effect of using cardiovascular risk scoring in routine risk assessment in primary prevention of cardiovascular disease: an overview of systematic reviews. *BMC Cardiovasc Disord.* Jan 9 2019;19(1):11.
24. Friis-Moller N, Ryom L, Smith C, et al. An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. *Eur J Prev Cardiol.* Jan 2016;23(2):214-223.
25. Allan KS, Morrison LJ, Pinter A, Tu JV, Dorian P, Rescu I. Unexpected High Prevalence of Cardiovascular Disease Risk Factors and Psychiatric Disease Among Young People With Sudden Cardiac Arrest. *J Am Heart Assoc.* Jan 22 2019;8(2):e010330.