Health Economics and Epidemiology Research Office
HE²RO
Wits Health Consortium
University of the Witwatersrand

HE²RO Policy Brief

Number 20 · February 2018

This policy brief is drawn from: L Jamieson, D Evans, AT Brennan, F Moyo, D Spencer, K Mahomed, M Maskew, L Long, S Rosen, MP Fox. Changes in elevated cholesterol in the era of tenofovir in South Africa: risk factors, clinical management and outcomes. *HIV Medicine* 2017. The full article can be accessed at http://dx.doi.org/10.1111/hiv.12495

CHANGES IN ELEVATED CHOLESTEROL IN THE ERA OF TENOFOVIR: RISK FACTORS, CLINICAL MANAGEMENT, AND OUTCOMES

Background

ART has led to great improvements in survival for HIV patients (1-3), but emerging evidence of associations between ART and increased risk of cardiovascular disease is raising concern. Long-term ART use has been closely linked to CVD risk factors like hypertension and distortions of metabolic pathways (4-9).

The impact of ART on lipid profiles depends on the ARV regimen used (8-15). Tenofovir has been associated with more favourable lipid outcomes than NNRTIs and PIs (10). Complicating the role of ARVs is the fact that HIV itself can affect lipid profiles (16, 17). We investigated incident elevated total cholesterol (TC) in a large South African population on first-line ART, as a measure of potential CVD risk.

Methods

This analysis was conducted among ART-naïve adults initiating a standard first-line ART regimen between April 2010 and April 2014. The most common regimen in use at that time was TDF/3TC/EFV. The patient cohort attended the Themba Lethu Clinic, a large urban HIV clinic at Helen Joseph Hospital in Johannesburg, South Africa (18).

Our primary outcome was incident high TC, defined as having a TC>6 mmol/l >90 days after ART initiation, in those who had a baseline TC<6 mmol/l. Baseline TC was defined as a TC measurement taken up to 90 days prior to and 7 days after ART initiation. We assessed risk factors associated with incident high TC, attrition, and clinical management of high incident TC and subsequent repeat TC.

Results

Of the 10,690 patients who initiated treatment, 5,308 (49.7%) were ART naïve, initiated a standard first-line ART regimen, were at least 18 years old, and had a baseline TC measurement during the required window. At baseline 113 (2.1%) patients had a high TC and were excluded from the analysis. Of the 4,091 patients with follow-up data, 60.7% were female, the median age at ART initiation was 38 (IQR: 32-45) years and the median baseline CD4 count was 158 (IQR: 76-231) cells/mm^3 (Table 1). The median follow-up time from ART initiation to either last visit date or database closure was 4.0 years (IQR: 3.0-4.8)

Table 1: Baseline characteristics of cohort

Variable (n, %)	Overall (N=4091)	Non-tenofovir regimen (N=609)	Tenofovir regimen (N=3482)
ART regimen at initiation			
3TC/TDF/EFV	3296 (80.6%)	0 (0.0%)	3296 (94.7%)
3TC/d4T/EFV	469 (11.5%)	469 (77.0%)	0 (0.0%)
3TC/TDF/NVP	186 (4.6%)	0 (0.0%)	186 (5.3%)
3TC/AZT/EFV	91 (2.2%)	91 (14.9%)	0 (0.0%)
Other	49 (1.2%)	49 (8.0%)	0 (0.0%)
CD4 count (cells/mm^3) (median, IQR)	158 (76-231)	160 (78-233)	144 (59-222)
Body mass index (kg/m^2)			
<18	374 (10.3%)	78 (14.9%)	296 (9.6%)
18-24.9	2106 (58.2%)	307 (58.7%)	1799 (58.1%)
25-29.9	728 (20.1%)	85 (16.3%)	643 (20.8%)
≥30	710 (11.3%)	53 (10.1%)	357 (11.5%)
Missing	473	86	387
Baseline TC (median, IQR)	3.8 (3.2-4.3)	3.8 (3.2-4.4)	3.8 (3.2-4.3)
No. TC measurements in follow-up (median, IQR)	3 (2-5)	3 (2-5)	3 (2-5)

Incident high total cholesterol

There were 595 incident cases of TC >6 mmol/l after ART initiation over 13,783 pyrs, corresponding to an incidence rate of 4.32/100 pyrs (95% CI: 3.98-4.68). Of these, 496 (83.4%) had a repeat TC available at a median of 11.6 months (IQR: 6.9-12.9) after their initial high TC, 61.7% (N=306) of whom had a TC <6 mmol/l at the repeat TC.

Clinical and demographic predictors of high incident TC

Factors associated with increased risk of incident high TC are shown in Table 2. Risk factors for an elevated TC included older age, high BMI, and low CD4 count. Patients who initiated on a non-tenofovir-based regimen, compared to those on a tenofovir-based regimen, had a 50% increased risk of having incident high TC (95%CI: 14%-108%). This association occurred early on after ART initiation; by one year post-ART the probability of incident high TC was 4.8% and 8.8% for tenofovir- and non-tenofovir-based regimens.

Clinical management and outcomes among patients with elevated total cholesterol

Of the 595 patients with incident high TC, 10 (1.7%) died and 34 (5.7%) were lost to follow-up at a median of 13.8 and 17.0 months after their high TC, respectively. Among the 496 patients with an initial elevated TC and a repeat TC measurement thereafter, rates of mortality for those with repeat TC <6mmol/l and ≥6mmol/l

were 5.82/1000 pyrs (95%CI: 1.89-13.58) and 7.08/1000 pyrs (95%CI: 1.93-18.12), respectively. Loss to follow-up rates in those with a repeat TC<6mmol/l and ≥6mmol/l were similar at 1.16/100 pyrs (95%CI: 0.56-2.14) and 1.24/100 pyrs (95%CI: 0.50-2.55), respectively.

Table 2: Predictors of incident high total cholesterol

Variable		No. incident high cholesterol cases, n/N (%)	Adjusted hazard ratio* (95% CI)
Initiating NRTI	TDF	473/3482 (13.6%)	1.00
	non-TDF	122/609 (20.0%)	**1.54 (1.14-2.08)**
Initiating NNRTI	EFV	567/3866 (14.7%)	1.00
	non-EFV	28/225 (12.4%)	0.90 (0.55-1.48)
Age (years)	18-29	45/680 (6.6%)	1.00
	30-39	191/1715 (11.1%)	1.49 (0.95-2.35)
	≥40	359/1696 (21.2%)	**3.22 (2.07-4.99)**
Gender	Female	379/2482 (15.3%)	1.00
	Male	216/1609 (13.4%)	1.01 (0.79-1.29)
Body mass index (kg/m^2)	<18	37/374 (9.9%)	0.75 (0.46-1.21)
	18-24.9	276/2106 (13.1%)	1.00
	25-29.9	131/728 (18.0%)	**1.70 (1.30-2.23)**
	≥30	88/410 (21.5%)	**1.65 (1.18-2.31)**
CD4 count (cells/mm^3)	≥200	181/1400 (12.9%)	1.00
	100-199	188/1290 (14.6%)	1.13 (0.86-1.48)
	50-99	84/574 (14.6%)	**1.40 (1.00-1.97)**
	<50	124/696 (17.8%)	**1.55 (1.10-2.20)**

*Adjusted model included all listed variables.

A third (36.5%) of patients with elevated TC were prescribed cholesterol-lowering drugs following their initial high TC. The majority (59.3%) probably received counselling only. A small proportion of patients had an ART regimen switch only (2.7%) or received both cholesterol-lowering drugs and an ART switch (1.5%). Most patients ultimately received cholesterol-lowering drugs after repeated TC measurements (61.0%), while fewer had only an ART switch (4.7%) or a combination of an ART switch and cholesterol-lowering drugs (2.5%).

Policy Relevance

We found South African adults on ART have increased rates of elevated total cholesterol but tenofovir affects total cholesterol less than do other NRTIs. Older patients and patients with increased BMI are at an increased risk of high cholesterol and should therefore be monitored closely and perhaps be prioritized for cholesterol-lowering drugs, while at the same time receiving lifestyle and dietary counselling. A concerted effort needs to be made in monitoring those who have recurrent or persistently high TC. We have also highlighted the importance of regular, robust and systematic monitoring of patients on long-term ART, especially after the initial high TC has been diagnosed and treated to ensure patients reach and maintain lower TC levels. For patients with an initial high TC, more frequent cholesterol monitoring is required, in order to treat those who need it sooner. Current South African ART guidelines do not call for regular TC monitoring in adults, but the risk of untreated high TC suggests that they should. The opportunity to monitor non-communicable disease risks should not be missed.

References

1. Bor J, Herbst AJ, Newell ML, Barnighausen T. Increases in adult life expectancy in rural South Africa: valuing the scale-up of HIV treatment. Science. 2013;339(6122):961-5.
2. Broder S. The development of antiretroviral therapy and its impact on the HIV-1/AIDS pandemic. Antiviral Res. 2010;85(1):1-18.
3. UNAIDS. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2013 UNAIDS report on the global AIDS epidemic http://www.unaids.org/sites/default/files/media_asset/UNAIDS_Global_Report_2013_en_1.pdf. 2013.
4. Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio Monforte A, et al. Cardiovascular disease risk factors in HIV patients--association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17(8):1179-93.
5. Hejazi N, Huang MS, Lin KG, Choong LC. Hypertension among HIV-infected adults receiving highly active antiretroviral therapy (HAART) in Malaysia. Glob J Health Sci. 2014;6(2):58-71.
6. Muhammad S, Sani MU, Okeahialam BN. Cardiovascular disease risk factors among HIV-infected Nigerians receiving highly active antiretroviral therapy. Niger Med J. 2013;54(3):185-90.
7. Shaffer D, Hughes MD, Sawe F, Bao Y, Moses A, Hogg E, et al. Cardiovascular disease risk factors in HIV-infected women after initiation of lopinavir/ritonavir- and nevirapine-based antiretroviral therapy in Sub-Saharan Africa: A5208 (OCTANE). J Acquir Immune Defic Syndr. 2014;66(2):155-63.
8. Souza SJ, Luzia LA, Santos SS, Rondo PH. Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. Rev Assoc Med Bras. 2013;59(2):186-98.
9. Troll JG. Approach to dyslipidemia, lipodystrophy, and cardiovascular risk in patients with HIV infection. Curr Atheroscler Rep. 2011;13(1):51-6.
10. Feeney ER, Mallon PW. HIV and HAART-Associated Dyslipidemia. Open Cardiovasc Med J. 2011;5:49-63.
11. Melzi S, Carenzi L, Cossu MV, Passerini S, Capetti A, Rizzardini G. Lipid Metabolism and Cardiovascular Risk in HIV-1 Infection and HAART: Present and Future Problems. Cholesterol. 2010;2010:271504.
12. Fontas E, van Leth F, Sabin CA, Friis-Moller N, Rickenbach M, d'Arminio Monforte A, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? J Infect Dis. 2004;189(6):1056-74.
13. George JA, Venter WD, Van Deventer HE, Crowther NJ. A longitudinal study of the changes in body fat and metabolic parameters in a South African population of HIV-positive patients receiving an antiretroviral therapeutic regimen containing stavudine. AIDS Res Hum Retroviruses. 2009;25(8):771-81.
14. Langat A, Benki-Nugent S, Wamalwa D, Tapia K, Ngugi E, Diener L, et al. Lipid changes in Kenyan HIV-1-infected infants initiating highly active antiretroviral therapy by 1 year of age. Pediatr Infect Dis J. 2013;32(7):e298-304.
15. Liu E, Armstrong C, Spiegelman D, Chalamilla G, Njelekela M, Hawkins C, et al. First-line antiretroviral therapy and changes in lipid levels over 3 years among HIV-infected adults in Tanzania. Clin Infect Dis. 2013;56(12):1820-8.
16. El-Sadr WM, Mullin CM, Carr A, Gibert C, Rappoport C, Visnegarwala F, et al. Effects of HIV disease on lipid, glucose and insulin levels: results from a large antiretroviral-naive cohort. HIV Med. 2005;6(2):114-21.
17. Fourie CM, Van Rooyen JM, Kruger A, Schutte AE. Lipid abnormalities in a never-treated HIV-1 subtype C-infected African population. Lipids. 2010;45(1):73-80.
18. Fox MP, Maskew M, MacPhail AP, Long L, Brennan AT, Westreich D, et al. Cohort profile: the Themba Lethu Clinical Cohort, Johannesburg, South Africa. Int J Epidemiol. 2013;42(2):430-9.

Funding Statement: This work was funded by United States Agency for International Development (USAID) through co-operative agreements 674-A-12-00029 to HE^{2}RO and 674-A-12-0002 to Right to Care. The authors' views expressed in this publication do not necessarily reflect the views of the United States Agency for International Development or the United States Government.

Acronyms used in this brief:

3TC	Lamivudine	CVD	Cardiovascular disease	TC	Total cholesterol
ART	Antiretroviral therapy	EFV	Efavirenz	TDF	Tenofovir disoproxil fumarate
ARVs	Antiretroviral medications	pyrs	person-years	CI	confidence interval
NRTI	Nucleoside reverse transcriptase inhibitor	NNRTI	Non-nucleoside reverse transcriptase inhibitor		