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Changes in Lipid Profile and Body Mass Index in HIV/AIDS Patients on Antiretroviral and Anti-Tuberculosis Therapies in Cameroon.

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ABSTRACT

The purpose of this study was to determine the changes in the lipid profile, CD4+ T cells, and Body Mass Index (BMI) in HIV and tuberculosis (TB) coinfected patients on antiretroviral therapy (ART) and/or anti-tuberculosis therapy (ATT). Consenting participants were enrolled into one of the six study groups including controls. The lipid profile, BMI and CD4+ T cell count were determined using standard procedures. At completion, 480 participants aged between 15 and 77 years (mean±SEM = 39.84±0.84) and mostly females (318, 66.3%) were enrolled. Comparative analysis revealed significantly lower mean values of High Density Lipoprotein cholesterol (HDL-c) in all the groups compared to the controls; with varied changes in the Triglycerides (TG), Total Cholesterol (TC), Low Density Lipoprotein cholesterol (LDL-c) and BMI. Compared to HIV-naïve group, mean HDL-c and TC values were significantly higher in HIV-ART. Meanwhile significantly lower mean HDL-c values were observed in the TB, HIV/TB-ATT, and HIV/TB-ART+ATT groups. The CD4+ T cell counts in the HIV/TB-ATT and HIV/TB-ART+ATT groups were significantly lower compared to the HIV-naïve group. Tuberculosis was observed to enhance the development of dyslipidaemia in HIV. ART in this study was observed to be associated with elevated levels of HDL-c which could be beneficial.

Keywords: HIV/AIDS; Tuberculosis; anti-tuberculosis therapy; antiretroviral therapy; lipid profile; Body Mass Index.

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INTRODUCTION

HIV/AIDS and tuberculosis (TB) are diseases of immense public health importance, which affects mostly people living in the poor and less developed parts of the world. Globally, approximately 46% of people living with HIV/AIDS (PLWHA) have concomitant infection with Mycobacterium tuberculosis, which causes tuberculosis [1]. Sub-Saharan Africa is the region most affected mirrored by the high HIV prevalence in the area [2, 3]. In 2009, it was estimated that approximately 1 of 3 TB-related deaths (29%) worldwide was related to HIV infection, meanwhile TB contributed to 26% of the estimated deaths due to HIV infection [4].

The advent of Highly Active Antiretroviral Therapy (HAART) has seen a general improvement in the life of PLWHA [5-8]. With the longevity of PLWHA, several other clinical conditions have developed, most of which are related to metabolic abnormalities including insulin resistance and disturbances in glucose homeostasis; adverse lipid profile changes (dyslipidaemia); altered body fat distribution, with lipoatrophy (loss of subcutaneous fat mostly in the face and periphery) and/or lipohypertrophy (localized fat gain most often central and visceral adiposity) [9,10]. Dyslipidaemia is a well-known complication of HIV and its development has been associated with certain components of antiretrovirals (ARV) – protease inhibitors (PI) and stavudine increase blood levels of total cholesterol (TC), Low density lipoprotein cholesterol (LDL-c) and triglycerides (TG) with variable effects on High density lipoprotein cholesterol (HDL-c) [11,12]. The risk of stavudine associated lipodystrophy has been shown to be higher in individuals with low body mass index (BMI) [13].

No association between anti-tuberculosis drugs and dyslipidaemia has been documented before. On the contrary, a study carried out on HIV/TB coinfected patients in India demonstrated a slight improvement of lipid profile (increased TC, HDL-c and LDL-c levels) after 6 to 12 months of simultaneous ART and Anti tuberculosis therapy (ATT) [14]. Information on the changes in lipid profile in HIV/AID patients co-infected with tuberculosis simultaneous o n ART and ATT in Sub-Saharan Africa is not readily available. Such information is completely absent in Cameroon. This study was therefore designed to determine the changes in lipid profiles in HIV/AIDS patients co- infected with tuberculosis on ART and ATT in order to generate data that may be useful in the management of PLWHA coinfected with tuberculosis.

MATERIALS AND METHODS

Study area

Participants were recruited from the HIV and tuberculosis treatment centers of the Regional Hospitals in Buea (Coordinates: 4°10'N 9°14'E) and Limbe (Coordinates: 4°01'N 9°13'E). These are the reference treatment centers in the South West region receiving patients from all over the South West region especially the Fako Division of the region.

Study design and duration

This was a comparative cross sectional study in which participants were enrolled between May and September 2013.

Study population

PLWHA of both sexes who attended the HIV and/or tuberculosis treatment centers were approached to take part in the study. To be included in the study, the participant was to be over 15years of age. Participants were required to give their signed informed consent which was duly explained to them in English, French or the local Pidgin English languages. In the case of children or minor who could not read or write, written informed consent was obtained from their parents or guardians or next of kin. Participants who consented were enrolled into one of the following 6 categories based on their clinical records as to whether they were on treatment or not;

- HIV negative apparently normal individuals: controls
- Newly diagnosed HIV infected individuals who were not ART: HIV-naïve
- HIV/AIDS patients already on ART: HIV-ART
- Tuberculosis patients on anti-tuberculosis therapy (ATT): TB

- HIV/TB coinfected patients on anti-tuberculosis therapy (ATT): HIV/TB-ATT
- HIV/TB coinfected patients who were simultaneously on ART and ATT: HIV/TB-ART+ATT

Excluded from the study were patients who were below 15years, hypertensive, diabetics, on lipid lowering drugs, or chronic smokers.

The study protocol was approved by the Faculty of Health Sciences Institutional Review Board of the University of Buea, Cameroon.

Sample collection

About 4ml of whole blood was collected from study participants following a 12 hour overnight fast into dry and EDTA anticoagulated test tubes each. The dry tubes were centrifuged at 4000rpm for five minutes to obtain serum. The serum samples were stored at -20°C until the time of analysis.

Laboratory investigations

Triglycerides (TRIG), High Density Lipoprotein Cholesterol (HDL-c) and Total Cholesterol (TC) were measured by Standard Spectrophotometry using CHRONOLAB® reagent kits according to the manufacturer's instructions after proper calibration and verification of the Spectrophotometer. Low Density Lipoprotein Cholesterol (LDL-c) values were calculated using the Friedelwald formula [LDL-c = TC – (TRIG/5) – HDL-c]. The values obtained were compared with the reference ranges laid down by the National Cholesterol Education Program (NCEP) [15].

Body Mass Index (BMI)

BMI was determined using the BMI formula [BMI = WEIGHT (KG)/HEIGHT^2 (M)]. The BMI were classified as underweight (BMI<18.5), Normal range (18.5<BMI<24.99), overweight (BMI≥25) and obese (BMI≥30) [16].

Measurement of CD4+ T cell count

Blood collected into the EDTA test tubes was used for the determination of the CD4+ T cell count by flow cytometry using BD FASCount™.

Statistical analysis

Statistical analysis were performed using the Statistical Package for the Social Sciences (SPSS) for windows version 17.0. Differences between group means were compared using analysis of variance (ANOVA) and the independent sample student's t-test where appropriate. Pearson correlation was also carried out to test for correlation between the different test parameters and CD4+ T cell counts. Statistical significance was set at $P < 0.05$.

RESULTS

At the end of the study, 480 participants were enrolled. Among the participants were 88 (18.33%) HIV-negative (controls), 120 (25%) HIV-naïve patients, 98 (20.42%) HIV patients on ART, 72 (15%) TB patients on ATT, 40(8.33%) HIV/TB coinfected patients on ATT, and 62(12.92%) HIV/TB coinfected patients on ART and ATT. Three hundred and eighteen subjects (66.3%) were females while 162 (33.8%) were males. Overall, the mean age (± SEM) of the participants was 39.84 ± 0.84, ranging from 15 to 77 years.

The ART comprised of combinations of lamivudine (L), stavudine (S), efavirenz (E), nevirapine (N), tenofovir (T), and zidovudine (Z). The mean (±SD) treatment time were 27.69±17.77 months for participants on ART and 22.45±26.77 months for participants that were simultaneously on ART and ATT (Table 1).

The ATT comprised of RHEZ (combination of Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide), Streptomycin (STR), and RH (combination of Rifampicin and Isoniazid). The mean (±SD) treatment time were

1.94±1.48 month, 3.85±0.65 months, 3.45±0.44 months for the TB, HIV/TB-ATT, and HIV/TB-ART+ATT groups respectively (Table 2).

Comparison of the CD4+ T cell counts to the HIV-naïve group revealed significantly lower mean values of CD4+ T cell counts in the HIV/TB coinfected group on ATT (P=0.001) and the HIV/TB coinfected group on both ART and ATT (P=0.001), with no significant difference in the HIV-ART group (Table 3).

When compared to the control group, significantly lower mean values of TC (P=0.026), HDL (P=0.034), LDL (P=0.005) and BMI (P=0.003) were observed in the HIV-naïve group; lower mean values of TC (P=0.022), HDL (P=0.001) and BMI (P=0.001) in the TB group; lower mean values of TC (P=0.003), HDL (P=0.001) and BMI (P=0.001) in the HIV-ART group; lower mean values of TC (P=0.001), HDL (P=0.001), LDL (P=0.044) and BMI (P=0.001) in the HIV/TB-ATT group; and lower mean values of HDL (P=0.001) and BMI (P=0.001) in the HIV/TB-ART+ATT group were observed (Table 4).

When compared to the HIV-naïve group, significantly lower mean values of BMI (P=0.001) were observed in the HIV/TB-ATT group; lower mean values of TG (P=0.02) and BMI (P=0.001) in the HIV/TB-ART+ATT group meanwhile significantly higher mean values of HDL (P=0.001) were observed in the HIV-ART group and higher mean values of TC (P=0.001) and LDL (P=0.036) in the HIV/TB-ART+ATT group (Table 4).

When the HIV/TB coinfected groups were compared to the HIV-ART group, significantly lower mean values of HDL (P=0.01) and BMI (P=0.001) were observed in the HIV/TB-ART+ATT group (Table 4).

Comparison of the lipid profile and BMI to the TB group revealed significantly lower mean values of TC (P=0.039), HDL (P=0.003) and BMI (P=0.014) in the HIV/TB-ATT group with no significant difference in all the parameters in the HIV/TB-ART+ATT group (Table 4).

Comparison of the lipid profile and BMI in the HIV-ART group (stratified according to the different combined ART regimens) to the controls revealed significantly lower mean value of TC in all the groups; lower mean values of HDL in the L+S+N (P=0.0001), L+Z+E (P=0.0001) and L+Z+N (P=0.0001) groups; lower mean values of LDL in the L+T+E (0.042) group, and lower mean values of BMI in the L+S+E (P=0.007), L+S+N (P=0.03), L+Z+E (P=0.0001) and L+Z+N (P=0.0001) groups (Table 5).

Comparison of the lipid profile and BMI in the TB group (stratified according to the different ATT regimens) to the controls revealed significantly lower mean values of TC in the RHEZ (P=0.004) and RHEZ+STR (P=0.029); lower mean values of HDL in the RH (P=0.046) and the RHEZ (P=0.0001) groups; lower mean values of LDL in the RHEZ (P=0.045) and RHEZ+STR (P=0.029) groups; and lower mean values of BMI in all the groups (Table 5).

Table 1: Distribution of HIV infected participants on ART with respect to the different ARV combinations

ARV combinations	HIV-ARV n(%)	HIV/TB-ARV+ATT n(%)
L+Z+N	52(53.06)	4(6.45)
L+S+N	12(12.24)	2(3.23)
L+Z+E	28(28.57)	8(12.9)
L+S+E	4(4.08)	22(35.48)
L+T+E	2(2.04)	0(0)
Others*	00(0)	26(41.94)
Total	98	62
L=lamivudine, S=stavudine, E=efavirenz, N=nevirapine, T=tenofovir, Z=zidovudine		

Table 2: The distribution of the TB patients with respect to the different ATT combinations

Anti-tuberculosis (ATT) regimens	TB only n(%)	HIV/TB-ATT n(%)	HIV/TB-ARV+ATT n(%)
RHEZ	60(83.33)	24(60)	34(54.84)
RHEZ + STR	2(2.78)	8(20)	8(12.9)
RH	10(13.89)	8(20)	20(32.26)
Total	72	40	62
RHEZ: Rifampicin+Isoniazid+Ethambutol+Pyrazinamide, STR: Streptomycin, RH: Rifampicin+Isoniazid			

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Table 3: CD4+ counts comparison in various HIV positive participants on treatments compared to naïve

Groups concerned	CD4+ Tcell counts (mean±SD)	Level of significance
HIV-naïve	382.70±26.77	1.00
HIV-ART	376.49±23.85	P=0.866
HIV/TB-ATT	115.35±26.12	P=0.001
HIV/TB-ART+ATT	136.06±32.02	P=0.001

Table 4: comparison of the mean Lipid profiles and BMI among the different groups of study participants

Groups Concerned	Mean±SEM of compared parameters P values				
	TRIG	TC	HDL	LDL	BMI
Controls	99.77±13.62	183.82±8.63	72.86±3.48	91.00±8.22	29.29±0.91
HIV-naïve	93.78±7.09	129.89±5.92	42.45±2.13	68.69±5.2	23.75±0.49
TB Only	103.64±1.56	154.48±8.97	54.86±2.59	75.52±6.26	21.71±0.43
HIV-ART	95.47±9.72	149.33±7.25	54.72±2.98	75.52±6.26	24.63±0.61
HIV/TB-ATT	110.89±8.11	125.00±9.34	40.94±3.59	62.54±9.73	19.72±0.70
HIV/TB-ART+ATT	129.61±15.93	165.73±8.63	49.17±3.84	88.18±7.86	20.82±0.52

Table 5: Comparison of the lipid profile and BMI in the different groups (stratified according to the different ART and ATT regimens) with the controls and the ARV-naïve groups

Groups concerned		Mean±SD of compared parameters P- values				
		TRIG	TC	HDL	LDL	BMI
Controls		99.78±89.82	183.82±56.9	72.86±22.93	91±54.19	29.29±6.01
ARV-naïve		93.78±7.09	129.89±5.92	42.45±2.13	68.69±5.2	23.75±0.49
HIV-ART	L+S+E	49.35±7.1	119.4±13.51	62±16.97	47.53±29.06	21.65±0.17
	L+S+N	96.72±37.27	129.45±15.29	44.42±17.71	65.69±13.41	25.78±6.02
	L+T+E	77.9±0	86±0	75.2±0	-4.78±0	24.2±0
	L+Z+E	73.72±40.79	138.54±57.15	53±15.48	70.79±51.49	23.72±3.06
	L+Z+N	111.11±82.7	164.46±49.43	56.67±23.62	85.57±40.81	25.12±4.45
TB-only	RH	81.46±38.36	177.9±56.91	60.46±4.47	99.15±49.11	24±2.73
	RHEZ	104.38±43.21	152.19±52.6	54.07±16.67	76.56±44.89	21.2±2.36
	RHEZ+STR	192.19±0	106.06±0	50.42±0	17.2±0	22.09±0
HIV/TB-ATT	RH	102.46±49.48	139.38±25.12	31.13±8.64	83.76±36.1	19.42±1.84
	RHEZ	107.97±35.01	125.47±49.16	43.15±17.38	63.22±48.69	19.75±3.83
	RHEZ+STR	128.09±14.63	109.22±19.32	44.1±14.01	39.26±6.7	19.95±1.47

Comparison of the lipid profile and BMI in the HIV/TB-ATT group (stratified according to the different ATT regimens) with the controls revealed significantly lower mean values of TC, HDL and BMI in all the groups; and lower mean values of LDL in the RHEZ (P=0.013), and RHEZ+STR (P=0.004) groups (Table 5).

Comparison of the lipid profile and BMI in the HIV-ART stratified according to the different ART regimens with the HIV-naive group revealed significantly higher mean values of TC for the L+Z+N (P=0.0001) group; higher mean values of HDL for the L+S+E (P=0.010), L+T+E (P=0.001) and the L+Z+N (0.0001) groups; higher mean values of LDL for the L+Z+N (P=0.006) group; and higher mean values of BMI for the L+Z+N (P=0.021) group (Table 5).

Correlation

Bivariate Pearson correlation analyses were performed between CD4+ T cell counts and the various lipid profile parameters as well as BMI. These analyses were performed in a subgroup composed of a combination of all HIV positive groups on treatment (HIV-ARV, HIV/TB-ATT and HIV/TB-ART+ATT). The HIV-naïve group was excluded from these collective analyses since they were not on any of the drug regimens (ATT and ART) considered in this study. A significant positive correlation was observed only between CD4+ T cell count and BMI (r=0.363, P=0.001) (Fig. 1).

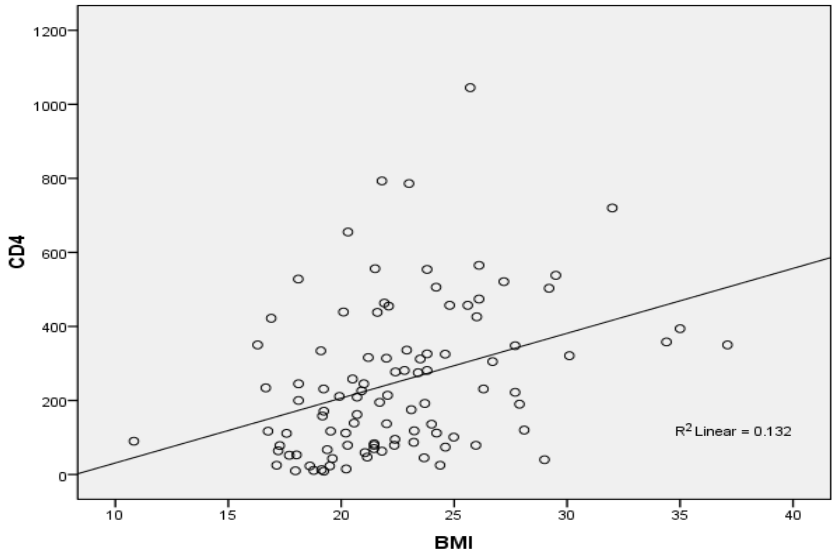

Figure 1: Scatter plot for correlation between CD_4^+ T cell count and BMI in HIV-infected participants on treatment.

DISCUSSION

In this study, mean BMI values were observed to be lower in all the study groups compared to the controls. HDL-c and TC values were also observed to be lower in all the groups except in HIV/TB coinfected patients on ART and ATT. There was no significant differences in TRIG in all the groups compared to the controls. HDL-c plays a very important role in the body by transporting cholesterol from cells to the liver for excretion or re-utilization thereby preventing the accumulation of excess cholesterol; individuals with lower levels of HDL-c are more at risk of cardiovascular diseases than individuals with higher levels [17]. The mechanism underlying the decrease of HDL-c in HIV is not clear but studies have shown that this change could be as a result of the replicating virus that needs cholesterol for the assembly of the viral envelop [18,19,20].
The finding of lower mean values of HDL-c, TC, LDL-c and BMI observed among HIV-naïve patients are in accordance with a study performed in India [21]. Among TB patients, lower mean values of TC and HDL-c with no significant change in the other parameters were observed compared to the controls, which is different from the study by Ghorbanihajo et al. [22] in which no significant difference was observed in any of the lipid profile parameters. The discrepancy in their results and ours could be attributed to the fact that the participants in their study were not on any treatment meanwhile ours were on ATT. The observation of lower mean values of TC, HDL-c and BMI, with no significant difference in the TRIG and LDL-c in HIV patients on ART compared to the controls is not in accordance with similar studies performed among European HIV patients where significantly

higher values of mean LDL-c, TC, and TRIG with varied HDL-c have been observed [11,12], but similar to a study performed in Nigeria [23]. This could be explained by the difference in the genetic makeup and feeding habits of the patients in the Caucasian studies compared to ours and the study in Nigeria. It also could be as a result of the fat redistribution observed in HIV/AIDS patients which is usually greater in the presence of ART [24]. The observation of lower mean values of TC, LDL-c and BMI, with extremely low values of HDL-c (highly atherogenic) and slightly raised values of TRIG are very similar to those reported in a study in India [14]. Furthermore, the lower mean values of HDL-c and BMI observed among TB and HIV patients on ART, with no significant differences in the other parameters suggest that TB alone has no significant effect on the lipid profile, which is in line with the study by Ghorbanihaghjo et al. [22]. This could reflect the severity of the compromised nutrition associated with these comorbidities. Relative to the HIV-naïve group, higher mean values of TRIG, TC, LDL-c and BMI with no significant difference in HDL-c were observed in HIV/TB coinfected patients on ART and ATT. This demonstrates an improvement on the lipid profile of coinfected patients as they start ART which confirms the study performed in India by Chandrasekaran et al [14].

In this study significantly lower mean values of HDL-c were generally observed in participants on combined ART except those that were on the combination of lamivudine, stavudine and efavirenz when compared to the controls. Both the nucleoside reverse transcriptase inhibitors (including lamivudine and stavudine) [25] and non-nucleoside reverse transcriptase inhibitors (including efavirenz and nevirapine) [26] have been observed to lead to changes in the lipid profile components, but the most prominent change associated with the non-nucleoside reverse transcriptase inhibitors is the increase in HDL-c [26] which may explain the increase of HDL-c in the efavirenz containing ART. Like the combined ART, significantly low HDL-c levels were also observed for all the ATT. In HIV/TB coinfected patients on ART and ATT, the effect was also lower HDL-c levels in almost all the groups, which confirms our previous hypothesis that ATT may also have a lowering effect on HDL-c. Our findings could be affected by the insufficient number of patients in the different groups which renders it inconclusive. However the effect of the non-nucleoside reverse transcriptase inhibitors on the lipid profile components, with raised values of mean TC, LDL-c and HDL-c have previously been documented [27].

In this study, relative to the HIV-naïve group, significantly lower values of mean CD4+ T cell counts were observed in all the groups of HIV/TB coinfected patients with the exception of HIV patients on ART. This is an indication that the presence of tuberculosis hasten the depletion of the CD4+ T cells as the immunocompromised system attempts to fight out the *Mycobacterium* and HIV at the same time [28].

In this study, a significant positive correlation was observed between CD4+ T cell counts and BMI ($r = 0.363$, $P = 0.001$) but no significant correlation was observed between the CD4+ T cell counts and TC, LDL-c, TRIG and HDL-c. These findings differ considerably from those of a similar study by Aricio *et al.* [29] in which a significant positive correlation was observed between CD4+ T cell counts and TC as well as between CD4+ T cell counts and HDL-c, meanwhile a significant negative correlation was observed between CD4+ T cell counts and TRIG. This discrepancy could be accounted for by the difference in genetic makeup and nutritional status between the Caucasian and African populations. However, a positive correlation between CD4+ T cell counts and BMI indicates a positive proportionality link between CD_4^+ and BMI implying that an increase in CD4+ T cell counts coupled to other factors could lead to a rise in BMI. This result should however be interpreted with caution taking in to consideration the fact that BMI is an anthropometric measurement and a positive correlation does not always imply that there is a cause-effect relationship between the parameters considered. It is also important to note that all the above comparisons were also performed by gender and no significant difference was observed in any of the cases as opposed to other long term gender based studies [30].

These findings have an important implication in the management of HIV and TB patients and necessitates routine monitoring of the lipid profile, and BMI in these patients. However the long term effect of the ART and ATT on the lipid profile of these patients could not be shown due to the cross sectional nature of the study. This serves as a major limitation to this study. However the long term effect of ART on the different lipid profile components have been well documented in the studies by Mankhatitham et al. [27] and Buchacz et al. [31].

CONCLUSION

Tuberculosis enhances the development of dyslipidaemia in HIV/AIDS patients in the absence of ART. Furthermore, the presence of ART leads to varied changes in the various lipid profile parameters including the elevation of HDL-cholesterol irrespective of the combined ART regimen, which could be beneficial. The presence of tuberculosis also worsens the immunosuppressed state of coinfected patients as demonstrated by the significant decline in the CD4+ T cell count compared to HIV-naïve patients.

We therefore recommend routine monitoring of the lipid profiles and BMI in HIV and HIV/TB coinfected patients which could be beneficial for a better prognosis.

Author's Contribution

ATT and TEK conceived of the study. ATT, FAN, MEC, and JFM participated in data collection. ATT, TEK, MEC, and LEB performed the analyses and interpretation. ATT, TEK, FAN, MEC, and JFM conducted the literature search and review, and wrote the first draft. ATT, TEK and LEB critically revised the manuscript. All authors read and approved of the final manuscript.

List Of Abbreviations

PLWHA: People living with HIV/AIDS
TB: Tuberculosis
TC: Total cholesterol
LDL-c: Low density lipoprotein cholesterol
TG: Triglycerides
HDL-c: High density lipoprotein cholesterol
BMI: Body Mass Index
ATT: Anti-tuberculosis therapy
ART: Antiretroviral therapy
ARV: Antiretrovirals

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