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Protease inhibitors are not associated with increased risk of dyslipidemia in HIV-1 infected patients initially treated with non-nucleoside reverse transcriptase inhibitors: a cross-sectional study

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Protease inhibitors are not associated with increased risk of dyslipidemia in HIV-1 infected patients initially treated with non-nucleoside reverse transcriptase inhibitors: a cross-sectional study

Short title: **Protease inhibitors and dyslipidaemia**

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Abstract

Objectives: Lipid abnormalities associated with antiretroviral therapy in people with HIV infection are more frequent with protease inhibitors (PI) based regimens. Whether effects extend to patients receiving a PI subsequent to failure on non-nucleoside reverse-transcriptase inhibitors (NNRTI) based regimen, is still unknown. We investigated the effects of secondary treatment with a PI on the lipid profile in a group of patients with HIV infection in Cameroon.

Design: This was a cross-sectional study.

Setting: This study was carried out at the registered centre for HIV treatment of the Yaounde Jamot hospital in Cameroon.

Participants: Participants were consecutively recruited between November 2009 and January 2010. There were 138 HIV-1 patients on initial treatment with a NNRTI regimen and 66 HIV-patients on secondary treatment with a PI for at least 12 months. Lipid abnormalities were based on the National Cholesterol Education Program, Adult Treatment Panel III criteria.

Outcome measures: Levels of lipid parameters among patients on PI and NNRTI.

Results: Median (interquartile range) levels (mg/dl), NNRTI-treated vs. PI-treated patients were 185 (149-225) and 189 (147-244) for total cholesterol, 46 (27-66) and 42 (28-82) for HDL-cholesterol, 121 (90-169) and 126.9 (71-176) for LDL-cholesterol, 134 (98-174) and 138 (111-167) for triglycerides, and 4.3 (2.9-6.2) and 5.1 (2.6-7.9) for total/HDL-cholesterol ratio (all $p>0.32$). The most frequent lipid abnormality in the two groups was high LDL-cholesterol [46.4% (NNRTI) vs. 54.5% (PI)]. Occurrence of lipid abnormalities was similar in the two groups (all $p>0.29$).

Conclusions: The use of PI does not appear to deteriorate the lipid profile of HIV patients above and beyond abnormalities induced by an unsuccessful initial treatment with NNRTI. Monitoring of lipid profile during HIV treatment regardless of the regimens would improve timely detection and management of abnormalities, to mitigate related risks.

Word count – 287

Key words – HIV infection, antiretroviral therapy, protease inhibitors, non-nucleoside reverse-transcriptase inhibitors, lipid profile

Article summary

Article focus:

- To investigate the effects of secondary treatment with a protease inhibitors on the lipid profile in a group of patients with HIV infection in Cameroon**.**

Key messages:

- The differential contribution of antiretroviral agents to lipid abnormalities suggests that hypothetically, switching patients from first-line to second-line treatment may have deleterious effects on their lipid profile.

- Effects of protease inhibitors on lipid profile among patients receiving the protease inhibitors subsequent to failure on non-nucleoside reverse-transcriptase inhibitors based regimen are still unknown.

- In this study, the use of protease inhibitors does not appear to deteriorate the lipid profile of HIV patients above and beyond abnormalities induced by an unsuccessful initial treatment with non-nucleoside reverse-transcriptase inhibitors.

Strengths and limitations:

- To our knowledge, such hypothesis has not yet been tested.

- This is a cross-sectional study which lacked of previous level of lipid parameters of participants.

INTRODUCTION

Antiretroviral treatments are associated with widely described abnormal changes in the lipid profile in people with HIV infection.[1,2] Although more frequent during treatment with protease inhibitors (PI),[1,3,4] these changes are also observed during treatment with stavudine and to a lesser extent with non-nucleoside reverse-transcriptase inhibitors (NNRTI).[1,5] Such changes include raised total and LDL cholesterol, raised triglycerides and variable effects on HDL cholesterol levels.[1,4]

The increasing rollout of antiretroviral treatment over the last ten years has significantly improved survival among people living with HIV.[6] This however has been achieved at the cost of increasing resistance to first-line antiretroviral therapies.[7,8] In sub-Saharan Africa (SSA), the epicentre of HIV pandemic, the widely used first-line antiretroviral regimen, inspired by the World Health Organisation (WHO), combines two nucleoside reverse-transcriptase inhibitors (NRTI) with a non-nucleoside reverse-transcriptase inhibitor (NNRTI).[9] Protease inhibitors (PI) are the compulsory component of the second line treatment subsequent to the failure of the first-line one in this setting.[9,10] The differential contribution of antiretroviral agents to lipid abnormalities suggests that hypothetically, switching patients from first-line to second-line treatment in SSA may have deleterious effects on their lipid profile. However, such hypothesis has not yet been tested.

We compared the lipid profile of HIV-1 patients receiving the WHO recommended 1st-line therapy with that of patients on 2nd-line therapy subsequent to first-line treatment failure.

PARTICIPANTS AND METHODS

Study setting and Participants

This cross-sectional study was conducted at the registered centre for HIV treatment of the Yaounde Jamot hospital in Cameroon. The study setting has been described in details elsewhere.[11] Participants were consecutively recruited between November 2009 and

January 2010. Two groups of HIV-1 positive participants were selected. The first group included individuals who had received antiretroviral treatment for the 12 preceding months or more, based on the WHO first-line regimens or NNRTI-based regimen (NNRTI-based group). The second group included individuals who were receiving second-line antiretroviral treatment or PI based regimen for at least 12 months after failure of the first-line regimen (PI-based group). First-line ART regimens applied to these participants combined lamivudine (3TC) and stavudine (d4T) or zidovudine (AZT) with nevirapine (NVP) or efavirenz (EFV). The PI-based regimens included abacavir (ABC), didanosine (DDI) and lopinavir/ritonavir (LPV-r) or indinavir (IDV). The choice of regimens is unrelated to potential factors that could induce a dyslipidemia, since lipid profile assessment is a requirement in routine pre-ART treatment evaluation in this setting.[12] Failure on 1st line antiretroviral therapy in the study setting is based on persisting plasmatic HIV-1 viral load of 5000 copies/ml or greater, after a year on antiretroviral treatment. Diagnosis of therapeutic failure to the first-line ART is always confirmed after a reinforcement of the adherence for a period of 3 months.[9] Patients who had had their treatment regimens changed during follow-up were excluded. Participants had to be at least 18 years of age and to have a treatment adherence rate $\geq$95%. Level of adherence was assessed by verbal administration of a standard series of questions adapted from Adult AIDS clinical trials group (AACTG) adherence instruments. The 95% rate of adherence is preferable to 4-day recall data.[13] Participants were also required not to be on lipid modifying therapies at their enrolment. All participants gave their inform consent and the study was approved by the Cameroon National Ethic Committee (ref N^{o}150/CNE/SE/09).

Procedures

For each participant, data were collected on the sociodemographic background, past medical history including the use of medications that could modify the lipid profile and active or history of tuberculosis. Lymphocytes count for all participants used flux cytometry methods

implemented with BD FASCOUNT automate (BD Biosciences, Le pont de Claix, France). Lipid profile was assessed through enzymatic methods (Linear chemicals, Montgat, Spain) and included total cholesterol (TC), HDL-cholesterol (HDL-c), LDL-cholesterol (LDL-c) and triglycerides (TG). To this end, blood sample was collected after an overnight fast (12 hours) and centrifuged at 3000 cycles/minute, and the serum obtained was then used for lipids determination. The TC/HDL-c ratio was also calculated. Abnormal lipid profile was defined in accordance with the US National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) guidelines, as TC ≥ 200mg/dl, HDL-c < 40mg/dl, LDL-c ≥130mg/dl, TG ≥150mg/dl and TC/HDL-c ratio ≥5.[14]

Statistical analysis

Sample size was determined assuming a 35% prevalence of total cholesterol ≥200 mg/dl in the NNTI based group, a minimum detectable unadjusted odds ratio (OR) of 2, a Type I error of 5% and a power of 80%.[15] Based on the above, the required sample size was 84 participants (42 NNTI treated patients and 42 IP treated patients). Data analysis used the Statistical package for social sciences (SPSS) version 17 for Windows (SPSS, Chicago, IL). Differences in means and proportions for participants' characteristics were assessed using Student t-test, Mann –Whitney U test and χ^2 tests. A probability threshold of $p < 0.05$ was used to characterise statistical significant results.

RESULTS

Study population

The total number of participants included in each study group was 138 (NNRTI-based regimen) and 66 (PI-based regimen). NNRTI-based regimens were d4T/3TC/NVP (61 patients), d4T/3TC/EFV (32 patients), AZT/3TC/NVP (31 patients) and AZT/3TC/EFV (14 patients); while PI-based regimens were DDI/ABC/INV (35 patients) and DDI/ABC/LPV-r (31 patients). The characteristic of participants are summarised in Table 1. The median

duration on ART was higher among participants in the PI-regimen group than among those on NNRTI-regimens (36 vs. 28 months, p=0.001). This included a 22-month period on NNRTI-regimens and 14-month duration on PI-based regimens. Sex distribution, mean age, body mass index and median CD4 count were similar between the two study groups (Table 1).

Table 1: Profile of 138 patients on NNRTI-based regimens and 66 patients on protease inhibitors based regimens

Characteristics	NNRTI-based regimen (n=138)	PI-based regimen (n=66)	p
Women, n (%)	90 (65.2)	39 (59.1)	0.396
Mean age, years (SD)	40.6 (8.7)	42.5 (8.7)	0.154
Mean body mass index, kg/m² (SD)	24.6 (4.7)	23.8 (3.9)	0.208
Median CD4 count, per mm³ (IQR)	333(206-459)	330 (172-451)	0.747
Median duration on ART, months (IQR)	28 (13-40)	36 (24-50)	0.001
Median duration on NNRTI-based ART, months (IQR)	28 (13-40)	22 (10-36)	0.001
Median duration on PI-based ART, months (IQR)	NA	14 (12-20)	NA

NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; ART, antiretroviral therapy; SD, standard deviation; IQR, interquartile range; NA, not applicable

Lipid profile

Median levels of TC, HDL-c, LDL-c, triglycerides and lipid ratio were similar between participants on PI-based regimens and those on NNRTI-based regimens (Table 2). The prevalence of lipid abnormalities (NNRTI-based vs. PI-based regimens) was 38% vs. 44% for TC≥ 200 mg/dl (p=0.39), 46% vs. 56% for LDL-c≥ 130 mg/dl (p=0.30), 40% vs. 46% for HDL-c< 40 mg/dl (p=0.54), 44 vs. 36% for triglycerides≥ 150 mg/dl (p=0.33) and 36% vs. 29% for TC/HDL-c≥ 5 (p=0.34). The pattern was similar in men and women, participants above and below median age, and after adjustment for age, sex, and total duration on ART in linear and logistic regression analyses.

Table 2: Median levels of different lipid parameters in patients on NNRTI-based and PI-based regimens in Yaounde, Cameroon

Lipid variable	NNRTI-based regimen (n=138)	PI-based regimen (n=66)	p
Total cholesterol, mg/dl	184.7 (149.3-225.0)	189.5 (146.7-243.8)	0.688
HDL cholesterol, mg/dl	45.84(27.0-66.0)	42.16(27.6-82.3)	0.568
LDL cholesterol, mg/dl	121.4(89.7-168.7)	126.9(70.8-176.5)	0.767
Triglycerides, mg/dl	134.5 (98.3-174.0)	138.0 (111.1-166.6)	0.468
Total/HDL-cholesterol ratio	4.3 (2.9-6.2)	5.1 (2.6-7.9)	0.329

Data are median (interquartile range); NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor

DISCUSSION

There is an abundant literature on the improvement of lipid profile of people with HIV subsequent substitution of NNRTI or NRTI for PI in the treatment regimens.[16] We are not aware of a study that has examined the effects of PI on lipid profile of patients initially treated with NNRTI. The current study was conducted in a setting where virtually all treated HIV-1 patients are almost always started on a NNRTI-based regimen as first-line therapy, and shifted to PI-based regimens only after failure of the first-line therapy. Our findings suggest that this transition to PI-based regimens may not be associated with significant deterioration of the lipid profile.[1,5] Indeed, median serum lipid levels and prevalence of lipid abnormalities were similar in patients on initial treatment with a NNRTI-regimen and those on secondary treatment with a PI-regimen. These findings were consistent by gender, age and CD4 count, and robust to adjustment for several covariates.

In sub-Saharan and other developing countries, NNRTI-based regimens not containing a PI are associated with pro-atherogenic adverse lipid changes.[15,17-19] However, the World

Health Organisation's recommendations,[9,10] enforced at the country level in Cameroon[12] and elsewhere, suggest that only those HIV patients on a PI should be screened for dyslipidemia. These recommendations are applied against a background of scarcity of comparative studies on lipid profile of patients and NNRTI with that of those on a PI. By demonstrating findings suggesting that continuation treatment with a PI may not necessarily induce lipid derangements above and beyond those induced by prior NNRTI, our study emphasizes the need to extend screening for dyslipidemia in this setting to any patient on antiretroviral therapy regardless of the regimens. Such an approach may help early detection of lipid abnormalities and mitigation of related risks.

High LDL-cholesterol was the most common lipid abnormality found in our study. High LDL-cholesterol is a major lipid abnormality, and a treatment target for cardiovascular prevention.[20] That lipid abnormalities in the general population in Cameroon and other countries in the region are generally rare, suggests that lipid abnormalities in our patients were induced by antiretroviral therapy. It is also possible that high LDL-cholesterol was at least in part the result of the 'catch-up phenomenon'. Indeed, untreated HIV infection is associated with low LDL-c,[21-23] and levels generally increase subsequent to starting antiretroviral therapy[17]. Total cholesterol/HDL cholesterol ratio, a commonly used indicator of the atherogenic potential of the lipid profile [24] was similar between patient on a PI and those on NNRTI-regimens. This suggests that, at least in medium term, treatment with a PI does not deteriorate the atherogenic potential of the lipid profile of patients previously on NNRTI-based regimens.

Our study has some limitations. The cross-sectional design precludes any inference about causality. It is unlikely that patients who failed on first-line antiretroviral therapy in this setting are those with favourable lipid profile, and that our findings may actually reflect subsequent deterioration, causing their profile to be similar to that of a broader population on

NNRTI. Indeed, our previous investigations in this setting suggest that markers of disease severity such as CD4 counts are not associated with lipid abnormalities.[17] It is also possible that with a much large sample, some of the small differences could become significant. This however, would not invalidate the conclusions from the study. Previous studies have demonstrated lipid abnormalities to be more frequent in NNRTI than in ART-naïve patients in this setting,[17] precluding the need for an ART-naïve control group in the present study. Our study also has major advantages, for instance, by demonstrating perhaps for the first time that transition from a NNRTI-based regimen to a PI-based regimen should not necessarily invite changes in the monitoring protocol for lipid abnormalities.

In conclusion, treatment of HIV-1 patients with protease-inhibitors based regimens subsequent to failure on NNRTI-based regimens may not deteriorate the lipid profile above and beyond derangements cause by prior NNRTI in our setting. Recommendations for lipid abnormalities in HIV patients on treatment should apply to everyone on antiretroviral treatment in this setting. Cohort data are needed to refine the findings from this study and monitor the adverse consequence of lipid derangements.

Competing interests – None for all authors

Source of funding – None

Authors' contribution – EWPY conceived the study, supervised data collection, co-analysed the data and drafted of the manuscript; APK contributed to study designed, data analysis, drafting and critical revision of the manuscript; GA critically revised the manuscript; AFB contributed to data collection and co-analysed the data; JN supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	/
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	/
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	/
		Case-control study—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	/
		(*c*) Explain how missing data were addressed	/
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	/
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	/
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	/
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	10

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Dyslipidemia in HIV-1 infected patients receiving protease inhibitors after initial treatment with first-line based non-nucleoside reverse transcriptase inhibitors: a cross-sectional study

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Dyslipidemia in HIV-1 infected patients receiving protease inhibitors after initial treatment with first-line based non-nucleoside reverse transcriptase inhibitors: a cross-sectional study

Short title: **Protease inhibitors and dyslipidaemia**

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References: 27

Abstract

Objectives: Lipid abnormalities associated with antiretroviral therapy in people with HIV infection are more frequent with protease inhibitors (PI) based regimens. Whether effects extend to patients receiving a PI subsequent to failure on non-nucleoside reverse-transcriptase inhibitors (NNRTI) based regimen, is still unknown. We investigated the effects of secondary treatment with a PI on the lipid profile in a group of patients with HIV infection in Cameroon.

Design: This was a cross-sectional study.

Setting: This study was carried out at the registered centre for HIV treatment of the Yaounde Jamot hospital in Cameroon.

Participants: Participants were consecutively recruited between November 2009 and January 2010. There were 138 HIV-1 patients on initial treatment with a NNRTI regimen and 66 HIV-patients on secondary treatment with a PI for at least 12 months. Lipid abnormalities were based on the National Cholesterol Education Program, Adult Treatment Panel III criteria.

Outcome measures: Levels of lipid parameters among patients on PI and NNRTI.

Results: Median (interquartile range) levels (mg/dl), NNRTI-treated vs. PI-treated patients were 185 (149-225) and 189 (147-244) for total cholesterol, 46 (27-66) and 42 (28-82) for HDL-cholesterol, 121 (90-169) and 126.9 (71-176) for LDL-cholesterol, 134 (98-174) and 138 (111-167) for triglycerides, and 4.3 (2.9-6.2) and 5.1 (2.6-7.9) for total/HDL-cholesterol ratio (all $p>0.32$). The most frequent lipid abnormality in the two groups was high LDL-cholesterol [46.4% (NNRTI) vs. 54.5% (PI)]. Occurrence of lipid abnormalities was similar in the two groups (all $p>0.29$).

Conclusions: The use of PI does not appear to deteriorate the lipid profile of HIV patients above and beyond abnormalities induced by an unsuccessful initial treatment with NNRTI. Monitoring of lipid profile during HIV treatment regardless of the regimens would improve timely detection and management of abnormalities, to mitigate related risks.

Word count – 287

Key words – HIV infection, antiretroviral therapy, protease inhibitors, non-nucleoside reverse-transcriptase inhibitors, lipid profile

Article summary

Article focus:

- To investigate the effects of secondary treatment with a protease inhibitors on the lipid profile in a group of patients with HIV infection in Cameroon**.**

Key messages:

- The differential contribution of antiretroviral agents to lipid abnormalities suggests that hypothetically, switching patients from first-line to second-line treatment may have deleterious effects on their lipid profile.

- Effects of protease inhibitors on lipid profile among patients receiving the protease inhibitors subsequent to failure on non-nucleoside reverse-transcriptase inhibitors based regimen are still unknown.

- In this study, the use of protease inhibitors does not appear to deteriorate the lipid profile of HIV patients above and beyond abnormalities induced by an unsuccessful initial treatment with non-nucleoside reverse-transcriptase inhibitors.

Strengths and limitations:

- To our knowledge, such hypothesis has not yet been tested.

- This is a cross-sectional study which lacked the previous level of lipid parameters of participants.

INTRODUCTION

Antiretroviral treatments are associated with widely described abnormal changes in the lipid profile in people with HIV infection.[1-4] Although more frequent during treatment with protease inhibitors (PI),[1,5,6] these changes are also observed during treatment with stavudine and to a lesser extent with non-nucleoside reverse-transcriptase inhibitors (NNRTI).[1,7] Such changes include raised total and LDL cholesterol, raised triglycerides and variable effects on HDL cholesterol levels.[1,6]

The increasing rollout of antiretroviral treatment over the last ten years has significantly improved survival among people living with HIV.[8] This however has been achieved at the cost of increasing resistance to first-line antiretroviral therapies.[9,10] In sub-Saharan Africa (SSA), the epicentre of HIV pandemic, the widely used first-line antiretroviral regimen, inspired by the World Health Organisation (WHO), combines two nucleoside reverse-transcriptase inhibitors (NRTI) with a non-nucleoside reverse-transcriptase inhibitor (NNRTI).[9] Protease inhibitors (PI) are the compulsory component of the second line treatment subsequent to the failure of the first-line one in this setting.[11,12] The differential contribution of antiretroviral agents to lipid abnormalities suggests that hypothetically, switching patients from first-line to second-line treatment in SSA may have deleterious effects on their lipid profile. However, such hypothesis has not yet been tested.

We compared the lipid profile of HIV-1 patients receiving the WHO recommended 1st-line therapy with that of patients on 2nd-line therapy subsequent to first-line treatment failure.

PARTICIPANTS AND METHODS

Study setting and Participants

This cross-sectional study was conducted at the registered centre for HIV treatment of the Yaounde Jamot hospital in Cameroon. The study setting has been described in details elsewhere.[13] Participants were consecutively recruited between November 2009 and

January 2010. Two groups of HIV-1 positive participants were selected. The first group included individuals who had received antiretroviral treatment for the 12 preceding months or more, based on the WHO first-line regimens or NNRTI-based regimen (NNRTI-based group). The second group included individuals who were receiving second-line antiretroviral treatment or PI based regimen for at least 12 months after failure of the first-line regimen (PI-based group). First-line ART regimens applied to these participants combined lamivudine (3TC) and stavudine (d4T) or zidovudine (AZT) with nevirapine (NVP) or efavirenz (EFV). The PI-based regimens included abacavir (ABC), didanosine (DDI) and lopinavir/ritonavir (LPV-r) or indinavir (IDV). The choice of regimens is unrelated to potential factors that could induce a dyslipidemia, since lipid profile assessment is a requirement in routine pre-ART treatment evaluation in this setting.[14] Failure on 1st line antiretroviral therapy in the study setting is based on persisting plasmatic HIV-1 viral load of 5000 copies/ml or greater, after a year on antiretroviral treatment. Diagnosis of therapeutic failure to the first-line ART is always confirmed after a reinforcement of the adherence for a period of 3 months.[11] Patients who had had their treatment regimens changed during follow-up were excluded. Participants had to be at least 18 years of age and to have a treatment adherence rate $\geq$95%. Level of adherence was assessed by verbal administration of a standard series of questions adapted from Adult AIDS clinical trials group (AACTG) adherence instruments. The 95% rate of adherence is preferable to 4-day recall data.[15] Participants were also required not to be on lipid modifying therapies at their enrolment. All participants gave their inform consent and the study was approved by the Cameroon National Ethic Committee (ref N^{o}150/CNE/SE/09).

Procedures

For each participant, data were collected on the sociodemographic background, past medical history including the use of medications that could modify the lipid profile and active or

history of tuberculosis. Lymphocytes count for all participants used flux cytometry methods implemented with BD FASCOUNT automate (BD Biosciences, Le pont de Claix, France). Lipid profile was assessed through enzymatic methods (Linear chemicals, Montgat, Spain) and included total cholesterol (TC), HDL-cholesterol (HDL-c), LDL-cholesterol (LDL-c) and triglycerides (TG). To this end, blood sample was collected after an overnight fast (12 hours) and centrifuged at 3000 cycles/minute, and the serum obtained was then used for lipids determination. The TC/HDL-c ratio was also calculated. Abnormal lipid profile was defined in accordance with the US National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) guidelines, as TC ≥ 200mg/dl, HDL-c < 40mg/dl, LDL-c ≥130mg/dl, TG ≥150mg/dl and TC/HDL-c ratio ≥5.[16]

Statistical analysis

Sample size was determined assuming a 35% prevalence of total cholesterol ≥200 mg/dl in the NNTI based group, a minimum detectable unadjusted odds ratio (OR) of 2, a Type I error of 5% and a power of 80%.[17] Based on the above, the required sample size was 84 participants (42 NNTI treated patients and 42 PI treated patients). Data analysis used the Statistical package for social sciences (SPSS) version 17 for Windows (SPSS, Chicago, IL). Differences in means and proportions for participants' characteristics were assessed using Student t-test, Mann –Whitney U test and χ^2 tests. A probability threshold of $p < 0.05$ was used to characterise statistical significant results.

RESULTS

Study population

The total number of participants included in each study group was 138 (NNRTI-based regimen) and 66 (PI-based regimen). NNRTI-based regimens were d4T/3TC/NVP (61 patients), d4T/3TC/EFV (32 patients), AZT/3TC/NVP (31 patients) and AZT/3TC/EFV (14 patients); while PI-based regimens were DDI/ABC/INV (35 patients) and DDI/ABC/LPV-r

(31 patients). The characteristic of participants are summarised in Table 1. The median duration on ART was higher among participants in the PI-regimen group than among those on NNRTI-regimens (36 vs. 28 months, p=0.001). This included a 22-month period on NNRTI-regimens and 14-month duration on PI-based regimens. Sex distribution, mean age, body mass index and median CD4 count were similar between the two study groups (Table 1).

Table 1: Profile of 138 patients on NNRTI-based regimens and 66 patients on protease inhibitors based regimens

Characteristics	NNRTI-based regimen (n=138)	PI-based regimen (n=66)	p
Women, n (%)	90 (65.2)	39 (59.1)	0.396
Mean age, years (SD)	40.6 (8.7)	42.5 (8.7)	0.154
Mean body mass index, kg/m² (SD)	24.6 (4.7)	23.8 (3.9)	0.208
Median CD4 count, per mm³ (IQR)	333(206-459)	330 (172-451)	0.747
Median duration on ART, months (IQR)	28 (13-40)	36 (24-50)	0.001
Median duration on NNRTI-based ART, months (IQR)	28 (13-40)	22 (10-36)	0.001
Median duration on PI-based ART, months (IQR)	NA	14 (12-20)	NA

NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; ART, antiretroviral therapy; SD, standard deviation; IQR, interquartile range; NA, not applicable

Lipid profile

Median levels of TC, HDL-c, LDL-c, triglycerides and lipid ratio were similar between participants on PI-based regimens and those on NNRTI-based regimens (Table 2). The prevalence of lipid abnormalities (NNRTI-based vs. PI-based regimens) was 38% vs. 44% for TC≥ 200 mg/dl (p=0.39), 46% vs. 56% for LDL-c≥ 130 mg/dl (p=0.30), 40% vs. 46% for HDL-c< 40 mg/dl (p=0.54), 44 vs. 36% for triglycerides≥ 150 mg/dl (p=0.33) and 36% vs. 29% for TC/HDL-c≥ 5 (p=0.34). The pattern was similar in men and women, participants

above and below median age, and after adjustment for age, sex, and total duration on ART in linear and logistic regression analyses.

Among patients on NNRTI, median (interquartile range) levels (mg/dl) of lipid variables, d4T-treated vs. AZT-treated patients were 180.3 (149.2-227.1) and 227.3 (187.7-270.7), p=0.632 for total cholesterol, 133.1 (96.4-167.7) and 136.0 (136.0-101.5-189.3), p=0.389 for triglycerides, 46.6 (27-67.2) and 45.2 (26.3-59.8), p=0.624 for HDL-cholesterol, 116.8 (87.7-163.7) and 134.9 (90.6-172.7), p=0.280 for LDL-cholesterol and, 4.1 (2.5-5.9) and 4.6(3.3-6.9), p=0.341 for total cholesterol/HDL-cholesterol ratio.

Among patients on protease inhibitors, median (interquartile range) levels (mg/dl) levels of lipid variables, IDV-treated vs. LPV/r-treated patients were 171.9 (146.8-253.0) vs 193.8 (146.0-239.8), p=0.959] for total cholesterol, [135.2(108.2-167.4) and 138.6 (112.4-162.2), p=0.96 for triglycerides, 45.1 (32.1-60.1) and 39.6 (24.0-53.8), p=0.23 for HDL-cholesterol, 114.7 (54.4-176.7) and 130.5 (85.6-171.5) , p=0.64 for LDL-cholesterol and, 4.8 (2.4-7.6) and 5.5 (2.9-8.0), p=0.576 for total cholesterol/HDL-cholesterol ratio.

Table 2: Median levels of different lipid parameters in patients on NNRTI-based and PI-based regimens in Yaounde, Cameroon

Lipid variable	NNRTI-based regimen (n=138)	PI-based regimen (n=66)	p
Total cholesterol, mg/dl	184.7 (149.3-225.0)	189.5 (146.7-243.8)	0.688
HDL cholesterol, mg/dl	45.84(27.0-66.0)	42.16(27.6-82.3)	0.568
LDL cholesterol, mg/dl	121.4(89.7-168.7)	126.9(70.8-176.5)	0.767
Triglycerides, mg/dl	134.5 (98.3-174.0)	138.0 (111.1-166.6)	0.468
Total/HDL-cholesterol ratio	4.3 (2.9-6.2)	5.1 (2.6-7.9)	0.329

Data are median (interquartile range); NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitor

DISCUSSION

There is an abundant literature on the improvement of lipid profile of people with HIV subsequent substitution of NNRTI or NRTI for PI in the treatment regimens.[18] We are not aware of a study that has examined the effects of PI on lipid profile of patients initially treated with NNRTI. The current study was conducted in a setting where virtually all treated HIV-1 patients are almost always started on a NNRTI-based regimen as first-line therapy, and shifted to PI-based regimens only after failure of the first-line therapy. Our findings suggest that this transition to PI-based regimens may not be associated with significant deterioration of the lipid profile.[1,7] Indeed, median serum lipid levels and prevalence of lipid abnormalities were similar in patients on initial treatment with a NNRTI-regimen and those on secondary treatment with a PI-regimen. These findings were consistent by gender, age and CD4 count, and robust to adjustment for several covariates.

In sub-Saharan and other developing countries, NNRTI-based regimens not containing a PI are associated with pro-atherogenic adverse lipid changes.[17,19-21] However, the World Health Organisation's recommendations,[11,12] enforced at the country level in Cameroon[14] and elsewhere, suggest that only those HIV patients on a PI should be screened for dyslipidemia. These recommendations are applied against a background of scarcity of comparative studies on lipid profile of patients and NNRTI with that of those on a PI. By demonstrating findings suggesting that continuation treatment with a PI may not necessarily induce lipid derangements above and beyond those induced by prior NNRTI, our study emphasizes the need to extend screening for dyslipidemia in this setting to any patient on antiretroviral therapy regardless of the regimens. Such an approach may help early detection of lipid abnormalities and mitigation of related risks.

High LDL-cholesterol was the most common lipid abnormality found in our study. High LDL-cholesterol is a major lipid abnormality, and a treatment target for cardiovascular

prevention.[22] That lipid abnormalities in the general population in Cameroon and other countries in the region are generally rare, suggests that lipid abnormalities in our patients were induced by antiretroviral therapy. It is also possible that high LDL-cholesterol was at least in part the result of the 'catch-up phenomenon'. Indeed, untreated HIV infection is associated with low LDL-c,[23-25] and levels generally increase subsequent to starting antiretroviral therapy. The derangements of the lipid profile were similar in our patients treated with the regimen containing IDV or LPV-r. Likewise, the levels of lipid fractions were similar between patients receiving d4T-based regimens and those receiving AZT-based regimens. Thus, d4T does not seem to induce more dyslipidaemia in our patients as described in other studies [1,5]. In this study, HDL-c level was similar between patients treated with NNRTI and those secondary treated with PI. Thus, switching of NNRTI regimens to PI regimens was not associated with increased of the HDL-c level. However, the results of the SMART study have shown that the use of PI is associated with a decrease of HDL-c level compared to the use of NNRTI, resulting in a higher atherogenic risk in patients treated with PI.[26]

Total cholesterol/HDL cholesterol ratio, a commonly used indicator of the atherogenic potential of the lipid profile [27] was similar between patient on a PI and those on NNRTI-regimens. This suggests that, at least in medium term, treatment with a PI does not deteriorate the atherogenic potential of the lipid profile of patients previously on NNRTI-based regimens. Our study has some limitations. The cross-sectional design precludes any inference about causality. It is unlikely that patients who failed on first-line antiretroviral therapy in this setting are those with favourable lipid profile, and that our findings may actually reflect subsequent deterioration, causing their profile to be similar to that of a broader population on NNRTI. Indeed, our previous investigations in this setting suggest that markers of disease severity such as CD4 counts are not associated with lipid abnormalities.[19] It is also possible

that with a much large sample, some of the small differences could become significant. This however, would not invalidate the conclusions from the study. Previous studies have demonstrated lipid abnormalities to be more frequent in NNRTI than in ART-naïve patients in this setting,[19] precluding the need for an ART-naïve control group in the present study. Our study also has major advantages, for instance, by demonstrating perhaps for the first time that transition from a NNRTI-based regimen to a PI-based regimen should not necessarily invite changes in the monitoring protocol for lipid abnormalities.

In conclusion, treatment of HIV-1 patients with protease-inhibitors based regimens subsequent to failure on NNRTI-based regimens may not deteriorate the lipid profile above and beyond derangements cause by prior NNRTI in our setting. Recommendations for lipid abnormalities in HIV patients on treatment should apply to everyone on antiretroviral treatment in this setting. Cohort data are needed to refine the findings from this study and monitor the adverse consequence of lipid derangements.

Competing interests – None for all authors

Source of funding – None

Authors' contribution – EWPY conceived the study, supervised data collection, co-analysed the data and drafted of the manuscript; APK contributed to study designed, data analysis, drafting and critical revision of the manuscript; GA contributed to study design and critically revised the manuscript; AFB contributed to data collection, co-analysed the data and drafting of the manuscript; JN supervised data collection and critically revised the manuscript. All authors approved the final version of the manuscript.

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Pages
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4,5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4,5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	/
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	/
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	4,5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	/
		Case-control study—For matched studies, give matching criteria and the number of controls per case	/
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5,6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	/
		(*c*) Explain how missing data were addressed	/
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	
		Case-control study—If applicable, explain how matching of cases and controls was addressed	
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	/
		(c) Consider use of a flow diagram	/
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,7
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*7*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Not applicable
		(*b*) Report category boundaries when continuous variables were categorized	/
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9,10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8,9,10,11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.