PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Pefura Yone, Eric Walter ; Kengne, Andre; Ashuntantang, Gloria; Betyoumin, Awa; Ngogang, Jeanne

VERSION 1 - REVIEW

REVIEWER	Signe Worm, MD, PhD Depart. of Infectious Diseases 5121, Rigshospitalet, Blegdamsvej 3B, DK-2100 Copenhagen Ø, DENMARK. I declare no conflicts of interest.
REVIEW RETURNED	11-Jun-2012

THE STUDY	No information on "time since failure", which could have influenced when lipids where measured. What was the average time after switching and measures of lipids? Follow-up is quite different between the PI and the NNRTI group. No information on use of lipidlowering drugs after switching. No information on weight/BMI, waist circumference of other important parameters that could affect lipid levels. Within the PI drug class the individual PI's have different propensity to cause dyslipedemia, there is no discussion of this. Importantly there is no discussion of use of NNRTIs and increase in HDL reported by the SMART study (A Phillips et al.) References from the SMART study, the D:A:D study and the ACTG trial are missing. The NCEP guidelines are available in more updated versions than the one quoted from 2001

REVIEWER	James Kohler, PhD Research Assistant Professor Dept. Pediatrics Emory University School of Medicine
REVIEW RETURNED	22-Jun-2012

THE STUDY	No supplemental docs are included. Manuscript alone is sufficient.
GENERAL COMMENTS	Overall the study reported is well-designed and carried out. Data

	are clearly summarized in table format. The minor revisions proposed are the following: 1) The authors indicate that the cholesterol/HDL cholesterol ratio were similar between the the 2 groups of patients (NNRTI vs PI regimens). However, it is important to note that while the ratios were similar, the median ratio for group on PI regimen was above the abnormal lipid profile guidelines of US National Cholesterol Education Program (ie: >5). Thus, this point should be made that biological relevance for greater lipodistrophy is likely in this cohort. 2) In addition, while the differences in the lipid profile parameters between the 2 groups were not statistically different (based upon the medians), it should be noted that both treatment groups had ~50% prevalence of lipid abnormalities. Therefore both groups are at increased risk and should be carefully monitored. 3) The NNRTI group consisted of 2 distinct subgroups (those that included d4T vs AZT in their 1st line regimens). As the authors noted, d4T treatment is also associated with abnormal lipid profiles. As they combined these 2 subgroups the results of the NNRTI group may be skewed. I would suggest reassessing the NNRTI group as 2 subsets: d4T inclusive vs AZT inclusive and also look to see what NNRTI regimen as first line treatment was used in the PI group. It is likely that the authors will find a reduced median level for AZT treated group compared to d4T group. Again, this report is important as it demonstrates that outcomes of substituting in PI in second line treatment. The data also emphasize the importance of monitoring lipid abnormality both in first-line and second line treatment regimens.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Signe Worm, MD, PhD
Depart. of Infectious Diseases 5121, Rigshospitalet, Blegdamsvej 3B, DK-2100 Copenhagen Ø, DENMARK.
I declare no conflicts of interest.

No information on "time since failure", which could have influenced when lipids where measured. What was the average time after switching and measures of lipids?
Our answer: Thank you for raising this point. The time since failure is equivalent to the second line treatment (i.e. protease inhibitors-based regimen in this case), which was already provided in Table 1 (14 months), and described towards the end of the first paragraph of the result section. It is of note that in this centre and other treatment centres in the country, HIV patients are directly started on a second line treatment once a diagnosis of treatment failure on a first regimen has been reached, without a wash-out window in-between.

Follow-up is quite different between the PI and the NNRTI group.
Our answer : Thank you for raising this point. There was indeed an expected difference in the length of follow-up between PI and NNRTI groups. PI patients indeed, are those who failed to respond to an

initial treatment with a NNRTI, and by design would be expected to have an overall exposure to ART longer than that in the NNRTI group. By design, we had no control on the time a patient spent on NNRTI before a transition to a PI regimen. The most we could do was to setup a minimum exposure time to the on-going treatment regimen, which was fixed at 12 months in this case. It is known that lipid abnormalities occur early after initiation of ART treatment and are found in most patients after one year of treatment.

No information on use of lipid lowering drugs after switching.
Our answer: Thank you for raising this important point. As described in the method section of the initial submission, we included in this study only those patients who were not receiving lipid modifying therapies or other medications that can potentially interfere with lipid metabolism. It reads:
"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 No150/CNE/SE/09)."
It is also of note that lipid profile is not included in the routinely pre-assessment for ART commencement in this setting, and therefore the choice of initial ART regimens is not affected by prior knowledge of the lipid profile. We had also already alluded to this in the methods section. It reads:
"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"

No information on weight/BMI, waist circumference of other important parameters that could affect lipid levels.
Our answer: Please, we had reported BMI data in Table 1, showing no difference by ART regimens. Unfortunately, we do not have data on other parameters.

Within the PI drug class the individual PI's have different propensity to cause dyslipedemia, there is no discussion of this.
Our answer: The PI that are associated with better/favourable lipid profiles (namely Atazanavir, Raltegravir, Maraviroc) were not used in this study. At the time of the study, patients were on IDV and LPV/r which all seem to have comparable effects on lipid profile as described elsewhere (Grunfeld C. Top HIV Med 2010;18:112-8, Melroe NH et al. J Assoc Nurses AIDS Care 1999, 10:22-30) and also found in our study. In fact, median (25th-75th percentiles) levels (mg/dl) of lipid variables, Indinavir-treated vs. Lopinavir/ritonavir-treated patients [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) vs 138.6(112.4-162.2), p=0.959] for triglycerides, [45.1(32.1-60.1) vs 39.6(24.0-53.8), p=0.232] for HDL-cholesterol, [114.7(54.4-176.7) vs 130.5(85.6-171.5) , p=0.639] for LDL-cholesterol and [4.8(2.4-7.6) vs 5.5(2.9-8.0), p=0.576] for total cholesterol/HDL-cholesterol ratio.
We have added the above to the result section and included the following note in the discussion.
"The derangements of the lipid profile were similar in our patients treated with the regimen containing IDV or LPV-r"

Importantly there is no discussion of use of NNRTIs and increase in HDL reported by the SMART study (A Phillips et al.)

Our answer: Thank you for raising this important point which we now address by adding the sentences below to the discussion.
“Likewise, 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]”.

References from the SMART study, the D:A:D study and the ACTG trial are missing.
Our answer : We have now included the 3 references [Phillips AN et al Antivir Ther. 2008;13:177-187; Haubrich RH et al. (ACTG A5142 Study Team) AIDS 2009, 23:1109-1118; Friis-Moller N et al. (DAD study group) N Engl J Med 2003, 349:1993-2003].

The NCEP guidelines are available in more updated versions than the one quoted from 2001
Our answer: This has been fixed. We have found the other guidelines published in circulation in 2002 (National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation. 2002;106:3143-3421). These guidelines provide similar definitions to those used in our study for the definition of lipid abnormalities.

Reviewer: James Kohler, PhD
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Overall the study reported is well-designed and carried out. Data are clearly summarized in table format.
The minor revisions proposed are the following:
1) The authors indicate that the cholesterol/HDL cholesterol ratio were similar between the the 2 groups of patients (NNRTI vs PI regimens). However, it is important to note that while the ratios were similar, the median ratio for group on PI regimen was above the abnormal lipid profile guidelines of US National Cholesterol Education Program (ie: >5). Thus, this point should be made that biological relevance for greater lipodistrophy is likely in this cohort.
Our answer: Thank you for raising this point. Actually, the median HDL-c/TC ratio > 5 in the PI group reflects the fact that more patients in the PI group had a high HDL-c/TC ratio. However, the prevalence of high atherogenic index was 44.2% in the NNRTI group and 54.5% in the PI group ($p = 0.166$). This difference in prevalence of high atherogenic index was not significant. It is possible that the statistical non significance is related to a lack of power as already acknowledge in the limitations paragraph of our discussion section.

2) In addition, while the differences in the lipid profile parameters between the 2 groups were not statistically different (based upon the medians), it should be noted that both treatment groups had ~50% prevalence of lipid abnormalities. Therefore both groups are at increased risk and should be carefully monitored.

Our answer: We agree with the reviewer and indeed, we have shown elsewhere that patients treated with first-line ART had lipid profile derangements potentially atherogenic compared to untreated HIV-positive patients (Pefura Yone et al., 2011, 8 : 33). We have already noted the suggestion of reviewer in the conclusion of this study.

3) The NNRTI group consisted of 2 distinct subgroups (those that included d4T vs AZT in their 1st line regimens). As the authors noted, d4T treatment is also associated with abnormal lipid profiles. As they combined these 2 subgroups the results of the NNRTI group may be skewed. I would suggest reassessing the NNRTI group as 2 subsets: d4T inclusive vs AZT inclusive and also look to see what NNRTI regimen as first line treatment was used in the PI group. It is likely that the authors will find a reduced median level for AZT treated group compared to d4T group.
Our answer: We thank the reviewer for this query. We have actually compared the level of different lipid fractions between patients treated with regimens containing d4T and those treated with AZT regimens and we have found no difference between the two groups of patients. In fact, Median (interquartile range) levels (mg/dl), d4T-treated vs. AZT-treated patients [180.3 (149.2-227.1) vs 227.3 (187.7-270.7), p=0.632] for total cholesterol, [133.1(96.4-167.7) vs 136.0(136.0-101.5-189.3), p=0.389] for triglycerides, [46.6(27-67.2) vs 45.2(26.3-59.8), p=0.624] for HDL-cholesterol, [116.8(87.7-163.7) vs 134.9(90.6-172.7), p=0.280] for LDL-cholesterol and [4.1(2.5-5.9) vs 4.6(3.3-6.9), p=0.341] for total cholesterol/HDL-cholesterol ratio.
We have added the above to the result section and alluded to it in the discussion section in the following terms:
“In our study, 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].”

Again, this report is important as it demonstrates that outcomes of substituting in PI in second line treatment. The data also emphasize the importance of monitoring lipid abnormality both in first-line and second line treatment regimens.
Our answer: We thank you for the appreciation

VERSION 2 – REVIEW

REVIEWER	James J Kohler, PhD Research Assistant Professor Emory University School of Medicine USA
REVIEW RETURNED	10-Jul-2012

- The reviewer completed the checklist but made no further queries.