Author's response to reviews

Title: Per oral Substitution with 300000 IU Vitamin D (Cholecaliferol) Reduces Bone Turnover Markers in HIV-positive Patients

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Author's response to reviews: see over
Dear Dr. Torti, dear Reviewers

We would like to thank the reviewers for their careful work and valuable suggestions. We have implemented most of their comments in the manuscript and given a detailed point-by-point comment in this letter below.

We would be delighted if the manuscript could be accepted in BMC.

Sincerely

Rein Jan Piso
Reviewer: Giovanni Guaraldi

1: Major concern of the study are the poor characterisation of the study population (particularly HCV and HBV infected individuals).

The problem was in our opinion the complicated table 1. Therefore we divided the table in two parts. So the baseline characteristics are easier to read.

2. Methods are not very clear. Inclusion criteria and collection of adverse events are poorly described.

Added in methods:
Patients were recruited in the outpatient infectious disease clinic of Kantonsspital Olten. Baseline characters are presented in table 1 and 2. Patients were excluded if a start or switch in ART had been performed in the last six months, as this may interfere with Vitamin D levels and bone turnover. In patients with urgent need of antiretroviral therapy, no intervention data were collected for the same reason. Patients with Hepatitis monoinfection were excluded if treated with interferon. Dexascans and nutrional data collection were not performed. Ad follow up visit, questionnaire concerning overall physical health including specific questioning pain (bone fractures, nephrolitiasis) or nausea was filled out. Blood testing including liver, renal, metabolic and immunological parameters was also performed.

Reviewer: Emanuele Focà

1. Knowledge of Vitamin D deficiency in HIV medicine is wide and is increasing in the last years: I found the cited references as poorly updated and focused on HIV uninfected people, while I believe that we have good knowledge also in HIV-medicine.

According to the suggestions, we changed following references. However, we are convinced that some comparisons with non-HIV patients should be done. Moreover, there are no data concerning Vitamin D supplementation and clinical endpoints in HIV patients. There are also no data about side effects in HIV patients. As the discussion concerning the method of supplementation (continuous low dose vs pulse therapy) is still ongoing, we believe that this point should not skipped in the paper.


2. Title: changed to: Per oral Substitution with 300000 IE Vitamin D(Cholecalciferol) reduces Bone Turnover Markers in HIV-infected Patients

3. Vitamin D supplementation is intended as cholecalciferol supplementation, I suppose, therefore I suggest to use for Cholecalciferol throughout the text.
We changed the manuscript according to the suggestions, using cholecalciferol for supplementation and 25-OH Vitamin D for measurements in serum.

4. Authors should better explain why they compared HIV infected patients only with hepatitis (B or C) mono-infected patients, and not to the general population
Changed to: Low levels of vitamin D in HIV-patients compared to the general population are well described. However it is still not understood if this is due to the HIV infection itself or to traditional
risk factors. Therefore, we compared vitamin D levels not with the general population, but with HBV and HCV monoinfected patients, postulating similar living conditions as well as chronic inflammatory status.

5. The introduction section is poor of information particularly on hepatitis mono-infected patients. Actually, osteoporosis is an important topic in hepatitis too, therefore the work could be interesting also for clinicians involved in hepatitis care.

We agree that we primarily focused on HIV patients. We tried therefore to add some information on Hepatitis patients too. However, we think that studies more specific focused on hepatitis patients should be design to answer these question. We added: Moreover, osteoporosis and low vitamin D level has also described in hepatitis B and C patients[7, 8],[9, 10]. 25-OH-vitamin D levels may also influence treatment outcome in Hepatitis C patients[11].

6. Tables are confusing and difficult to read. Efavirenz based regiments should be underlined and EFV use should be insert as variable in the logistic regression model.

We agree that the table 1 is difficult to read and therefore, we divided it in two tables. As only two patients were on nevirapine and nobody on etravirine, we do not think it appropriate to add efavirenz separately. However, we admit that it should be stated that 34/36 NNRTI patients were on efavirenz. We also changed the appearance of the table to make it easier to read.

7. The circannual rhythm formula needs to be better clarified; I underline that vitamin D variability is due to seasonality and not to fixed annual convention.

Most studies measuring Vitamin D look at winter vs. summer. However, if we conclude that sunlight exposure is an important factor of Vitamin D level, we are convinced that in temperate climazones it is more a circannual rhythm, shown also in a paper from Woitge et al.


As we gave for example Vitamin D in January and measured the effect in march, just using seasonal differences would not exactly give the effect of supplementation. However, the differences in Vitamin D before and after supplementation would also have been significant if no correction would have performed.

Changed to: 25OH-vitamin D was corrected for circannual rythm [12], bone turnover markers were not corrected. According to the method published by Bolland who could show that the concentration of 25(OH)-vitamin D follows a sinus curve, we corrected the values for : baseline + amplitude x sine (angular frequency x day of the year + phase shift). Angular frequency was 2 x π/365, and the phase shift is the translation from x axis. As the minimum/maximum concentrations were in february resp. august, phase shift was calculated
accordingly. Amplitude was calculated from minimum and maximum monthly mean values (before supplementation).

8. Authors used the term “postulated” to much and often improperly (sometimes it is too strong): please substitute with “suggested”, “demonstrated”, “observed” etc. 
   4/5 times, postulate was changed.

9. Please use the term “HIV-infected” instead of HIV positive
   done as requested.

10. Have the Authors data on 1,25OH-Vitamin D? It would be interesting to compare 25 OH vitamin D with the final product.
   No, we did not measure 1,25 Vitamin D, therefore we cannot give data on this question, unfortunately.

11. We actually recommend...” in the discussion section, please substitute the word recommend with “suggest”. It is difficult to draw recommendation as conclusion in a study that is not a RCT and not so powerful.
   We agree, the term recommend is to strong and did as requested.

12. In the discussion section, authors must be more quantitative when they compare their work with the literature.
   Done where possible. However, as there exists a variety of bone turnover markers, direct quantitative comparison is often difficult.

References
