Reviewer's report

Title: Therapeutic drug monitoring of nevirapine in saliva in Uganda using high performance liquid chromatography and a low cost thin-layer chromatography technique

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Reviewer: Bernd Rosenkranz

Reviewer's report:

The authors report the results of a cross-sectional study to assess the use of TDM of nevirapine in a clinical environment in Uganda. 40% of the patients were recruited as sub-study of the Pan African Studies to Evaluate Resistance (PASER) cohort. Nevirapine levels in plasma and saliva were determined by HPLC in 297 HIV infected adults, and results were compared to virological response. In addition, a previously developed low-cost TLC method was used, but this assay was not feasible in this setting. The study showed a mean saliva-plasma ratio of 0.58 which is consistent with the fact that 40% of the drug is unbound in plasma and the previously reported CSF:plasma ratio of 0.45. Only 15/287 patients had nevirapine plasma levels below 3 mg/L considered to be sub-therapeutic. Patients with sub-therapeutic levels had an odds-ratio of 3.29 (1.00-10.74) for virological failure, and only 2 patients with genotypic resistance mutations had sub-therapeutic plasma concentrations. The authors concluded that TDM of nevirapine may be justified for patient monitoring in specialist centres.

This study is of interest, since it provides information about the feasibility and use of TDM of nevirapine in a major provider of ART in Uganda. However, the pharmacokinetic results are limited because of the cross-sectional nature of the study allowing only a single pharmacokinetic sampling time point for each patient. Therefore the data do not provide enough information about long-term treatment adherence. Also, there is no clear correlation between adherence assessments and the TDM data. Table 2 shows that all 5 patients with virological failure and nevirapine levels below 5 mg/L had a reported 30 day adherence of at least 95%. The relevance of this finding should be discussed.

Since the study was not prospective, no conclusions can be made about the effectiveness of the TCM approach to improve patient management.

- Major Compulsory Revisions

1. The authors should provide a more detailed statistical evaluation of the correlation between the plasma and saliva concentrations, such as ROC analysis.

2. More details of the results of the plasma and saliva concentrations (e.g. Mean (SD)) should be reported.

3. The limitations of the study as discussed above should be addressed in the
discussion.

- Minor Essential Revisions

1. Abstract, background: It should be made clear that TLC was only used for plasma, not saliva samples (same for last paragraph in the introduction).

2. Abstract, Conclusions, Discussion, first sentence and last paragraph: The conclusions should be re-phrased to state that the HPLC TDM method currently only should be considered in a research setting in specialist centres, instead of “feasible and potentially useful in clinical practice in Uganda”.

3. Accuracy of the TLC method should be included in the Methods section. The reference to L’Homme et al for the details of the analytical method is adequate.

4. A few typos should be corrected (Methods: Sartstedt should be Sarstedt; Results: copies/mL and cps/mL are used interchangeably; consistent terms should be used; Five percent should be 5 percent).

- Discretionary Revisions

1. The comparison of the detected mean saliva-plasma ratio of 0.58 with known protein binding and CSF:plasma ratio of 0.45 could be included in the discussion.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.