

**Author's response to reviews**

**Title:** Renal AA-amyloidosis in intravenous drug users - A role for HIV-infection?

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**Author's response to reviews:** see over
Dear Editors,

We would like to thank the editors and both reviewers for their constructive and fair criticism of our work. We hope that you agree that the suggested changes improved the quality of our manuscript. Please find below our point-by-point response to the concerns raised.

With kind regards,
Markus Bickel

Reviewer 1:
Jung and colleagues present a retrospective analysis of intravenous drug users (IVDU) that underwent a renal biopsy. The study is well structured and presented but some serious methodological issues and other limitations must be considered.

Methods section
# The analysis is retrospective and this is always an important source of bias that must be considered and mentioned as a limitation of the study.
# All patients with ongoing or with a prior history of IVDU were included. How did you identify and select the IVDU from the study period?
Answer: Patients with IVDU were identified by using the Patient Data management System of the renal units of the GU and AMK. Primary and secondary diagnoses are based on the international Classification of Diseases 10th Revision (ICD-10). This information is now included into the methods section.
How did you collect the information regarding drug use (ongoing vs. prior)? Did you review medical records?
Answer: Clinical as well as the medical history were obtained by reviewing the medical records. We changed the corresponding sentence in the manuscript
# Only patients that underwent renal biopsy were included. Patients with end-stage renal disease (ESRD) without a kidney biopsy were excluded and this may be another important source of bias. In my opinion all patients diagnosed with ESRD (with clinical and/or histological diagnosis) should be included in the analysis.
Answer: Within the time range of our study three additional patients with IVDU were referred to our centres because of progressive renal failure. Out of these three patients only one patient experienced ESRD within the time range of our study. This patient (HIV negative) refused kidney biopsy. Clinical diagnosis in this patient was chronic interstitial nephritis.
The second patient (HIV negative) refused renal biopsy and died 2 months later because of methadone intoxication. An autopsy was performed and histological evaluation demonstrated membranoproliferative GN type I.
The third patient (HIV positive) had severely impaired coagulation because of hepatitis B-associated liver cirrhosis and kidney biopsy was therefore not performed. This patient is still alive and free from dialysis, returning frequently to follow-up visits (latest CKD stage: IV).
We had decided not to include this data in our analysis, as performance of renal biopsy requires a certain degree of adherence to medical advice. To us it appears reasonable, that only patients with some basal level of adherence will present at our units for evaluation of renal disease, whereas IVDU with low adherence only present when acutely ill and most often fail to return to follow-up visits (as indicated in the manuscript). Adding - only partially available - post-mortem data from non-adherent patients into this evaluation might therefore represent a source of bias to our study.
We included the data of the total number of patients seen in the study period into the methods section of the manuscript. Probably, the decision of performing a kidney biopsy is based on the centers policy, the patient life expectancy, performance status, etc. For this reason, patients with a biopsy-proven diagnosis are not representative of all ESRD-IVDU patients.

Answer: We agree with the reviewer that performing a kidney biopsy might be a subject to bias by centre politics or others factors. At our centers we advocate renal biopsy - whenever possible - in any case of uncertainty of renal failure, which is especially true for patients with IVDU or HIV, because of the paucity of data. This more liberated attitude towards renal biopsy is underlined by the high percentage of patients with biopsy-proven diagnosis at our centres (see above).

# Last paragraph (Statistical methods): continuous variables should be expressed as median and IQR and also range if you want to.

Answer: We changed these parts of the manuscript. All continuous data are now expressed as median and IQR.

When continuous variables are expressed as proportions? This is usually for categorical variables.

Answer: This mistake has been corrected in the revised version of the manuscript.

Results section

# It would be very interesting to know how many patients with prior or ongoing IVDU were attended in your hospitals during the study period and how many of them had progressive renal failure or proteinuria (you would be able to know the prevalence of chronic kidney disease in this population).

Answer: We agree, but such a study is quite challenging, as it is difficult to obtain the relevant information. As mentioned above, most IVDU only seek medical help when acutely ill and often leave hospitals despite physicians’ recommendation and do not return to follow-up visits. E.g., in the case of an observed impairment of renal function on presentation at the hospital, it is difficult and highly speculative to discriminate acute renal failure (because of acute illness) from chronic renal disease, when there is lack of any follow-up data. In our opinion, such a study could be conducted prospectively.

Only 24 patients underwent a renal biopsy. The number of patients included in the final analysis is too low and this should be mentioned as a limitation.

Answer: We agree that 24 patients is a small number. But, we are not aware of any larger renal biopsy study in such a population within the last decade. We addressed this issue in the new limitations paragraph.

# Self reported duration of IVDU was 3-33 years. How did you collect the information? Did you review medical records? In my opinion this information is difficult to collect retrospectively.

Answer: Data concerning duration of IVDU were obtained by reviewing the medical records. The standardized medical history worksheets at our hospitals include questions concerning drug abuse. However this information is patient dependent. We therefore used the term “self-reported” in our manuscript, to strengthen the point that this data rely on the information patients were giving to us.

# Table 2 is not necessary. Information is clear in the text.

Answer: We deleted table 2.

# In my opinion figure 1 and probably figure 2 are not necessary.

Answer: We deleted figure 1.

# Figure 4: a survival comparison (using the Kaplan-Meier method and the log-rank p value) with patients with other diagnoses it’s highly recommended

Answer: A survival comparison as well as log-rank p-value is now included.
In addition, a new table comparing the characteristics of patients with and without amyloidosis could be useful.

**Answer:** All data comparing characteristics of patients with and without amyloidosis are now provided in table 2.

**Discussion**

The authors compare their findings with another retrospective cohort of 25 HIV-infected patients without a history of IVDU that underwent a kidney biopsy. This comparative analysis was not mentioned in the objectives and methods section of the study. These two groups are probably not properly matched and the conclusions of this comparison must be interpreted cautiously.

**Answer:** This comparative analysis is now included into the methods section and the limitations of this comparison are addressed.

A “limitations” paragraph is highly recommended at the end of the discussion.

**Answer:** We included a limitations paragraph at the end of the discussion section.

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

**Answer:** We addressed these issues in the point-by-point answers above.

**Reviewer 1:**

Quality of written English: Needs some language corrections before being published

**Answer:** We found and deleted several language mistakes.