Reviewer’s report

Title: Impact of tenofovir disoproxil fumarate plus ritonavir-boosted protease inhibitor-based regimens on renal function in HIV-infected individuals: a prospective multicenter study

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Reviewer: Amit Achhra

Reviewer's report:

Cao et al present the prospective observational study evaluating the impact of 2nd line TDF+PI/r vs. other 1st line agents on the renal function. Although comparing treatment experienced patients receiving TDF with treatment naive individuals is not an ideal design, the study does provide the rare and valuable data on TDF use in Asian HIV-infected individuals. However, a few concerns regarding methodology should be addressed:

MAJOR:

(i) Given that patients in TDF group were HIV-infected for a longer duration and had been exposed to other ART agents in the past, how might this would have impacted your results? Authors should discuss and/or provide additional analysis adjusted for HIV duration if possible. Present discussion is unclear/insufficient.

(ii) How do your results compare to the TDF-associated change in eGFR in western population?

(iii) Given that some PI agents could be nephrotoxic (such as indinavir, atazanavir and possibly lopinavir/r), at very least provide description of which PIs were being used in the TDF group.

(iv) Statistics: Comparing differences, as well as difference in changes in creatinine and eGFR at 48 weeks using Wilcoxon rank-sum test seem appropriate. However, methods used for second part (Results paragraph 3) focused on trends in creatinine and eGFR need improvement. The conclusion that “.. creatinine rapidly increased in first 4 weeks and then stabilised..” and “.. eGFR declined in first 4 weeks and then stabilised..” are not sufficiently backed up by statistical analysis. Ideally, a random effect model (to account for repeat measurements and matching) having exposure group variable and time variable (categorised at say < or > 4 weeks) and possibly the interaction between time and exposure group, should be assessed for each of the endpoints (creatinine and eGFR).

(v) It seems counter intuitive that the impact of TDF was largely in first 4 weeks and then stabilised. Results from larger cohorts (see EUROSIDA study) suggest cumulative exposure to TDF could result in increasing renal toxicity. Similarly, negligible impact of TDF in those with abnormal baseline eGFR (n=23) is also surprising. It is possible that the study was simply not powered to pick up these differences given that expected impact of TDF on GFR is generally small.
Authors should attempt to make a statement on power of their study or discuss in limitations.

Also in Discussion, Paragraph-4 “In TDF+PI/r group...” is unclear.

(vi) Since this was a prospective study designed for renal endpoints, other risk factors (smoking, diabetes, hypertension) were surprisingly absent. They should be presented if available, else discuss this important limitation.

Minor:
- It seems the abstract is missing.
- Clearly state if both the groups were initiating (i.e. not already receiving) respective ART regimen at baseline.
- Confirm if ethics approval was obtained from the mentioned review board.
- Mention full form of all abbreviations at first use.
- Mention if matching was 1 to 1 or based on frequencies of the matched variables?
- Methods Paragraph 1, Inclusion criteria point 2: Mention frequencies of given cART regimens.
- Discussion: Discussion on mechanism of TDF toxicity could be reduced/minimised as it was not the main focus of the study.
- Replace all P values given as “0.000” to “<0.001”.
- Fig-1 and Fig-2 presentations are different (p values in fig-1 and actual eGFR values fig-2). Please be consistent.
- Figure-3: change “90>eGFR>=group” to “90>eGFR>=50” in the table.
- There were other several minor grammatical errors which I have mentioned as track changes in the word document as they were too many to be populated here.

Discretionary comment:
It would be of interest to give the sensitivity analysis after calculating eGFR using Thai eGFR formula (recently validated and published, see Praditpornsilpa et al AIDS 2012 26:1781-1788). This eGFR calculation may be more closer to Chinese population than that derived on white and black populations.

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

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

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

Declaration of competing interests:
I have received research funding grant from Gilead Australia.