PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Predictors of HIV Virologic Failure And Drug Resistance In Chinese Patients After 48 Months Of Antiretroviral Treatment, 2008-2012 : A Prospective Cohort Study
AUTHORS	Kan, Wei; Teng, Tao; Liang, Shujia; Ma, Yanling; Tang, Heng; Zuohela, Tuerdi; Sun, Guoqing; He, Cui; Wall, Kristin; Marconi, Vincent; Liao, Lingjie; Leng, Xuebing; Liu, Pengtao; Ruan, Yuhua; Xing, Hui; Shao, Yiming

VERSION 1 - REVIEW

REVIEWER	Dr. Matilda Michael Ngarina Muhimbili National Hospital, Tanzania
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	The abstract is okay except for the conclusion and limitation of the study sections. The first sentence of the conclusion is very good but the following sentences are a repetition of the results. The conclusion in the main body is well structured. It is not common to have limitations of the study in the abstract unless this is what is recommended by the journal itself. The ethical issues were not well elaborated. HIV is a stigmatizing disease in many countries so it's good to elaborate what confidentiality precautions was taken. It is not well stated in design as to which sampling method was used. Also it is not clear as to what were the profession and/or level of education of the data collectors. The discussion is a bit longish, repetitive and sometimes discusses things that are out of the scope of this paper. Otherwise the manuscript is very good.

REVIEWER	Jan Weber Head of the Virology Research-Service Team Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences Czech Republic
REVIEW RETURNED	11-Mar-2017

GENERAL COMMENTS	Kan and colleagues analyzed predictors of HIV virologic failure and development of HIV drug resistance in Chinese patients after 4 years of ART during 2008-2012 period. They analyzed extensive number of covariates and found several interesting gender-specific associations. Although this study does not bring any breakthrough findings it can benefit HIV professionals in resource-limited settings. The major limitations of this study (as authors correctly admit) is missing the transient virologic failures during the first years of ART (2008-2010). During the 4-years period almost one third of patients switched therapy, many probably due to virologic failures resulting in their underreporting. This limitation diminishes authors' claims of first long-term study of evaluation of virologic failures on 3TC-based regimens. Here are my additional comments/corrections. 1. Author list: Remove extra comma after fourth author 2. Result section of abstract line 48: remove the X after 7 3. Result section of abstract line 56: add 95% CI for non-Han men risk for VF 4. Introduction Page 7 line 12: article by Wang et al. Current HIV research 2011 found 75.3% prevention of HIVDR not prevalence. They found 4.1% of VF (VL>1000 copies/ml). 5. Study design page 8 line 52: please correct feedback to feedbacked or synonym. 6. Laboratory analysis page 9: Please clarify if only one blood sample per patient was collected. 7. Laboratory analysis page 9 line 7: please chnage "test" to determine or synonym 8. Data analysis page 10 line 30: delete / between the words for and removal 9. Results: Quite large number of patients was lost to follow up because of death (139). How many were HIV/AIDS related? 10. Results page 10 line 50 add "to" between lost and follow-up 11. Demographic and ART Information page 11 line 27: Please clarify if all 536 patients were on 3TC based therapy up to the point of blood collection. 12. Demographic and ART Information page 11: There were 169 patients who switched therapy during 2008-2012 - 55 to RTV-boosted LPV based regimen and 66 to TDF based regimen, that leaves 48 patients with no information about their new regimen. In addition, please consider for clarity to state complete regimen instead of just LPV/r based or TDF based. 13. Multivariate model results page 12 line 43: add 95% CI 14. Discussion page 13 line 37: Liu et al ClinInfDis 2014 reported HIVDR prevalence at 37-48 months from 3.04% to 47.92% 15. Discussion page 13 line 39: in the work of Xing et al PLoS One 2013 it was estimated that only HIVDR (not VF) incidence in 2009 was 3.5 per 100 person-years. 16. Discussion page 13: Reviewer is missing discussion of work from Wang et al. PLoS One 2014 Feb 7;9(2):e88305 "Virological outcomes and drug resistance in Chinese patients after 12 months

	of 3TC-based first-line antiretroviral treatment, 2011-2012" 17. Discussion page 13, line 52: the 2.4% of HIVDR for male patients is not correct - based on table 2 there were 13 cases of HIVDR among 278 male patients resulting in 4.7% of HIVDR. Also it would not lead to average 5% of HIVDR in all participants. Make same correction also in the table 2. Please consider to verify all calculations in your tables 1 to 3. 18. Discussion page 14 line 46: remove "a" before possible 19. Discussion page 15 line 4: delete "enough" 20. Discussion page 15 line 9: delete "our" 21. Discussion page 15 line 22: correct researches to research 22. Discussion page 15 line 51 change "the amount is not sufficient for us to test" to the number is not sufficient to test 23. Discussion page 15-16: Please revise sentence 'There is no association between HIVDR…."to be clear

REVIEWER	Habtamu Wondifraw Baynes University of Gondar, Ethiopia
REVIEW RETURNED	13-Apr-2017

GENERAL COMMENTS	Please address the comments forwarded to you

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr. Matilda Michael Ngarina
Institution and Country: Muhimbili National Hospital, Tanzania
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
The abstract is okay except for the conclusion and limitation of the study sections. The first sentence of the conclusion is very good but the following sentences are a repetition of the results. The conclusion in the main body is well structured.
It is not common to have limitations of the study in the abstract unless this is what is recommended by the journal itself.
Strength and limitation required by the journal.

Reviewer: 2
Reviewer Name: Jan Weber
Institution and Country: Head of the Virology Research-Service Team, Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Czech Republic
Please state any competing interests or state 'None declared': None declared

9. Results: Quite large number of patients was lost to follow up because of death (139). How many were HIV/AIDS related?
Unfortunately, we don't have detailed data between 2010 and 2011.

12. Demographic and ART Information page 11: There were 169 patients who switched therapy during 2008-2012 - 55 to RTV-boosted LPV based regimen and 66 to TDF based regimen, that

leaves 48 patients with no information about their new regimen. In addition, please consider for clarity to state complete regimen instead of just LPV/r based or TDF based.
48 patients included those who switch from EFV to NPV and/or from AZT to TDF. There were many combinations of the ART regimen if we want to test switching regimen, so we only put in the table if it's statistically significance if one drug was switched.

Reviewer: 3
Reviewer Name: Habtamu Wondifraw Baynes
Institution and Country: University of Gondar, Ethiopia
Please state any competing interests or state 'None declared': no conflict of interest
1. There are different studies conducted in your area (china) with similar topics, but what is your new finding that may contribute for the scientific world in addition to the other studies? What is the purpose of conducting this project?

2. The abstract is ok but why you omit the background one?
BMJ have 300 words limit on abstract.

3. Why only you enforced to measure the outcome variable in 2011 and 2012? Why not measure in all study years?

We didn't have sufficient fund to continue this study between 2011 and 2012.

4. Study Design and Data collection

- Why you consider having been on ART for 36±6 months in 2011 as inclusion criteria, since you already enroll the participants in 2008? need clarification
We have a ±6 month time window for enrolling participants, however we have participants who had been on ART for less than 30 months or more than 42 months in our dataset. For example, if a participant initiating ART at Dec 2008, and came to clinic at March 2011, he/she would still be enrolled but no longer eligible for this study.

5. At laboratory analysis,

- If you conduct the analysis within 24 hours of collection, what is the importance of preserving at -80 oc?
Only CD4 cell count was determined in local CDC within 24hrs, VL and HIVDR was transported to NCAIDS.

VERSION 2 – REVIEW

REVIEWER	Matilda Ngarina Muhimbili National Hospital
REVIEW RETURNED	28-Jun-2017

The reviewer completed the checklist but made no further comments.

REVIEWER	Jan Weber Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Czech Republic
REVIEW RETURNED	23-Jun-2017

GENERAL COMMENTS	Manuscript has been improved. It is suitable for publication after one correction.All my previous comments and corrections were addressed except for number 17. It was corrected in he table but not in the text. On page 50 line 12 correct 2.4% to 4.7%.

REVIEWER	Hbatamu Wondifraw Baynes University of Gondar, Ethiopia
REVIEW RETURNED	24-Jun-2017

GENERAL COMMENTS	I have reviewed the document twice and it has scientific valuable results & better to be published. So I have no comment if the paper is published

VERSION 2 – AUTHOR RESPONSE

Your coment is highly appreciated. Thank you and have a wonderful day!