Reviewer comments: 2013-0009	
Title	Variation between Canadian centres in the uptake of treatment for hepatitis C by patients coinfected with HIV: a prospective cohort study
Authors	Jim Young, Martin Potter, Joseph Cox, Curtis Cooper, John Gill, Mark Hull, Sharon Walmsley, Marina B. Klein
Reviewer 1	**Linghua Yu**
Institution	The First Affiliated Hospital of Jiaxing Medical College, Department of Infectious Diseases and Hepatology Unit, The First Affiliated Hospital of Jiaxing Medical College, Jiaxing, Zhejiang, China
General comments	There're two figures in Figure 1, but the legend does not explain the difference between them clearly. Does these two figures stand for the difference in treatment uptake between provinces or between the magnitude of centre? The author should add additional illustration about these two figures.
Reviewer 2	**Naveed Janjua**
Institution	BC Centre for Disease Control, Epidemiology, Vancouver, BC
General comments	This is a really well-timed paper in the Canadian context and provides an important insight about HCV treatment for high risk population. Here are few comments: Methods: 1. It would be useful to expand section on information collected from investigators/providers providing details on provider/institution level variables that were assessed especially for variables not described in previous publications. 2. Why don't you add investigator/provider related variable in the model to assess if these are related to treatment on the top of individual level factors. 3. There was variation in access to various services especially availability of elastography and addiction services at the treatment centre? It may be worth assessing their effect on the treatment uptake? 4. There may be value in creating a score of responses from investigators on criteria used for offering treatment presented in table 4. Results 5. Females were less likely to start treatment while in you intro mentioned males are less likely to start treatment. Why it's different in this cohort?
Reviewer 3	**Aranka Anema**
Institution	British Columbia Centre for Excellence in HIV/AIDS, St. Paul's Hospital, Vancouver, BC
General comments	This paper has great potential to inform improved understandings of HCV treatment uptake issues in Canada, but is not publishable in its current form. The manuscript requires more attention to detail - particularly in description of methods and in interpretation of results. Please find comments attached. All the best. **INTRODUCTION** Authors should cite current estimate of the number of people living with HCV in Canada, and prevalence range among IDU based on reports by previous cohorts. Overall Introduction is nicely written. **METHODS** Overall this section could be significantly strengthened by inclusion of more detail about study cohort, variable selection/definition and statistics used: **Description of CCC:** Authors should write a few more descriptive sentences about the CCC to clarify: i) Date range for participant enrollment; ii) Specific provinces involved; iii) What types of questions were included in survey (e.g. socio-demographic, behavioral clinical) and whether survey was self- or interviewer-administered; iv) Variables should be better defined (e.g. how were psychiatric morbidity, homelessness and current drinking measured? What is clinical threshold for end stage liver? What is recall time for crack/cocaine use?). Epidemiological cut-offs and references should be cited for each, where possible. v)It would have been interesting if authors included rural/urban residence as a potential covariate, based on population size of participant/provider-reported post code. vi) What types of information was extract from blood samples. Clinical/laboratory cut-offs should be explained/justified. vii) Presumably informed voluntary consent was obtained participants and should be mentioned; viii) Include institutions from which REB approval was obtained.

Statistics:
Authors currently only describe Weibull modeling technique, and have not explained how baseline characteristics were analyzed. If bivariable comparison is not preferred by the authorship team, there should at least be a mention of the fact that baseline characteristics were explored by calculating mean for continuous variables, and proportions for dichotomous ones.

INTERPRETATION

Interpretation could be significantly strengthened by explaining how and where their results are consistent with or diverge from previously published studies. This section is very weak in terms of inclusion of relevant / current references and comparison to existing evidence:

i) First line of interpretation is overstating descriptive results and should be removed.

ii) Given that access to elastography and harm reduction services are cited as potential explanations for variations in HCV treatment uptake, authors should dedicate a paragraph in discussion to exploring this further and cite basic descriptive data on availability of such services at CCC sites. Other factors that may explain findings, that were not explored in analysis include type of front-line clinical provider at CCC sites. Authors should describe potential role of different HCV service modalities in HCV treatment uptake and response - e.g. nurse led http://www.ncbi.nlm.nih.gov/pubmed/23362288 vs other modalities; combination with addiction treatment services, e.g. http://www.ncbi.nlm.nih.gov/pubmed/23298178; http://www.ncbi.nlm.nih.gov/pubmed/23036920

iii) In discussion around importance of individual patient decision-making to explain differences between centres, authors should elaborate on potential roles of :
- Education to increase HCV-infected individuals' knowledge of and uptake of treatment and to improve patient-provider communication:
http://www.ncbi.nlm.nih.gov/pubmed/23509897
-Psychosocial treatment readiness:
http://www.ncbi.nlm.nih.gov/pubmed/22564797
-Creation of an enabling environment for, gaining trust of, and negotiating flexibility with patients:
http://www.ncbi.nlm.nih.gov/pubmed/23465200
- Peer support, nutritional guidance, and weekly provider contact:
http://www.ncbi.nlm.nih.gov/pubmed/23420134
-Cultural and linguistic stigma:
http://www.ncbi.nlm.nih.gov/pubmed/22440043
-Fact that homelessness did not appear to be a relevant individual-level factor for HCV treatment uptake is inconsistent with literature, including in Canada – e.g.
http://www.ncbi.nlm.nih.gov/pubmed/23121361 - and should be described.

iv) Authors should speak to additional potential provider-related characteristics that may be influencing outcomes, such as:
-patient to provider ratio
-provider experience

iv) What are authors saying when they state that survey was 'relatively informal' - was it a semi-structured interview?

v) Authors should contextualize findings within Canada' current clinical and policy atmosphere, for example by citing innovative models of care;
http://www.ncbi.nlm.nih.gov/pubmed/22001894. Where appropriate, relevance of findings to policy and practice should be extrapolated beyond Canada to the US:
http://www.ncbi.nlm.nih.gov/pubmed/22715216

vi) Limitations sections is completely missing. Authors should describe biases inherent in study design, variable definitions and participant recall; potential biases introduced by failure to account for known or unknown potential confounders; and suggest ways in which analysis could be improved in future studies.

ADDITIONAL MINOR COMMENTS:

Typos:
-Aboriginal should be consistently capitalized throughout manuscript;

Tables 1 & 2:
-Reference for sex variable changed from male (in Table 1) to female (in Table 2). While this isn't a big deal, it would be a cleaner read and provide more consistency if authors maintain a consistent reference;
-To be consistent with Table 1, Table 2 should write include ART (as acronym), rather than spell

	out entire word; -Table 2 should be reviewed for use of consistent significant figures – e.g. for age variable, should read: 0.75 – 1.00;
Author response	Reviewer: 1 Comments to the Author There are two figures in Figure 1, but the legend does not explain the difference between them clearly. Do these two figures stand for the difference in treatment uptake between provinces or between the magnitude of centre? The author should add additional illustration about these two figures. [Editors' note: this information may be better presented as a table.] We have expanded the legend to better explain what each plot shows and the (lack of) difference between them and the legend now reads: "Median rank (and 95% credible interval) for each of the 16 cohort centres: rank was ordered from best (1) to worst (16) at starting an average patient on treatment for hepatitis C during follow up. There was considerable uncertainty about which centres were best but Centres 8 and 15 appeared particularly effective at getting patients started on treatment. The graph on the right shows these centre ranks when data on hepatitis C treatment prior to or at enrolment was included in the Weibull model as prior information. Including this prior information did not materially reduce the uncertainty about which centres were best." Reviewer: 2 Comments to the Author This is a really well-timed paper in the Canadian context and provides an important insight about HCV treatment for high risk population. Here are few comments: Methods: 1. It would be useful to expand section on information collected from investigators/providers providing details on provider/institution level variables that were assessed especially for variables not described in previous publications. In the new Table 1, we include information on the availability of transient elastography (Fibroscan) and addiction services at each centre. 2. Why don't you add investigator/provider related variables in the model to assess if these are related to treatment on the top of individual level factors? We carried out an analysis to see if there was appreciable variability between centres in treatment uptake after adjusting for case mix. We were surprised by the degree of residual variability and explored why this could be. So the second part of our analysis was exploratory. The risk of adding every provider related variable to the model is that we could be misled by 'false positives' if we indiscriminately consider many variables. We therefore just consider the variables we identified as of interest - elastography and addiction services – as suggested below. But even then, this post-hoc analysis is data-driven and consequently, these additional results cannot confirm the importance of these covariates. 3. There was variation in access to various services especially availability of elastography and addiction services at the treatment centre? It may be worth assessing their effect on the treatment uptake? We carried out this additional analysis and report the results in the Discussion (because this was not a planned analysis). The new text reads: "As suggested by a reviewer, we added additional covariates to our Weibull model representing access to transient elastography and addiction services: adding the latter had no effect, but adding the former reduced the estimated residual variation in treatment uptake between centres ($\sigma 2$ = 0.7, 95% CI 0.4 to 1.4)." 4. There may be value in creating a score of responses from investigators on criteria used for offering treatment presented in table 4. We think this is beyond the scope of our study. In addition we doubt we have sufficient data for both a development and a testing data set and without testing, a score would be of unknown reliability. Results 5. Females were less likely to start treatment while in you intro mentioned males are less likely to start treatment. Why is it different in this cohort? We expect the difference arises because of different settings: the studies cited in the Introduction were in US war veterans. Our results may not apply in other setting – we now note

this as a limitation and illustrate with this as an example. We now write:

"Our results may not apply in other settings: for example, in this study females were less likely to start HCV treatment but in a study of (mostly male) American war veterans, males were less likely to start treatment."

Reviewer: 3
Comments to the Author
This paper has great potential to inform improved understandings of HCV treatment uptake issues in Canada, but is not publishable in its current form. The manuscript requires more attention to detail - particularly in description of methods and in interpretation of results.

INTRODUCTION
Overall Introduction is nicely written.
1. Authors should cite current estimate of the number of people living with HCV in Canada, and prevalence range among IDU based on reports by previous cohorts.

We have added this information to the Introduction along with suitable references.

METHODS
Overall this section could be significantly strengthened by inclusion of more detail about study cohort, variable selection/definition and statistics used:

Description of CCC:
Authors should write a few more descriptive sentences about the CCC to clarify:
2. Date range for participant enrollment;
3. Specific provinces involved;
4. What types of questions were included in survey (e.g. socio-demographic, behavioral clinical) and whether survey was self- or interviewer-administered;
5. Variables should be better defined (e.g. how were psychiatric morbidity, homelessness and current drinking measured? What is clinical threshold for end stage liver? What is recall time for crack/cocaine use?). Epidemiological cut-offs and references should be cited for each, where possible.
6. It would have been interesting if authors included rural/urban residence as a potential covariate, based on population size of participant/provider-reported post code.
7. What types of information were extracted from blood samples? Clinical/laboratory cut-offs should be explained/justified.
8. Presumably informed voluntary consent was obtained participants and should be mentioned;
9. Include institutions from which REB approval was obtained.

First we should say that the manuscript has always had a reference to a cohort profile with background information on the CCC. Some of this information has now been updated and included in the new Table 1. This table gives the province of each centre (point 3).

We have added new material on the CCC to the Introduction, to address points 2, 4, 7, 8 and 9, and this new material reads:

"Patients have been enrolled at 16 centres across Canada since 2003, with centres in university hospitals and community based clinics in both small and large urban areas (Table 1). All eligible patients at each centre were invited to participate. Patients giving informed consent underwent an initial evaluation followed by study visits scheduled every six months. At each visit, socio-demographic and behavioural information were self-reported in questionnaires; blood was taken for biochemical, virologic and immunologic analyses; medical treatments and diagnoses were collected by research personnel. The AUDIT-C questionnaire was used to measure alcohol use.{Bush 1998} The Cohort's research was approved by the community advisory committee of the Canadian HIV Trials Network and by all institutional ethics boards of participating centres."

In Table 2, we have amended variable descriptions and added footnotes to address points 5 and 7.

Statistics:
10. Authors currently only describe Weibull modeling technique, and have not explained how baseline characteristics were analyzed. If bivariable comparison is not preferred by the authorship team, there should at least be a mention of the fact that baseline characteristics were explored by calculating mean for continuous variables, and proportions for dichotomous ones.

We report descriptive statistics for patients at cohort enrolment – this is not an analysis of data but a summary of data. What we have done is so very common in the medical literature that no further explanation should be necessary.

INTERPRETATION
Interpretation could be significantly strengthened by explaining how and where their results

	are consistent with or diverge from previously published studies. This section is very weak in terms of inclusion of relevant / current references and comparison to existing evidence: 11. First line of interpretation is overstating descriptive results and should be removed. This first sentence is not the interpretation of a descriptive result. In the second paragraph of the Methods we state "We fitted a Weibull time to event model with a normally distributed random intercept for each centre so we could estimate the variation between centres in treatment uptake." In the second paragraph of the Results, we give the results of this exercise: "Even with case mix adjustment, there was still appreciable variation in treatment uptake between centres (estimated between centre variance [$\sigma 2$] = 0.9, 95% credible interval [CI] 0.5 to 1.5, without informative centre priors; $\sigma 2$ = 0.9, 95% CI 0.5 to 1.5, with informative centre priors)." Hence the first sentence of the Interpretation is a summary of what our modeling implies: "There is variation in the uptake of HCV treatment between our cohort centres that cannot be explained by differences in the patients seen at each centre." 12. Given that access to elastography and harm reduction services are cited as potential explanations for variations in HCV treatment uptake, authors should dedicate a paragraph in discussion to exploring this further and cite basic descriptive data on availability of such services at CCC sites. Other factors that may explain findings, that were not explored in analysis include type of front-line clinical provider at CCC sites. Authors should describe potential role of different HCV service modalities in HCV treatment uptake and response - e.g. nurse led http://www.ncbi.nlm.nih.gov/pubmed/23362288 vs other modalities; combination with addiction treatment services, e.g. http://www.ncbi.nlm.nih.gov/pubmed/23298178;http://www.ncbi.nlm.nih.gov/pubmed/23036920 See our responses to Reviewer 2: we include information on the availability of elastography and addiction services at each centre in our new Table 1; we have carried out additional modelling with respect to access to these services. As noted above, we carried out an analysis to see if there was appreciable variability between centres in treatment uptake after adjusting for case mix. The risk of then adding numerous provider related variable to the model is that we could be misled by 'false positives' if we indiscriminately consider many variables. 13. In discussion around importance of individual patient decision-making to explain differences between centres, authors should elaborate on potential roles of : - Education to increase HCV-infected individuals' knowledge of and uptake of treatment and to improve patient-provider communication: http://www.ncbi.nlm.nih.gov/pubmed/23509897 - Psychosocial treatment readiness: http://www.ncbi.nlm.nih.gov/pubmed/22564797 - Creation of an enabling environment for, gaining trust of, and negotiating flexibility with patients:http://www.ncbi.nlm.nih.gov/pubmed/23465200 - Peer support, nutritional guidance, and weekly provider contact: http://www.ncbi.nlm.nih.gov/pubmed/23420134 -Cultural and linguistic stigma: http://www.ncbi.nlm.nih.gov/pubmed/22440043 -Fact that homelessness did not appear to be a relevant individual-level factor for HCV treatment uptake is inconsistent with literature, including in Canada – e.g. http://www.ncbi.nlm.nih.gov/pubmed/23121361 - and should be described. When adjusting for case-mix, it is probable that many covariates are correlated. For the purposes of case-mix adjustment, that does not matter. However it may then appear that homelessness is not a relevant factor in treatment uptake, when in fact it is likely that homelessness is associated with other risk factors such as infection drug use or Aboriginal ethnicity and these other risk factors are strongly associated with treatment uptake. We have added to the Discussion to note the potential role of these patient level interventions in efforts to improve treatment uptake. The relevant text now reads (with new material underlined): "Programs designed to increase HCV treatment uptake in injection drug users are being introduced in Canada,26 when it is not clear how best to improve the unacceptably low uptake in this key patient population.7 Community based primary care, peer support groups and multidisciplinary care are all approaches that may help.{Grebely 2010}{Grebely 2011} Patient related barriers to treatment uptake are important but difficult to overcome. Our study suggests provider barriers are as important …" 14. Authors should speak to additional potential provider-related characteristics that may be influencing outcomes, such as: -patient to provider ratio -provider experience We have slightly amended our discussion of this issue which now reads:

	"We did not survey all clinicians working at each centre, and between centre differences could be due, at least in part, to different levels of experience at each centre or different workloads." 15. What are authors saying when they state that survey was 'relatively informal' -was it a semi-structured interview? The way data are collected can influence responses. For example, social desirability bias is likely to be an issue for face to face interviews but much less an issue for a web based survey. Such differences are known as mode effects (http://en.wikipedia.org/wiki/Mode_effect). We suspect that a web based survey is perceived by respondents as a relatively informal environment. This has both advantages (lower social desirability bias) and disadvantages (quick completion possibly with less introspection) and the rapidly increasing use of web surveys may lead to survey fatigue (so respondents take them less seriously). There is a rapidly growing literature on how web surveys might compare to other modes of data collection. We can do little more than alert the reader to the issue. We amend this sentence and provide an appropriate reference so the sentence now reads: "Web surveys are a relatively quick and anonymous method of data collection and this can influence responses.(Couper 2011)" 16. Authors should contextualize findings within Canada' current clinical and policy atmosphere, for example by citing innovative models of care; http://www.ncbi.nlm.nih.gov/pubmed/22001894. Where appropriate, relevance of findings to policy and practice should be extrapolated beyond Canada to the US: http://www.ncbi.nlm.nih.gov/pubmed/22715216 We think this is beyond the scope of this particular study. 17. Limitations sections is completely missing. Authors should describe biases inherent in study design, variable definitions and participant recall; potential biases introduced by failure to account for known or unknown potential confounders; and suggest ways in which analysis could be improved in future studies. Our paragraph of limitation did not have a subheading. We have added this, and the paragraph also includes new material on the choice of covariates for case mix adjustment, on loss to follow up and on whether our results can be expected to apply in other settings. ADDITIONAL MINOR COMMENTS: Typos: 18. Aboriginal should be consistently capitalized throughout manuscript; Changed as suggested. Tables 1 & 2: 19. Reference for sex variable changed from male (in Table 1) to female (in Table 2). While this isn't a big deal, it would be a cleaner read and provide more consistency if authors maintain a consistent reference; Changed as suggested. 20. To be consistent with Table 1, Table 2 should write include ART (as acronym), rather than spell out entire word [Editor's note: Please spell out antiretroviral therapy] Abbreviations removed throughout the manuscript (except for HIV and HCV, with the latter defined when first used). 21. Table 2 should be reviewed for use of consistent significant figures – e.g. for age variable, should read: 0.75 – 1.00; We have reviewed the entire manuscript according to the following conventions: "Results should be presented with only as much precision as is of scientific value. For example, measures of association, such as odds ratios, should ordinarily be reported to two significant digits." [http://www.nejm.org/page/author-center/manuscript-submission] "All non-zero digits are considered significant." [http://en.wikipedia.org/wiki/Significant_figures]