Response to Reviewers' Comments

Non-Initiation of HCV Antiviral Therapy in Patients with HIV/HCV Co-Infection

Reviewer #1

Reviewer's Comments		Authors' Response	Manuscript Changes
#	**Comments**		
Reviewer #1 Comment: In the retrospective cohort study, the author aimed to document reasons for non-treatment with HCV therapy and assess how they differentially affected racial and ethnic minorities in 121 patients with HIV/HCV co-infection. It was found that race/ethnicity alone was not predictive of reasons for HCV therapy non-initiation. In conclusion, targeted intervention might improve access to therapy for all patients with HIV/HCV co-infection.			
General:	The topic of this paper is not novel		
General: (study cohort)	There remain several problems in the retrospective cohort study. All of the patients number of Caucasian, Hispanic/other, genotype 2, 3, 4 and the total sample size are too small.	Per comments received from the other reviewers, we have revised our study methodology to include patients that died, into the analyses. This change has increased our overall sample size to 171 patients. We have also included "death" as a non-modifiable medical reason for not receiving therapy, but we welcome the reviewers' thoughts on this approach and we will revise our methodology accordingly. Given the study sample (HIV/HCV coinfected patients in North Carolina), it is expected that most patients would be African-American and that few patients would have genotypes 2,3,4. We better describe this in the Discussion section.	We have now increased the sample size to 171 patients. We have added references to the Discussion to corroborate our findings regarding race/ethnicity and patient genotype.
	Moreover, only 22 patients had HCV RNA data among 121 patients with HIV/HCV co-infection.	It is likely that most patients had HCV RNA data at some point during the study period. However, the reason	The Methods have been revised accordingly:

		for fewer patients (n=22) with HCV RNA data is that HCV RNA was measured at baseline (± 30 days of positive HCV antibody test result) to standardize the variable for patients entering the cohort at varying times during the study period. As we have revised our inclusion criteria, this number is now n=35. We now clarify this definition of baseline in the Methods.	"Baseline clinical characteristics were measurements taken proximal (allowing a 30-day window) to the date of the first positive HCV test."
Conclusion	In the first sentence of conclusion, "modifiable, potentially modifiable, and non-medical reasons for non-treatment did not differentially affect racial and ethnic minorities co-infected with HIV/HCV", "modifiable" should be "non-modifiable"	Agreed.	We have simplified this sentence as follows: "In summary, reasons for non-treatment did not differentially affect racial and ethnic minorities co-infected with HIV/HCV."
Figure 1	The description of "whites" in the last two figures of Figure 1 is inappropriate that should be replaced with "Caucasians".	Agreed.	"Whites" has been changed to "Caucasians."

Reviewer #2

Reviewer's Comments		Authors' Response	Manuscript Changes
#	**Comments**		
Reviewer #2 Comment: Oramansionwu wt al, carried-out a retrospective cohort study to analyse the effect of different medical and social variables on non-starting anti-HCV treatment in HIV/HCV patients. They selected retrospectively a cohort of co-infected patients that did not start treatment and they registered in this cohort non-modifiable and potentially modifiable medical variables, as well as non-medical variables. They did not find any relation between the racial/ethinc origin and the causes involved in not starting treatment. The study is well written and the design and objectives are perfectly described. Nevertheless, in my opinion there are two shortcomings.			
General:	Firstly, the authors excluded patients that did not start treatment if they couldn't find information about genotype or the patient died. They should analyse the medical and social features of the excluded patients, because the non-enrolled patients could bias the results if these patients were predominantly from the same ethnic origin. Therefore, these cases should be either included in the analysis or another analysis in this cohort should be performed to show that there is no a selection bias.	We have added patients that died into the analyses. We purposely listed genotype as an inclusion criterion, as genotype may influence treatment initiation (and ultimately treatment response) given the therapies that were available during the study period.	We have now included patients that died into the study and have increased the sample size to 171 patients. This is now reflected in the Methods and the Results. We have revised the Methods accordingly: "Patients were included in the study if they had the following: 1) a concomitant diagnosis of HCV based on positive HCV serostatus (as determined by HCV antibody test enzyme-linked immunosorbant assay [ELISA]/enzyme immunoassay [EIA]) and 2) a positive HCV recombinant immunoblot assay (RIBA) test, detectable HCV RNA, or HCV genotype test results."
General:	Another issue is that authors analysed only non-starting treatment cases, but it could be very informative to know what happened with cases starting treatment. Since it	We agree that it is possible that with the advent of newer DAAs, some of these patients have now (as of today) initiated HCV therapy. But if we were to include this information	The following text has been added to the Methods: "For each reason type (non-modifiable medical, potentially

	could be possible that some patients starting treatment could have some of the reasons for not starting treatment and this could be related with the ethnic origin. To sort out this problem, the authors should have considered the independent variable as a categorical variable (treatment indication: positive or negative) and the dependent variable as the ethnic origin. They should have carried out a logistic regression controlled by the other co-variables (modifiable and non-modifable medical and non-medical reasons). In my opinion the quality of the study would increase if they also record the data from patients starting treatment and if they analyse the features of the non-enrolled cases.	(patients who initiated treatment), this would impact our study design and impede the ability to address our study objectives. Our intent was to restrict the sample to non-treated patients and to document common reasons for treatment non-initiation in that sample of patients. We now clarify our dependent variables and independent variables in the Methods to be in line with our study objectives.	modifiable medical, and non-medical), risk factors such as age, gender, race/ethnicity, insurance status, and select HIV clinical characteristics were analyzed using multivariate logistic regression. Three separate regression models were fit for each reason type; the three reason types were the dependent variables in the respective models.”

Reviewer #3

Reviewer's Comments		Authors' Response	Manuscript Changes
#	**Comments**		
Reviewer #3 Comment: : I enjoyed reading the manuscript of "Non-initiation of HCV antiviral therapy in patients with HIV/HCV co-infection" by Oramasionwu et al. The manuscript evaluated the reasons for non-treatment with HCV antiviral therapy and to assess how they differentially affect racial and ethnic minorities with HIV/HCV co-infection. It may help to recognize and overcome potential treatment barriers in order to improve treatment uptake and eradicate HCV in this patient population in the era of DAAs. The study period is from 2004 to 2011, when PR therapy was the standard of treatment for HCV patients with or without HIV co-infection. Although the study has some limitations, it may be interest to the readers of the journal. And I think this manuscript maybe accepted with a major revision.			
Major 1a:	Although patients with different genotype have a different efficacy may a reason of non-initiation of HCV antiviral therapy in this patient population. In view of vast majority of patients were genotype 1 (92%), patients lack of HCV genotype results should not excluded in this study.	Given the study sample (HIV/HCV coinfected patients in North Carolina), it is expected that most patients would be African-American and that few patients would have genotypes 2,3,4. We better describe this in the Discussion section. We purposely listed genotype as an inclusion criterion, as genotype may influence treatment initiation (and ultimately treatment response) given the therapies that were available during the study period.	We have added references to the Discussion to corroborate our findings regarding race/ethnicity and patient genotype. The Methods have been changed as follows: "Patients were included in the study if they had the following: 1) a concomitant diagnosis of HCV based on positive HCV serostatus (as determined by HCV antibody test enzyme-linked immunosorbant assay [ELISA]/enzyme immunoassay [EIA]) and 2) a positive HCV recombinant immunoblot assay (RIBA) test, detectable HCV RNA, or HCV genotype test results."
Major 1b	Also, the patients died during the study period should not excluded in this study, since the study just to document reasons of non-initiation of HCV antiviral therapy. In this way, the	Agreed.	We have now included patients that died into the study and have increased the sample size to 171 patients.

	sample size will be significantly increased.		

Major 2:	Advanced immunosuppression (CD4<200) was a common reason for non-treatment for HCV, and was an indication for HAART. A considerable portion of patients with advanced immunosuppression and received HAART, how does the author rule out the effect of this confounding factor on non-initiation of HCV antiviral therapy in different racial/ethnic group.	We are not able to fully rule out this confounding effect. We attempted to adjust for baseline HAART in regression analyses, but inclusion of the variable demonstrated poor model fit. Rather, in our final model, we controlled for baseline CD4, which was not associated with having a non-modifiable medical reason for non-treatment. There was a high proportion of HAART at baseline among all patients (73%), but we did not measure HAART at later time points, nor did we assess continuity of HAART among patients with advanced immunosuppression. It is possible that patients who had advanced immunosuppression documented as a reason for non-treatment were maintained on HAART, but did not experience the full clinical benefits of HAART due to regimen adherence, regimen appropriateness, and/or due to inability to achieve immune reconstitution (all unmeasured factors in our study. We address these limitations in the Discussion section.	We have revised the Discussion section to address this limitation.
Major 3:	As described by the authors, the main shortcoming of the article is that authors did not evaluate differences in HCV treatment by race/ethnicity.	We agree that it is possible that with the advent of newer DAAs, some of these patients have now (as of today) initiated HCV therapy. But if we were to include this information	No changes made.

		(patients who initiated treatment), this would impact our study design and impede the ability to address our study objectives. Our intent was to restrict the sample to non-treated patients and to document common reasons for treatment non-initiation in that sample of patients. We now clarify our dependent variables and independent variables in the Methods to be in line with our study objectives.	
Major 4:	Why only a few patients have HCVRNA data,17 patients (14%) and 5 patients (4%) before and after May 1, 2007, respectively.	It is likely that most patients had HCV RNA data at some point during the study period. However, the reason for fewer patients (n=22) with HCV RNA data is that HCV RNA was measured at baseline (± 30 days of positive HCV antibody test result) to standardize the results for patients entering the cohort at varying times during the study. As we have revised our inclusion criteria, this number is now n=35. We now clarify this definition of baseline in the Methods.	The Methods have been revised accordingly: "Baseline clinical characteristics were measurements taken proximal (allowing a 30-day window) to the date of the first positive HCV test."
Minor 1:	Reference 11 and 29 is the same literature, please delete one.	Agreed.	Reference 29 is deleted.
Minor 2:	The language is excellent, exclude a few typing mistakes, such as Page 4, Line 5 of Core tip: 'modifiable medical reasons' should be 'non-modifiable medical reasons'; Page 13, first Line of Conclusion: 'modifiable' should be ' non-modifiable', etc	Agreed. We have reviewed the manuscript and addressed any other typographical errors.	These changes have made throughout the manuscript.