The authors appreciate the helpful reviews and have responded to each reviewer individually below:

1. *Reviewer 00034635 – Minor Revision*

Hunt et al retrospectively examined an electronic recorded cohort of 19,304 patients who received Anti-CD20 agents and analyzed the pre-treatment testing of HBsAg, HBsAb and HBcAb status. The authors broadly categorized 2 groups of patients according to their serological profile (HBV + and HBV-). Despite testing coverage was 80% of the whole cohort, only ? 37% of those at risk (HBV +) received anti-viral treatment. As expected, those categorized as HBV+ suffered higher rate of acute hepatitis, however, there were no difference rate of liver failure or overall mortality among groups. Interestingly, 16 cases of HBV-negative patients developed hepatitis which suggest that profound immunosuppression may render HBV-negative subjects more susceptible to HBV infection. Unfortunately, the effect of preemptive treatment could not be assessed due to a low number of patients under treatment.

a. Minor Comments: Could the authors identify differences of effectiveness between the different antiviral drugs? adefovir, entecavir, lamivudine, tenofovir, and telbivudine

   The authors appreciate your helpful review. Due to the very low use of hepatitis B antivirals in the analysis, these small numbers precluded an analysis to assess the effectiveness of different hepatitis B antiviral treatments.

2. *Reviewer 00506601 – Major Revision*

This is a record review study of Veteran electric health records from 2002-14 who received anti-CD20 treatment looking at hepatitis B status. The data base used is impressive and the population examined is ideal for such a review.

a. Specific comments: In the Abstract the authors say that most veterans have HBV testing prior to anti-CD20 treatment, but only 64% were screened for HBsAg and 56% for HBcAb. With 44%-36% veterans not being screened I don't think you can say that most veterans are being screened.

   The authors agree that "most" could be more accurately in the conclusions as: "*While HBV testing of Veterans has increased prior to anti-CD20 Ab, few HBV+ patients received HBV antivirals, suggesting electronic health record algorithms may enhance health outcomes.*"

b. On page 10, first paragraph; the authors state that the HBV assays were qualitative and as normal ranges were not provided in CDW (the data warehouse) numerous serology results were indeterminate. I don't know what they mean by this statement. Most HBV test are qualitative and there are no

normal ranges because 1=positive, 2=negative, 3=indeterminate or whatever convention the lab uses. This is the standard for these tests so what are the authors talking about?

The authors agree that many hepatitis B tests are qualitative. We are referring to quantitative hepatitis B DNA (to determine hepatitis B reactivation), quantitative hepatitis B surface antigen (increasingly used to assess hepatitis B viral burden and antiviral treatment response), and quantitative hepatitis B surface antibody (to evaluate protective antibody response to hepatitis B vaccine). Specifically, hepatitis B viral reactivation is most accurately identified increases in quantitative hepatitis B DNA of 1 logarithm or greater.

c. Statistical Analysis In reading this section I really wonder if the authors ever read or wrote another scientific paper before. They start out the section by mentioning the name of their statistician as if that was adequate for describing the statistics used in the paper.

The World J. Gastro. Manuscript guidelines request (Section 1.18 Biostatistics): "Any manuscript describing a study (basic research and clinical research) that used biostatistics must include a statement in the Materials and Methods section affirming that the statistical review of the study was performed by a biomedical statistician." Therefore, the authors have retained the following test: "*A biomedical statistician performed the statistical analyses and completed pre-submission statistical review.*"

d. They need to state what statistical software was used to perform the analysis and what type of analysis was done. What p values were used to connote significance and if they did multivariate analysis.

The Methods have been updated to include: "*Statistical analyses were performed using Stata MP-64 version 13.1 (StataCorp LP, College Station, Texas), and differences were considered statistically significant when the p-value(s) were less than 0.05.*" Multivariate analyses are not included.

e. No one cares about the name of their statistician.

We have deleted our statistician's name in Methods.

f. They have 0% and 1% in their tables, there should be Standard Errors (SE) around these percentages since these numbers appear to be very unstable. Even if they didn't have small numbers all %s need SE.

We agree and have added standard error (SE) for the mean age data in Table 1, and to Figure 4, which profiles peak ALT and bilirubin by hepatitis B category during anti-CD20 antibody treatment and 12 month followup.

g. On all the Figures there need to be titles.

As the reviewer's suggestions conflict with the World J. Gastro. Manuscript guidelines, we complied with the guidelines in (Section 1.20 Illustrations): "The figure's title and legend must be presented on a separate page from the figure itself."

h. Figure 1a is missing. Figure 1b is a change over time but there is no discussion in the paper about the change over time when the figure is discussed. Why?

The authors included Figures 1a and 1b in the uploaded manuscript for review, and are unclear how Figure 1a was missing. However, we identified a numeric error in Figures 1a and b which has been corrected in the enclosed version. We agree that it's important to discuss these figures – and have included the following in Results (Hepatitis B Testing): *"Prior to anti-CD20 Ab treatment, 62-73% had HBsAg and HBcAb tested at any time pretreatment in 2014 (Figure 1). During the study period, the rates of HBsAg and HBcAb testing increased more than two-fold (Figure 1) with overall pretreatment HBsAg and HBcAb measured in 53% (10,224/19,304) and 41% (7903/19,304), respectively".*

i. Page 13, Antiviral Treatment during High-Risk Period for HBV Reactivation: In the first sentence the authors state that across all HBV disease categories 2-22% of the HBV antiviral treatment in the high-risk period was associated with HIV infection. 2-22% is an awfully large range. This seems to be dropped in the paper out of nowhere. They mention Figure 2 but figure 2 seems to have nothing to do with HIV.

Few patients receiving hepatitis B antivirals exhibited concomitant HIV infection. We have clarified the HIV data in Results as follows: *Across all HBV disease categories, few patients receiving HBV antiviral treatment in the high-risk period had concomitant HIV infection (ranging from 1 in 59 to 2 in 9, or 2 to 22%). Overall HBV antiviral use throughout the study period ranged from 10-37% in HBV positive patients at risk for reactivation (Figure 2); the highest rate of HBV antiviral use was 37% in those with definite chronic HBV."*

j. Actually I have no idea what figure 2 is portraying with decimal points on the y axis and years on the x axis. The discussion of figure 2 in the paper seems unrelated to the actual figure since no mention of time over the years anywhere

in the paper except to say this is a record study of VA data from 2002-2014 but the years in the table are 2004-2014.

Figure 2 portrays hepatitis B antiviral treatment during anti-CD20 Ab treatment and 12 month follow-up period by hepatitis B category during the study period 2002-2014. Figure 2 is now better described in Results as:
"Overall HBV antiviral use <u>throughout the study period</u> ranged from 10-37% in HBV positive patients at risk for reactivation (Figure 2); the highest rate of HBV antiviral use was 37% in those with definite chronic HBV."

k. There is an unlabeled figure between Figure 2 and 3 portraying who knows what??? This all just very sloppy writing and proof reading on the part of the authors.

The authors are unclear about the unlabeled figure (which does not appear in their manuscript version). No figures are unlabeled in the revised paper.

l. On page 17 the authors list as a weakness the predominately qualitative HBV serology tests. They need to become more familiar with HBV serology tests so they are aware that this is what you get from the standard serology tests.

The authors have clarified the reference to quantified hepatitis B DNA (to detect hepatitis B reactivation), as revised in Discussion:
"Study limitations include the lack of VHA standardization of HBV serology resulting in some indeterminate results, and the predominantly qualitative HBV serologies. While HBV reactivation is generally identified by logarithmic increases in HBV DNA, reverse seroconversion (newly appearing HBeAg or HBsAg), or increases in ALT,[27] the very limited <u>quantified</u> HBV DNA and HBeAg data required us to focus our evaluation on hepatitis – which occurs less frequently than HBV DNA increases in reactivation.[4]"

m. I was also not sure why on Page 17 the authors described antiviral practice in a Spanish medical center. It made no sense since we are talking about U.S medical treatment.

While we described U.S. medical treatment, we sought results of successful implementation programs to effectively prevent hepatitis B reactivation globally. As the Spanish medical center provided the best such example, it was included in the discussion.

3. **Reviewer 00006789 – Accept without revisions**

The retrospective study presented by Hunt et al demonstrate the necessity to screen patients for HBV before anti-CD20 Ab treatment, and most likely, prior to the

administration of any immunosuppressive treatment; in order to determine if the patient will benefit from HBV vaccination or preventive antiviral treatment. This simple measure will reduce the number of HBV-related deaths occurring in a number of patients. It is an interesting and relevant study.

a. **The authors appreciate your helpful review**