Answer to reviewer's comments:

Reviewer #1: The manuscript, "Remdesivir investigational trials in COVID-19: a critical reappraisal", addresses an extremely important issue of the most important infectious disease of our time, namely evaluation of a proposed antimicrobial treatment for COVID-19. The authors aptly point out the critical need to identify effective therapy for infection with SARS COV-2 in the setting of pandemic disease that has thus far killed >300,000 persons. In that context, a critical evaluation of the impact of the antiviral drug remdesivir on outcomes of this disease is timely and extremely important. Nonetheless, the work presents data in a way that makes it somewhat difficult for a reader to come to similar conclusions. In addition, in several places the language is more editorial than neutral, which detracts from the most important message, i.e, that it is far too premature to identify remdesivir as a curative or life-saving intervention. Some comments for the authors consideration.

1. In several places the manuscript contains language that verges on editorialization.
Line 18-20: "...the competition appears to be the fight between repurposing low-cost generic products and assess the efficacy of newly developed extremely expensive products.....not exclusively guided by science and public health."
Author response: We agree with the reviewer and we remove this sentence.

Lines 77-80: "The bad scientific quality of this paper sponsored and written by Gilead employees...."
Author response: we change the sentence for "Scientific veracity and credibility of this paper sponsored and written by Gilead employees is questioned as well as the quality of the review by the N Eng J Med , ethical consideration of what is compassionate used and the role of industrial funding in trials bias"
Line 110: "...no future investment should be made."
Author response: Still few studies have been reported on evaluation the new drug remdesivir. In many aspects, data from a case report or series without controls mean little to nothing in the context of evaluating efficacy of an experimental drug. On the other hand, RCTs takes time and rarely bring usable information during time of outbreak. Three RCTs have data available, but two share the same aims and give contradictory data. Only one is methodologically adequate with both IPP and PP analysis on a cohort of patient having completed the study demonstrating the absence of difference between drugs and standard of care.

As today no study convincingly supports the use of remdesivir in severe patients. It is likely that, such as for influenza, the major key for COVID-19 outcome is the early treatment of patient at the time of diagnosis. However serious adverse reactions, some leading to interruption of treatment, and the IV route, would probably limit the use of remdesivir in this indication.

Although these statements could be valid and appropriate in an editorial, the inclusion in a scientific evaluation detracts somewhat from an otherwise non-biased presentation of facts. In that context, recommend that the authors focus entirely on these studies, and present the flaws of each a more neutral, fact-based tone. Alternately, the work could be presented as an editorial, which could be appropriate, but would then need to be identified as such rather than a peer-reviewed scientific paper.

2. It would be helpful for the authors to define specifically what they consider important outcome/endpoint measures (e.g., survival, days hospitalized, days on mechanical ventilation, thromboembolic sequelae, etc.) and then evaluate these studies against these metrics. As written, the 11 reports appear to be summarized and critiqued individually, which misses an important

opportunity to evaluate the efficacy (or lack thereof) of this drug in reducing morbidity and mortality. A table summarizing these measures would perhaps be more concise and powerful than dissecting each study separately in the text.
Author response: we agree with the reviewer but at this time only three RCTs have been made available, two of them share the same goal (Remdesivir versus placebo) but only one as an adequate methodology. Not enough data are available to merit meta-analysis. We add a table summarizing the available outcomes at endpoints.

As pointed out appropriately by these authors, treating patients early in disease has always been a crucial issue in treating potentially life-threatening infectious diseases. This point should be highlighted earlier, and particularly in the critique of these studies, as it is often lost by persons outside of the clinical arena.
Author response: we add this information in the introduction but also in the conclusion.

3. Where possible, there should be some statistical analysis of the data from different studies, or when that is not possible, document that flaw. In many aspects, data from a case report or series of 12 patients without controls mean little to nothing in the context of evaluating efficacy of an experimental drug. That would be a fair statement.
Author response: we include this in the discussion

4. Some work is needed to correct word choice and grammatical errors.
Introduction: quotation marks are not needed for severe acute respiratory syndrome, coronavirus disease 2019, Middle East respiratory syndrome coronavirus.
Line 11. Unclear what is meant by the word "decried" in this context.
Author response: we changed for discussed
Line 12. Replace "aware" with "inform".
Author response: ok
Line 26, Replace "deposit" with 'deposited"
Author response: OK
Line 40. "Negativation" not a word--suggest replacement.
Author response: normalization
Line 107. Suggest replacing "decried" with "criticized".
Author response: We have removed this word