Title: Is there continued evidence for an association between abacavir usage and myocardial infarction risk in individuals with human immunodeficiency virus (HIV)?: a cohort collaboration

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Author’s response to reviews:
Reviewer #2:

First I would like to thank the authors for allowing me to review their work. The objective of this manuscript is to provide more evidence with regards to the relationship between abacavir and the risk of MI among HIV+ people. Of concern for the authors is the potential of "channelling bias" that may be associated with the use of abacavir over time particularly given reports in some but not all studies that abacavir is associated with increased AMI use. This study uses the well phenotyped DAD cohort.

I think the paper overall is interesting and will add to the literature but I don't think it solves the issue at hand as to whether abacavir is truly associated with an increased CVD risk or not. As the authors report in their conclusion, confounding by indication is still potentially a very large player in this study and cannot be easily removed even with the thoughtful study design. That is to say these observational data are not valuable but SMART and results from the Women's health initiative ( HIV+ and uninfected people examples) thought us with regards to medications to be very careful hanging our hat on observational data.

We do appreciate that we can never eliminate the potential role of unmeasured confounders (and as the reviewer notes, we have acknowledged this in our Discussion). However, we believe that the weight of evidence that is now available, both from our own lengthy and varied analyses and from other, independent methodological and mechanistic studies, would suggest that confounding is unlikely to be a possible explanation for our findings.

Comments I would like the authors to address

Table 3 has same ARR between pre and post 2008 but the absolute rates are 50% less for both groups... person time is less but not proportionately...this pattern is again noted in Table 4. Why would the rates drop so substantially? My initial thought was difference in exposure risk to the drug but follow up time is less but not 50% less. In low risk people of which this most of the people are in this sample based on Table 1, suggests extremely low risk post 2008. Even with a high "relative risk" such a low absolute rate may make the relative risk meaningless in the context of risk stratifying and treating people... I think the authors should comment on this phenomenon and explain what it means in the context of treating people with HIV if abacavir were used.
We have continued to see a drop in the risk of MI in the cohort over time, similar to that which has been seen in the general population. Much of this has been due to the increased use of preventive medications and interventions (e.g. lipid-lowering drugs, anti-hypertensives, coronary artery bypass grafting, etc.), as reported in a previous publication from the cohort (Data Collection on Adverse Events of Anti-HIV Drugs Study Group. Clin Infect Dis 2008;46:1101-1110). However, we have also seen a certain level of smoking cessation in the cohort which has also been associated with a reduced MI risk (see Petoumenos K et al. HIV Med 2011; 12:412-21). Secondly, it is likely that we would expect to see a ‘cohort effect’ as we do not continually refresh the cohort (only on three separate occasions prior to 2008), and thus those at highest risk of MI will experience an event soon after enrolment. Finally, as in any observational study, there is always a concern about under-ascertainment of events in the most recent year of follow-up (which invariably occurs as some MI events may not be reported to the clinician until some months after they have occurred). Thus it is likely that the lower rate in the second period of study is a combination of these three phenomena.

Whilst it is true that a high relative rate may have little clinical relevance if the absolute rate is low, such information on potential drug associations with serious outcomes is extremely important. Our research focuses on whether abacavir does, indeed, increase the risk of MI – clearly the clinical relevance of these findings in a given situation will always be dependent on the underlying risk of the event in an individual patient. We note that the relative rate that we see is similar even in the high CVD risk group and this is the group where focus should primarily lie. We have added a short section to the first paragraph of the Discussion to clarify this issue.

Second issue: the fact that the rates of AMI increase so dramatically with increasing FRS suggests that comorbidity and not abacavir is what is really driving AMI risk in this population. Rates increase 10 fold with increasing risk factor burden! This point should also be made in the manuscript. While addressing the abacavir is important, these data strongly support the need for risk factor control to reduce AMI risk perhaps even more than the concern for abacavir. No evidence was provided that suggests ABC is interacting with risk factor burden nor does that seem likely.

We have demonstrated on several occasions that individuals with an MI in the cohort DO generally have established CVD risk factors and the role of these risk factors in determining MI risk is similar to that which would be expected in the general population (e.g. smokers are at about two-fold risk of MI, say). As such, we agree with the reviewer that traditional CVD risk factors contribute significantly to CVD risk in this population. However, an investigation of the role of these traditional risk factors was not the aim of this present manuscript – rather, our aim
was to investigate whether abacavir exposure continues to be associated with an excess risk of MI in a period when any confounding by indication would be expected to be reduced – and, indeed we saw that this was the case. Of note, and as noted above, even in the group with a high Framingham risk score, the current use of abacavir is associated with an almost doubling in the risk of MI and this isn’t explained by the underlying CVD risk factors. Thus, it is not the case that traditional risk factors alone are driving the AMI risk within these individuals. As such, in these high risk patients, both traditional risk factors and abacavir are major drivers of CVD risk. At a cohort level, of course, the attributable risk associated with abacavir use is likely to be lower than that of the standard risk factors as a smaller proportion of the participants will be receiving this drug (compared to the proportion that are smokers, say). However, it is at least a risk factor that appears to be modifiable (unlike some of the other established risk factors) and therefore deserves attention.

Reviewer #4:

This study provides an update to the 2008 D:A:D analysis demonstrating an association between abacavir use and MI, and examines changes in the use of ABC that followed the publication of the original D:A:D study results. The association of abacavir and MI continues to be a controversial topic, with mixed results across various study populations and designs. This study is particularly germane given the recent approval of a single-pill ART regimen that includes abacavir, which is likely resulting in an increase in its use. Furthermore, the D:A:D study is one of the few that are powered to examine the association between abacavir and MI specifically, rather than a composite CVD event outcome. This is overall a well-conducted study and well-written manuscript. Most of my comments are minor, but I do have a few major comments about the analytic approach:

1) There is no discussion of the potential selection bias that can be introduced by adjustment for factors on the causal pathway that may also be confounders (see Hernan et al., Epidemiology 2004), as was done in the sensitivity analyses here. For example, renal function may be both 1) on the causal pathway from abacavir to MI and 2) a predictor of both abacavir initiation/discontinuation and MI, and thus a time-dependent confounder. Several studies on abacavir and CVD have specifically tried to address this problem using marginal structural models (Brouwer et al., Epidemiology 2014; Young et al., JAIDS 2015; Marcus et al., JAIDS 2015; Desai et al., CID 2015). I would suggest either adding an analysis to address this potential bias or at least highlighting this in the discussion as a limitation of this study.
Whilst others have had some success with this approach, an analysis of this type would be very difficult with the approach that we’ve taken to the categorisation of the use of abacavir and other ART drugs (where current exposure states can change repeatedly in an individual). Our primary analyses specifically did not adjust for factors thought to be on the causal pathway for exactly this reason, and we have now further clarified this in the Methods section. However, whilst we recognise that the failure to adjust for some of these factors could be seen as a limitation of the study, we don’t believe that our findings would be altered dramatically. Had these factors been on the causal pathway, then we would have expected the RR associated with current abacavir use to be attenuated after adjustment for these factors – the fact RR associated with current abacavir use was virtually unchanged from analyses that did not include these additional factors suggests that these factors do not actually lie on the causal pathway. This is also supported by mechanistic studies which suggest that the abacavir association acts through a very different pathway. At the same time, causal models themselves make several major assumptions that may not be testable. Thus, we do not agree that this is a limitation of the study. We have, however, added some further text to the end of the Discussion around this point.

2) I question the collapsing of the low and unknown CVD risk groups into one category. Figure 1 suggests that receipt of abacavir differs substantially between these groups, and the unknown CVD risk group may be driving the results presented in Table 2 on changes in initiation and discontinuation of abacavir. There is no discussion of what this group may represent; do we think they are likely to be low or high CVD risk? Furthermore, while their CVD risk, as measured by the Framingham risk score, is unknown to the authors (perhaps due to missing blood pressure or smoking data), it may have been known to the clinicians making decisions about their abacavir use (e.g., because of reduced renal function or other known CVD risk factors). If the unknown CVD risk group is included, I think the ORs should be presented separately for the low and unknown comparison groups, data should be provided on how many subjects were in each CVD risk category, and there should be some discussion about what this group may represent.

Note that the only time that we have combined the low and unknown groups into a single category is for the analysis that looks at factors associated with initiation and/or discontinuation of abacavir. All remaining analyses that incorporate CVD risk either incorporate it as a four-category variable or exclude the unknown group on the basis that the association within this group would have been of limited clinical interest as well as the fact that (as explained below) it would be of limited size in the post-2008 dataset.
To clarify, the group with unknown CVD risk largely reflects patients who were recruited to the study in the earlier calendar years at a time when many of the components that are required to calculate the Framingham risk score were not routinely monitored – as this is a time-updated covariate, much of this missing information has become available over time and therefore the proportion of follow-up time spent with missing CVD risk drops from 63.5% <2000 and 42.3% in the period 2001-2003, to only 15.7% in the post-2008 period. In the early years of the study, it is likely that those with missing information on Framingham risk score would not have been perceived to be at high CVD risk. Thus, it does not seem unreasonable to assume that they would most closely resemble the low risk group as far as the clinician choice as to whether to start or stop abacavir (ie. if the clinician isn’t aware of the raised CVD risk then it is unlikely to affect his/her prescribing). We don’t believe that there would be much additional information on CVD risk that would be available to the clinician that isn’t already captured on the database – for example, renal monitoring was relatively rare until 2004, and tenofovir was not used widely until later in the study – however, if renal monitoring had been performed, then the information would be captured on the database. The analyses are also adjusted for all other standard, non-FRS, CVD risk factors.

At the reviewer’s suggestion we have, however, repeated the analyses reported in Table 2 after excluding those with unknown CVD risk. The aOR (95% CI) for initiation of abacavir in those with moderate/high risk was 0.99 (0.74-1.32) in the pre-March 2008 period and 0.68 (0.43-1.06) in the post-March 2008 period (interaction p-value 0.0007). For discontinuations of abacavir in those with low or suppressed viral load, the aRR (95% CI) were 1.16 (1.02-1.31) and 1.48 (1.33-1.66) in the two periods, respectively (interaction p-value 0.0001). Finally, for discontinuations of abacavir in those with non-suppressed viral load, the aRR (95% CI) were 0.99 (0.89-1.11) and 1.25 (1.03-1.51) in the two periods (interaction p-value 0.05). Thus, the changes in the aOR/RR over the two periods were, if anything, stronger in this analysis and we hope that this will reassure the reviewer that these findings are not driven by the group with unknown CVD risk. However, due to the reduction in power in the earlier calendar period when missing data are excluded, we have retained our original analyses in the paper.

3) The authors focus on current abacavir use as the exposure of interest, arguing that the state of the evidence is consistent with a short-term effect. However, several studies have found an increased risk per year of abacavir use (see review by Bavinger et al., PLOS ONE 2014), with several finding that the risk increased after about three years of use (Brouwer, Marcus, Young). This study would be strengthened by the addition of an analysis that explores duration of abacavir use and risk of MI. A survival curve would be particularly helpful. At the very least, there should be some discussion of the possibility of a cumulative effect that would not have been identifiable with the approach used.
We have previously reported several analyses of associations with duration of abacavir use (as a continuous covariate) and have not found this to be a significant predictor of MI risk. As we argue in the paper, we do not believe that the mechanistic data support such a cumulative association and therefore do not wish to repeat previous published analyses without any reasonable hypothesis. Furthermore, it is not clear what the interpretation would be of any stratified analysis that includes cumulative exposure (as the exposure to abacavir in the post-2008 group could have occurred both prior to and after 2008 – this is not the case with current exposure).

We are not clear how a survival curve would be appropriate in the current analysis as patients stopping abacavir may restart at later periods and it is not clear what the appropriate time zero would be (nor how we would stratify this by calendar period as far fewer patients have started the drug in the post-2008 period and these patients are substantially different). Of note, we have previously published a figure showing the unadjusted MI rate stratified by year of exposure to abacavir (Worm SW et al, J Infect Dis 2010; 201:318-330) – whilst this figure suggests that in unadjusted analyses there is an increasing trend to the risk with increased exposure to the drug, this association disappears completely after adjustment for other drugs in the ART regimen and for age.

Minor comments:

Background

1) The first paragraph of the paper is unnecessary and a bit confusing, and could be omitted.

We have removed this paragraph as suggested.

2) There are other recent studies on abacavir and CVD outcomes that could be referenced in the second paragraph (Desai, Marcus).

We have not currently referenced all studies in the paper as there are now many (and our reference list is already very long). Therefore the papers cited are examples of the total published literature. However, we have added these two references as suggested.
3) It may be worth mentioning in the third paragraph that subsequent analyses adjusted for renal dysfunction not only because it is a marker of CVD risk, but because it is associated with channeling away from tenofovir.

That is true, but as tenofovir did not become available in many of the participating cohorts until sometime during the study (by which time there was already some evidence of an association with abacavir), this wasn’t the primary reason for us to include this as a covariate in the model.

Methods

4) According to the methods, "the proportion of follow-up time in each year that was contributed by individuals receiving ABC" was calculated, but I don't see this in the results. Figure 1 shows the proportion of participants receiving ABC, not follow-up time.

Actually, the figure is generated based on the total follow-up in each year and the proportion of that which is spent on abacavir. However, as most people generally received abacavir for the full year, this is essentially the same as the proportion of patients on abacavir in the year. However, as this may be confusing, we have modified the y-axis label to Figure 1.

5) Why was follow-up through 6 months after the last clinic visit, rather than the date of the last clinic visit? This should be explained.

The censoring strategy (pre-defined for all D:A:D analyses) is based on the usual time by which a patient would be expected to re-attend clinic, and information on death would become available to clinicians through routine means. As some cohorts obtain mortality data from death registries, following all patients until death, including those who had been lost to follow-up, could introduce differential censoring between those who did and did not die. We have described this approach in a previous publication from the study (see: Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group. AIDS 2008; 22:2143-2153).

Tables

6) Personally, I prefer footnotes that include the factors included in adjusted models so that readers don't have to reference the methods section.
We are happy to change this if the Editor thinks this is appropriate (and it fits with journal style). However, this is very much a personal preference and other reviewers may feel the opposite.

Discussion

7) There should be some acknowledgment of the lack of statistical significance for some of the results shown in Table 1. For example, "somewhat less likely" in the second sentence is a bit vague.

Whilst we appreciate the reviewer’s point, the key hypothesis being tested here is not that those with moderate or high risk have a significantly lower odds of initiating abacavir in the 2008 period compared those with low or unknown risk, but that the association between CVD risk group and initiation of abacavir significantly changed in the post-2008 period (as demonstrated by the interaction p-value). The wording was carefully chosen to avoid any over-interpretation of a non-significant finding and so we prefer to retain it.

8) Another reason the abacavir and MI association has not been observed in trials may be the shorter duration of follow-up, particularly if there is a cumulative rather than short-term effect.

This is true although, as noted above, we do not believe that the evidence (from several sources) points to a cumulative effect, and our earlier findings have suggested that the risk of MI increased soon after initiation of abacavir.

References

9) References seem to be off, at least toward the end (49, 50…).

We apologise – these have been updated.