This article by Y Jiang et al. describes an analysis of the frequency of KIR genes, HLA-B antigen subsets and combinations of KIR3DL1/S1 and HLA-Bw4*80I combined genotypes in 132 HIV infected individuals, which include 40 long term non progressors (LTNP). These individuals are classified as having either high or low CD4 counts, high or low viral load or being LTNP versus typical progressors (TP). Overall they find that carriage of the KIR3DL1+KIR3DS1+HLA-Bw4*80I+ is more frequent in LTNP than TP, that Bw6 homozygotes are more frequent in TP and that carriage of the KIR3DL1+KIR3DS1-HLA-Bw4*80I- genotype is associated with higher viral load and lower CD4 counts. They also observe higher levels of mRNA for KIR3DS1 in LTNP and low levels of KIR3DL1 mRNA in TP.

The question posed by the authors could be better defined. The methods are in general appropriate but should be better described. There are some questions regarding the data as discussed below in the review. The discussion and conclusions are in general well balanced and supported by the data. The limitations of the work are not clearly stated. The authors acknowledge work upon which they are building but because they have categorized study subjects in a manner that is different from what has been done by other it is difficult to place this article in the context of the field as it stand at present. The title needs to be changed. The abstract accurately conveys what has been found. The writing is acceptable but needs to ne gone over again to make language usage more rigorously what is being reported and to make additional corrections.

Overall, this manuscript needs to be reorganized and refocused in order to build on what has already been published on KIR3DL1/S1 HLA-B and HIV infection. In its present state it is difficult to appreciate how the information presented relates to previous work because the alleles and genotypes studies are not categorized as others have done and because no rationale is provided for why they are categorized differently in this manuscript. These points should be addressed before this manuscript is accepted for publication.

Major Compulsory Revisions
1) The main critique I have with this manuscript is that it uses language that pushes their interpretation of the results that certain genotypes are the cause of a phenotype (whether that be low or high CD4 count, low of high VL or LTNP versus TP status). Their data only show associations between certain genotypes
and HIV outcomes and it is an over interpretation of their results to assume a causal relationship between the 2.

The title is an example of this: “KIR3DS1/L1 and HLA-Bw4-80l affect HIV disease progression among HIV typical progressors and long-term nonprogressors” should be changed to soften the idea that these genotype “affect” disease progression. Other examples of this can be found on page 14 par 2 (“…play a vital role in slowing…”) page 16 paragraph 2 (“…in inhibiting HIV disease progression…”) and par. 3 (“…mRNA has an impact on HIV disease progression…”), page 18 par 3 line 1, page 20 par. 2 line 5 and in other parts of the discussion. The authors need to change the text to remove language that reflects a causal relationship between their data and HIV outcome.

2) KIR3DL1 and KIR3DS1 have a high degree of homology. The description of the relative quantitative analysis for KIR mRNA expression section on page 9-11 was difficult to follow. Please clarify this section by adding additional detail linking the data generated with the data shown in Figure 2. The authors should include in this manuscript examples of the raw data that was used to generate Figure 2 that demonstrate that the reactions are specific for KIR3DL1 and KIR3DS1. Does this methodology pick up the copy number variation for KIR3DS1 and KIR3DL1 reported by Pelak et al? If so this should be mentioned and reported.

3) On page 12 1st and 2nd paragraphs the gene frequency of KIR3DS1 and KIR3DL1 in subjects having different outcomes is reported. I do not think that the terminology used here is correct. KIR3DL1/S1 is a locus (or a gene) within the KIR region that encodes both KIR3DL1 and KIR3DS1 alleles. When reporting that the KIR3DS1 gene is more frequent in those with high versus low CD4 counts the authors apparently mean alleles since they consider the 5 individuals who only have KIR3DS1 alleles as being KIR3DS1 homozygotes and having 2 allele copies (Table 2 for KIR3DS1 consider 44 alleles from 34 heterozygotes and 10 homozygotes). What is being analyzed for the KIR3DL1 “gene” in the text and Table 2 is confusing. The sum of KIR3DL1+ observations adds up to 127 for CD4 counts and viral load and 118 for LTNP+TP. This does not correspond to the number of KIR3DL1 alleles in homozygotes + heterozygotes. One would expect that this is what should be analyzed given that this is what was analyzed for KIR3DS1. What do these KIR3DL1 “gene” numbers correspond to? This section and Table 2 either need to be clarified to justify the use of the word gene to describe KIR3DL1 and KIR3DS1, which I think is incorrect. The results should be reanalyzed by considering alleles (usually 2 copies per locus) in which case the denominator for their analyses would be 132 subjects X 2 alleles per subjects = 264 alleles (unless they have access to copy number variation information) or analyse between group differences in genotypes (KIR3DS1 homozygotes, KIR3DL1/S1 heterozygotes and KIR3DL1 homozygotes). Also Table 1 line 1 “KIR allele” should be “KIR gene” for most of the data presented in this table excluding that for the KIR3DL1/S1 locus is reporting the frequency with which each gene is present.

4) On page 13 paragraph 3 states that persons who are HLA-Bw4*80l have higher CD4 counts. HLA-B*57 belongs to this group, which is an allele well
recognized to be associated with LTNP status and viral load control. Since 40 LTNP are included in this study a high frequency of HLA-B*57 would be expected and may be driving the results the authors attribute to HLA-Bw4*80I. Do the authors have information on the HLA-B locus allotype? If so please report whether the frequency of HLA-B*57 explains these observations. This point should be discussed in the discussion section as well.

5) On page 14 paragraph 3 this section would be much clearer if the genotypes were better described. Lines 1/2 and 4 KIR3DS1/3DL1 “gene” should be “genotype”. On line 5 does KIR3DS1+HLA-Bw4-80I+ genotype describe genotypes with at least 1 copy of KIR3DS1 (i.e. heterozygotes and homozygotes?) Who is included in the KIR3DS1-HLA-Bw4*80I- genotype group (Only KIR3DL1 homozygotes?). On page 15 par 1 line 5/6 are not KIR3DS1-HLA-Bw4*80I- and KIR3DL1+KIR3DS1-HLA-Bw4*80I- the same group? And so on…. These paragraphs would benefit from better organization and synthesis and this would follow from a better definition of groups in the methods section or by reporting on the 3 generic genotypes with and without co carriage of Bw4*80I. Another issue not addressed is that HLA-Bw4 alleles that are not *80I, i.e. those that have a threonine at position 80 of the HLA heavy chain are ligands for KIR3DL1 and can educate NK cells through the KIR3DL1 receptor for activity upon encountering targets with reduced HLA-B expression. This is not considered by in this manuscript at all. Why?

6) For the data appearing in Figure 2 the number of datapoints shown indicates that this represents a subset of the study population with approximately 30 data points shown. How were these selected? Are all those tested KIR3DL1/S1 in this figure heterozygotes? Add this information to the text.

7) For the data shown in Figure 3A there is one data point that is an outlier with relative KIR3DS1 mRNA levels between 9 and 12. Does the statistical significance of the correlation between CD4 counts and KIR3DS1 mRNA levels survive when this point is removed? If not this should be mentioned in reported.

Minor Essential Revisions

1) There are several instances where references have been incorrectly cited. Reference 4 by Pelak et al in not a correct references for the statement on page 4 that “…the polygenic KIR gene complex codes for varying numbers of inhibitory and activating receptors.” It may be if the author mean the KIR3DL1 locus specifically. The statement one on page 5 regarding NK activation status being regulated by interactions between KIR and HLA class I gene products. I do not think that reference 8 is appropriate for the statement that KIR and HLA exhibit remarkable diversity and rapid evolution as this reference describes work done in non human primates.

2) On page 5 and later in the text the authors need to be cautious regarding whether HLA-Bw4*80I is a ligand for KIR3DS1 as there is no direct evidence for this statement and much against this possibility. I would refer then to JP Vivien et al in Nature 2011.
3) The statement made on page 6 that KIR2DL3 has a strong protective effect in HIV infected individuals preventing them from becoming immunological non responders is too strong a statement for an observation that found an association between presence of a KIR/HLA genotype and an outcome after starting HAART. The authors did not show that carrying the genotype was the cause of the outcome measured.

4) LTNP are HIV infected and therefore not resistant to HIV infection. Rather they exhibit a slower rate of disease progression. The statement to this effect on page 6 par 2 line 4 should be corrected.

5) Also on page 6 the authors reference a manuscript by Bostik at al. The mRNA levels that are increased and reported to be associated with high SIV viral load is KIR3DL and not KIR3DL1.

6) The authors study a cohort of 132 HIV positive subjects of which 40 were LTNP. This is a very high frequency of LTNP since one would expect that only approximately 5% of HIV infected individuals would fit the criteria for being LTNP, i.e. only 6 or 7 among 132 subjects. If this is a selected population it should be mentioned in the manuscript. The definitions for high versus low viral load and high versus low T cell counts are arbitrary. Is there a rationale for setting the cut offs where they did for these groups?

7) Regarding KIR and HLA genotyping please state what information the KIR Genotyping SSP kit provides. Is it KIR3DL1/S1 generic genotyping? Does the kit also give information on KIR3DL1 allotyping? Is the HLA typing done to a 2 digit or 4 digit resolution? Is HLA-A considered in assigning whether an individual has a Bw4*80I allele?

8) On page 11 paragraph 3 line 1 the word “detected” should be changed to “screened” since it is unlikely that they detected all the KIR genes and pseudogenes in each person tested.

9) On page 18 the authors mention that others have shown that KIR3DS1 independently associates with higher CD4+ T cell counts but does not have an effect on viral load. Please add the reference for this statement.

10) Multiple analyses were done that should be subjected to Bonferonni’s correction for multiple comparisons. This has not been done in this manuscript. This should be addressed in the discussion as a limitation of the data or the correction should be applied in order to see which comparisons remain statistically significant.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests