We sincerely thank reviewer #1 for the detailed review comments. We have adjusted the manuscript accordingly. Following are the answers in regards to the concerns and questions raised by the reviewer:

**Reviewer 1**

Major Concerns:  
1) The manuscript was difficult to read. Major editing for clarity is needed. For example, the second authors affiliation is written "Coty" of Hope, not "City". I had to re-read sentences several times to figure out exactly what was meant. Also, a lot of very subjective or "jargon" terminology was used throughout. I would avoid use of the words "decent," "good," and "properly." What is "decent" engraftment? >5%? >50%? Again, very subjective. You can say one model engrafts better than another, but not that one model has "good" engraftment. Also, please use a single verb tense within a sentence.

We have gone through detailed proof-reading, typos and wording issues have been addressed.  
2) Please define SRC in the text (SCID repopulating cell) and PBL (peripheral blood leukocyte). You define BLT but not the other two abbreviations.

We have defined the other two humanized mice models accordingly.  
3) In lines 51-52, you make the statement that HIV infects B cells (not true) and DCs (rarely). You could make the statement instead that CD4+ T cells are the major target for HIV infection but other cell types can also be infected, such as myeloid cells.

We have changed the content to “HIV primarily infects human CD4+ T cells, impacts the developments and immune responses in other immune cells such as B cells, macrophages, and dendritic cells, therefore small animal models transplanted with functional human immune system are highly demanded..”  
4) In reference to line 233, the CD4 receptor serves as the primary cellular receptor for HIV entry, not as a cofactor.

We have changed the context to “Significant decrease in CD4+ cell count in expected as CD4 antigen serves as coreceptor for viral entry.”, since CD4 binding does not necessarily lead to viral entry, depending on the tropism of the HIV viruses, coreceptor CCR5 or CXCR4 is required for infection of CD4+ cells.  
5) How many weeks post-engraftment is the mouse shown in Figure 1?

Figure 1 shows the peripheral blood profile at week 10 post-engraftment. We have added the information in the figure legend.  
6) In Figure 2, why are there so few total events in the middle and right panels in comparison to the left panel? Did engraftment levels drop? Also, you state that cART started on Day 28, but the shaded box starts around Day 31. Also, if you want to discuss a restoration of CD4 levels, should also show the pre-HIV levels in Figure 2b.

Thank reviewer #1 for the comments. Since HIV only targets human cells in the presented mice model, as the infection progresses, the CD45 level as well as progenitor immune cell levels in peripheral blood drops with the same volume of blood analyzed.

The shadow box is arranged so that the blood analysis on Day 28 is presented as prior to cART and the shadow box does not cover the data points for the Day 28 analysis. The box is just representing the stage of cART treatment in the model development. Further, it has been clearly stated in the manuscript that cART starts right after blood analysis.

Figure 2a dot-plots have indicated the CD4 percentage prior to the infection, during infection and after cART, which sufficiently identifies the cART responsiveness in the reported mouse model. Figure 2b is to further compare the cART group with non-cART group, showing both the cART response and the latency development in the reported model.   
  
Minor Concerns:  
1) In lines 54-57, I would make it clear that the deficiencies are in murine cell development.

Context has been changed accordingly  
2) The word "researches" is not typically used (found in abstract and conclusion) as "research" is already plural.

Context has been changed accordingly  
3) For protocol, if anticoagulants are being used, then plasma not serum is isolated from blood samples. "Serum" should be replaced with "plasma" throughout (including all text and figure legends).

Context has been changed accordingly  
4) In Figure 3, should read vRNA not vRNa. Also, why are the undetectable viral loads from day 56 shown so far below the LOD when the undetectable points from day 42 are shown just below the line? Also, the corresponding figure legend is worded oddly.

Context has been changed accordingly. Day 42 shows viral loads with 2 weeks of cART treatment, the analyzed results is at or slightly above the LOD, Day 56 is 4 weeks into cART treatment, as typically observed in patient, the viral loads is undetectable. In our qPCR data no trace appears within the amplification cycles, hence the viral load has a value of 0.

**Reviewer #2:**

Manuscript Summary:

The manuscript describe a protocol for reconstitution of humanized NSG mice with human CD34+ HSC cells and utilization of the model for HIV research.

Major Concerns:

Not applicable

Minor Concerns:

Though manuscript is very well written, additional informations could also be included to increase the reproducibility of the protocol by others.

Line 75: Remove the musical word.

Line 142: Please mention the collagenase concentration and incubation time.

Line 150: For the freezing of HSCs, include the name or composition of freezing medium. It would also be useful for the readers if the viability of cells are also mentioned after thawing.

Line 156: What is irradiator source and nature of radiation, gamma rays or x-rays?

Line 146: Correct the name of Miltenyl biotech to miltenyi biotec.

Line 194: Please mention the catalog number of the antibodies, as different antibodies may have different working concentrations, also it would assist in making multicolor panel for immunophenotyping.

Line 218: Please provide the catalog number of p24 ELISA kit used.

Line 235: Provide the sequence of HIV-1 LTR specific primer and probe.

We thank the reviewer for the detailed review and the positive feedback. All the minor concerns have been addressed accordingly.