Author's response to reviews

Title: Transmission of HIV Infection from an Elite Controller to a Patient who Progressed to AIDS: a case report

Authors:

   Michael S Killian (scott.killian@ucsf.edu)
   Girish N Vyas (girish.vyas@ucsf.edu)
   Rochak Mehta (rochak.mehta@roche.com)
   Karen Young (karen.young@roche.com)
   Osman Ebrahim (osman.ebrahim@telkomsa.net)

Version: 3 Date: 21 February 2012

Author's response to reviews: see over
February 18, 2012

Dear Editor:

We thank the reviewers for their helpful critiques. As a result, additional analyses have been performed and the manuscript has been revised as detailed in the following responses:

Reviewer A:

We are pleased by the comment that the “topic is highly interesting to the community”.

1. “... the evidence for the event of the transmission from an elite controller to his wife is relatively low.”

We agree that, relative to experimental findings, the evidence is low. However, relative to most studies of HIV transmission, the evidence is fairly strong. Many studies of HIV transmission are based on self-reported exposures that include multiple sex partners and needle sharing. In this case report, there is a man who had a blood transfusion in South Africa and his wife who tested negative for HIV prior to this event. Nonetheless, this limitation is stated in the discussion (see p.5).

2. “... contamination during nucleic acid extraction and PCR has to be excluded.”

The nucleic acid extractions and PCR reactions were performed at the Roche Molecular Diagnostics (RMD) laboratory in California where HIV-1 clade C is very rare. Roche is a leader in PCR technology and in HIV diagnostics. RMD holds licenses, certifications and registrations with multiple national and international quality assurance agencies. Thus, we are confident that safeguards are in place and that PCR contamination is not likely.

3. “Please refer to HIV-1 instead of HIV.”

HIV-1 is now used throughout the text.

4. “Introduction: Please specify how long elite controller at least must have undetectable viral load and be asymptomatic to fulfill elite controller criteria having been used in the paper.”

There is no consensus on the definition of an elite controller in terms of the duration of the aviremic period. In general, the definition requires having <50 HIV RNA copies/ml for the large majority of test results spanning 1 or more years. This is now stated on p.3. Having undetectable plasma viral loads for 10 years, MM is clearly an elite controller.

5. “Results: What is the reason to report about the neutralization capacity of MM’s serum? The paper is not addressing the topic of potential reasons for MM’s elite controller status. So skip the phrase.”

The phrase has been omitted in the revised manuscript.

Reviewer B:

We appreciate that Reviewer B has also found the topic interesting.

1. Is the age (31 years) of both partners the age at diagnosis (i.e. in 2001) or the current age?
Both partners were 31 years old at the time of presentation/diagnosis. This is now stated in the text (see p 3-4).

2. At what time point were the samples for sequence analysis obtained?

Samples for sequencing analysis were obtained in 2008 as now indicated on p.4.

3. The major issue that needs to be clarified in my opinion is the following: Was the male partner also interviewed about his sexual history? The manuscript only states that he “gave no history of any infectious diseases” and only “surgery 3 years previously for treatment of an abdominal gunshot wound” is reported as a potential transmission route. If a sexual history was not obtained this has to be clearly stated because it weakens the argument of transmission during the aviremic phase. I would assume that he did have sexual contacts before, which are at least as likely to pose him at risk of HIV-1 infection as the surgery is. Another question is if he did require blood transfusion during surgery, because without this, transmission of HIV via this event is very unlikely. Thus, the surgery is clearly not the only possibility for him to have acquired HIV infection, and he may well have transmitted the infection to FF during acute infection acquired much less than the 3 years before when he had surgery.

The text has been revised to include a more detailed description of MM’s history (see p.4). Indeed, he reported having a monogamous relationship with FF and that he had no prior sex partners. He also reported having received a blood transfusion.

4. How was sequencing accomplished in the male partner when “On at least eight separate occasions spanning this 10 year period, MM tested negative for HIV DNA by PCR.”? What was different in the PCR method used to amplify for sequencing from the PCR method used in detection? The only difference I could notice is that for sequencing “total nucleic acids (both DNA and RNA)” were extracted, whereas for the detection attempts probably only DNA was extracted.

Roche used a nested PCR approach that involves 2 rounds of PCR amplification. Also, recent studies indicate that HIV DNA and RNA tests have comparably low sensitivities (~0.55) when the virus levels are very low (J Pediatr. 2012 Jan;160(1):6).

5. A final issue I want to raise is about the sequence comparisons to determine the relationship of the sequences from MM and FF. Wouldn’t it have been possible to do a phylogenetic analysis even with those short sequence fragments? Although from a conserved region, the heterogeneity of the sequences used is quite substantial. Furthermore, the distance from other sequences may have been overestimated in the analysis shown here using only sequences from a sequence database. If one would also include local sequences from the same area, the relationship of the sequences of MM and FF might not be as unique as it is presented here.

This good suggestion prompted us to include a phylogenetic analysis in the revised manuscript. For this task, we used the LANL HIV database, an exceptional resource that contains more than 414,398 HIV sequences collected from the major sequence repositories (e.g., GenBank, EMBL, and DDBJ). It is true that the sequences of MM and FF are most similar to other clade C sequences from South Africa. Still, this analysis confirms that their viruses are similar enough to constitute a transmission pair.