Reviewer's report

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

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Reviewer: Hauke Walter

Which of the following best describes what type of case report this is?: New associations or variations in disease processes

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is the case report ethical?: Yes

Is there any missing information that you think must be added before publication?: No

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: Yes

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: No

Is the anonymity of the patient protected?: Yes

Comments to authors:

The paper improved a lot. I understand now, that the authors do not try to say there is, but there may have been a transmission from an elite controller to his wife, because there is some evidence. To be sure, there is a need to prove not only that the viruses are so closely related that a chain of infection is likely but also to show the direction of infection was without a doubt from the elite controller to his wife and not vice versa. Still, the data cannot support this second hypothesis without any doubt. Therefore, the title of the manuscript is misleading and should reflect the remaining limitations of the conclusion. E.g.: Evidence for Transmission of HIV-1 infection by an Elite Controller to a Patient who progressed to AIDS: a case report.

In order to the same argument, there are still some parts of the manuscript that
need to be rephrased:

Abstract: “His plasma HIV-1 RNA levels were measured and have remained undetectable for the past decade.”

This phrase could be misunderstood indicating that the “past decade” is dated before the transmission occurred. If so, the direction of transmission would be obvious. But this is not the case, so the phrase is misleading. Exchange “past” by “next”.

Results: “In comparison to the consensus HIV-1 clade C sequence, MM differed at 1 of the 255 bases, while FF differed at 6 of the 255 bases. Importantly, the 1 difference in MM’s sequence was present in FF’s sequence. Further analyses, performed using the QuickAlign tool in the HIV database, revealed that the majority of published clade C sequences differ from MM’s sequence in this region at greater than 10 of 255 nucleotides (Fig. 2C). Moreover, less than 1 percent of the 400 published clade C viruses differed at 6 or less bases in this region.”

I appreciate that you performed phylogenetic analyses. But what does it show? I had to enlarge your figure 6-fold to make the tiny MM knob visible showing the minimal distance of the two strains MM and FF. Please focus in the figure on clade C strains preferentially while keeping on the total number of strains in the analysis (all of them clade C). It is not necessary in this paper to show that clade C is distant from other HIV-1 clades (as long as your isolates obviously cluster in clade C).

“Even fewer would be expected to share only the discrepant nucleotide.”

As already mentioned in the last review, the relative proximity of strains cannot be shown adequately by the presence of a single common nucleotide, even if it is unpresent in the clade C consensus sequence. Now me, I checked the frequency of this particular G base within clade C sequences and detected approx. 35% (n=200) of strains harbouring this nucleotide (which is not the majority and therefore not present in clade C consensus sequence). In South Africa live approximately 6 million people infected with HIV-1, of which approx. the moiety is infected by clade C strains. 0.5% of 3 million are 15,000, resulting in 5,000 individuals in whole South Africa, being HIV 1 infected by a clade C strain including the exceptional G nucleotide of MM and FF, as well as with a difference in sequence homology of 6 or less bases in the gene region you sequenced. E.g. in Johannesburg do live approx. 3.9 million people, of which 12% may be infected by HIV resulting in >45,000 HIV-infected individuals living in Johannesburg. Assuming, there would be no cluster of “Johannesburg-strains”, which is certainly wrong, this already results in approx. 400 HIV-infected people living in Johannesburg and having HIV-1 strains with a similar homology like FF and MM, just by incidence and not by being part of a particular infection chain.

Therefore, show a more detailed analysis for the exceptionally interesting area of sequences with 6 or less nucleotides difference to the reference strain in the figure. It is ok to argue for the group of 6 or less bases differences together (in the text), because the data covers the maximal difference of FF’s and MM’s sequences. Of note, the difference between MM and FF is not 6 but only 5 nucleotides, because the G is common between the two relevant sequences.
This minimizes the number of sequences with similar low homology further and should be clearly addressed by you to improve your argumentation.

Discussion: “Though unlikely, it remains possible that we are incorrect in our assessment of the transmission history. This would require an improbable sequence of events, the inaccurate reporting of FF’s sexual history, and that mere chance explains the shared divergent mutations between the virus sequences of FF and MM.”

Many people do often lie about having had sex with a person other than their partners. This is not unlikely but regular if somebody is cheating on someone (Of note, >10% of all children seem not to know their real father!).

In addition, FF could have been infected after the last negative HIV-test during her previous pregnancy and before her marriage with MM, without having lied. The sequence homology between MM’s and FF’s viruses is not “mere chance” but easily to explain as long as you simply assume MM was infected by FF (which would be in accordance of being faithful). This would explain perfectly the high similarity of both strains. This is the most probable explanation for your case in my eyes. You cannot ignore this in your discussion.

Of note, following your scenario, MM was infected by an unknown source, which was either by the blood transfusion or by another sexual contact or by another - totally unreported - risk behaviour. I do not know exactly how safe blood transfusion in Johannesburg was more than a decade ago, but I would assume it was quite safe (according to literature, in South Africa about 10-20 units / (year + country), as long as PCR methods have not been used, (which I cannot confirm for the relevant time)). You think that it is most likely that MM was infected by blood transfusion than that he is lying about either having had sex only with his wife ever or having not reported any other risk behavior, he might have had. This is mere chance.

I strongly suggest to provide an honest and cautious argumentation about the two relevant questions, simply admitting that as long as you believe FF and MM that they had no other sexual contacts in the relevant time, and if you take into account that FF was sero-negative approx. one year before she was diagnosed (with AIDS!), in comparison to MM who could be infected for decades because he obviously is an elite controller, the high homology of their sequences supports the idea that FF was infected by MM, an elite controller.

**Quality of written English:** Acceptable

**Declaration of competing interests:**

No competing interests.