nature portfolio

Peer Review File

Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a CCR5Δ32/Δ32 Sibling Donor

Corresponding Author: Professor Marius Trøseid

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The manuscript by Myhre et al. documents a case report of a 62-year-old man, treated for myelodysplastic syndrome, whom they have identified to be in viral remission for HIV for greater 4 years following hematopoietic stem cell transplantation (HSCT) by homozygous CCR5 delta 32 mutation sibling donor-matched cells. While there are at least 6-7 people living with HIV (PLWH) that have been identified to have achieved a “functional cure” of infection, all involving HSCT treatment for a malignancy, this study has significance in the relative rarity in achieving a functional cure for HIV, the unique use of HLA matched cells from an older sibling, the older ages of the donor and patient (60 and 58, respectively), and in the identification of rapid donor cell reconstitution/chimerism in multiple tissues, including the gut. Comparisons are made between this case and other cure cases in a helpful and insightful manner. The data largely support the notion of a functional cure in this individual, which is historically important. There are a few minor issues that could strengthen this manuscript:

While it is acknowledged in the manuscript that there are limitations in the availability and quantity of cells in the tissue samples, the inclusion of more data points, if available, would strengthen this study.

More data detailing the cellular parameters following lymphodepletion/myelodepletion and the hematopoietic recovery, if available, would strengthen this study, providing greater insight in the use of the indicated conditioning regiment on lymphocyte subsets and allowing better comparison to other approaches.

It would be helpful in the actual Table 1 if it were clarified that, in the “undetectable” samples, the limit of detection is indicated in the HIV copies column, perhaps by an asterisk or a different font. The way it appears is that DNA is present in these samples while it is indicated in the legend and text of the manuscript that it is not. This would better represent the data.

There are reports of several PLWH that received CCR5 delta 32 HSCs that died as a result of complications following the transplantation procedure or due to relapse of the malignancy. It should be clarified that this procedure has been attempted other times and carries significant risks.

In sum, this is an interesting identification of an individual that appears to have achieved a "functional cure" of HIV, which would be of broad interest to the biomedical field.

Reviewer #2

(Remarks to the Author)
This manuscript describes the clinical course and findings of a PWH and myelodysplastic syndrome who underwent an allogeneic transplant, with a sibling donor who was CCR5delta 32 homozygous, who has no evidence of HIV on detailed testing and is no longer on ART.
There are a number of important highlights of this article to be noted, including:
-This work describes a patient transplanted using a sibling donor, which is a unique donor type compared to other reports of PWH undergoing transplant.
-The study team performed extensive reservoir testing with leukapheresis and gut biopsies
-The detailed testing performed by this group replicates other evaluations of potential HIV cure post-allogeneic transplant, although the patient did undergo colonoscopy with extensive biopsies that were studied in detail as well, which has not been reported previously.
-The study team did access and report on features of other PWH undergoing allogeneic transplant that have been reported and compared/contrasted findings with their reported patient.

As an area to add to this work, this patient received vedolizumab as part of the treatment for acute GVHD early after transplant. Vedolizumab has been studied in HIV and shown to have impact on HIV gut reservoir. Given this patient was treated with vedolizumab, I recommend more detailed description of their treatment course and analysis and discussion of how this could have potentially played a role for this patient. Below are just a few references regarding this drug in HIV:
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Gabrielle Meyers, MD

Reviewer #3

(Remarks to the Author)
This is a very well-written paper describing another rare case of HIV cure via SCT. The methodologies applied are state of the art.

A novel aspect is the measurement of donor chimerism in the terminal ileum, which is considered one of the most relevant HIV reservoirs. This makes this case of interest to the readers of this journal. It would have been of added value to assess potential dynamics of the proviral reservoir in plasma in relation to tissue chimerism, or to evaluate CCR5 expression levels of the host in relation to proviral DNA prior to SCT. However, as is often the case with these rare opportunities for cure, the available material was limited.

Remarks:

Case report: It is indicated that the virus was CCR5-tropic. According to the methods, this was determined genotypically by Sanger sequencing, which provides only limited insights and represents a prediction rather than a direct phenotypic assessment. This should be made clear in the text (eg “the virus was predicted to be CCR5-tropic, FPR XX"

Although from a hematological perspective full donor chimerism in tissues is generally considered to be >95%, the question arises whether this definition is equally applicable in the context of HIV cure. Given the emphasis of the paper on tissue chimerism, this issue warrants more attention in the discussion.
The discussion is rather lengthy and could be shortened to improve clarity and focus on the new findings such as the chimerism in the terminal ileum.

Minor points:
In Figure 1, the apparent plateau of viral load at low levels is likely due to the detection threshold of the viral load assay. This should be noted in the figure legend.

Decision Letter:

4th September 2025

*Please ensure you delete the link to your author homepage in this e-mail if you wish to forward it to your co-authors.

Dear Professor Trøseid,

Thank you for your patience while your manuscript "Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a CCR5Δ32/Δ32 Sibling Donor" was under peer-review at Nature Microbiology. It has now been seen by 3 referees, whose expertise and comments you will find at the end of this email. Although they find your work of some potential interest, they have raised a number of concerns that will need to be addressed before we can consider publication of the work in Nature Microbiology.

In particular, we think it would be important to address all the reviewers reports including some directed only to the editor regarding the addition of references for the data presented in supplementary tables 1 and 2. It should also be clear that given the limited number of cells that were available to measure the viral reservoir at the time of donor chimerism and at the start of the JAK inhibitor, firm conclusions about its effect cannot be drawn.

Should further experimental data allow you to address these criticisms, we would be happy to look at a revised manuscript.

We are committed to providing a fair and constructive peer-review process. Please do not hesitate to contact us if there are specific requests from the reviewers that you believe are technically impossible or unlikely to yield a meaningful outcome.

We strongly support public availability of data. Please place the data used in your paper into a public data repository, if one exists, or alternatively, present the data as Source Data or Supplementary Information. If data can only be shared on request, please explain why in your Data Availability Statement, and also in the correspondence with your editor. For some data types, deposition in a public repository is mandatory - more information on our data deposition policies and available repositories can be found at https://www.nature.com/nature-research/editorial-policies/reporting-standards#availability-of-data.

Please include a data availability statement as a separate section after Methods but before references, under the heading "Data Availability". This section should inform readers about the availability of the data used to support the conclusions of your study. This information includes accession codes to public repositories (data banks for protein, DNA or RNA sequences, microarray, proteomics data etc…), references to source data published alongside the paper, unique identifiers such as URLs to data repository entries, or data set DOIs, and any other statement about data availability. At a minimum, you should include the following statement: "The data that support the findings of this study are available from the corresponding author upon request", mentioning any restrictions on availability. If DOIs are provided, we also strongly encourage including these in the Reference list (authors, title, publisher (repository name), identifier, year). For more guidance on how to write this section please see: http://www.nature.com/authors/policies/data/data-availability-statements-data-citations.pdf

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* If you have not done so already we suggest that you begin to revise your manuscript so that it conforms to our Article format instructions at http://www.nature.com/nmicrobiol/info/final-submission. Refer also to any guidelines provided in this letter.

* Include a revised version of any required reporting checklist. It will be available to referees (and, potentially, statisticians) to aid in their evaluation if the manuscript goes back for peer review. A revised checklist is essential for re-review of the paper.

When submitting the revised version of your manuscript, please pay close attention to our href="https://www.nature.com/nature-portfolio/editorial-policies/image-integrity">Digital Image Integrity Guidelines. and to the following points below:

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-- that control panels for gels and western blots are appropriately described as loading on sample processing controls
-- all images in the paper are checked for duplication of panels and for splicing of gel lanes.

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Finally, please ensure that you retain unprocessed data and metadata files after publication, ideally archiving data in perpetuity, as these may be requested during the peer review and production process or after publication if any issues arise.

Please use the link below to submit a revised paper:

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If you wish to submit a suitably revised manuscript we would hope to receive it within 6 months. If you cannot send it within this time, please let us know. We will be happy to consider your revision, even if a similar study has been accepted for publication at Nature Microbiology or published elsewhere (up to a maximum of 6 months).

In the meantime we hope that you find our referees' comments helpful.

Yours sincerely,

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Reviewer Expertise:

Referee #1: Stem cell therapies to cure HIV
Referee #2: Allogeneic hematopoietic stem cell transplantation
Referee #3: Clinical, HIV

Reviewer Comments:

Reviewer #1 (Remarks to the Author):

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Gabrielle Meyers, MD

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The discussion is rather lengthy and could be shortened to improve clarity and focus on the new findings such as the chimerism in the terminal ileum.

Minor points:
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Version 1:

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(Remarks to the Author)
The responses to the reviewer's concerns have sufficiently addressed the issues. I would recommend acceptance.

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I appreciate the authors' thorough review of the comments, with each of these items addressed in the revised manuscript.

Gabrielle Meyers

Reviewer #3

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The authors have addressed the comments very well, and the revisions have clearly improved the manuscript. However, I have one remaining relevant issue regarding newly added information on transplant-related mortality.
I was triggered by the quoted low mortality in this particular statement:
“Although the procedure carries a treatment-related mortality of approximately 10–20%, this risk is considered acceptable given the underlying disease” (Discussion, page 11, lines 236–239)
is ambiguous. It is unclear whether this mortality estimate refers specifically to people living with HIV or to allogeneic stem cell transplantation in the general population, and no time frame for this estimate is provided.
Moreover, the cited reference (Arslan et al., 2019; PMID: 30926447) reports substantially higher mortality in people with HIV

undergoing allogeneic transplantation, with approximately 43% mortality at 12 months (12-month overall survival 56.6%) and ca 51% mortality over total follow-up.
Clarification of the population (HIV-positive vs. general allo-HCT cohorts), the time horizon, and reconciliation with the findings of Arslan et al. would improve accuracy and avoid potential underestimation of risk in this context.

Decision Letter:

Our ref: NMICROBIOL-25062257A

8th January 2026

Dear Dr. Trøseid,

Thank you for submitting your revised manuscript "Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a CCR5Δ32/Δ32 Sibling Donor" (NMICROBIOL-25062257A). It has now been seen by the original referees and their comments are below. The reviewers find that the paper has improved in revision, and therefore we'll be happy in principle to publish it in Nature Microbiology, pending minor revisions to satisfy the referees' final requests and to comply with our editorial and formatting guidelines.

If the current version of your manuscript is in a PDF format, please email us a copy of the file in an editable format (Microsoft Word or LaTex)-- we can not proceed with PDFs at this stage.

We are now performing detailed checks on your paper and will send you a checklist detailing our editorial and formatting requirements in about a week. Please do not upload the final materials and make any revisions until you receive this additional information from us.

Thank you again for your interest in Nature Microbiology Please do not hesitate to contact me if you have any questions.

Sincerely,

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Version 2:

Decision Letter:

19th February 2026

Dear Professor Trøseid,

I am pleased to accept your Article "Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a CCR5Δ32/Δ32 Sibling Donor" for publication in Nature Microbiology. Thank you for having chosen to submit your work to us and many congratulations.

Over the next few weeks, your paper will be copyedited to ensure that it conforms to Nature Microbiology style. We look particularly carefully at the titles of all papers to ensure that they are relatively brief and understandable.

Once your paper is typeset, you will receive an email with a link to choose the appropriate publishing options for your paper and our Author Services team will be in touch regarding any additional information that may be required. Once your paper has been scheduled for online publication, the Nature press office will be in touch to confirm the details.

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Marius Trøseid
Oslo University Hospital

Nature Microbiology
Editorial Office

Oslo, Dec 4th, 2025

Dear Editor,

Please find enclosed our revised manuscript "Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a CCR5Δ32/Δ32 Sibling Donor". We are very grateful for the thorough assessment provided by the reviewers and the Editorial Office. We have revised the manuscript in accordance with their suggestions, with the following main changes:

- Inclusion of additional data on leukocyte subsets and proviral reservoir measurements at several critical time points, including proviral reservoir in gut biopsies at two time points during his GvHD diagnosis.
- Highlighted that, due to the limited amount and quality of tissue available to measure the viral reservoir at the time of donor chimerism and at the start of the JAK inhibitor, firm conclusions about its effect cannot be drawn.
- Strengthened discussion of the procedure-related risks associated with hematopoietic stem cell transplantation.
- Addition of a new section on vedolizumab and its potential impact on the HIV reservoir in the Results and Discussion sections.
- Clarification that virus tropism was predicted genotypically rather than assessed phenotypically.
- A more concise discussion section with greater emphasis on key new findings, particularly donor chimerism in the terminal ileum, and a clearer description of the study's limitations within the broader context of HIV cure research.
- Minor revisions to Table 1 and to the figure legends.
- Corrected References to supplemental tables.

In addition, we have gone carefully through the manuscript in accordance with the Editorial policy checklist. Page and line numbers cited refer to the clean version.

We hope that the revised manuscript will be acceptable for publication in its current form.

Sincerely, on behalf of the Oslo HIV Cure Study group,

Professor Marius Trøseid, MD PhD

(Corresponding author)

Reviewer #1 (Remarks to the Author):

The manuscript by Myhre et al. documents a case report of a 62-year-old man, treated for myelodysplastic syndrome, whom they have identified to be in viral remission for HIV for greater 4 years following hematopoietic stem cell transplantation (HSCT) by homozygous CCR5 delta 32 mutation sibling donor-matched cells. While there are at least 6-7 people living with HIV (PLWH) that have been identified to have achieved a “functional cure” of infection, all involving HSCT treatment for a malignancy, this study has significance in the relative rarity in achieving a functional cure for HIV, the unique use of HLA matched cells from an older sibling, the older ages of the donor and patient (60 and 58, respectively), and in the identification of rapid donor cell reconstitution/chimerism in multiple tissues, including the gut. Comparisons are made between this case and other cure cases in a helpful and insightful manner. The data largely support the notion of a functional cure in this individual, which is historically important.

Response
We thank the reviewer for the overall positive evaluation of our work and for highlighting the unique aspects of this case compared with previously reported cases of sustained HIV remission.

There are a few minor issues that could strengthen this manuscript:

While it is acknowledged in the manuscript that there are limitations in the availability and quantity of cells in the tissue samples, the inclusion of more data points, if available, would strengthen this study.

More data detailing the cellular parameters following lymphodepletion/myelodepletion and the hematopoietic recovery, if available, would strengthen this study, providing greater insight in the use of the indicated conditioning regiment on lymphocyte subsets and allowing better comparison to other approaches.

Response
We thank the reviewer for this excellent suggestion. Although our initial focus was to apply state-of-the-art technologies to confirm sustained HIV remission 24 months after ATI, we agree that the inclusion of more data points would strengthen the study. In accordance with this suggestion, we have now added data on lymphocyte subsets and myeloid cells measured in fresh blood at several follow-up time points (Fig. 3A, B). We believe this has substantially strengthened the study and facilitates comparison with other cases and approaches.

It would be helpful in the actual Table 1 if it were clarified that, in the “undetectable” samples, the limit of detection is indicated in the HIV copies column, perhaps by an asterisk or a different font. The way it appears is that DNA is present in these samples while it is indicated in the legend and text of the manuscript that it is not. This would better represent the data.

Response
We thank the reviewer for this good suggestion. We agree that the data presentation in table 1 could be confusing and have indicated samples below the limit of detection with an asterisk, as suggested. We believe this improves clarity and more accurately presents the underlying data.

There are reports of several PLWH that received CCR5 delta 32 HSCs that died as a result

of complications following the transplantation procedure or due to relapse of the malignancy. It should be clarified that this procedure has been attempted other times and carries significant risks.

Response
Again, we agree with the reviewer. Allogeneic transplantation is primarily performed to prevent malignant relapse, which is otherwise frequently fatal. Although the procedure carries a treatment-related mortality of approximately 10-20%, this risk is considered acceptable given the underlying disease. Nevertheless, relapse continues to be the leading cause of death after transplant for malignant diseases, both in people living with HIV and in the general transplant population, and we have added references to support this. (Discussion, page 11, lines 236-239).

In sum, this is an interesting identification of an individual that appears to have achieved a "functional cure" of HIV, which would be of broad interest to the biomedical field.

Response
Again we thank the reviewer for the positive feedback on our manuscript.

Reviewer #2 (Remarks to the Author):

This manuscript describes the clinical course and findings of a PWH and myelodysplastic syndrome who underwent an allogeneic transplant, with a sibling donor who was CCR5delta 32 homozygous, who has no evidence of HIV on detailed testing and is no longer on ART. There are a number of important highlights of this article to be noted, including:
-This work describes a patient transplanted using a sibling donor, which is a unique donor type compared to other reports of PWH undergoing transplant.
-The study team performed extensive reservoir testing with leukapheresis and gut biopsies
-The detailed testing performed by this group replicates other evaluations of potential HIV cure post-allogeneic transplant, although the patient did undergo colonoscopy with extensive biopsies that were studied in detail as well, which has not been reported previously.
-The study team did access and report on features of other PWH undergoing allogeneic transplant that have been reported and compared/contrasted findings with their reported patient.

Response
We thank the reviewer for the overall positive evaluation of our work and for highlighting the unique features and translational work-up of this case compared to previous cure cases published.

As an area to add to this work, this patient received vedolizumab as part of the treatment for acute GVHD early after transplant. Vedolizumab has been studied in HIV and shown to have impact on HIV gut reservoir. Given this patient was treated with vedolizumab, I recommend more detailed description of their treatment course and analysis and discussion of how this could have potentially played a role for this patient. Below are just a few references regarding this drug in HIV:

- Santangelo PJ, Cicala C, Byrareddy SN, Ortiz KT, Little D, Lindsay KE, Gumber S, Hong JJ, Jelicic K, Rogers KA, Zurla C, Villinger F, Ansari AA, Fauci AS, Arthos J. Early treatment of SIV+ macaques with an α4β7 mAb alters virus distribution and preserves CD4+ T cells in

later stages of infection. Mucosal Immunol. 2018 May;11(3):932-946. doi: 10.1038/mi.2017.112. Epub 2017 Dec 20. PMID: 29346349; PMCID: PMC5976508.

- Arthos J, Cicala C, Nawaz F, Byrareddy SN, Villinger F, Santangelo PJ, Ansari AA, Fauci AS. The Role of Integrin α4β7 in HIV Pathogenesis and Treatment. Curr HIV/AIDS Rep. 2018 Apr;15(2):127-135. doi: 10.1007/s11904-018-0382-3. PMID: 29478152; PMCID: PMC5882766.

- Jimenez-Leon MR, Gasca-Capote C, Roca-Oporto C, Espinosa N, Sobrino S, Fontillon-Alberdi M, Gao C, Roseto I, Gladkov G, Rivas-Jeremias I, Neukam K, Sanchez-Hernandez JG, Rigo-Bonnin R, Cervera-Barajas AJ, Mesones R, García F, Alvarez-Rios AI, Bachiller S, Vitalle J, Perez-Gomez A, Camacho-Sojo MI, Gallego I, Brander C, McGowan I, Mothe B, Viciana P, Yu X, Lichterfeld M, Lopez-Cortes LF, Ruiz-Mateos E. Vedolizumab and ART in recent HIV-1 infection unveil the role of α4β7 in reservoir size. JCI Insight. 2024 Jul 9;9(16):e182312. doi: 10.1172/jci.insight.182312. PMID: 38980725; PMCID: PMC11343594.

Response
We thank the reviewer for this excellent suggestion. As noted by the reviewer, a substantial amount of work has previously been published on vedolizumab and HIV reservoir both in humans and non-human primates. However, the patient received only a single dose before treatment was discontinued due to CMV infection, and we therefore believe vedolizumab likely had limited impact on the viral reservoir in this case. In the revised manuscript, we have added further details regarding vedolizumab treatment in the Results section (page 5, line 85-86) and expanded the Discussion section accordingly (page 9, line 181-185), including two of the references suggested by the reviewer. We believe these additions have improved the manuscript.

Reviewer #3 (Remarks to the Author):

This is a very well-written paper describing another rare case of HIV cure via SCT. The methodologies applied are state of the art.

A novel aspect is the measurement of donor chimerism in the terminal ileum, which is considered one of the most relevant HIV reservoirs. This makes this case of interest to the readers of this journal.

Response
We thank the reviewer for the overall positive evaluation of our work, and for highlighting the measurement of donor chimerism in the terminal ileum, which is a novel aspect compared to previous cases of sustained HIV remission.

It would have been of added value to assess potential dynamics of the proviral reservoir in plasma in relation to tissue chimerism, or to evaluate CCR5 expression levels of the host in relation to proviral DNA prior to SCT. However, as is often the case with these rare opportunities for cure, the available material was limited.

Response
We thank the reviewer for this excellent suggestion. Despite limitations in the availability of stored material, we have now added analyses of proviral reservoir measurements from the available gut biopsies at two early time points (days 45 and 155 post-SCT) during the patient's GvHD episode (Results, page 6, lines 121-125 and Table 1; Methods, page 15, lines 330-336).

According to the pre-specified protocol, proviral DNA was scheduled to be assessed in blood every three months. Thus, the first planned analyses of proviral HIV DNA and donor chimerism were performed three months post-SCT, at which time full donor chimerism had already been achieved and proviral HIV DNA was undetectable. As the patient's GvHD began shortly before this time point, the new analyses of gut biopsies from days 45 and 115 are potentially informative, both showing undetectable proviral HIV DNA. These findings, however, must be interpreted with caution due to DNA fragmentation inherent to formalin-fixed tissue.

Although we believe that an early and sustained allo-immune reaction contributed substantially to depletion of the patient's viral reservoirs, we are unable to determine the relative contribution of full donor chimerism, GvHD, or GvHD-directed therapy, given that proviral DNA remained undetectable throughout. We have expanded on this important point in the Discussion (page 9, line 185-188) and have now added this explicitly as a study limitation (page 10, lines 217-222).

Finally, no suitable pre-SCT material was available to allow assessment of CCR5 expression in relation to proviral DNA levels.

Remarks:

Case report: It is indicated that the virus was CCR5-tropic. According to the methods, this was determined genotypically by Sanger sequencing, which provides only limited insights and represents a prediction rather than a direct phenotypic assessment. This should be made clear in the text (eg “the virus was predicted to be CCR5-tropic, FPR XX"

Response
Thanks for pointing out this limitation. In the revised manuscript we have explicitly clarified that the tropism of the virus was predicted genotypically, rather than phenotypically assessed (page 3-4, line 58-59).

Although from a hematological perspective full donor chimerism in tissues is generally considered to be >95%, the question arises whether this definition is equally applicable in the context of HIV cure. Given the emphasis of the paper on tissue chimerism, this issue warrants more attention in the discussion. The discussion is rather lengthy and could be shortened to improve clarity and focus on the new findings such as the chimerism in the terminal ileum.

Response
Thanks for your suggestion. We have amended the Discussion to focus more clearly on the new findings, including chimerism in the terminal ileum, with more emphasis on whether the general definition of full donor chimerism also applies in the context of HIV cure. The conservative consensus definition of full donor chimerism reflects variability in analytical techniques and their sensitivity, cell type and sample purity, underlying disease, and

transplantation method. Results must therefore be interpreted in the context of disease risk, kinetics, and sample type. For example, a decline to 96% donor chimerism in the myeloid blood compartment in high-risk myeloid neoplasia typically indicates imminent disease relapse, whereas the same result in unseparated bone marrow or bone marrow CD34+ cells (which may also be expressed on endothelial cells) is less informative due to inevitable contamination with recipient-derived stromal cells. Chimerism analysis of gut leukocytes is not performed routinely, and exclusive DNA purity from CD45+ cells cannot be conclusively ensured. Thus, the conservative consensus definition remains justifiable, as discussed in the revised manuscript (page 9, lines 198-203).

Minor points:
In Figure 1, the apparent plateau of viral load at low levels is likely due to the detection threshold of the viral load assay. This should be noted in the figure legend.

Response
We thank the reviewer for this suggestion and have revised the figure legend accordingly.

Marius Trøseid
Oslo University Hospital

Nature Microbiology
Editorial Office

Oslo, Feb 6th, 2026

Dear Editor,

Please find enclosed our revised manuscript "Long-term HIV-1 Remission Achieved Through Allogeneic Hematopoietic Stem Cell Transplant from a *CCR5*Δ32/Δ32 Sibling Donor". We are very happy with the reviewers' endorsement of the manuscript, and have performed the following minor revisions to satisfy the referees' final requests:

- We have made minor clarifications in the Discussion to specify the time frame and populations relevant to reported transplant-related mortality estimates, thereby improving precision and avoiding potential ambiguity

In addition, we have gone carefully through the manuscript in accordance with the Editorial policy checklist. Page and line numbers cited refer to the clean version.

We hope that the revised manuscript will be acceptable for publication in its current form.

Sincerely, on behalf of the Oslo HIV Cure Study group,

Professor Marius Trøseid, MD PhD

(Corresponding author)

Reviewer #1 (Remarks to the Author):

The responses to the reviewer's concerns have sufficiently addressed the issues. I would recommend acceptance.

Response:

We thank the reviewer for their positive assessment and helpful comments.

Reviewer #2 (Remarks to the Author):

I appreciate the authors' thorough review of the comments, with each of these items addressed in the revised manuscript.

Response:

We thank the reviewer for their positive assessment and helpful comments.

Reviewer #3 (Remarks to the Author):

The authors have addressed the comments very well, and the revisions have clearly improved the manuscript. However, I have one remaining relevant issue regarding newly added information on transplant-related mortality.
I was triggered by the quoted low mortality in this particular statement:
“Although the procedure carries a treatment-related mortality of approximately 10–20%, this risk is considered acceptable given the underlying disease” (Discussion, page 11, lines 236–239)
is ambiguous. It is unclear whether this mortality estimate refers specifically to people living with HIV or to allogeneic stem cell transplantation in the general population, and no time frame for this estimate is provided.
Moreover, the cited reference (Arslan et al., 2019; PMID: 30926447) reports substantially higher mortality in people with HIV undergoing allogeneic transplantation, with approximately 43% mortality at 12 months (12-month overall survival 56.6%) and ca 51% mortality over total follow-up.
Clarification of the population (HIV-positive vs. general allo-HCT cohorts), the time horizon, and reconciliation with the findings of Arslan et al. would improve accuracy and avoid potential underestimation of risk in this context.

Response:
We thank the reviewer for their positive assessment of the revised manuscript and for raising this important point regarding mortality.

We agree that the originally quoted mortality estimate was ambiguous with respect to both the population and the time horizon. In response, we have revised the Discussion to explicitly clarify that the reported mortality refers to procedure-related (non-relapse) mortality within the first year after allogeneic HSCT, and that this time point is used in the cited literature. We have also clarified that the statement applies to both people living with HIV and the general allogeneic HSCT population, thereby avoiding potential misinterpretation.

Regarding the apparent discrepancy with Arslan et al. (2019, PMID: 30926447), we acknowledge that overall mortality at 12 months in that study is higher when relapse-related

deaths are included. However, as now made clearer in the revised text, our discussion refers specifically to procedure-related (non-relapse) mortality, which in Arslan et al., as well as in Kwon et al. (2019, PMID: 30932952), and Ambinder et al. (2019, PMID: 31279752), is reported at approximately 20%, 14% and 12% at one year, respectively. These estimates are in line with contemporary expectations in the general transplant population.

We further emphasize in the revised Discussion that relapse remains the leading cause of death after transplantation in malignant disease, both among people living with HIV and in the general allogeneic HSCT population, and that without transplantation these malignancies would, in the vast majority of cases, be fatal. While it is theoretically possible that relapse-related mortality could be increased in people living with HIV, for example through impaired graft-versus-leukaemia effects, there is currently no substantial evidence to support this.