

## Transient CD4-cell-depletion therapy for HIV/AIDS cure

Min Wei<sup>1,2</sup>, Yi-Ming Shao<sup>1,3</sup>

<sup>1</sup>Department of Pathogenic Biology, School of Medicine, Nankai University, Tianjin 300071, China;

<sup>2</sup>Nankai University Second People's Hospital, Nankai University, Tianjin 300192, China;

<sup>3</sup>State Key Laboratory for Infectious Disease Prevention and Control, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 102206, China.

Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is still a threat to global public health, with around 38 million people living with HIV by the end of 2019 (<http://www.unaids.org>). Until now, there is not a routine cure therapy available for HIV/AIDS.<sup>[1]</sup> Anti-HIV inhibitors, such as reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry inhibitors, were all applied in HIV/AIDS patients.<sup>[1]</sup> Combined antiretroviral therapy (cART) can effectively control HIV replication, but cannot eradicate the HIV reservoir.<sup>[1]</sup> HIV reservoir is the major barrier for HIV cure and is the major cause for HIV rebound after anti-HIV treatment interruption.<sup>[1,2]</sup> HIV reservoir, here defined as resting CD4<sup>+</sup> cells that harbor replication-competent HIV, is established in 2 to 3 days of HIV primary infection.<sup>[2]</sup> HIV remains quiescent in long-lived memory CD4<sup>+</sup> cells, and therefore is not sensitive to cART.<sup>[1,2]</sup>

Currently, the “Berlin patient,” who received bone marrow transplantation from a donor with CCR5-tropic-HIV-resistant homozygous CCR5  $\Delta$ 32 mutation for the treatment of HIV infection and acute myeloid leukemia, is the only worldwide-acknowledged HIV cure case.<sup>[3]</sup> The “London patient” received similar therapy and had no HIV rebound after the stop of cART in 2019.<sup>[4]</sup> It is still too early to conclude an “HIV cure” for the London patient. Absolutely, bone marrow or stem cell transplantation is not suitable for each HIV patient, especially when the current cART does very well.

The success of “Berlin patient” makes global scientists focus on CCR5  $\Delta$ 32 mutation. Even us, we have successfully converted wild-type CCR5 to homozygous CCR5  $\Delta$ 32 in lymphocytes *in vitro* using CRISPR-Cas9 gene-editing technology.<sup>[5]</sup> This approach can supply the autologous homozygous CCR5  $\Delta$ 32 cells.<sup>[5]</sup> However, this

approach cannot clear wild-type CCR5<sup>+</sup> CD4<sup>+</sup> cells in HIV patients, which still support HIV replication. This disadvantage results in the failure of the HIV/AIDS cure.<sup>[6]</sup>

In the success of “Berlin patient,” scientists always ignore the treatment before bone marrow transplantation. To inhibit graft-*vs.*-host disease, anti-T cell antibody (anti-T cell globulin), and cyclophosphamide were applied, which cleared all T cells, including CD4<sup>+</sup> cells, of course, the HIV reservoir in the Berlin patient.<sup>[3]</sup>

Therefore, here, we raise a hypothesis, a therapy “transient CD4-cell-depletion therapy (TCDT)” to eradicate HIV reservoir.

The detailed steps of TCDT are as follows: (1) The HIV/AIDS patients are treated with current cART, such as two reverse transcriptase inhibitors and one protease inhibitor. Wait until the plasma viral load of HIV/AIDS patients is 0 copy/mL or lower than the detection limit of commercial kits. Keep the patients in good conditions without infections, if antibiotics are needed. (2) The patients will be injected with a specific anti-human CD4 monoclonal antibody. This treatment will deplete all of the CD4<sup>+</sup> cells, including CD4<sup>+</sup> T cells, CD4<sup>+</sup> macrophages, CD4<sup>+</sup> dendritic cells, etc, despite HIV<sup>-</sup> or HIV<sup>+</sup> status. The aim of this step is to eradicate the HIV reservoir. Treat the patients until their peripheral blood CD4<sup>+</sup> cells are zero or very close to zero. During this period, cART will continue. (3) Stop TCDT of anti-CD4 therapy. Wait several weeks until human CD4<sup>+</sup> cells recover to normal. cART still continues. (4) Stop cART therapy. Observe if HIV will rebound [Figure 1].

TCDT is a therapy of transiently depleting CD4<sup>+</sup> cells in HIV-infected patients. Antibody-based TCDT can not only deplete CD4<sup>+</sup> T cells but also CD4<sup>+</sup> macrophages,

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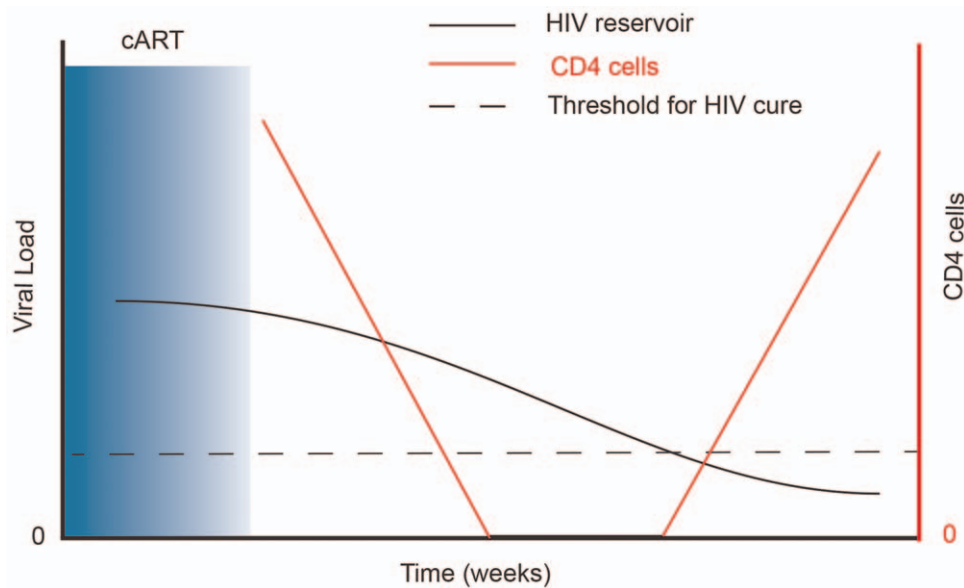
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**Correspondence to:** Min Wei, Department of Pathogenic Biology, School of Medicine, Nankai University, Tianjin 300071, China  
E-Mail: [weimin@nankai.edu.cn](mailto:weimin@nankai.edu.cn)

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**Figure 1:** Schematic diagram of TCDT to eradicate HIV reservoir for HIV/AIDS cure. The detailed steps are as follows: (1) The HIV/AIDS patients are treated with current cART. Wait until the plasma viral load of HIV/AIDS patients is 0 copy/mL or lower than the detection limit of commercial kits. Keep the patients in good conditions without infections if antibiotics are needed. (2) The patients will be treated with specific anti-human CD4 monoclonal antibody. This treatment will deplete all of the CD4<sup>+</sup> cells. The aim of this step is to eradicate the HIV reservoir. Treat the patients until their peripheral blood CD4<sup>+</sup> cells are zero or close to zero. During this period, cART will continue. (3) Stop TCDT of anti-CD4 therapy. Wait several weeks until human CD4<sup>+</sup> cells recover to normal. cART still continues. (4) Stop cART therapy. If the HIV reservoir is lower than the threshold, HIV/AIDS is possible to be cured. cART: Combined antiretroviral therapy; CD4: Cluster of differentiation 4; HIV/AIDS: Human immunodeficiency virus/acquired immunodeficiency syndrome; TCDT: Transient CD4-cell-depletion therapy.

dendritic cells, etc. TCDT can clear HIV-infected and HIV-uninfected CD4<sup>+</sup> cells; however, the stem cells producing CD4<sup>+</sup> cells are still normal and can produce more CD4<sup>+</sup> cells. TCDT will deplete CD4<sup>+</sup> cells in peripheral blood, as well as in lymph nodes, brain, bone marrow, and gut-associated lymphoid tissues, which are HIV sanctuaries.<sup>[2]</sup>

In the last three decades, TCDT has never been tested in HIV/AIDS patients. However, an anti-CD4 monoclonal antibody (zanolimumab) was applied in a human phase II clinical trial in T cell lymphoma therapy.<sup>[7]</sup> This human trial also showed zanolimumab was safe and tolerated with no major toxicity in humans.<sup>[7]</sup>

The biggest risk of TCDT is temporary immunodeficiency in patients and opportunistic infections after the clearance of CD4<sup>+</sup> cells. We can make some preparations before starting TCDT, such as putting the patients in a clean sterile room, and using antibiotics for anti-bacterial infections and anti-viral agents for reactivation of cytomegalovirus, or Epstein-Barr virus, etc. The TCDT-caused immunodeficiency is transient and recoverable.

The second question is whether the human CD4<sup>+</sup> cells can recover after depletion. It has been confirmed in the above phase II clinical human trial that the CD4<sup>+</sup> cells can return to normal after about 12 weeks of clearance.<sup>[7]</sup> In fact, the stem cells that produce CD4<sup>+</sup> cells are not damaged, so CD4<sup>+</sup> cells can recover. Another evidence is that CD4<sup>+</sup> cells in the late stage of AIDS patients, whose CD4<sup>+</sup> cell counts already reach zero or close to zero, can recover after cART treatment. Therefore, the strategy of TCDT is applicable. On the other hand, although CD4<sup>+</sup> cells have reached zero in the late stage of AIDS patients, the patients will die rather than cure, due to a large number of free viruses and

immunodeficiency in the absence of cART treatment. Thus, to remove free viruses, cART is a very important prerequisite for TCDT.

Third, what will we do if CD4<sup>+</sup> cannot reach zero, and there are some residual CD4<sup>+</sup> cells after anti-CD4 antibody treatment? In the phase II clinical trial mentioned above, many patients already dropped to zero, but it was true that some patients' CD4<sup>+</sup> cells did not reach zero.<sup>[7]</sup> Even if the clearance is not complete and CD4<sup>+</sup> cells are more than zero, HIV/AIDS cure is still possible when the HIV latent reservoir is dramatically reduced. The residual virus and HIV-infected cells could be cleared by the patient's immune system. At present, we do not expect TCDT therapy to cure all HIV/AIDS patients. If only 30%, that is, 10 million patients are cured, it is great progress toward HIV/AIDS cure.

The fourth question is whether the use of anti-CD4 antibodies will induce autoantibodies. Anti-CD4 antibody itself is autoantibody, and the human body will not produce. No autoantibodies were reported in the above human experiments. No serious case of autoimmune disease was reported in the monoclonal antibody that has been approved for clinical usage, such as rituximab.<sup>[8]</sup>

Fifth, after HIV infection, HIV expressed accessory protein – negative factor (Nef). Nef can downregulate CD4, major histocompatibility complex, and other molecules.<sup>[9]</sup> Cleaning up the CD4<sup>+</sup> cells will miss the CD4<sup>-</sup> HIV-infected cells. Overcome of this problem depends on cART. Because Nef production requires viral replication, cART can inhibit Nef production. Therefore, in the early stage of TCDT therapy, cART must be applied to inhibit HIV replication and deplete free viruses as much as possible.

The newly generated CD4<sup>+</sup> cells are still sensitive to HIV. TCDT therapy is not suitable for patients in the late stage of AIDS, because their CD4<sup>+</sup> cells are already very low, it will even worse if applied.

The sixth problem is that the immune memory of CD4<sup>+</sup> T cells may be lost after the clearance of CD4<sup>+</sup> cells, that is, the previously injected vaccines are no longer effective. If so, for such patients, when they recovered completely, they can be vaccinated again to stimulate the immune response.

The advantage of this therapy is that TCDT can clear the resting CD4<sup>+</sup> T cells and monocytes/macrophages of HIV reservoir in peripheral blood, lymph nodes, and other tissues. Although normal CD4<sup>+</sup> cells were cleared, it was only temporary, transient, tolerable, and recoverable. If HIV reservoir size is smaller than that before cART, TCDT is effective. When the HIV reservoir is dramatically reduced by 10,000 times (4 Log), HIV/AIDS may be cured. Actually, in the HIV-infected cells, around 93% of the pre-viruses are replication-defective, and only the remaining 7% can replicate.<sup>[2]</sup> Therefore, it is not necessary to clear all CD4<sup>+</sup> cells, and it is good enough to clear replication-competent HIV reservoir by TCDT. TCDT is much specific than anti-T cell antibody and cyclophosphamide used in “Berlin patient.”

In 2018, the US Food and Drug Administration approved an anti-HIV drug, anti-CD4 monoclonal antibody ibalizumab (Commercial name: Trogarzo). Ibalizumab only binds to CD4 and prevents the binding of HIV and CD4 receptor; however, does not deplete CD4<sup>+</sup> cells.<sup>[10]</sup> Now there is no evidence that ibalizumab can cure HIV/AIDS. In the published paper, other investigations of depletion of CD4<sup>+</sup> cells are to observe the function of CD4<sup>+</sup> cells, which is different from this TCDT.

In the past 2019–2020 year, the pandemic of novel coronavirus – severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread in China and globally. The successful control of the pandemic in China is due to the lockdown of Wuhan City, traffic restriction, quarantine of close contact patients, and cure of infected patients, summarized as “strategy of clearing to zero” (<http://www.nhc.gov.cn>). If an infected person is uncontrolled, SARS-CoV-2 infection may break out again. Similarly, HIV/AIDS cannot be cured if HIV still exists, and HIV-producing cells still exist in the human body. Theoretically, HIV/AIDS will be cured after the HIV latent reservoir is

cleared by TCDT. Up to now, TCDT is still an idea and a hypothesis. TCDT cannot be used in HIV patients until it passes the animal tests and clinical trials.

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### Conflicts of interest

None.

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