



A novel approach to HIV therapy: Highly active antiretroviral therapy and autologous hematopoietic cell transplantation

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Summary Highly active antiretroviral therapy dramatically decreases in vivo viral replication to levels below the level of clinical detection, but does not eradicate HIV-1 infection on the basis of persistent low-level or cryptic viral replication and latent provirus in resting CD4⁺ T lymphocytes.

Immune activation therapy has begun to be used in attempts to increase the turnover rate of the latent virus reservoir through activation of infected cells that comprise this reservoir, in order to promote cell death and accelerate virus clearance. Recent reports have not demonstrated complete virus ablation.

Autologous hematopoietic cell transplantation now appears as a safe, feasible, and reasonable approach for Aids-related lymphoma in patients who meet criteria for transplantation.

The hypothesis is based on the possibility that hematopoietic stem cells from a HIV-positive patient could be collected before the patient becomes infected with HIV.

Then, the proposed treatment consists of the following assumptions. HAART keeps viral replication below the level of detection, limiting the infection to latent provirus in resting CD4⁺ T lymphocytes. It is presumed here that myeloablative conditioning regimen can lead to the killing of all the cells that, in theory, harbour the virus. The following transplantation of the autologous hematopoietic stem cells, collected before HIV infection, would allow the complete recovery.

The hypothesis is to be tested on a suitable animal model. After the collection of hematopoietic stem cells, the animal is experimentally infected with the immunodeficiency virus. HAART is given after plasma viral RNA becomes detectable. By myeloablative conditioning regimen all the cells harbouring the virus are supposed to be killed.

Then, as the viral load is kept undetectable by HAART, the animal undergoes autologous hematopoietic stem cell transplantation. Antiretroviral therapy is interrupted a month after engraftment has taken place.

Although hematopoietic stem cells from man before infection with HIV are unlikely to be available, a successful test on the animal would suggest a new approach which could allow the cure of HIV in future.

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Background

Highly active antiretroviral therapy (HAART) dramatically decreases *in vivo* viral replication to levels below the level of clinical detection (typically, to <50 HIV-1 RNA copies per mL of blood plasma), but does not eradicate HIV-1 infection on the basis of persistent low-level or cryptic viral replication and, of importance, latent provirus in resting CD4+ T lymphocytes [1,2]. The peripheral blood of HIV-1 infected individuals remains populated with persistently infected, nonactivated CD4+ T lymphocytes, despite HAART [3], and plasma viral RNA rebounds rapidly if therapy is discontinued in patients receiving HAART [4].

This replication-competent but latent HIV-1 proviral DNA resides in resting memory (CD45RO) CD4+ T lymphocytes and, also, in resting naive (CD45RA) CD4+ T lymphocytes, albeit at lower levels [5]. Rebound virus appears to be identical to the latent virus pool in those instances in which patients exhibit no detectable HIV-1 replication during receipt of HAART. In other words, virus evolution is restricted if antiretroviral therapy can maintain virus loads at undetectable levels for a prolonged period [6].

New approaches are now being developed for stimulation of "HAART-persistent" reservoirs. Immune activation therapy (IAT) has begun to be used in attempts to stimulate the HIV-1 latent reservoir. This strategy aims to increase the turnover rate of the latent virus reservoir through activation of infected cells that comprise this reservoir, in order to promote cell death and accelerate virus clearance [7,8]. Recent reports, although they demonstrate that IAT achieves an overall reduction in the HIV-1 infected T cell reservoir, have not demonstrated complete virus ablation [9,10].

Several authors have reported on small series of patients treated at single institutions for Aids-related lymphoma (ARL) with autologous hematopoietic cell transplantation (HCT) [11]. It now appears that sufficient numbers of patients with ARL have undergone autologous HCT to state that it is a safe, feasible, and reasonable approach for ARL patients who meet criteria for transplantation [11].

The hypothesis

The hypothesis is based on the possibility that hematopoietic stem cells from a HIV-positive patient could be collected before the patient becomes infected with HIV.

Then, the proposed treatment consists of the following assumptions. HAART keeps viral replica-

tion below the level of detection; viral spread can be prevented by intensifying therapy with enfuvirtide [12]: under this therapeutic regimen no virion should appear in blood plasma, since the infection is limited to latent provirus in resting CD4+ T lymphocytes. In this scenario, we suppose that myeloablative conditioning regimen can lead to the killing of all the cells that, in theory, harbour the virus (at least in the first phases of infection) [9]. The following transplantation of the autologous hematopoietic stem cells, collected before HIV infection, would allow the complete recovery, with no need of immunosuppressive regimen.

Testing the hypothesis

The hypothesis is to be tested on a suitable animal model. After the collection of hematopoietic stem cells, the animal is experimentally infected with the immunodeficiency virus. HAART is given after plasma viral RNA becomes detectable. As the viral load is kept at undetectable level by HAART (intensified with enfuvirtide to prevent viral spread), the animal undergoes myeloablative conditioning regimen. As a consequence, all the cells harbouring the virus (at least in the first phases of infection) are supposed to be killed, and no virion in blood plasma should appear if HAART is not discontinued.

Then, as the viral load is still kept undetectable by HAART, the animal undergoes autologous hematopoietic stem cell transplantation. Antiretroviral therapy is interrupted a month after engraftment has taken place. The follow up will show if a complete virus eradication has been achieved.

Consequences of the hypothesis

A successful test of the hypothesis on the animal would demonstrate a chance in eradicating HIV infection. Although hematopoietic stem cells from man before infection with HIV are unlikely to be available, this new finding would suggest a novel approach which could allow the cure of HIV in future.

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