

CAN HIV BE CURED?

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Earlier, it was observed that certain individuals do not get infected with HIV, even though they are classified as high risk individuals for HIV, as some of them were previously exposed to HIV numerous times. Surprisingly, these individuals did not show any signs and symptoms of HIV infection, even though they were not under any anti-retroviral treatment. These individuals considered as having “natural resistance” against HIV infections. Natural resistance against microbial infections is not a new phenomenon, resistance against other microorganisms is well known in case of other diseases like small pox [1], etc. Certainly occurrence for natural resistance in case of HIV is a new observation with enormous clinical implications. Further studies revealed that the main reason for this natural resistance against HIV is due to the requirement of other receptors, which are expressed on T-cells and essential for HIV infectivity. Commonly, CD4 is the primary receptor for HIV infections, but chemokine receptors like CXCR4 and CCR5 has been shown to be essential for HIV infection and known as co-receptors. HIV strains are also classified into two categories as per their preferences for co-receptors like X-4 and R5 strain of HIV. It was realized that natural resistance against HIV infection is attributable to mutation in co-receptor CCR5. Among resistant individuals CCR5 gene has a deletion of 32 bp sequence. Some of resistant individuals are homozygous for $\Delta 32$ deletion, while some are heterozygous for $\Delta 32$ deletion. Individual with homozygous deletion have shown to be resistant with HIV, while individual with heterozygous deletion have shown an extremely slow progression of disease after exposure to HIV. This mutation was reported with low frequencies of ~1-3% that is only among Caucasians. Certainly, it was a significant finding to revisit the mechanism for HIV infections, which may offer new insights for the development of new therapeutic strategies to treat HIV.

This important observation remained a matter of laboratory studies and this has to wait another ~10-12 years to see its implications in real-life situation. Hutter *et al.* [2] published their findings in Feb. 12, 2009 issue of New England Journal of Medicine about bone marrow transplantation in a HIV seropositive patient. They performed allogenic bone marrow transplantation in February of 2007 in a HIV seropositive. The patient was a 40 year old male HIV seropositive under HAART regimen with no signs and symptoms of HIV infection that means HIV infection was under control due to HAART. But,

this patient was presented with acute myelogenous leukemia (AML) and tried with chemotherapy to treat AML. Due to toxicity of drugs, HAART was stopped during chemotherapy of AML, as a result of which rebound of HIV was noticed. Unfortunately, chemotherapy for AML was not very helpful for this patient because AML relapsed. So the best option to treat the patient was to perform bone-marrow transplantation. Hutter being a hematologist in the team of clinicians took a cognizant decision to perform bone marrow transplantation. Apart from matching donor, Hutter opted to have a donor with homozygous mutation in CCR5 co-receptors, i.e., CCR5 $\Delta 32/\Delta 32$. There were two reasons for Hutter to opt for this particular combination, 1) it reduces chances for GVHD rejection, and 2) possibilities are there that this patient may become naturally resistant to HIV. Therefore, bone marrow transplantation can treat this patient for AML as well as HIV, it is like hitting two birds with one stone.

Successful bone marrow transplantation in this patient led to discontinuation of HAART. This patient remained negative for HIV infection. But an episode of AML relapse was the reason for another bone marrow transplantation on 391th day after the first bone-marrow transplantation. This patient was closely followed for 20 months, and during observation period this patient did not show any signs and symptoms of HIV infection. On the one hand, these results showed a success for the cure for HIV, while on the other hand it has left many questions unanswered. These questions have valid scientific and theoretical foundations some of them are like chimerism, activation of long-term HIV reservoirs in body, conversion of one form of HIV into another, etc. The answers for all these question will have to wait for its time for long term observations with this patient.

Recently in December 2010 issue of Blood [3] have published the results for 4 year follow up of the this patients, who had received CCR5 $\Delta 32/\Delta 32$ bone marrow transplantation. In this report Allers *et al.* has declared that “Cure for HIV has been achieved”. By February, 2011, this patient has lived almost ~4 years post-bone marrow transplantation and remained free of HIV without any anti-retroviral treatment. Chimerism was achieved in this patient, while no conversion of HIV has been observed, so far. A successful immune-reconstitution was also observed in this patient, which was comparable to other

transplanted patient. A milder form of Graft-vs-Host Disease (GVHD) reaction was noticed, which is not unexpected and that was treated appropriately. HIV RNA and HIV cDNA was found to be absent in all samples, tested so far from this patient.

Without any doubts and debate, this experiment has raised a possible hope toward cure for HIV. It is also certain that just 4 years is not long enough to answer all the possible questions and concerns. However, a long term survival will have answers for all these uncomfortable and complicated questions to assure success of this procedure. These types of therapeutic interventions may have far reaching implications, which warrants further investigations with more number of patients. This strategy can be helpful for those, who do not respond to anti-retroviral treatment due to one reason or another. Some of the possible applications of this have been discussed earlier [4]. Nevertheless, one of the major limitations for this mode of treatment is the availability of limited pool of donors with this specific mutation. This mutation is restricted only to Caucasians, while ~66% of HIV infected people live in Africa. Expansion of search program to identify this mutation among different races will serve as a consolation for ever expanding numbers due to longer survivability among HIV seropositives. There is a need of active research programs to develop universal stem cell with CCR5 deletion, which can be administered to any HIV seropositive without any restriction of matching.

Possibilities are limitless to make real use of this breakthrough in treatment of HIV patient.

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