Timing it right

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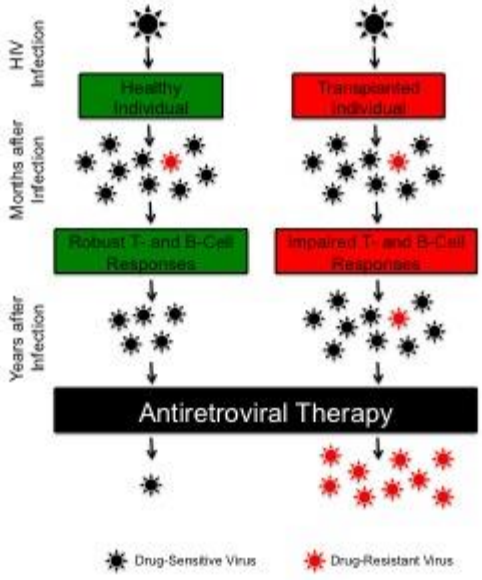

Model for the proposed mechanism leading to establishment of ART resistant virus in post-transplant group.

Image provided by Dr. Christopher Peterson.

Last month's spotlight edition featured a publication supporting safety and efficacy of maintaining regimens of combination antiretroviral therapy (ART) in subjects undergoing bone marrow transplantation. This month, a paper published by Fred Hutch scientists explains why it is important to maintain ART in the period around transplantation. There are multiple reasons to focus on this topic. First, recent improvements mean that HIV infection can be controlled by antiretroviral drugs; therefore, infected subjects are more likely to live longer and face additional health issues that may be related to HIV infection, antiretroviral therapy, or non-HIV related causes. Second, the only person who has so far been declared free from HIV was cured as a result of bone marrow transplantation. The marrow donor in this case was resistant to HIV infection, due to a genetic mutation of the HIV co-receptor. In the future, more cases similar to this might present; therefore, it is important to know when the therapy should be interrupted to evaluate whether the subject can control viral replication in the absence of therapy. A paper published this month on *AIDS* by Dr. Christopher Peterson, a staff scientist in Dr. Hans-Peter Kiem's Lab at Fred Hutch, shows the importance of carefully evaluating when ART can be interrupted after transplantation.

The work utilizes the simian/human immunodeficiency virus (SHIV) model of HIV infection to understand the effects of starting antiretroviral treatment after bone marrow transplantation. Three

groups were compared in the study: one that received a SHIV challenge but no transplantation, a second that received a SHIV challenge before bone marrow transplantation and the third that received a SHIV challenge after bone marrow transplantation. ART was initiated immediately after the SHIV challenge to control viremia and was found effective in reducing the viral load in the first two groups, but not in the third. In this group, the presence of resistance-linked mutations, especially in the pol gene, was detected by deep-sequencing analyses. To explain the reason of the elevated frequency of ART-resistance mutations, the researchers evaluated three possible mechanisms. Neither reduced bioavailability of the drugs due to intestinal damage caused by the myeloablative regimen, nor the prevalent infection of myeloid subsets that could serve as drug sanctuaries were affected by the myeloablative conditioning followed by the viral challenge. Therefore, the researchers explored the possibility that the depletion of CD4 and CD8+ T cells due to myeloablative and immune suppressive therapy allowed for the establishment of ART-resistant mutants. Indeed, the third group, where SHIV challenge followed transplantation, was characterized by depletion of naïve CD4+ and CD8+ T cells in the blood, while less marked differences were noted for memory T cells. Naive T cells rebound after ART initiation, but their expansion was not followed by a viral load decrease. Finally, the group was characterized by a low production of antibodies to SHIV.

The clinical relevance of this study is summarized in the comment from Dr. Peterson: "In order to know whether or not a patient has been cured of HIV infection in future clinical trials, we will need to briefly take them off of their antiretroviral treatment to confirm that the virus does not come back; this is known as an analytical treatment interruption'. Understanding when to do this is particularly important in our work with patients who undergo stem cell transplantation and are immunosuppressed. Our study shows that these analytical treatment interruptions should not occur until the patient's immune system has completely recovered from the transplant procedure or immunosuppressive therapy".

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Peterson CW, Haworth KG, Polacino P, Huang M-L, Sykes C, Obenza WM, Repetto AC, Kashuba A, Bumgarner R, DeRosa SC, Woolfrey AE, Jerome KR, Mullins JI, Hu S-L, Kiem H-P. 2015. Lack of viral control and development of combination antiretroviral therapy escape mutations in macaques after bone marrow transplantation. *AIDS*. 29(13):1597-606.