Valproic acid and HIV eradication—many questions remain

Although the amount of HIV in resting CD4+ cells clearly decreased when an intensive regimen of HAART and valproic acid was used, researchers are concerned that their laboratory equipment and techniques may not be sensitive enough to detect very low levels of latently infected cells. However, as interest in eradication studies grows, it is likely that HIV detection technologies and techniques will improve. This work will be time-consuming and labour-intensive, particularly because it involves assessing millions of cells.

Here are some issues that need to be explored in future eradication studies.

**Time**

Future studies will need to be longer. Already researchers are planning studies that last at least one year in the hope that this will improve the chances of eradication.

**Intensification**

Is the use of T-20 helpful? Researchers are not certain about the need for including this drug in eradication protocols. In the present study, two participants had “persistent, low levels of [HIV]” despite the use of T-20, according to the research team. To resolve this issue, future eradication studies may need a comparison group, where one receives T-20 and another does not. T-20 must be injected twice daily. But recent Canadian research suggests that a gas-powered needle-free delivery system (Biojector 2000) is as effective as the injections. No matter what method is used to deliver the drug, participants will have to be highly motivated and adherent. Future studies may also use different anti-HIV agents. For instance, boosted protease inhibitors such as lopinavir + ritonavir (Kaletra) and atazanavir (Reyataz) + ritonavir are candidates for this.

**The measure of success**

A major question for both scientists and PHAs is, “How will success in HIV eradication protocols be measured?” To answer this, at some point after the course of an eradication study, participants will have to stop using HAART. Levels of HIV antibodies, viral proteins and RNA (viral load) will be tracked at subsequent time points. There is some debate about the sensitivity of currently available technology and laboratory techniques to detect HIV when it is at very low levels.

For instance, two different teams of researchers, one in the United States and the other in the Netherlands, have found very low levels of HIV in men who have engaged in unprotected intercourse. Using readily available tests, these men did not have antibodies to HIV or any obvious traces of the virus in their blood. However, intensive and time-consuming lab investigation did find HIV in resting CD4+ cells. The implications of these findings need further exploration, but they suggest that HIV can hide quietly within cells.

**Will toxicity occur?**

Because valproic acid has the potential to interact with AZT, future eradication protocols may not use this nuke. This leaves the following options:

- 3TC
- FTC (available in the U.S. and E.U.)
- ddi
- d4T
Both “d” drugs—ddI and d4T—can cause pancreatitis and nerve damage and may be toxic to the liver. Also, d4T is associated with the loss of fat (lipoatrophy) under the skin. In rare cases, valproic acid is associated with the development of pancreatitis. So combining the “d” drugs with valproic acid may require that participants be closely and frequently monitored so that doctors can detect this problem in its infancy.

Beyond valproic acid, future studies of eradication may include the use of cytokines such as IL-7 (interleukin-7), which can help stimulate HIV out of hiding without also ramping up the immune response and making CD4+ cells more susceptible to infection. Most experiments with IL-7 in people have been halted because their immune systems produced antibodies that attacked this chemical messenger and neutralized its effect. So, attempts are underway to make artificial IL-7 more like the form found naturally in the human body and, therefore, hopefully less likely to provoke an immune response. The new formulation of IL-7 will not likely be available until late 2006 (J-P Routy MD, personal communication).

**HDAC-1 inhibitors**

Valproic acid is one inhibitor of the enzyme HDAC-1. But researchers in the United States and European Union are working on developing other potential inhibitors of this enzyme that may be more effective than valproic acid. These new HDAC-1 inhibitors may be tested in PHAs if valproic acid is found to be insufficient.

**Bone marrow transplants**

The bone marrow is rich in white blood cells and lymphocytes and, not surprisingly, serves as a reservoir for HIV. In the late 1980s, researchers tried to destroy the bone marrow of PHAs with intensive doses of chemotherapy and/or radiation, after pre-treatment with AZT. The destruction of the bone marrow and its HIV-infected cells would be followed by a bone marrow transplant to help kick-start that organ into producing healthy, HIV-free cells. Unfortunately, none of these studies cured HIV infection. Moreover, such regimens can be very difficult to tolerate.

In this century, with a choice of potent anti-HIV agents at their disposal, some scientists are beginning to reconsider the idea of bone marrow ablation once again.

**REFERENCES:**


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