Emerging early in the 1980s, a new virus called HIV would be linked to the development of weakened immunity and the appearance, at least until that time, of uncommon infections and cancers. One of the striking features of this new syndrome was that it affected previously healthy people, mostly men, in the prime of their lives, without any obvious risk factors for life-threatening complications. This collection of symptoms, infections and cancers—together with lab tests indicative of immune deficiency—would later be called AIDS.

In the early days of the AIDS epidemic, hopes were high that a cure would soon be found. Doctors and people with HIV/AIDS (PHAs) held great expectations for the first drug licensed against HIV—AZT (Retrovir, zidovudine). Unfortunately, AZT, when used by itself (monotherapy), wasn’t strong enough to destroy HIV-infected cells and had limited effects suppressing the symptoms of HIV disease.

Some researchers thought that HIV would be effectively suppressed only by intensifying therapy with AZT—using doses that are much higher than those used today. Although high doses might damage the bone marrow, a transplant of bone marrow tissue after high-dose AZT would help this organ regenerate, perhaps free of HIV. However, experiments with high doses proved to have very little benefit—HIV infection was never cured and this therapy was associated with a great deal of toxicity. AZT belongs to a class of drugs called nucleoside analogues (nukes) and as more nukes became available, combination therapy with this class of drugs also did not fully suppress HIV.
It was only in the mid-1990s, as more researchers gained experience with a new, more potent class of drugs called protease inhibitors (PIs), that thoughts of curing HIV infection returned. When PIs were used as part of combination therapy with other anti-HIV drugs, for the first time since the appearance of the AIDS epidemic doctors were able to return many PHAs to a better state of health.

Because some virologists found that triple-drug therapy with PIs was able to strongly suppress the production of new viruses, they hoped that if this suppression could be sustained for several years, then perhaps the body might rid itself of HIV. Unfortunately, this has not been the case.

Faced with a history of setbacks, it is not surprising that more recent attempts at curing (or eradicating) HIV infection have been announced or carried out with little fanfare.

New class, new hope
What makes the slowly growing enthusiasm for studying HIV eradication different now than from previous efforts is that this time researchers have the following:

- at least one easily available drug—valproic acid—that can help tease HIV out of hiding from resting T-cells
- four classes of licensed anti-HIV drugs, including the fusion inhibitor T-20 (enfuvirtide, Fuzeon)
- one new class of anti-HIV drugs called CCR5 receptor blockers. One drug from this class, maraviroc has entered the final stage of clinical trials before approval is sought.

A tall barrier
There are formidable barriers, both biological and personal, that could affect the ability of eradication protocols to work successfully. Because of these barriers—details of which appear in the next story—it will be several years before researchers can be sure that eradication efforts planned or underway will be effective.

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B. Overcoming barriers to a cure

Protocols involving highly active antiretroviral therapy (HAART) and valproic acid will likely become more commonplace in 2006 as researchers race to see which team can come closest to eradicating HIV. There will likely be a variety of approaches that attempt to rid the body of this virus. Understanding how HIV interacts with the immune system and these drugs is important when trying to make sense of the different protocols that will appear.

Different from others
HIV infection is different from many common viral diseases because it infects, disables and destroys cells of the immune system that would ordinarily control this virus. Moreover, another unusual aspect of HIV is that it appears to cause the immune system to suppress its own ability to respond to infections, including those caused by HIV.

Deep inside the cell
Once HIV infects a cell it inserts the instructions for making new viruses (HIV’s genetic material) and overwrites the cell’s DNA. This infected cell is now a potential virus factory. Because the cell’s genetic material now contains instructions for making HIV, getting rid of HIV’s incorporated genetic material becomes almost impossible unless the cell is destroyed.

Within two weeks after HIV has entered the body, the virus becomes well established in many cells throughout the body as well as in lymph nodes and tissues. This rapid and wide distribution adds to the difficulty of eradication.
HAART as a barrier
To keep HIV from infecting more cells over time, PHAs have to take HAART every day, continuously. Once therapy with a combination of anti-HIV drugs begins, the ability of HIV to infect more cells is gradually reduced over a period of months. Regrettably, HAART does not affect the reproduction of HIV-infected cells that can quietly carry the instructions for making new viruses. These cells are called resting CD4+ T cells and their persistence is a barrier to eradicating HIV.

Different cells, different uses
The cells that researchers think are a part of the permanent reservoir for HIV in the body include the following:
- a group of T-cells called resting CD4+ lymphocytes
- “memory” CD4+ cells
- monocytes, macrophages and dendritic cells

A memory of the past
As their name suggests, memory cells help the immune system to remember its previous encounter with a germ. The next time that particular microbe infects the body, the immune response is faster, quicker and more effective because of this immunologic memory. Memory cells have a long life span—perhaps decades.

The early-warning system
Monocytes, macrophages and dendritic cells all can act as the body’s early warning system against infection. These cells alert the immune system to the presence of invading germs and help to amplify the response against them. All of these cells can be infected by HIV.

In the brain
Experiments on monkeys with an AIDS-like condition and brain samples taken from deceased PHAs suggest that the central nervous system—the brain and spinal cord—is a reservoir for HIV. The lining of the blood-brain barrier has many tiny pumps that flush out anti-HIV drugs if they manage to get inside the brain. So the brain and its protective barrier remains a formidable obstacle to eradication of HIV. Despite all of these obstacles, some scientists have forged ahead trying to find a cure for HIV.

Squashing the bug
To increase the chances that an eradication protocol might succeed, an intensive combination of anti-HIV drugs may need to be taken. Moreover, PHAs participating in eradication research will need to engage in a high degree of adherence so that viral load is fully suppressed. To monitor changes in viral load, studies of eradication will likely use specially developed laboratory techniques and equipment that can accurately assess very low viral loads.

Key to a cure
Some researchers believe that the key to curing HIV infection lies in coaxing HIV from resting T cells. HAART is not able to do this, but researchers in North America and the European Union have been trying to find drugs with this capability. The substances that they have tested all suppress an enzyme called HDAC-1 that keeps HIV from becoming activated. Examples of compounds with this potential include the following:
- compound Q (tricosanthin)—an extract of Chinese bitter melon
- valproic acid—a commonly used anti-seizure drug

In lab experiments with cells and HIV, HDAC-1 inhibitors have triggered the replication of HIV in formerly resting T cells. And, experiments in a handful of PHAs suggest that it has the same potential. Researchers have used valproic acid because it is licensed for managing people with seizures and it has a long history of use, so its side effects and interactions are well known. The next report provides details about a pilot study of valproic acid in HAART users.

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C. Can valproic acid help flush HIV from hiding?

Researchers in Dallas, Texas, conducted an HIV eradication study and recently published an account of their work. Between 2002 and 2005, four PHAs whose viral load was very low (less than 50 copies) for several years, were enrolled in a study to try to reduce the level of HIV infection of their cells. In addition to their treatment regimens, all participants also received T-20 (enfuvirtide, Fuzeon) and the anti-seizure drug valproic acid. This last medication appears to help release HIV from resting T cells. After three months, researchers found that the level of HIV in resting cells fell significantly in three of the four PHAs. This last medication appears to help release HIV from resting T cells. After three months, researchers found that the level of HIV in resting cells fell significantly in three of the four PHAs. This is the first time that any therapy has appeared to reduce the body’s reservoir of HIV. The news of this development raised hopes that that a route to flushing HIV out of the body may be a possibility if the Dallas protocol were applied for several consecutive years.

However, readers should be cautious in interpreting the results from these and similar studies that are underway. Many issues need to be resolved before researchers can prove that a cure for HIV is indeed at hand. It may take several years before they can be certain about eradication. These and other related issues are explored later in this issue of *Treatment Update*.

**Study details**

Researchers recruited four adult participants who had been diagnosed with HIV infection between 1985 and 1999. All of them had been taking HAART for at least two years before entering the study and during that period their viral load was below the 50-copy mark. Having this degree and duration of viral suppression was a requirement for entering this clinical trial. The CD4+ cell counts of participants at the start of the study and the combinations of HAART used were as follows:

- **Participant 1**—1,285 CD4+ cells: tenofovir (Viread), abacavir (ABC, Ziagen), d4T (stavudine, Zerit) and amprenavir (Agenerase) boosted with a small dose of ritonavir (Norvir)
- **Participant 2**—558 CD4+ cells: ddI (didanosine, Videx), FTC (emtricitabine, Emtriva) and efavirenz (Sustiva, Stocrin)
- **Participant 3**—350 CD4+ cells: tenofovir, ABC, 3TC (lamivudine, Epivir), efavirenz and nelfinavir (Viracept)
- **Participant 4**—372 CD4+ cells; AZT, 3TC and nevirapine (Viramune)

Once in the study, participants self-injected T-20 twice daily at standard doses. The purpose of adding T-20 to their regimens was to hopefully intensify the anti-HIV activity of their treatment. After confirming participants’ adherence to this intensified therapy, researchers added another drug, valproic acid, to the regimen. This was taken at a dose between 500 and 750 mg twice daily for three months, at which point the study ended. Valproic acid levels in the blood were monitored to keep them within the range of 50 to 100 mg/L.

**Results—Side effects**

According to the study team, the four participants tolerated the protocol and adhered to it well.

Participant 4 was taking AZT and his bone marrow was temporarily weakened as he developed less-than-normal levels of red blood cells. This may have occurred because valproic acid can decrease the body’s ability to get rid of AZT.

**Results—Viral load**

In three of the participants, the intensified treatment regimen was able to keep viral load below the 50-copy mark. Participant 3 developed a minor chest infection after initiating T-20 therapy. His viral load rose to about 75 copies during this
illness but then fell back below the 50-copy mark and remained there for the duration of the study.

**Misunderstanding viral load results**
The currently available tests for assessing viral load generally have a lower limit of 50 copies. There is a common misunderstanding that viral load results below the 50-copy mark are "undetectable." In reality, these tests can often detect viral loads that are lower than 50 copies but cannot accurately count (or quantify) viral loads that are there. So a more accurate way to refer to the 50-copy limit is to say the viral load is BLQ—below the level of quantification.

**Breaking the 50-copy barrier**
To be able to accurately assess viral loads less than 50 copies, the study team developed their own test to be used in the lab. It could accurately assess viral loads as low as 1 copy.

Using this ultra-sensitive assay, researchers found that, for the most part, participants 1, 2 and 3 had viral loads as low as 1 copy or less. Participant 4 had viral loads that ranged between 9 copies and 1 copy at different times during the study.

**Searching for HIV**
Researchers took blood from participants and filtered out the lymphocytes, focusing on CD4+ cells. They maintained and grew these cells in the lab, then stimulated them with interleukin-2 to activate the cells and force HIV out of hiding. Three weeks later, technicians assessed CD4+ cultures for any HIV.

In general, during the study, the level of resting T cells with HIV fell by "at least 29%," according to the researchers. But when participants stopped taking valproic acid and T-20, the number of latently infected CD4+ cells appeared to increase.

In theory, if participants remained on the study regimen for several years, it may have been possible that the pool of resting HIV-infected CD4+ cells could have been removed from the body. However, even this research team notes that there are many issues about this study that need to be explored before they can be certain that HIV infection has been cured. These issues and ideas about different HIV eradication protocols are discussed later in *Treatment Update*.

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D. 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
- tenofovir

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.

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**E. Canadian trial of valproic acid**

In late 2005, the Canadian HIV Trials Network (CTN) will consider launching a study of an eradication protocol using valproic acid in HAART users. This trial, to be called CTN 205, will recruit at least 75 HAART-using PHAs who will be randomly assigned to one of three arms where valproic acid will be provided for:

- 4 months
- 6 months
- 12 months

The reason for the different lengths of exposure to valproic acid is so that researchers can assess its impact on the amount of HIV in the body. So far, researchers in Montreal, Ottawa and Vancouver have expressed interest in this study, which has been largely designed by Dr. Jean-Pierre Routy.

The CTN will soon have more details about this study at:

- [http://www.hivnet.ubc.ca/e/home/index.html](http://www.hivnet.ubc.ca/e/home/index.html)
- 1.800.661.4664

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**F. Study finds PEP not 100% effective in preventing HIV infection**

Some doctors and nurses who care for PHAs may sustain needle-stick injuries. This raises the possibility that they may develop HIV infection. To prevent this, a number of studies have been conducted in which health care workers exposed to HIV have received anti-HIV drugs for four weeks. For instance, in the 1990s, researchers found that giving AZT to health care workers who were exposed to HIV was able to prevent HIV transmission in about 81% of cases. Taking anti-HIV drugs to prevent this form of transmission is called PEP, or post-exposure prophylaxis.

In studies with monkeys, treatment within 72 hours of exposure to SIV (Simian Immunodeficiency Virus, which causes AIDS in those animals) reduces their risk of infection. Based on this and other results, researchers in San Francisco conducted a study about the ability of PEP to prevent sexual and needle-use transmission of HIV in people. In analyzing data from 702 participants who were given PEP within 72 hours of exposure, they found that most were protected from developing HIV infection. It is important to note that PEP did not provide 100% protection in cases of sexual exposure. Why this might have happened is explored in the report below.

**Study details**

Researchers in San Francisco conducted two studies of PEP and combined the data they collected for this analysis.

In both studies, participants received PEP within 72 hours of possible exposure to HIV. Some participants received two counseling sessions, while others received up to five counseling sessions, focusing on reducing the risk of transmitting HIV, along with other messages, including adherence to PEP.

**Routes of infection**

Eligible participants had to have engaged in sex without condoms as follows:

- receptive or insertive anal intercourse
- unprotected vaginal intercourse
- receptive oral intercourse with ejaculation

Also, certain other potential routes of exposure were considered, including:

- sharing of needles for street drug use
- contact with a potentially infectious body fluid on a mucosal membrane or skin that was damaged because of a cut, scrape or abrasion

The potential exposure must have occurred with a partner who had one of the following characteristics:

- HIV infection
- was a man who had sex with another man
- injected street drugs
- engaged in sex work
- was an anonymous sexual partner

Participants who entered the study were given the following therapies:

- AZT coformulated with 3TC (Combivir)
- d4T and 3TC
- d4T and ddI
Whenever possible, researchers also interviewed the person who was the potential source of exposure. Based on the source person’s history of using anti-HIV drugs, researchers could modify their prescription of PEP. If the treatment history of the potential source was unavailable, researchers gave participants Combivir. In cases where the potential source of infection had a recent viral load above the 50-copy mark, researchers provided Combivir and nelfinavir (Viracept) for PEP.

Technicians assessed blood samples before participants began PEP and then three months later, checking for antibodies to HIV, viral load, interferon-gamma and, in some cases, strains of HIV that were resistant to therapy.

Results
Analysing data from 702 participants, researchers found that there were a total of seven people who became infected with HIV (seroconverters) — about 1% of the group. Here’s a look at the profile of study participants:

- The vast majority (95%) was exposed through unprotected sex and were men.
- The remaining participants were exposed through a combination of sex and needle use or needle use alone.

The research team divided participants into two groups — seroconverters and non-seroconverters — to try to find factors that were linked to HIV infection.

All seven seroconverters were men and all had engaged in unprotected, receptive anal intercourse. By comparison, among non-seroconverters, 50% had engaged in similar sex acts.

Timing
On average, people who seroconverted initiated therapy 46 hours after exposure. Notably, three of seven seroconverters began to take PEP more than 56 hours after exposure. People who did not seroconvert initiated therapy earlier — on average 33 hours after exposure. This difference may be important because animal experiments suggest that the sooner PEP is started, the lower the risk of infection.

Therapy
Of the 14 people (2%) who began PEP with a nelfinavir-containing regimen, none seroconverted. There were no significant differences in the proportion of seroconverters who used Combivir (86%) and non-seroconverters who used Combivir (94%).

Adherence
Although all seroconverters took PEP for four consecutive weeks, at least three reported that they missed “a substantial number of doses,” according the research team.

Repeated infection(s)?
Prior to entering the study, all seroconverters had other, potential exposures to HIV, including unprotected, receptive anal intercourse.

To check for the possibility of infection before entering the study, technicians analysed blood samples from participants for HIV viral load. Six of the seven seroconverters were later found to have a viral load less than 50 copies — the lower limit of the test, suggesting that there was little chance of prior infection. The remaining participant had a viral load of about 400 copies at the time he entered the study. None of the seroconverters had evidence of HIV that was resistant to any therapy.

Why did PEP fail?
The researchers note that, as is the case with health care workers, PEP is not 100% effective for preventing infection from sexual exposure to HIV.

In this study, there may be several reasons why PEP failed for the seven participants who became HIV seropositive.

1. Better prevention?
A possible source of failure is that all people who seroconverted received just two drugs, usually AZT and 3TC. A more robust regimen consisting of a protease inhibitor in addition to two nukes conferred protection to all participants who used it. Other studies have found that a potent protease inhibitor (Kaletra) when used as part of combination therapy for PEP prevented seroconversion in all 88 evaluable people.

2. Continuous exposure
Three participants who seroconverted reported that they continued to engage in unprotected, receptive anal intercourse while taking PEP. This may have increased their exposure to HIV, overwhelming their immune systems and PEP.

3. Earlier is better
In at least one study with monkeys and simian immunodeficiency virus (SIV), the earlier that PEP
was initiated after exposure, the less likely that infection occurred. For instance, PEP was more effective when given at 12 hours post-exposure rather than at 72 hours.

4. Adherence
More intensive counseling and monitoring of adherence may be a useful intervention to make when conducting future studies of PEP.

5. Route of infection
Some researchers said that unprotected, receptive anal intercourse is “a severe test for prevention of HIV infection.” This arises because of the very high risk of transmission with which this type of sex is associated. However, perhaps more robust PEP regimens may deal with this issue.

The San Francisco researchers acknowledge that their study does not allow a true test of the efficacy of PEP because there was no comparison group—participants who did not receive PEP. And they emphasize that when exposed patients are being counseled in the future, they should be told that PEP does not provide 100% protection from HIV infection.

Continued research on PEP for preventing sexual transmission is needed to find out which combinations of drugs are best for this situation. As well, research with animals to better understand the immunology of the mucosal immune system (in the lining of the anus, mouth, penis and vagina) may provide some insight as to how to strengthen the immune response against HIV in the first hours after infection.

Here are some links to guidelines about sexual exposure and PEP from the following countries:

- United States: http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=68
- United Kingdom http://www.bashh.org/guidelines/draft_04/pepse[1]_010404.doc

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