



HIV and AIDS: Myths, Facts, and the Future

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The first cases of HIV* infection in the United States began to be reported to physicians almost 25 years ago, although at the time, physicians did not know what agent was responsible for the onset of what appeared to be the emergence of an immunodeficiency syndrome. These initial reports in 1981, described unexplained cases of *Pneumocystis carinii* pneumonia (PCP) and Kaposi's sarcoma (KS) among young homosexual and bisexual men.^{1,2} The cause or reason for the clustering of these conditions among homosexual and bisexual men, particularly along the coastal areas of the United States, was unknown at the time, but subsequent reports that pneumonia and KS were also increasing among hemophiliacs and injecting drug users, which were such separate and distinct populations, suggested that an infectious agent might be involved.³ The first myths surrounding the syndrome that eventually would become known as AIDS, caused by the HIV retrovirus, began to emerge at this time. The most common are listed in the sidebar (see Page 13) along with information to dispel the myth.

This article looks at the demographics of HIV/AIDS in the United States, before going into a detailed discussion of how the infection manifests itself in the body. The remainder of the article touches on co-infection with other viruses.

A Cumulative Portrait of AIDS

The cumulative number of AIDS cases reported in the United State to the US Centers for Disease Control and Prevention (CDC) and found in their December 2002 semi-annual HIV/AIDS Surveillance Report was 886,575. Distribution by age is found in Table 1.

| AGE | NUMBER OF CASES |
|----------------|-----------------|
| under 13 years | 9,300 |
| 13-24 | 36,299 |
| 25-34 | 301,278 |
| 35-44 | 347,860 |
| 45-54 | 38,386 |
| 55-64 | 40,584 |
| 65 and older | 12,868 |

Table 1: Distribution by age of US cases of HIV/AIDS reported to the CDC by December 2002.

*Note: In this article HIV refers to human immunodeficiency virus type 1 (HIV-1), the more prevalent strain of HIV infection.

From this data, we can see the impact of the disease on those age groups that would have been most sexually active during the rapid spread of the infection in the 1980s. Transmission began to plateau in the 1990s, in large part because of educational efforts promoting "safe sex," abstinence, or the use of condoms, particularly among high-risk populations. Unfortunately, these data also show an apparent recent up-surge of new infections among those in their late teens and early twenties, apparently due to increased sexual promiscuity.

HIV Infection by Occupational Exposure

In fact, the spread of HIV to healthcare workers within their occupational settings is very uncommon in the United States. Accidental or unintentional needlesticks are the most common causes of occupational exposure leading to HIV infection of healthcare workers. All healthcare providers, how-

| Occupation | Total Number |
|------------------------|--------------|
| Nurses | 23 |
| Laboratory technicians | 19 |
| Physicians | 6 |
| Surgical technicians | 2 |
| Dialysis technician | 1 |
| Respiratory therapist | 1 |
| Health aide | 1 |
| Embalmer | 1 |
| Housekeeper | 2 |

Table 2: The cumulative numbers of individuals by profession or occupation infected by HIV following a clear case of accidental occupational exposure as of 1999, as reported to the CDC.

ever, should always wear protective gloves during routine care of their patients as there have been reports of HIV transmission from exposure to patient blood or body fluids that have come in contact with chapped skin or small, unprotected wounds or blisters. Such events, however, are exceedingly rare.

HIV: A Retrovirus

Retroviruses, including HIV, are unique among animal viruses because of their ability to convert the RNA genome within the infectious virus particle into a double-stranded DNA form shortly after the virus infects the cell, as illustrated in Figure 1. This ability to convert viral RNA to double-stranded viral DNA is accomplished by the viral enzyme reverse-transcriptase (RT).⁴ RT is a target for which effective clinical therapies have been developed. These therapies are small molecule nucleoside and non-nucleoside

structural inhibitors and function on the basis of impeding the conversion of viral RNA into a DNA copy by reverse-transcriptase. RT is found in the cell within a protein/nucleic acid (viral RNA) complex after viral infection. It is within this complex that HIV-1 RNA is converted into a double-stranded viral DNA form capable of being integrated into host cell chromosomal DNA. As shown in Figure 1, the viral DNA is then shuttled into the nucleus of the cell where HIV integrase inserts the viral DNA into the DNA of the host cell.⁵ This event is significant because the viral DNA is stably integrated into the host chromosomal DNA and serves as a permanent template for the production of new virus particles.

The integrated HIV DNA is referred to as the HIV provirus or HIV proviral DNA. The chromosomal location of the HIV proviral DNA can affect the level of virus produced from within the infected cell. This production of viral components first starts with the synthesis of viral RNA from the viral DNA provirus and the viral components are then directed toward the cell's plasma membrane for assembly into new viral particles and subsequent release from the cell.

Viral messenger RNAs (mRNAs) serve as templates for viral protein synthesis. Some of these viral RNAs code for the synthesis of viral polypeptides, which must be cleaved into functional forms by the HIV protease, which itself, is part of the Gag-Pol polyprotein.^{6,7} The cleavage of the viral polypeptides by the viral protease must occur prior to release of newly synthesized virus particles from the infected cell. An effective therapeutic regimen referred to as highly-active antiretroviral therapy (HAART) includes orally administered inhibitors that impede the functions of both the HIV RT and protease enzymes.

HIV Cytopathicity

HIV infection causes the steady decline of immune cell functions and appears to be strongly related to the direct and indirect

killing of CD4+ T cells within an infected individual.⁸ HIV appears cytostatic or cytopathic for many cell-types. It is well known that infected T cells can form large aggregates, referred to as syncytia, triggered by fusion of the plasma or outer cell membranes of cells within the aggregate. Syncytia represent multinucleated collections of fused cells that have a short lifespan.

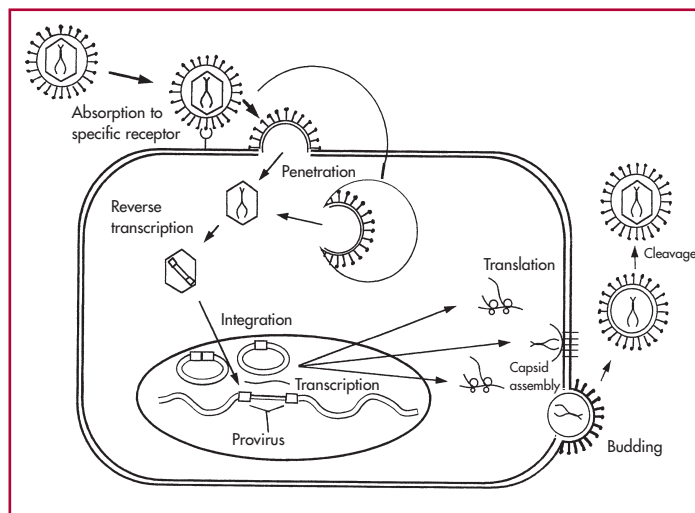


Figure 1: The life cycle of HIV—The HIV particle attaches to the primary CD4 receptor and one of two co-receptors on the plasma membrane of the cell the virus is infecting. The viral membrane fuses with the cell membrane and the viral bullet-shaped core is deposited into the cytoplasm of the cell. Reverse-transcriptase converts the viral RNA into a double-stranded DNA molecule, which then enters the cell nucleus. The HIV enzyme, integrase, inserts the HIV DNA into the cell chromosomal DNA from which viral RNA is synthesized. Viral RNAs serve as templates for the production of viral proteins. Full-length HIV genomic RNA and viral proteins coalesce at the outer cell membrane to form new HIV particles that are then released from the infected cell.

Certain HIV-infected cells also undergo programmed cell death or apoptosis. The HIV envelope protein (ENV) and the HIV accessory protein, Vpr, appear to be the prime candidates for initiating the direct killing of cells. Neurons exhibit unusual sensitivity to the cytotoxic and cytopathic after exposure to the virus.⁹ There is considerable evidence that regeneration of CD4+ lymphocytes from bone marrow sources is compromised in HIV-infected individuals, although it is likely that natural immune clearance of virus-infected cells is the main contributor to the steady decline of CD4+ lymphocytes

in the absence of therapeutic intervention. These immune responses to the presence of virus-infected cells occur in the form of HIV-specific cytolytic T lymphocytes, antibody-dependent cellular cytotoxicity, and the scavenger functions of natural killer cells.¹⁰

T-Lymphocyte Count and Viral Load

CD4 is the protein receptor for cell entry of the virus that is displayed on the surface of a specific class of T cells and healthy individuals have a CD4+ T-lymphocyte count of approximately 1,200 cells per cubic milliliter of blood.¹¹ In the absence of treatment, the CD4+ T-lymphocyte count gradually decreases in the blood of HIV-infected individuals at a rate of about 50-100 cells per year. Opportunistic infections, such as pneumonia, begin to arise in individuals whose CD4+ T-lymphocyte count is around 200 or less; severe damage to the immune system has already occurred as a consequence of viral replication when T-cells fall to this level.



The actual level of HIV virus particles or virions in an infected individual's blood is typically determined by measuring the amount of viral RNAs contained within the free blood-born virions. This is accomplished primarily by the use of two assays—bDNA and the polymerase chain reaction (PCR)—that accurately measure what is referred to as the “viral copy number” (see Fig. 2). PCR is used to measure extremely low levels of viral RNA from blood cell samples, typically less than 50 copies of viral RNA per milliliter of blood. The bDNA is less costly than PCR and has been shown to be accurate in measuring higher levels of virus in the blood. Viral load measurements, like T-cell counts, are good indicators of disease progression. The higher the viral load and the lower the T-cell count, the greater the progression of the disease.

Highly-active Antiretroviral Therapy (HAART)

The introduction of HAART dramatically changed the natural history of HIV infection and had a profound effect on mortality and morbidity. As shown in Figure 2, a drastic reduction in blood plasma HIV RNA levels (typically <50 copies/ml of blood plasma) can be achieved in most patients.^{12, 13} There is also a parallel reduction of HIV in genital secretions as well.¹⁴ Nonetheless, HAART does not lead to absolute viral eradication. Retroviral latency and continuous low levels of viral replication can still be detected not only as a cell-free virus, but also in different cell-types of distinct compartments within patients despite undetectable plasma HIV RNA levels.^{15–22}

HIV Latency and Viral Persistence

Virus persists in cells of HIV-infected patients even through prolonged administration of HAART. Resting CD4+ T-lymphocytes likely represent the most long-lived source of cells bearing viral DNA, however, other cell-types including CD14+ monocytes also have fairly long life-spans that may contribute to

the overall pool of cells that persist and contain HIV viral DNA. Indeed, it is quite unclear whether the administration of HAART will ever be capable of eradicating HIV completely from an infected patient. Some models indicate a progressive, but very slow elimination of the virus in certain patients.²³ These models provide some hope that continued use of current therapies

could eventually eliminate the virus, however other projections suggest that an HIV infection should be regarded as a life-long disease.²⁴ Indeed, the duplication of HIV CD4+ effector T-lymphocytes and their reversion back to a resting state, where virus expression becomes quiescent, supports a scenario whereby HIV persistence within resting cells could be maintained indefinitely in the HIV-infected individual. Viral latency and persistent or cryptic viral replication in specific microenvironments shielded by blood tissue barriers, such as in the central nervous system, retina, or testes, may occur and serve as potential

HIV reservoirs despite the use of virally-suppressive HAART.

HIV in Semen and Vaginal Secretions

The presence of replication-competent HIV has been demonstrated in seminal cells, indicating that they may not only play a role in the transmission of the virus, but may also act as a sanctuary for the HAART-resistant virus.²⁵ These infected cells may serve as a source for re-infecting the peripheral bloodstream and lymphoid tissue, especially when HAART is discontinued.

HIV has also been recovered from vaginal fluids and vaginal and cervical cells. Genital associated lymphoid tissue, composed of endo- and exo-cervical stromal lymphocytes, monocytes, and dendritic cells, is considered to be a potential source of HIV replication.

A recent study analyzed the HIV viral load in cervical-vaginal secretions from 122 HIV-positive women using a sensitive

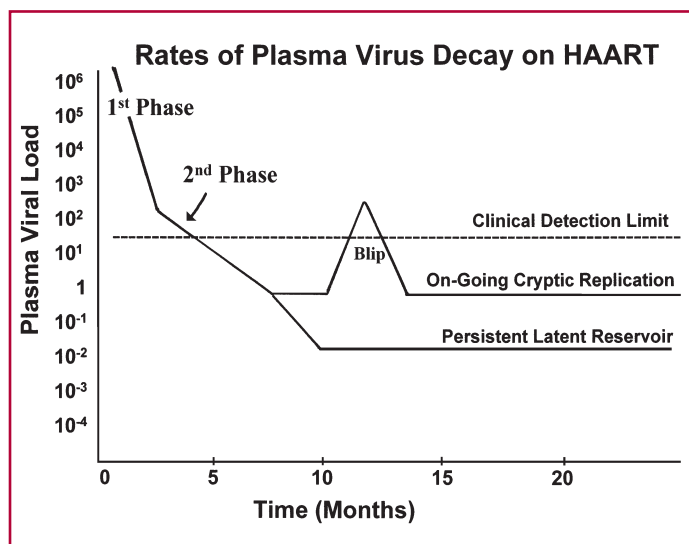


Figure 2: The effect of HAART on viral replication—Highly-active antiretroviral therapy (HAART) is a therapeutic combination of small molecule inhibitors that impede the functions of the HIV reverse transcriptase and protease enzymes. In the first phase of treatment, there is a rapid and steep decline of HIV particles present within blood plasma. This occurs within the first few months of therapy. In the second phase, a latent viral reservoir is established that can consist of HAART-resistant virus or latent virus that is not expressed in the absence of activation signals. This latent HAART-persistent reservoir appears highly stable. The presence of HIV particles presumably are produced from the latent reservoir.

technique with a low detection limit of 80 copies of viral RNA/ml of blood to investigate whether HIV shedding correlates with plasma HIV-viral load. The authors reported that in 40 percent of women on a HAART regimen, cervical lavage samples were still positive for the presence of HIV RNA. Moreover, in 25 percent of women with undetectable virus in their plasma a cervical-vaginal shedding was demonstrated, suggesting not only that blood plasma viral load may fail to predict the infectivity of genital secretions, but also the possibility of viral sequestration or compartmentalization.²⁶

The latter finding is in agreement with previous studies where higher HIV RNA levels were present in genital fluids relative to those found in blood plasma. HIV shedding occurs in the cervicovaginal fluids for the majority of HIV infected women with plasma viral load <50 copies/ml despite virally-suppressive HAART. The presence of cell-free HIV RNA in cervicovaginal secretions emphasizes the importance of continuing to practice protected sex even in the era of HAART.

Co-infection with Other Viruses

Herpes and HIV

Herpes is the most common sexually transmitted infection; the two most common types are herpes simplex type-1 and type-2 (HSV-1 and HSV-2). Either can infect the mouth or genital area. The CDC has advised that persons infected with HIV and HSV appear to be more readily able to transmit HSV to another person than those who are infected with HSV, but not HIV. Current treatments specifically for herpes include acyclovir (Zovirax), valcyclovir/valacyclovir (Valtrex), and famciclovir (Famvir).

Human Papilloma Virus and HIV

Treatment for genital warts, which are the result of a human papilloma virus (HPV) infection, may include one or a combination of the following compounds or procedures: podofilox 5 percent solution or gel, imiquimod 5 percent cream, bichloroacetic acid, cryotherapy (freezing), or surgical removal. Infection with HPV is associated with a higher risk of cervical cancer for women, even without an HIV co-infection. Both HIV-infected men and women co-infected with HPV appear to be at increased risk for anal cancer.

Hepatitis and HIV

Persons with any combination of HIV and hepatitis B (HBV) or C (HCV) should stop drinking alcohol and get vaccinated against

PERSISTENT MYTHS SURROUNDING AIDS AND HIV INFECTION

MYTH 1: AIDS ONLY OCCURS IN HOMOSEXUAL MEN AND DRUG ABUSERS.

Response: At the onset of the epidemic in the United States, AIDS clustered in these populations. It is now known that anyone infected with HIV can get AIDS if they are not treated with medications to stop replication of the virus in their bodies.

MYTH 2: AIDS CAN BE TRANSMITTED THROUGH FOOD SOURCES, CASUAL HUMAN CONTACT, OR INSECT BITES.

Response: HIV infection, which leads to the symptoms of AIDS, can only be transmitted by the direct exchange of bodily fluids such as blood, semen, and vaginal secretions. Sharing food, hugging an infected person, or getting bitten by an insect does not lead to infection. Those who engage in unprotected intercourse, share needles, or are born to an HIV-infected mother are at high risk.

MYTH 3: OLDER PEOPLE DON'T GET AIDS.

Response: Anyone infected with HIV can develop AIDS. Older people are less likely to be infected by HIV because they are less likely to be sexually promiscuous or injecting drug users.

MYTH 4: AIDS IS ALWAYS FATAL.

Response: Before the mid-1980s, AIDS was considered to be a lethal syndrome for those infected with HIV. Now, a regimen of medications called HAART stops almost all of the virus from replicating in infected persons. Patient T-lymphocyte counts return to essentially normal levels shortly after HAART treatment and the occurrence of opportunistic infections is reduced greatly.

MYTH 5: HIV-INFECTED WOMEN SHOULD NOT HAVE CHILDREN.

Response: There is concern of transmission, but certain steps, including medications, can be taken to greatly reduce transmission from mother to child and infected mothers can bear children that are not infected by the virus.

MYTH 6: HIV AND AIDS INFECTION CAN BE CURED.

Response: There is no current "cure" for HIV. Medications reduce replication of the virus which reverses the immunodeficiency syndrome so patients rarely die of opportunistic infections now.

hepatitis A. Hepatitis viruses damage the liver, which is largely the result of the immune system attacking hepatitis-infected liver cells. Ironically, some HIV and hepatitis co-infections may exhibit a slower rate of liver damage because HIV suppresses the immune system. Persons co-infected with HIV and hepatitis who follow a HAART regimen must be cautious, however, as immune response rebound—which is the result of HAART suppressing HIV replication—may normalize the rate of liver



damage caused by hepatitis virus. Vaccines are available for hepatitis A and B; treatment for hepatitis C typically involves administration of pegylated interferon plus ribovirin for approximately 48 weeks or standard interferon plus ribovirin.

Current Strategies to Eradicate HIV

Immune activation therapy (IAT) is a potential strategy to eliminate persistent HIV in conjunction with HAART. In general, IAT aims to activate HIV-infected cells synchronously to “force” the expression of viral products from quiescent HIV proviruses. It is believed that the activation of cells bearing quiescent HIV could accelerate the elimination of these cells. This would occur largely through natural immune surveillance within the patient as a consequence of newly synthesized viral proteins that would be deposited on the outer plasma membrane of the infected cell. Furthermore, activation may hasten turnover of HIV-infected cells by shortening their natural life span or by direct induction of apoptosis for this population of cells. To date, the results of using clinical administration of anti-T-cell receptor antibodies and cytokines—such as interleukin 2 (IL-2) or interferon gamma—in the IAT approach have not been very encouraging.

Another approach currently under research involves studying the effectiveness of a naturally occurring agent called prostratin that has been used in Samoa for the treatment of jaundice.²⁷ Prostratin is a non-tumor promoting phorbol ester that has two unusual properties. The compound alters the metabolic activities of cells and thereby “forces” the production of higher levels of HIV components within the cell. The production of virus components from latent viral DNA within an infected cell would not otherwise occur from silent or latent HIV viral DNA. This property of prostratin has potential clinical utility because cells that are triggered to make the virus become exposed to immune surveillance and removal. The compound also lowers the levels of receptors required for HIV to enter and infect cells. This property is only useful if the cell has not already been infected. The clinical toxicity index for this compound must first be determined before it can be used in a clinical setting. Such studies are underway.

HAART, or even the use of new classes of viral inhibitors, may not be able to purge the latent virus from resting cells. Given this, there may be no other clinical options but to employ immune activation therapy in attempting to eradicate the vestigial virus that persists in patients despite lengthy periods of use with the therapeutics now available.²⁸

New therapeutic agents to halt HIV replication are currently in clinical trials and there are a number of trials assessing the effectiveness of anti-HIV vaccines. Until the benefits or efficacy of new classes of HIV therapeutics are known or an anti-HIV prophylactic vaccine is developed, it remains best for individuals to practice protected sex. Healthcare professionals or others who routinely come in contact with blood or bodily fluids in their occupation are advised to wear gloves and perhaps other protective garments depending on the circumstances of their potential exposure.

The outlook for the eradication of HIV or at least reasonable management of the disease is optimistic. Until the mid-1990s, HIV in the United States was thought to invariably lead to death, but it is now considered a manageable disease with vastly reduced lethality. There is no other option but to await the development of new HIV therapeutics, an effective vaccine, or other clinical interventions such as IAT. The latter may be of benefit to those individuals already infected with the HIV retrovirus. The success of research activity for the last two decades suggests there is indeed promise for the future in combating this contagion. ■

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References

1. US Centers for Disease Control and Prevention, “Pneumocystis pneumonia—Los Angeles,” *MMWR* **30**, pp. 250-2 (1981).
2. US Centers for Disease Control and Prevention, “Kaposi’s sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California,” *MMWR* **30**, pp. 305-8 (1981).
3. US Centers for Disease Control and Prevention, “Update on Kaposi’s sarcoma and opportunistic infections in previously healthy persons—United States,” *MMWR* **31**, pp. 294-301 (1982).
4. A.M. Skalka and S.P. Goff, *Reverse Transcriptase* (Cold Spring Harbor Press, Cold Spring Harbor, NY, 1993).
5. J. Kulkosky and A.M. Skalka, “Molecular mechanisms of retroviral DNA integration,” *Pharmacology and Therapeutics* **61**, pp. 185-203 (1994).
6. N.E. Kohl *et al.*, “Active human immunodeficiency virus protease is required for viral infectivity,” *Proc. Natl. Acad. Sci. USA* **85**, pp. 4686-90 (1988).
7. R.A. Katz and A.M. Skalka, “The retroviral enzymes,” *Ann. Rev. Biochem.* **63**, pp. 133-73.
8. G. Pantaleo *et al.*, “The immunopathogenesis of human immunodeficiency virus infection,” *N. Eng. J. Med.* **328**, pp. 327-35 (1993).
9. C.A. Patel *et al.*, “Lentiviral expression of HIV Vpr induces apoptosis in human neurons,” *J. Neurovirology* **5**, p. 121 (2001).
10. Pantaleo *op cit.*, 1993.
11. A.G. Dagleish *et al.*, “The CD4 (T4) receptor antigen is an essential component of the receptor for the AIDS retrovirus,” *Nature* **312**, pp. 763-7 (1984).
12. F.J. Palella *et al.*, “Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection,” *N. Engl. J. Med.* **338**, pp. 853-60 (1998).

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13. S.M. Hammer *et al.*, "A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less," *AIDS Clinical Trials Group 320 Study Team, N. Engl. J. Med.* **337**, pp. 725-33 (1997).
14. P. Gupta *et al.*, "High viral load in semen of human immunodeficiency virus type 1-infected men at all stages of disease and its reduction by therapy with protease and nonnucleoside reverse transcriptase inhibitors," *J. Virol.* **71**, pp. 6271-5 (1997).
15. T.W. Chun *et al.*, "Quantification of latent tissue reservoirs and total body viral load in HIV infection," *Nature* **387**, pp. 183-8 (1997).
16. G. Dornadula *et al.*, "Residual HIV RNA in blood plasma of patients taking suppressive highly active antiretroviral therapy," *JAMA* **282**, pp. 1627-32 (1999).
17. D. Finzi *et al.*, "Identification of a reservoir for HIV in patients on highly active antiretroviral therapy," *Science* **278**, pp. 1295-300 (1997).
18. H. Zhang *et al.*, "Human immunodeficiency virus type 1 in the semen of men receiving highly active antiretroviral therapy," *N. Engl. J. Med.* **339**, pp. 1803-9 (1998).
19. R.J. Pomerantz, "Residual HIV infection during antiretroviral therapy: the challenge of viral persistence," *AIDS* **15**, pp. 1201-11 (2001).
20. S. Sonza *et al.*, "Monocytes harbour replication-competent, non-latent HIV in patients on highly active antiretroviral therapy," *AIDS* **15**, pp. 17-22 (2001).
21. A. Valentin *et al.*, "Persistent HIV infection of natural killer cells in patients receiving highly active antiretroviral therapy," *Proc. Natl. Acad. Sci. USA* **99**, pp. 7015-20 (2002).
22. K. Saha *et al.*, "Isolation of primary HIV that target CD8+ T lymphocytes using CD8 as a receptor," *Nat. Med.* **7**, pp. 65-72 (2001).
23. M.G. Mascio *et al.*, "In a subset of subjects on highly active antiretroviral therapy, human immunodeficiency virus type-1 RNA in plasma decays from 50 to <5 copies per milliliter, with a half-life of six months," *J. Virol.* **77**, pp. 2271-5 (2003).
24. D. Finzi *et al.*, "Latent infection of CD4+ T cells provides a mechanism for life-long persistence of HIV, even in patients on effective therapy," *Nature Med.* **5**, pp. 512-7 (1999).
25. Zhang *op cit.* (1998).
26. J. Fiore *et al.*, "Correlates of HIV-1 shedding in cervicovaginal secretions and effects of antiretroviral therapies," *AIDS* **17**, pp. 2169-76 (2003).
27. J. Kulkosky *et al.*, "Prostratin: Activation of latent HIV expression suggests a potential inductive adjuvant therapy for HAART," *Blood* **98**, pp. 3006-15 (2001).
28. J. Kulkosky and R.J. Pomerantz, "Approaching eradication of highly active antiretroviral therapy – persistent human immunodeficiency virus type-1 reservoirs with immune activation therapy," *Clin. Inf. Dis.* **35**, pp. 1520-26 (2002).