



HEPP NEWS

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EDUCATION
PRISON
PROJECT

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ABOUT HEPP

HEPP News, a forum for correctional problem solving, targets correctional administrators and HIV/AIDS and hepatitis care providers including physicians, nurses, outreach workers, and case managers. Continuing Medical Education credits are provided by the Brown University Office of Continuing Medical Education to physicians who accurately respond to the questions on the last page of the newsletter.

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IMMUNOTHERAPY OF HIV: ON THE HORIZON?

Anne S. De Groot, M.D.*, *Brown Medical School, Editor, HEPP News*
*The assistance of Jesse Creel** with this article is gratefully acknowledged*

Why should the correctional HIV provider care about T cells, T cell epitopes, and HLA molecules? Because the use of Strategic Treatment Interruption (STI) and therapeutic vaccines for the treatment of HIV – particularly acute HIV infection – may be on the horizon for our patients. This article will describe the components of immune response to HIV and explain why STI is more likely to provide benefit in acute HIV infection and less likely to benefit patients who have chronic HIV infection, at least until more effective forms of STI, such as STI given in conjunction with effective therapeutic HIV vaccines, are developed. It should be noted that STI is not an FDA approved use of any of the HAART drugs, and that STI should never be attempted outside of well-established experimental protocols run by experts in the field.

HIV IMMUNOLOGY 101

The cellular immune response is the first arm of the immune system to respond to HIV infection (see HEPPiagram). Cellular immune response is provided by T helper cells (also known as CD4+ cells or T4 cells) and cytotoxic T cells (also known as CTL, or CD8+ or T8 cells). Studies of acutely infected HIV patients have shown that each individual mounts a cellular immune response to HIV that determines the individual's "set point", the point of stabilization of viral load after acute infection has been controlled. This set point is closely linked to progression to AIDS.¹ Patients whose immune systems do not successfully control HIV during acute infection have higher set points and more rapid progression to AIDS than patients whose immune systems do not perform as well during acute infection.

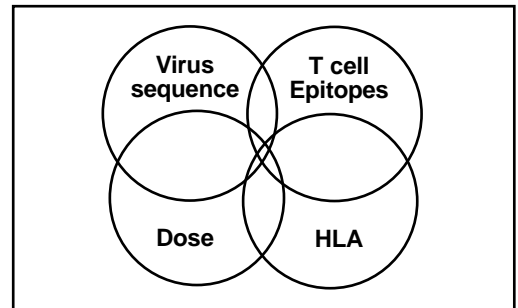
The ability to control HIV and obtain a lower set point is determined by several factors (illustrated in Figure 1). These factors include the initial dose of HIV during infection, the type of virus transmitted, i.e. the specific viral DNA and protein sequences, the HLA of the infected individual, and the number of T cell epitopes that can be recognized by the individual's T cells.

DOSE OF HIV

Numerous studies have clearly demonstrated that the initial dose of infecting virus can determine outcome. For example, patients who received blood donations containing large

amounts of HIV (such as hemophiliacs, prior to screening of factor VIII) appear to progress more rapidly than patients who are infected via sex or through minor intravenous exposures.² Mother to child transmission is also dependent on viral

FIGURE 1 . Factors determining "set point" and viral load in the setting of acute HIV infection



load (particularly at the time of delivery). Individuals who are infected with smaller doses may have a lower viral burden at the outset, and perhaps more importantly, may be infected with fewer quasiespecies or viral variants. Just as it is easier to control HIV with HAART when starting from a lower total viral load, it may be easier to obtain immune control of HIV when there are fewer viral variants.

HLA AND INHERITANCE

The HLA molecule carries pieces of HIV viral proteins in its central "binding groove" to the surface of infected cells. When T cells see a piece of an HIV protein (a short piece called a peptide) on the surface of the cell, carried by the HLA protein, they react, either by killing the infected cell (the function of CTLs) or by secreting messages that amplify the immune response to HIV (T helper cells). HIV peptides that bind to HLA and turn on T cells are called epitopes. These epitopes tell the immune system that HIV is present, and it needs to begin to fight. So HIV epi-

Continued on page 2

WHAT'S INSIDE

HEPPiagram	pg 5
Ask the Expert	pg 6
HIV 101	pg 7
Self-Assessment Test	pg 9

IMMUNOTHERAPY OF HIV... (continued from page 1)

topes are the "key" that turns on the immune defense against HIV.

There are many different types of HLA molecules (different alleles of the following HLA genes: HLA A, B, C, DR, DQ, DP). Different HLA molecules present different epitopes; the epitopes they are able to present are determined by the pattern of the amino acids in the HIV peptide. (If the HLA is a lock, only certain epitopes with a particular pattern fit the lock). Since HLA are genetically encoded, some individuals may be able to use epitopes (that have the right pattern for their HLA) that others cannot (because the sequences don't match the pattern for their HLA).

NEW INFORMATION ON THE ROLE OF HLA

One of the key findings in HIV over the past two years has been that the genetic background (HLA) of an HIV-infected individual can determine how well they are able to control their HIV. The role of HLA has been reported previously^{3,4} but the mechanism of interaction between the HLA and the outcome of infection was less clear until recent data was published in the *New England Journal*. Mary Carrington, one of the lead authors, demonstrated the link between selected HLA molecules (a variant of B35) and HIV virus sequence.⁵ She showed that the HLA variant in question did not effectively present a T cell epitope. (To use our metaphor, the key did not fit the lock). Other HLA were able to present the epitope. This epitope appeared to play a critical role in the immune response to HIV for these patients.

Thus, a person's genetic background (HLA) determines how many epitopes their immune system is able to recognize. The ability to recognize some specific epitopes appears to be linked to control of infection. One of the HLA types that appears to be associated with more rapid progression so far is a variant of HLAB35.⁶ HLA Types that are associated with better outcomes include HLA B27 (a rare haplotype) and HLA B57⁷. It may not be long before we begin HLA typing our HIV patients so as to predict the course of their infection.

T CELLS AND EPITOPES

T cell response to HIV epitopes has been shown to be a critical determinant of outcome: patients who have more T cell responses to many different pieces of HIV (epitopes) appear to be more likely to contain HIV infection.^{8,9} Broad T cell response to many HIV epitopes appears a major determinant of the HIV setpoint.⁸ Broad T cell response is also seen in long-term non-progressors.¹⁰ Most of the epitopes that have been mapped are cytotoxic T cell (CTL) epitopes. T helper cells (Th) also play an important role in early immune response to HIV, but since they are destroyed in chronic HIV

infection, researchers are only beginning to understand their role in HIV. They appear to play an important role in early infection. Th cells that respond to HIV are destroyed or inactivated in the setting of chronic infection since it is these Th or CD4+ T cells that are the target of the virus. Rebuilding the supply of Th and CTL that respond to HIV epitopes is one of the goals of STI and therapeutic vaccination.

VIRUS SEQUENCE AND QUASISPECIES

Different HIVs have different DNA sequences, due to the error-prone RT enzyme whose function is to enable the virus to replicate in the host cell. The RT makes mistakes, and as a result, variants of the original HIV are created. Some of these variants are not viable, however, others are. In acute infection, the variability of the strain is minimal. In chronic infection, the variability of HIV infecting the individual host expands. The swarm of variants that develop in the course of HIV infection are called quasispecies. The number of quasispecies expands as infection progresses.¹¹

The development of quasispecies appears to have an adverse impact on the ability of the immune system to contain the virus. In early infection, response to a few epitopes may effectively contain the virus. In late HIV infection, response to many different epitopes may still fail to contain infection, because of the number of variant viruses. Furthermore, if the patient has HLA that cannot present epitopes contained in the virus sequence, there will be only the minimum CTL response. Alternatively, as the HIV evolves into quasispecies, some isolates evolve in which the original epitopes recognized by the host immune system have been altered and no longer bind to the host HLA (these are called escape mutants).

THE THEORY BEHIND STI: BOOST AND BROADEN T CELL RESPONSES

The goal of STI is to "broaden immune response". From the above discussions, it is clear that the type of immune response that needs to be broadened is the T cell response. This can be achieved by vaccination, however, there only a few HIV vaccines under study in clinical trials (see HIV 101). In the absence of effective vaccines, proponents of STI have argued that allowing the patient to develop a response to his or her own virus, by "autologous vaccination" is a reasonable approach. Opponents of STI note that autologous vaccination involves allowing live, virulent autologous virus that has already been poorly controlled in the absence of drug treatment to replicate and potentially seed more sites in the body.

In general, patients who are undergoing STI are given HAART until viral replication has been completely suppressed below detectable levels (< 50 copies per ml), for

long durations of time (eight months in some cases). Then the HAART is stopped, and the patient's virus is allowed to rebound up to a certain level (up to 50,000 copies on one occasion or above 5,000 copies on two occasions, for example). This cycle of HAART treatment followed by treatment interruption is continued until there is sustained suppression of the viral load. Following several cycles of STI, in most cases, the viral rebound is smaller.

One potential benefit of STI that has been observed is that rebound virus tends to be "wild type", a strain lacking any viral mutations that had been developed in the course of HAART. However, when HAART is resumed in the course of STI, some researchers have observed that mutant drug resistant strains re-emerge (since they have only been archived in resting T cells). The same may be true for CTL escape mutants, however, data is lacking.

According to STI theory, subjects who are undergoing HAART treatment are able to recover immune function during the period of viral suppression. Stopping HAART allows autologous virus to rebound, and expands the number of T cells that respond to the virus. If the viral load reaches a dangerous level, HAART is restarted and the viral load returns to baseline (below 50 copies in most cases). Opponents of STI have pointed out that HAART may allow CD4 T cell counts to increase but few, if any, of these T cells are programmed to fight HIV.¹² Suppression of viral rebound may be due to broader CTL response, but it may also be due to assistance by T helper cells, particularly in early HIV infection.¹³

The role of CD8+ T cells (CTL) in containing HIV infection was recently confirmed in an animal model.¹⁴ In this model, acutely infected rhesus macaques who were treated with tenofovir (the new Gilead drug) and demonstrated subsequent suppression of a highly virulent strain of the SIV (simian HIV) also showed substantial resistance to subsequent intravenous rechallenge with homologous and highly heterologous SIV isolates, up to more than one year later, despite the absence of effective (neutralizing) antibody directed against the virus. However, when CD8 T cells were depleted by the researchers, the amount of viremia rose by as much as 100,000 fold. Viremia returned to low levels as soon as CD8+ cells were restored. This study showed a positive effect of STI in early infection and confirmed the critical role of CD8 T cells (CTL) in controlling infection after STI.

STI AND ACUTE INFECTION

The most successful studies of STI have focused on the treatment of acutely infected HIV subjects. Bruce Walker and colleagues (Boston, MA) have reported on 14 subjects who underwent repeated cycles of STI.¹⁵ Of

Continued on page 4

LETTER FROM THE EDITOR

Dear Colleagues,

Many of our correctional patients experience recurring cycles of excellent viral suppression followed by interruption of therapy (in parallel with their cycles of release and reincarceration). These cycles of therapy are a form of "unsupervised and unstructured treatment interruption" (USTI). Since USTI is a recurring theme of correctional HIV care, we chose to describe recent studies of Strategic Treatment Interruption (STI) and the interactions between T cells, HLA, and HIV for our main article this month. This article also gives our Chief Editor an opportunity to wear her immunology hat. When not providing care to incarcerated women in the Connecticut prison system, she is involved in the development of HIV vaccines for prevention and treatment of HIV at Brown University.

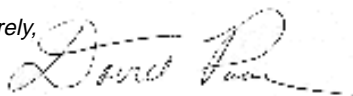
Our main article in this issue describes the components of immune response to HIV and explains why STI is more likely to provide benefit in acute HIV infection and less likely to benefit patients who have chronic HIV infection, at least until more effective forms of STI, such as STI given in conjunction with effective therapeutic HIV vaccines, are developed. Our HIV 101 lists vaccines that are currently under investigation for use with STI. The HEPPigram describes the course of immune response to HIV infection over time, and in response to HAART.

In this issue, the Ask The Expert piece is on HIV-1 non-clade B infections. The case discusses the specific issues of recognizing, testing for, and treating HIV-1 non-clade B infections. This month's expert is our own Chief Editor, Dr. Anne De Groot.

Since correctional HIV patients frequently experience what may be called USTI, correctional HIV providers have an opportunity to contribute some information on the effect of USTI on our patients. How would we expect USTI to compare to STI? Poorly. For example, many of our patients do not achieve suppression of viral replication of long enough duration prior to interrupting therapy (typically, in STI, treatment is continued for at least 8 months before STI is attempted). Secondly, the duration of HAART cessation may occur over periods of months (sometimes years), much longer than the duration of treatment interruption evaluated in STI studies. Furthermore, our patients frequently resume therapy, when they are reincarcerated, with viral loads vastly exceeding the limits used in STI studies. In addition, our patients usually resume illicit drug use when they interrupt their HAART. Resumption of injection drug use and the associated life circumstances may adversely impact the immune response to "autologous immunization." In short, USTI has none of the features that may contribute to the success of STI in acute HIV infection. Experts in the field caution against the application of STI until more information can be obtained on the optimal duration of the individual cycles, the role of HLA, the role of T cell epitopes, and the role of adjunctive treatments such as vaccines.

As always, we encourage your feedback and submissions for future issues of HEPP News!

Sincerely,



David P. Paar, M.D.

Published monthly and distributed by fax, HEPP News provides up-to-the-moment information on HIV and hepatitis treatment, efficient approaches to administering treatment in the correctional environment, national and international news related to HIV and hepatitis in prisons and jails, and changes in correctional care that impact HIV and hepatitis treatment.

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IMMUNOTHERAPY OF HIV... (continued from page 2)

the first 14 subjects, seven were able to achieve persistent control of viremia. Four achieved control after a single treatment cessation, two after a second STI, and one after a third STI. Several other studies have been reported where treatment was ceased entirely (Treatment cessation, not equivalent to STI), after initial optimal or suboptimal treatment of acute infection. Many of the subjects in these two studies appeared to be able to control viremia (4 out of 10 in one study¹⁶, 2 out of 7 in another study¹⁷). Whether the number of patients who controlled infection following treatment cessation is any different than the number that would be able to control infection without therapy is unknown at this point.

STI AND CHRONIC INFECTION

In general, studies of the use of STI in chronically infected patients have not shown any benefit. One reason may be that HAART does not as effectively suppress HIV replication in chronic HIV. In a large study of 128 subjects¹⁸, only 54 subjects were able to completely suppress HIV replication during the cycles of HAART therapy, only 9 of these had viral loads lower than 5,000 copies after completion of the STI cycles. Chronically infected patients also have greater viral diversity, so boosting immune responses to the virus by "autologous immunization" may not have the same effect as this treatment in the setting of acute infection, where viral variability is less and response to the same number of CTL epitopes may be able to contain infection.

VACCINES AS IMMUNOTHERAPY

HIV-1 vaccines in development fall roughly into three categories: recombinant proteins, vectored vaccines, and "replicons" (highly engineered viral vectors).

The vaccine that has been used most often in the setting of immunotherapy is Remune, a vaccine developed by the Salk Institute and now licensed to a subsidiary of Agouron (Immune Response Corp). Remune is an inactivated, protein-depleted, HIV virus. Several cycles of inactivation are carried out so as to assure the safety of the vaccine. Studies of Remune in the treatment of chronic infection have been recently published. Although CD4 T cell counts were significantly higher, no impact on viral load, or clinical course could be demonstrated.¹⁹ The vaccine may have a role when used in conjunction with STI (see below). Thus far, studies of therapeutic vaccination of chronically infected patients with any of the vaccines approved for human use have failed to demonstrate substantial benefits.

VACCINATION AS AN ADJUNCT TO STI

Investigators from the Aaron Diamond AIDS

Research Center have explored the potential for therapeutic vaccination in 14 subjects started on HAART within 90 days of HIV infection. This study was reported at the 8th CROI in Chicago, 2001, and reviewed in HEPP (February 2001). Subjects received 4 doses of a vaccine cocktail that included the canary pox vector vCP1452, expressing HIV gag, pol, env, and nef genes, as well as a recombinant HIV protein, gp160. This was the first study to incorporate a vaccine protocol into STI; while the results weren't altogether exciting, the procedure appeared to be safe.²⁰

A second study was carried out combining STI and Remune vaccination. This study was reported at the AIDS Vaccine 2001 meeting in September of this year.²¹ The slope of the initial rise in plasma vRNA was significantly slower (0.16 vs. 0.21 log₁₀ copies/day) in the Remune vs. control group ($p < 0.05$). The frequency of cells that produce IFN-gamma when stimulated with several HIV proteins was significantly increased in the Remune group. Therapeutic immunization with Remune appeared to increase both CD4 and CD8 T-cell immunity to HIV antigens and altered the kinetics of viral rebound during the treatment. Viral load and T cells returned to baseline after cessation of HAART, so the long term benefits of this approach are not yet clear.²²

STI AND USTI

Correctional HIV patients frequently experience what may be called unstructured treatment interruptions (USTI) because of numerous barriers to effective care that may exist in prisons today. Our patients more often experience interruptions because they experience side effects or have comorbidities such as liver disease that are exacerbated by HAART. Furthermore, these patients may be mentally ill and stop taking prescriptions or choose to drinking or taking drugs again and this interferes with their adherence. Bad care while incarcerated does occur but is just one of many reasons that patients have USTI. How does USTI compare to STI? Poorly. For example, many of our patients do not achieve suppression of viral replication of long enough duration. Secondly, the duration of HAART cessation may occur over periods of months (sometimes years), much longer than the duration of treatment interruption evaluated in STI studies. Furthermore, our patients frequently resume therapy, when they are reincarcerated, with viral loads vastly exceeding the limits used in STI studies. In addition, our patients usually resume drug use when they interrupt their HAART. Resumption of injection drug use and the associated life circumstances may adversely impact the immune response to "autologous immunization". In short, USTI has none of the features that may contribute to the success of STI in acute HIV infection. Experts in

the field caution against the application of STI until more information can be obtained on the optimal duration of the individual cycles, the role of HLA, the role of T cell epitopes, and the role of adjunctive treatments such as vaccines.

In conclusion, STI is a treatment that is on the horizon, particularly for modulation of acute HIV infection. Much remains to be learned about the optimal use of this strategy. Investigations related to these new treatments have expanded our understanding of immune response to HIV, and therefore may help us understand why some patients do well, and others worse, in the setting of a standardized approach to HIV treatment. Providers practicing in correctional settings probably have much greater experience with unstructured treatment interruption (USTI) than providers practicing in with non-incarcerated populations do. We may be in an excellent position to perform observational studies and teach our non-correctional peers about the outcomes of USTI. The next potential venue for this type of report would be the 9th CROI to be held in Seattle, Washington. (<http://www.retroconference.org>.) On the topic of treatment interruptions we have much to learn from our academic colleagues, and perhaps, even more to contribute.

GLOSSARY

T cell- Lymphocyte possessing either helper properties, assisting other cells in the body to respond to infection (a.k.a. T helper cells) or lytic properties (a.k.a. killer T cells, or Cytotoxic T cells /CTL).

MHC- Short for the Major Histocompatibility Complex. This is the molecule present on the outside of cells that presents peptides to the immune system. It acts as the carrier for pieces of the HIV virus (or any other virus or bacteria in the cell). Each person has six MHC genes (and may be heterozygous at all six loci). These molecules determine transplant rejection (hence the MHC name) and response to infections.

HLA- Short for Human Leukocyte Antigen. These proteins are genetically determined molecules that sit on the surface of antigen presenting cells. They play a key role in the presentation of immune stimuli to T cells. Essentially, HLA is the name that refers to the human MHC.

T cell epitope- Only a small piece of a virus, a peptide known as an epitope, will bind in the binding groove of each MHC. Mutations of the peptide can make binding, and hence immune response, impossible to detect (escape mutations). Alternatively, the patient can possess a variant of HLA to which critical HIV epitopes cannot bind. (see NEJM).

Continued on page 5

IMMUNOTHERAPY OF HIV... (continued from page 4)

Viral quasi species- The HIV virion's error-prone RT makes mistakes, and as a result, variants of the original infecting isolate of HIV are created. The swarm of variants that develop in the course of HIV infection are called quasi species. The number of quasispecies expands as infection progresses.

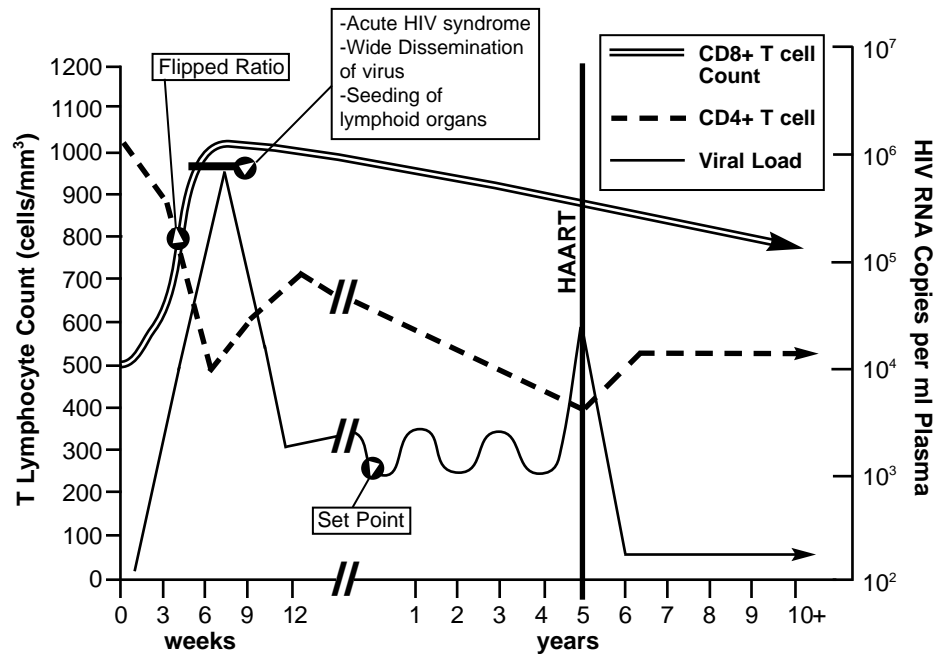
Escape mutation- HIV isolates that have evolved in which the original epitopes recognized by the host immune system have been altered or replaced and the new peptides no longer bind to the host HLA or are not recognized by the T cells.

Treatment cessation- Arresting HAART after initiation. (Without further cycles of intermittent therapy).

Structured Treatment Interruption (STI)- Cycles of HAART followed by cycles of no treatment. Viral load is closely monitored and treatment is resumed when viral load rises to a detrimental level.

Unstructured Treatment Interruption (USTI)- Not an investigational regimen, however one that is observed for many incarcerated individuals, due to failure to resume therapy (for any number of reasons) after release from prison or jail. Cycles of HAART of inconsistent duration followed by cycles of interruption of variable duration. Viral loads often achieve very high levels before treatment is resumed.

HEPPIGRAM: Natural Course of HIV Infection Plus Antiretroviral Therapy



Modified from Bartlett JG, Gallant JE. 2001-2001 Medical Management of HIV Infection. Online at <http://aids-hopkins.edu>

Flipped Ratio: The CD4:CD8 ratio is usually approximately 2:1 but in HIV-infected people, the ratio flips and is approximately 1:2.

HAART: Highly Active Antiretroviral Therapy

Set Point: The point around which viral load levels off without anti-HIV treatment. This point is different for different individuals, i.e. rapid progressors generally have higher set points. The idea of treatment is to lower the set point, lowering the viral load in the patient's body.

* Consultant & Speaker's Bureau: Agouron Pharmaceuticals, Dupont, Merck, Roche, Boehringer-Ingelheim/Roxane Laboratories.

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REFERENCES:

- Updated HHS guidelines on the web at http://www.hivatis.org/guidelines/adult/Aug13_01/pdf/AAAug13S.PDF
- CDC. MMWR 1998; 47 (RR-17):3. <http://www.cdc.gov/mmwr/PDF/rr/rr4717.pdf>
- Saah AJ, Hoover DR, Weng S, Carrington M, Mellors J, Rinaldo CR Jr, Mann D, Apple R, Phair JP, Detels R, O'Brien S, Enger C, Johnson P, Kaslow RA. AIDS. 1998 Nov 12;12(16):2107-13.
- Gao X, Nelson GW, Karacki P, Martin MP, Phair J, Kaslow R, Goedert JJ, Buchbinder S, Hoots K, Vlahov D, O'Brien SJ, Carrington M. N Engl J Med. 2001 May 31;344(22):1668-75.
- Musey L, Hughes J, Schacker T, Shea T, Corey L, McElrath MJ. N Engl J Med. 1997 Oct 30;337(18):1267-74.
- Carrington M, Nelson GW, Martin MP, Kissner T, Vlahov D, Goedert JJ, Kaslow R, Buchbinder S, Hoots K, O'Brien SJ. Science. 1999 Mar 12;283(5408):1748-52.
- Bender TJ, Tang J, Rivers C, Muligan MJ, Kaslow RA. Program and abstracts of the 8th Conference on Retroviruses and Opportunistic Infections, February 4-8, 2001, Chicago Illinois. Abstract 193.
- Walker BD. On medscape at http://www.medscape.com/medscape/cno/2001/RETRO/Story.cfm?story_id=2053
- Koup RA, Safrit JT, Cao Y, Andrews CA, McLeod G, Borkowsky W, Farthing C, Ho DD. J Virol. 1994 Jul;68(7):4650-5.
- Shankarappa R, Margolick JB, Gange SJ, Rodrigo AG, Upchurch D, Farzadegan H, Gupta P, Rinaldo CR, Learn GH, He X, Huang XL, Mullins JJ. J Virol. 1999 Dec;73(12):10489-502.
- Ruiz L, Carcelain G, et al. AIDS-Hagerstown, June 15 2001; 15 (9): F19-F27.
- Norris PJ, Rosenberg ES. AIDS. 2001 Feb;15 Suppl 2:S16-21.
- Lifson JD. J Virol. 2001 Nov; 75 (21): 10187-10199.
- Rosenberg ES, Altfeld M, Poon SH, et al Nature. 2000; 407:523-526.
- Reported by Bruce Walker in his talk: Structured treatment interruption: novel strategy or oxymoron? State-of-the-art lecture and summary. 8th CROI; February 4-8, 2001. Abstract 266.
- Yang OO, Kalams SA, Rosenzweig M, et al. J Virol. 1996;70:5799-5806.
- Tsomides TJ, Walker BD, Eisen HN. Proc Natl Acad Sci U S A. 1991;88:11276-11280.
- Yang OO, Walker BD. Adv Immunol. 1997;66:273-311.
- Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. JAMA. 2000 Nov 1; 284 (17): 2193-2202.
- Jin X, Ramanathan M Jr, Barsoum S, et al. 8th CROI; February 4-8, 2001. Abstract 21.
- AIDS Vaccine 2001, Sept 5th -8th, 2001, Philadelphia PA. See review by Nicodemus, Sbai, and De Groot on AIDSscience, October 2001, <http://www.AIDSscience.com>, for more information on the meeting.
- Bucy RP, Moss R, Gersten M, and the 806A Study Team. AIDS Vaccine 2001 Abstract 243.

ASK THE EXPERT: A New Infection with an Undetectable Viral Load

Anne S. De Groot, M.D., *Brown Medical School, Editor, HEPP News*

Question: A 40 year-old woman is referred to you by the prison HIV counselor because she had a recent positive HIV test. She was tested by one of the astute internists at your institution because she developed Bell's Palsy about two months into her incarceration (a condition not uncommonly associated with early HIV infection). She is surprised and dismayed by the diagnosis, since she never used injection drugs and was monogamous during the period prior to her incarceration. She had, in fact, been tested for HIV when she applied for her immigration waiver, and she was HIV seronegative. That test was performed about two months prior to incarceration, about six months ago.

You do your best to reassure her, by explaining how a viral load test and CD4 T cell count will assist you both with a decision on the course of treatment. You decide to repeat the HIV ELISA and Western Blot, just to be sure that the diagnosis is correct. You then arrange to have her HIV studies drawn, and schedule a follow up appointment.

When her blood work returns, it is your turn to be surprised. She has an undetectable viral load. You recheck her HIV test, and it is indeed positive (all the Western blot bands light up). Her CD4 T cell count is squarely in the normal range, however, on closer inspection you notice that her CD8 to CD4 ratio has "flipped" (CD8 cells > CD4 cells). You worry that the viral load assay was mislabelled, so you repeat it, along with another CD4 T cell count. Again, the viral load is undetectable but the CD4 is now slightly lower, at the low end of the normal range. You repeat the test again, and the CD4 returns even lower. She is now five months into her incarceration, and you have evidence of fairly rapid CD4 decline and no detectable viral load. What is going on and what should you do?

Answer: Either the patient is an exception to the rule and a lucky member of the "long term non-progressor" club, or the patient has ongoing viral load replication not identified by viral load PCR of viral replication. The latter is unfortunately more likely since you have already seen a decline in the CD4 T cell count in a relatively short period of time. Thus, you must consider the possibility that the viral load assay is not detecting the virus, as it would in a case of non-clade B infection.

What is non-clade B infection? As discussed in the main article in this issue, HIV is a very variable virus. Just as the virus may evolve during the course of an individual infection to become a "swarm" of different but related viruses, it has evolved into different but related subtypes in different regions of the world over the course of the HIV epidemic.

HIV-1 is broken down into 3 large groups, each believed to have arisen from a distinct transmission event, from 3 different chimpanzee viruses. The M group is the main group, which has dispersed throughout the world. The other two groups, O (outlier) group and a rarely noted non-O, non-M group are only found in West Africa and Cameroon. The M group of HIV-1 has been further broken down into various subtypes, or clades, designated A through K based on variability in the *env* and *gag* regions of the viral genome. The predominant subtype in the United States and Western Europe is HIV-1 subtype (clade) B. A is dominant in Eastern Africa, C is dominant in Southern Africa, and a slightly different set of clade C viruses are dominant in India. In Southeast Asia, B and E are the most prevalent. Intersubtype recombinations, or "chimeras," also known as circulating recombinant forms (CRFs) are spreading in China and other areas of the world where the epidemic is just taking off. In the US and Europe, the epidemiology of non-clade B infections is in flux, and recent reports suggest that non-clade B subtypes are becoming more prevalent.^{1,2}

On closer questioning, you find out that your patient's sexual partner formerly lived in New York City, where non-clade B viruses have

been detected. Since some viral load assays can be insensitive to the presence of circulating virus, you repeat the viral load using a branched chain DNA assay and you are now able to detect a positive viral load (75,000 copies per ml).

Although HIV antibody tests do detect non-clade B viruses, not all viral load assays can detect virus in the presence of non-B subtypes (eg, Roche Amplicor Version 1.0 or reverse transcriptase-polymerase chain reaction [RT-PCR] 1.0). Those that can detect it (branched DNA [b-DNA], Nuclisens, Ultradirect Monitor) may do so but there is a lot of variability between the tests.³ Now that you have found a test that is able to detect the patient's virus, you need to stick with that assay to follow the course of infection. You can also send her virus to be identified at the state Department of Health laboratories.

Since she has acute HIV infection, she should probably be treated with the goals of suppressing the initial burst of viral replication and decreasing the magnitude of virus dissemination throughout the body. This will potentially alter the initial viral set point which may ultimately affect the rate of disease progression, possibly reducing the rate of viral mutation, and preserving immune function.⁴ You consult an expert in your community about whether it would be appropriate to initiate treatment and with which medication. Your colleague tells you that there may be some variability in the response to treatment by clade or subtype, but that type of information is simply not available because large numbers of individuals with non-clade B subtypes have yet to be studied in detail. Thus there is no reason to modify her regimen by subtype. Early information from treatment of non-clade B infections in Africa suggest that treatment responses are similar to those seen with clade B strains.

The duration of treatment for acute HIV infection is currently not known, however, if her VL becomes undetectable after about 6 months, it may be acceptable to stop treatment. You would of course consult with your colleague, since you are not able to enroll her in a study of STI (see main article).

REFERENCES:

1. de Oliveira CF, Diaz RS, Machado DM, et al. Surveillance of HIV-1 genetic subtypes and diversity in the US blood supply. *Transfusion*. 2000;40:1399-1406.
 2. Barin F, Pillonel J, Buzelay L, Courouge AM. Increasing diversity of HIV-1 serotypes in French blood donors (1985-1996). In Program and abstracts of the 12th World AIDS Conference; June 28-July 3, 1998; Geneva. Abstract 13204.
 3. Holguin A, de Mendoza C, Soriano V. Comparison of three different commercial methods for measuring plasma viraemia in patients infected with non-B HIV-1 subtypes. *Eur J Clin Microbiol Infect Dis*. 1999;18:256-259.
 4. HHS HIV Treatment guidelines, available on the web at www.hivatis.org
- Additional information from Ball SC. "HIV-1 Non-B Subtypes in Clinical Practice." 2001 *The AIDS Reader* 11 (8): 339-400.

HIV Vaccine Candidates *by HEPP News Staff*

Adapted from Johnston MI, Flores J. Progress in HIV Vaccine Development. Current Opinion in Pharmacology. 2001;1(5):504-520. On the web at www.niaid.nih.gov/daids/vaccine/pdf/pc1506.pdf. Additional Information from Science Magazine 2001 293 (5537): 1973.

As drug-resistant HIV virus becomes more and more common, physicians will need alternative methods of treating the virus. One of the most promising of these methods is the development of a prophylactic or therapeutic vaccine. The following table provides information on vaccines currently in the development pipeline.

VACCINE NAME	HIV SUBTYPE TARGETED	PRODUCING COMPANY	STATUS
gp120	B/B, B/E	Vaxgen	Ongoing phase III trials in the United States and Thailand
ALVAC-HIV	B, E	Aventis Pasteur	Ongoing phase II trials in the US, Haiti, Brazil, Trinidad (subtype B); Thailand (subtype E); used alone or in combination with gp120
ALVAC-HIV	A	Aventis Pasteur	Ready for Phase I trials in Uganda
Lipopeptides LP5, LP6	B	ANRS: National Agency for AIDS Research, France	Ongoing phase I trials in France
Vaccinia TBC-3B	B	Therion	Ongoing phase I trials in the US
DNA-HIV	B	Apolion	Completed phase I trials
DNA-HIV, MVA-HIV	A	University of Oxford	Ongoing phase I trials in the UK and Kenya
NYVAC-HIV	B	Aventis Pasteur	Ready for phase I in the US
DNA-HIV, Adenovirus HIV	B	Merck	Ongoing phase I trials in the US
VaxGen Canarypox with HIV gag, protease, and env +gp120	B/E	U.S. Military, Royal Thai Govt., Mahidol U., Aventis Pasteur, VaxGen	Earliest phase III start date: Summer 2002, Thailand*
Canarypox with HIV env, gag, protease, pol, and nef, +gp120	B/?	NIH HVTN, Aventis Pasteur, VaxGen	Earliest phase III start date: December 2002, U.S., Brazil, Haiti, Peru, Trinidad (Possible: Argentina, Dominican Republic, Honduras)*

*proposed AIDS vaccine efficacy trials (See Newsflashes)

phase I trial: first stage trial, focusing on safety and toxicity, very small cohort

phase II trial: second stage trial, measures efficacy of vaccine in small cohort

phase III trial: last stage of experimental testing, pivotal trial measures efficacy on a larger scale

gp120: recombinant HIV envelope protein

ALVAC-HIV: a recombinant canarypox virus expressing multiple HIV genes

MVA-HIV: modified vaccinia Ankara (an attenuated vaccinia vector) expressing multiple HIV genes

NYVAC-HIV: an attenuated vaccinia vector expressing multiple HIV genes

TBC-3B: an attenuated vaccinia vector expressing multiple HIV genes

RESOURCES & WEBSITES

AIDS VACCINE WEBSITES:

NIH AIDS Vaccines Page

<http://www.niaid.nih.gov/daids/vaccine>

AIDS Clinical Trial Information Service

<http://www.actis.org/>

The Economics of AIDS Vaccines

<http://www.iaen.org/vaccine/>

The Body: AIDS Vaccines

<http://www.thebody.com/treat/vaccines.html>

AIDS Vaccine 2001 Conference

<http://63.84.172.40/>

The Global Alliance to Immunize against AIDS

<http://www.gaiavaccine.org>

AIDS TREATMENT WEBSITES:

Updated Adult and Adolescent HIV Treatment guidelines

http://www.hivatis.org/guidelines/adult/Aug13_01/pdf/AAAUG13S.PDF

AIDS Action: Publications on HIV and Corrections

<http://www.aidsaction.org>

Hopkins AIDS Service: Medical Management of HIV Infection

http://hopkins-aids.edu/publications/book/book_toc.html

HEPATITIS PACKETS AVAILABLE:

NATAP: 15-page handbook on HCV and HIV/HCV co-infection. Also available in Spanish. Contact JuLev@aol.com

Hepatitis C Awareness Project: 14-page packet on HCV targeted for and available inmates and others. Contact pkbeckinor@aol.com

SAVE THE DATES

National Conference on Correctional Health Care

November 10-14, 2001
Albuquerque, New Mexico

Fee: \$275 member,
\$325 non-member
Call: 773.880.1460
Fax: 773.880.2424

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Preconference Symposium
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1:30pm-5:00pm
Fee: Free with NCCHC
Conference Registration

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\$650 corporate
Registration (Oct. 20-Nov.18):
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Call: 520.626.5243

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Visit: www.NCTC2001.com
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3rd International Hepatitis C Update for the New Millennium

November 30-December 1, 2001
Houston, Texas

Fee: Physicians- \$165; Other
Health Care Professionals- \$135
Visit: www.uth.tmc.edu/cme
Email: Kristen.K.Brockman@uth.tmc.edu
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41st Interscience Conference on Antimicrobial Agents and Chemotherapy

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until November 19
Visit: www.icaac.org

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February 24-28, 2002
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Call for Abstracts: Deadline:
October 23, 2001
Registration: Dec. 10, 2001-
Jan. 23, 2002
Call: 703.535.6899
Visit: www.retroconference.org

NEWS FLASHES

HEPATITIS

Giving Interferon Early: An Improved HCV Treatment?

Washington Post, 10/02/01

According to the CDC, approximately 6,500 people in the United States are infected with Hepatitis C every year and 8,000-10,000 die annually. A new study that will be published in the *New England Journal of Medicine* in November states that treatment with interferon alfa-2b soon after infection may be an effective anti-HCV therapy. In the study, 42 of 453 newly infected patients received the full six months of interferon treatment and became virus-free and remained so after therapy termination. After 24 weeks of treatment, virus was undetectable in 42 out of 43 patients. Side effects include muscle and joint aches, fever, headache, and sometimes depression or a reduction in white blood cell count. The six-month treatment costs \$6000.

New Treatment Regimen for Hepatitis C

Lancet 2001; 358:958-65

A new study has shown that treating HCV with peginterferon alfa-2b plus ribavirin is more effective than treating with interferon alfa-2b plus ribavirin. The study measured the sustained virological response rate (SVR) and among genotype 1 HCV-infected individuals found a SVR of 42% for patients on the new treatment regimen compared to a SVR of 33% among patients on the old drug regimen. The new treatment regimen consists of 1.5mg/kg peginterferon (PEG-Intron, Schering Corp) subcutaneously once a week and 800mg oral ribivirin (Rebetol, Schering Corp) daily for 48 weeks. Oral ribivirin (Rebetol) is also available seperately.

HIV

Genetic Variation and HIV Progression

NEJM 2001;344:1668-1675

In a study of 850 HIV-positive people, researchers found a genetic variation that may be linked to the difference in progression time from initial HIV infection to full-blown AIDS. The gene is associated with the HLA locus (see main article) and is called Px, and a certain variation in this gene appeared to accelerate the onset of full-blown AIDS to 4-5 years. The 12% of patients in this study who had the genetic variation experienced full blown AIDS about 7 years post-infection compared to those without the variation who progressed to AIDS 11-12 years post-infection.

Possible New Vaccine Trials

Science, 14 September 2001; 293: 1973

Both the NIH and the U.S. military have plans to begin phase III efficacy trials of virtually identical HIV vaccines. The vaccines consist of two parts: the first is the "prime" dose that consists of HIV genes in a canarypox vector and to trigger the immune system to produce CTLs directed against HIV infected cells. The second part of the vaccine is genetically engineered gp120 used to trigger the immune system to produce antibodies

that protect cells from becoming infected in the beginning. Phase II trials, however, have shown that approximately 30% of people develop the CTL response the vaccine aims to produce. This has caused controversy as to whether the phase III trials should proceed. Some scientists doubt the scientific basis of this trial while others have taken the stance that 30% efficacy is better than none.

Mortality Due to HIV Drops

CDC Release, 10/10/01

According to a CDC release entitled "Deaths: Preliminary Data for 2000," the percentage of deaths due to HIV declined 3.7% in 2000. This is the fifth year in a row that deaths due to HIV have declined, although HIV remains the leading cause of death for all races in the 25 to 44 year-old age group. The full report is available online at the CDC's National Center for Health Statistics website at <http://www.cdc.gov/nchs/releases/01news/mort2k.htm>.

Abused Women at Higher Risk for HIV Infection

Family Planning Perspectives, September/October 2001

According to a new report from the Alan Guttmacher Institute's Family Planning Perspectives, women who experienced various "household dysfunctions," including abuse, as children are more likely to engage in risky sexual behaviors putting them at higher risk for contracting HIV. The study looked at how any one of seven "household dysfunctions" women experienced in childhood correlated with having more than 30 sexual partners, having had sexual intercourse before the age of 16, and perceiving oneself as at risk for HIV infection. Findings correlated the household dysfunctions with increased risk for infection with HIV, indicating a long-term effect of childhood experiences on sexual behavior.

Terrorist Attacks Affect Prisons

Tharp, New York Post, 10/4/01

In response to the terrorist attacks of September 11, 2001 stock prices of private prison companies sky rocketed in expectation of an increasing number of detainees. Coincidentally, the Federal Bureau of Prisons let out requests for bids for two prisons to hold criminal aliens in Georgia. This contract is the largest award this year from the BOP with a requests for three more bids early next year for prisons in the Southwest deserts for over 1500 detainees. Additionally, private prisons are looking to benefit from an expected Supreme Court ruling that would make it illegal for prisoners to sue private prisons for civil rights violations. In the wake of the attacks, private prisons are benefitting.

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1. STI is an FDA approved use of HAART.
 - a) True
 - b) False

2. Which of the following tests do NOT have the ability to detect non-clade B HIV-1 infections?
 - a) RT-PCR 1.0
 - b) branched-DNA (b-DNA)
 - c) Nuclisens
 - d) Amplicor Version 1.0
 - e) a and d

3. Which of the following factors determines the set point for HIV infection?
 - a) Viral Dose
 - b) HLA
 - c) T cell Epitopes
 - d) Viral Sequence
 - e) all of the above

4. HIV viral quasispecies:
 - a) develop due to mistakes made by the RT enzyme
 - b) allow the immune response to effectively contain the virus
 - c) develop due to mistakes of the protease enzyme
 - d) lead to greater transmission of the virus from mother to child
 - e) contribute to the destruction of CD8+ T cells

5. Which of the following HLA types are associated with a better outcome in HIV infection (i.e. slower progression to AIDS)?
 - a) HLA B57
 - b) HLA B35
 - c) HLA B27
 - d) a and c
 - e) a and b

6. Interruption of effective HAART therapy, in the context of STI:
 - a) allows autologous virus to expand without being controlled by HAART
 - b) allows virus to potentially seed new sites in the body
 - c) forces T cells that have been unable to contain autologous infection to confront the virus again in the absence of any assistance from HAART
 - d) allows the patient to develop T cell responses to autologous virus
 - e) all of the above

HEPP NEWS EVALUATION

5 Excellent 4 Very Good 3 Fair 2 Poor 1 Very Poor

1. Please evaluate the following sections with respect to:

	educational value					clarity				
Main Article	5	4	3	2	1	5	4	3	2	1
HEPPigram	5	4	3	2	1	5	4	3	2	1
HIV 101	5	4	3	2	1	5	4	3	2	1
Save the Dates	5	4	3	2	1	5	4	3	2	1

2. Do you feel that HEPP News helps you in your work? Why or why not?

3. What future topics should HEPP News address?

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5. Do you have specific comments on this issue?

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