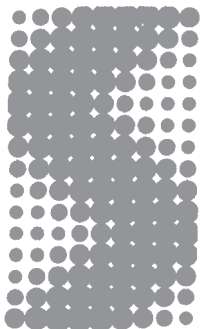


SEARCHLIGHT

NEWS FROM AIDS RESEARCH ALLIANCE

A National Leader in Fast-Track AIDS Research



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In This Issue—

HIV-Related Peripheral Neuropathy; Diagnosis and Treatment

Peripheral neuropathy is a disorder of the nervous system affecting many people living with HIV infection. Despite the lack of adequate treatment, early diagnosis may lead to more effective treatment. In this article Dr. Seymour Young reviews the symptoms and pathology of this disease, as well as the latest neurological examinations necessary for early diagnosis.

(Article starts on cover)

* * *

New Clinical Trials

We are currently enrolling volunteers (naïve patients, HAART-experienced patients and patients with painful neuropathy) for several new clinical trials. We are also beginning a new trial of an HIV preventive vaccine.

(Announcements pages 5, 7, 12, 13)

* * *

Prostratin Update

An outline of the progress that has been made to forward the development of prostratin as an anti-HIV drug targeting the viral reservoirs.

(Article on page 14)

* * *

HIV-Related Peripheral Neuropathy; Diagnosis and Treatment

By Seymour Young, M.D.

Many people living with HIV infection carry a diagnosis of peripheral neuropathy. In fact, some estimates suggest that over thirty percent of this population have clinical symptoms of neuropathy, while an even larger percentage may have sub-clinical neuropathy.

Peripheral neuropathy is a disorder of the nervous system that affects the endings of that system. That is to say, that while the nervous system begins with the brain, it ends with small fibers reaching throughout the body. Unlike many other systems, the nervous system relies not solely on the bloodstream for maintenance of good health, but on factors that come directly down the system from the brain and spinal cord. Thus, the nervous system is complex in both its physiology and pathology. This complexity is a challenge in designing treatments for illnesses of the nervous system, but also provides opportunities for novel interventions as well. The past decade has seen great progress in understanding this system, which will eventually allow for the development of more effective therapies.

In the vast majority of previous clinical trials investigating peripheral neuropathy the focus has been on diabetic neuropathy, *post-herpetic neuropathy* (the residual effect of "shingles" for many people), and *trigeminal neuralgia* (a form of facial pain). Very few studies have focused strictly on the HIV-related peripheral neuropathies. It is not entirely clear that the results of treatment for other conditions will be applicable to HIV patients, and thus our need for specific HIV-related peripheral neuropathy trials.

(Continued on page 6)

SEARCHLIGHT

NEWS FROM AIDS RESEARCH ALLIANCE

A National Leader in Fast-Track AIDS Research

ARA envisions a future in which HIV and its effects are eliminated from infected individuals, and research yields effective and accessible methods to prevent new infections—eradicating the virus.

ARA's mission is to find and accelerate the development of effective treatments for HIV and its complications. We do this by conducting cutting-edge research and clinical trials in order to improve the longevity and quality of life for all people with immune deficiency.

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George C. Fareed, M.D.

Stephen J. Brown, M.D.

CONTRIBUTORS TO THIS ISSUE

Marjan Hezareh, Ph.D.

Seymour Young, M.D.

PROOFREADER

Michelle Simek

SUBSCRIPTION COORDINATORS

Helen Macias

ART DIRECTOR

Chris Davies

ART PRODUCTION

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AIDS RESEARCH ALLIANCE OF AMERICA
621-A North San Vicente Blvd.
West Hollywood, CA 90069
TAX I.D. 95-4264845

Telephone: (310) 358-2423

Fax: (310) 358-2431

www.aidsresearch.org

info@aidsresearch.org



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Message from the Executive Director

By now you've heard the numbers countless times—over 40 million dead from HIV/AIDS, with the numbers still surging upwards in Africa, and the pandemic just reaching a harrowing pitch in Asia. You've heard it said that “nations will fall” as a result of the disease (by Colin Powell, no less), and that HIV/AIDS is so destabilizing a force that it is the first disease to be listed by the United States Government as a threat to national security.

But did you know that only 1% of those living in developing nations have access to drugs that many living in more developed nations take for granted? Did you also know that the culture of some developing nations is such that women do not control their own sex lives, exposing them to infection and to pregnancy that will likely result in one more child infected from birth?

What if there were a simple technology that could prevent sexual transmission of HIV? It could be used by those in developing nations as well as by those in the west. Ideally it could be used by both women and men at risk of infection.

Did you know that such products are already being tested in clinical trials in the U.S. and elsewhere? They are. What are they? *Microbicides*: topical agents that prevent HIV from being infectious when used during sex. While the search for a vaccine is crucial, a simple intervention such as a microbicide is needed in the meantime.

You can help make microbicides a reality by asking your congressional representatives to support the *Microbicide Development Act of 2003*, a bill with a good chance of passage.

The *Microbicide Development Act of 2003*

- Amends the Public Health Service Act to require the Director of the *Office of AIDS Research* to expedite the development of a Federal strategic plan for the conduct and support of microbicide research.
- Requires the Director of that office to expand, intensify, and coordinate the activities of all appropriate institutes and components of the *National Institutes of Health* with respect to research on the development of microbicides to prevent the transmission of HIV and other sexually transmitted diseases.
- Requires the Director of the *National Institute of Allergy and Infectious Diseases* to establish within the Vaccine and Prevention Research Program of the Division of AIDS in the Institute, a branch charged with carrying out microbicide research and development.
- Requires the Director of the *Centers for Disease Control and Prevention* to fully implement the Centers' five-year topical microbicide agenda to support microbicide research and development.

This is an easy call. Please do your part in helping this essential piece of legislation send a message about the importance of preventing HIV while we wait for an effective vaccine. Call your senators and congressional delegate today.

Warmly,

Irl Barefield

Executive Director

irl@aidsresearch.org

For more information on the Microbicide Development Act of 2003, visit www.aidsaction.org.

NEWS & VIEWS

How HIV-Infected cells avoid immune eradication¹.

In this elegant review, Peterlin and Trono discuss immune evasion strategies (including the infection of immunological sanctuaries, establishment of latency, and perturbation of antigen processing and presentation) used by HIV to avoid the immune defense. They conclude that it is unlikely that therapeutic approaches based solely on inhibition of HIV replication could cure the disease, because of the HAART-associated side effects and the realization that complete eradication of the virus would require both complete inhibition of viral replication as well as stimulation of strong immune responses. Therefore more effort should be expended on new therapeutic strategies, such as development of an anti-Nef agent promoting stimulation of an efficient cellular immune response that in turn would inhibit establishment of viral reservoirs. Another approach would be the use of gene therapy to engineer virus-resistant cells through the expression of antisense RNA, ribozymes and RNA interferences. A successful use of this approach in HIV/AIDS management will also advance treatment of other infectious agents which cause life long infection through their ability to escape the immune response.

Monoclonal antibody as a microbicide to protect against vaginal transmission of HIV².

Veazey and colleagues investigated whether HIV transmission could be prevented by vaginal application of monoclonal antibody b12, specific for HIV-gp120, in rhesus macaques. Two hours after vaginal application of b12 (5 mg), either in a gel form or in saline, rhesus monkeys were challenged with simian-human immunodeficiency virus (SHIV)-162P4. This virus used CCR5 to enter cells, so that the results of the study would

be applicable to human transmission. In this study, 3 out of 12 monkeys that received b12 became infected when compared to 12 out of 13 monkeys that received a control human monoclonal antibody. Lower doses of the b12 antibody were less effective. Therefore local application of b12 can protect monkeys from HIV infection and are potential modalities to be explored for microbicides to prevent HIV transmission.

HIV-1 Rev protein is involved in HIV immune evasion by reducing CTL-mediated cell killing³.

This study demonstrated for the first time the involvement of HIV-1 Rev protein, a regulatory protein that is required in expression of HIV late proteins (such as gag, pol, env), in immune evasion. First, Bobbitt and colleagues tested whether cells infected with different viruses differ in their susceptibility to CTL-mediated immune responses. Cells infected with HIV clone NL-PI were less susceptible to CTL recognition and cytotoxicity than cells infected with HXB-PI. They found that the protection against CTL-mediated response is due to a single mutation in the coding sequence of Rev NL-PI (Leu60Phe). Furthermore, they showed that the expression of mutated Rev in transfected cells decreased the expression of gag protein and to a lesser extent the env protein, but had no effect on the expression of Nef protein. Therefore, mutated Rev protects HIV infected cells from CTL responses through two mechanisms: by decreasing the source of antigen for CTL recognition (through reduction of the expression of Gag protein) and/or by maintaining the expression of Nef, which promotes MHC-I downregulation. They further analyzed primary viral isolates from asymptomatic AIDS patients. They discovered that virus from these patients had lower Rev activity, and cells infected with these viruses had a lower level of Gag protein and were resistant to CTL-mediated responses.

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NEWS & VIEWS

Therefore, in asymptomatic individuals (in contrast to patients with AIDS), immune pressure might select for mutated form of Rev, which is involved in immune evasion.

Lentiviral as a vehicle to deliver small interfering RNA (siRNAs) directed against CCR5⁴.

Small, double stranded RNAs (siRNA) can be a powerful, sequence-specific catalyst for targeted RNA destruction, followed by reduction in specific gene expression, through a process called RNA interference (RNAi) (see "RNA Interference", *Searchlight*, Spring 2003). However, in order to use them as treatment for viral diseases, effective techniques for introduction of siRNAs into primary cells are needed. In this study, Quin and colleagues described the use of a lentivirus-based vector to introduce siRNAs against CCR5, the HIV-1 co-receptor, into human peripheral T-lymphocytes. The choice of lentiviral as a vehicle for delivery was based on the fact that they can stably infect non-dividing cells and are not subject to the silencing imposed on other types of vectors. High titers of this vector were able to transfect greater than 40% of peripheral blood lymphocytes and the expression of siRNA against CCR5 resulted in a 10-fold decrease in cell surface expression of the co-receptor over a period of 2 weeks. This reduction in CCR5 expression provided protection of the T-lymphocytes against infection by CCR5-tropic HIV-1 virus (3-7 fold compare to control).

Although 3-fold reduction in an *in vitro* model is modest, clinical effectiveness of this technique would be through transplantation of hematopoietic (blood) stem cells. These cells would give rise to mature progeny T cells, dendritic cells and/or macrophages that are relatively protected against HIV-1 infection. Furthermore, the rapid turnover of HIV-1 infected T-lymphocytes should then lead to selection of CCR5-negative cells, resistant to virus infection. There was no change in the sur-

face expression of CXCR4 and the infection with CXCR4-tropic virus was slightly reduced. This study demonstrated the feasibility of lentiviral-mediated delivery of siRNAs against specific HIV-Ig gene and is an important step in development of siRNAs as a mean for treatment of HIV and other viral diseases.

sCD4-17b, a single-chain chimeric protein has potential use in passive immunization⁵.

Several studies demonstrated the protective potential of anti-env antibodies against the establishment of HIV infection in the context of passive immunization. However, efforts to elicit potent neutralizing antibodies against diverse HIV-1 isolates were unsuccessful, since potential neutralizing epitopes at the surface of env are masked by glycosylation and the presence of variable loops. Furthermore, the conserved region that forms CD4 binding sites is located within a pocket that is not accessible to antibodies and the highly conserved "bridging sheet" which constitutes a critical component of the coreceptor binding site is masked prior to CD4 binding. In this study, Dey and colleagues successfully engineered a single-chain chimeric protein, sCD4-17b, that contains two domains of soluble CD4 (sCD4) connected via a flexible polypeptide linker to a single-chain variable region of 17b (human monoclonal antibody that targets a conserved CD4-induced epitopes on gp120, overlapping the coreceptor binding region). The sCD4 moiety binds to gp120 and exposes the 17b epitope, allowing binding of 17b and blocking of coreceptor binding. They showed that sCD4-17b potently neutralizes R5 and X4 primary isolates as well as two previously known neutralizing resistant isolates. The effects of individual sCD4 and 17b to neutralize viral isolates were minimal, demonstrating that a single chimeric molecule is able to bind gp120 simultaneously through two independent moi-

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A New Study for Treatment of Neuropathic Pain Associated with HIV.

Savient Pharmaceuticals, Inc. and Neuro-AIDS Research Consortium (NARC)

Title

A randomized, double-blinded, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety of prosaptide over 6 weeks of treatment for the relief of neuropathic pain associated with HIV.

Background

Neuropathy is the most frequent neurological complication of HIV infection and its treatment with antiretrovirals. Antiretroviral-associated neuropathy (ATN) affects 30% of patients with advanced HIV disease. The most common symptom of HIV-associated neuropathy is pain in the feet. Although patients with HIV-associated neuropathic pain represent a large population, there are few effective treatments and all of them work primarily by decreasing pain, while reparative mechanisms are not currently used. Previous studies in animal models showed that prosaptide is efficient in the treatment of neuropathic pain.

Study Design

Volunteers will be randomly assigned to one of the following five groups:

prosaptide compared to placebo during 6 weeks of treatment in volunteers with painful HIV-associated neuropathy. The secondary objectives of this study are to determine the safety and tolerability of prosaptide compared to placebo and to determine the pharmacokinetic profile of the drug.

Dosing

HIV-positive volunteers who meet the inclusion criteria will be randomly assigned to groups 1,2,3,4, and 5.

Inclusion Criteria (*partial list*)

1. ≥ 18 years old
2. Currently taking antiviral regimens for greater than 4 months prior to visit 1.
3. Volunteer has painful HIV-associated sensory neuropathy confirmed by a neurologist.
4. Volunteer must be willing to stop their current neuropathy treatment

Number of Volunteer Slots estimated at ARA

26

GROUPS	1,2,3,4	5
WASHOUT PERIOD	5 Weeks	5 Weeks
RANDOMIZATION	Prosaptide (2, 4, 8, and 16 mg/day)	Placebo
PATIENT NUMBER	5 per group	5
STUDY DURATION	6 weeks	6 weeks
DOUBLE-BLIND CROSS-OVER PERIOD	Placebo	Prosaptide (4mg/day)
DURATION	2 weeks	2 weeks

Neurologic examinations, neuropathic assessment, pain assessment and laboratory results will be monitored during the study.

Primary Objective & Endpoints

The primary objective of this study is to determine the efficacy of 2, 4, 8, and 16 mg per day of

Principal Investigator

Seymour Young, M.D.

Co-Investigator

Stephen J. Brown, M.D.

HIV-Related Peripheral Neuropathy; Diagnosis and Treatment

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“Affliction of the sensory functions will lead to alteration in the perception of pain, temperature, and posture.”

The peripheral nerves subserve both motor and sensory functions for the body. Most neuropathies will afflict these two functions to varying degrees. Affliction of the motor functions will lead to weakness, atrophy, and reflex loss. Affliction of the sensory functions will lead to alteration in the perception of pain, temperature, and posture. Additionally, peripheral neuropathy not only leads to deficits in neural function, but also gives rise to increased excitability of the nerve endings; this can lead to the “positive” signs of neuropathy that include burning or stabbing pain, tingling, numbness, spasms, and twitching. The so-called “negative” signs, while not necessarily painful, are equally debilitating and lead to muscle loss, gait disturbance, and imbalance. Long-standing reflex loss can result in damage to the joints of the limbs as well.

“...the “positive” signs of neuropathy that include burning or stabbing pain, tingling, numbness, spasms, and twitching.”

Given that the nerves down to the feet are the farthest from the central nervous system, it is not

surprising that the majority of neuropathy signs and symptoms occur in the feet or in the hands before progressing elsewhere. As the system is symmetrical, so are signs and symptoms for most people. Thus, the most common HIV-related peripheral neuropathy is coined DSPN, for *distal sensorimotor peripheral neuropathy*.

“HIV-related peripheral neuropathies can occur at any stage of infection, and in some cases appear even when the subject has not been particularly immuno-compromised.”

In its earliest stages, the process may only affect the insulating sheaths around the nerves, known as *myelin*. However, with ongoing disease the actual nerve cylinder itself, known as the axon, may be injured. Fortunately, myelin is capable of regeneration, and even though some people may suffer axonal injury, each limb is subserved by thousands of axons, which work in concert.

HIV-related peripheral neuropathies can occur at any stage of infection, and in some cases appear even when the subject has not been particularly immuno-compromised. This is in part due to the use of certain antiviral agents and other medications that also produce neural injury and dysfunction. Furthermore, any HIV-related nutritional deficiencies or toxic exposures such

as alcohol would contribute to neuropathy. With the recent development of glucose intolerance or frank diabetes in many people with HIV infection, there is an increased risk of diabetic-related peripheral neuropathy. Accordingly, not every person with an HIV-related neuropathy will experience the same signs and symptoms and no singular intervention will be appropriate for all. Given this reality, much research is needed to develop multiple and varying treatment options.

“...not every person with an HIV-related neuropathy will experience the same signs and symptoms and no singular intervention will be appropriate for all.”

Clearly, all patients with HIV infection need to be screened by their care provider for neuropathy. As with most illnesses, earlier diagnosis may lead to more effective treatment. Certainly, earlier diagnosis provides an opportunity to correct any reversible contributory factors. A general neurological examination can easily suggest a subclinical or asymptomatic peripheral neuropathy. By examining a person’s reflexes, sensation, strength, gait, and balance skills, a bedside diagnosis can usually be made. However, care providers will often suggest neurodiagnostic testing to confirm, characterize, and quantify the neuropathy.

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A New Study for Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)-Naïve Patients

Bristol-Meyers Squibb

Title

VEST-QD: A phase IV, open-label, randomized, multi-center study switching HIV-1 infected volunteers with a viral load <50 copies/ml on a first PI-based regimen to an Efavirenz substitution regimen.

Background

Current antiretroviral (ARV) therapy focuses on decreasing viral replication below the limit of detection, thereby slowing disease progression. In addition to potency, success of a regimen is also a function of the tolerability, safety, and adherence to the ARV therapy. With current guideline recommending life-long therapy, there is a need for simpler and potent regimen that enhances adherence by reducing pill burden, while ensuring long-term efficacy, safety, and tolerability. Efavirenz (Sustiva™) is an NNRTI displaying high potency, safety, tolerability and reduced pill burden.

Study Design

Volunteers will be randomly assigned to one of the two treatment groups:

Primary Objective & Endpoints

The primary efficacy measure will be the proportion of volunteers who continue to have plasma HIV-1 RNA levels <50 copies/ml after switching to an efavirenz substitution regimen from a protease inhibitor (PI)-based regimen at week 48. The secondary outcome measures change from baseline in CD4/CD8 cells counts, virologic rebound (increase in plasma viral RNA), change from baseline in fasting lipids, adherence and quality of life.

Dosing

HIV-positive volunteers who meet the inclusion criteria will be randomly assigned to group 1 and 2.

Inclusion Criteria (partial list)

1. Two consecutive qualifying plasma HIV RNA < 50 copies/ml
2. ≥ 18 years old
3. On HAART over 6 months period prior to study entry, and must include a PI and ≥ 2 NRTIs.

GROUPS	1	2
DURATION	48 Weeks	48 Weeks
PATIENT NUMBER	3	3
DOSES	Efavirenz (600 mg, once per day (QD)) + lamivudine (3TC, 300 mg QD)+ didanosine-EC (DDI, 400mg orally QD)	Efavirenz (600 mg QD) + continuing of current NRTIs

Number of Volunteers Slots/estimated at ARA

6

Principal Investigator

Stephen J. Brown, M.D.

CURRENT RESEARCH AT ARA

STUDY	DESCRIPTION	STATUS
<p align="center">Pre-Clinical & Basic Research AIDS RESEARCH ALLIANCE</p>	<p>AIDS ReSearch Alliance is engaged in a number of ongoing preclinical and basic research projects necessary prior to human clinical trials. For example, see the <i>prostratin update</i> on page 14 outlining important progress that has been made to advance the development of prostratin as an anti-HIV drug.</p>	<p align="center">Ongoing</p>
<p align="center">Experimental HIV Vaccine MERCK & CO., INC.</p>	<p>A phase I dose-ranging study of the safety, tolerability, and immunogenicity of the Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine in a prime-boost regimen in healthy adults.</p>	<p align="center">Enrollment ongoing; study ongoing</p>
<p align="center">BMS AI266-406 BRISTOL-MYERS SQUIBB</p>	<p>Vest-QD: a phase IV, open-label, randomized, multicenter study switching HIV-1 infected subjects with a viral load <50 copies/ml on a first PI-based regimen to an efavirenz substitution regimen.</p>	<p align="center">Enrollment ongoing; study ongoing</p>
<p align="center">BMS AI424-067 BRISTOL-MYERS SQUIBB</p>	<p>A phase IIIB, open-label, randomized, multicenter study evaluating the effect on serum lipids following a switch to the protease inhibitor (PI) atazanavir in HIV-1 infected subjects evidencing virologic suppression on their first PI-based antiretroviral therapy.</p>	<p align="center">Enrollment ongoing; study ongoing</p>
<p align="center">C0603 SAVIENT PHARMACEUTICALS, INC. AND THE NEURO-AIDS RESEARCH CONSORTIUM (NARC)</p>	<p>A randomized, double-blind, placebo-controlled, multicenter, dose-ranging study to evaluate the efficacy and safety of prosapide over 6 weeks of treatment for the relief of neuropathic pain associated with HIV-1.</p>	<p align="center">Enrollment ongoing; study ongoing</p>
<p align="center">Micronutrient Neuropathy Study INTEGRATIVE HEALTH CONSULTING, INC.</p>	<p>Broad-spectrum micronutrient supplementation in HIV-infected patients who develop peripheral neuropathy while taking stavudine and/or didanosine antiviral therapy.</p>	<p align="center">Enrollment complete; study ongoing</p>

STUDY	DESCRIPTION	STATUS
<p>Capravirine A4311002 PFIZER/AGOURON PHARMACEUTICALS, INC.</p>	<p>A double-blind, randomized, placebo-controlled study of capravirine (AG1549) in combination with Viracept™ and two nucleoside reverse transcriptase inhibitors in HIV-infected patients who failed an initial nonnucleoside reverse transcriptase inhibitor containing regimen.</p>	<p>Enrollment complete; study ongoing</p>
<p>Capravirine A4311006 PFIZER/AGOURON PHARMACEUTICALS, INC.</p>	<p>A phase II, randomized, double-blind, dose-ranging study of capravirine (AG1549) in combination with Kaletra™ and least 2 nucleoside reverse transcriptase inhibitors in HIV-infected subjects who have failed antiretroviral regimens containing protease inhibitors, nonnucleoside reverse transcriptase inhibitors, and nucleoside reverse transcriptase inhibitors.</p>	<p>Enrollment complete; study ongoing</p>
<p>Zerit® (Stavudine) BRISTOL-MYERS SQUIBB</p>	<p>Evaluation of the safety and antiviral activity of stavudine extended release formulation as compared to stavudine immediate release formulation, each as part of potent antiretroviral combination therapy.</p>	<p>Enrollment complete; study ongoing</p>
<p>Serostim™ SERONO LABORATORIES</p>	<p>A study testing the safety and effectiveness of a growth hormone in treating HIV-associated lipodystrophy.</p>	<p>Study complete; report pending</p>
<p>BioMerieux 226034 BIOMERIEUX, INC.</p>	<p>Clinical evaluation of Vironostika HIV-1 Plus O Microelisa System on serum/plasma and dried blood spots enrolling HIV-negative volunteers.</p>	<p>Study completed; report pending</p>

For information about enrolling in any of our studies, contact Corie Castro at 310.358.2429. Assistance with transportation to our clinical research facility is usually available upon request. For priority notification of new clinical trials, sign-up for our Priority Notification Program when you call.

HIV-Related Peripheral Neuropathy; Diagnosis and Treatment

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Neurodiagnostic testing involves the external measurement of nerve conduction velocities. Most commonly, a very light electrical stimulus (such as you might experience upon touching a doorknob after sliding your feet on carpeting) is applied to the peripheral nerves in the lower legs, and the response time is measured at the foot level. The most superficial of all human nerves in the legs, the *sural* nerve, is the most convenient and standard choice for evaluation. The size of the electrical response to stimuli as well as the speed of that response is helpful diagnostic data. In a few instances, nerve conduction tests may be supplemented by *electromyography* (EMG), but it is not routinely indicated. Confirmation and characterization of neuropathy expands the database and allows for more specifically tailored treatment plans. Additionally, quantification allows for a more objective follow up assessment of the neuropathy.

“Peripheral and central pain receptors may respond to certain medications, but unfortunately, those medications are rarely specific for any one set of pain receptors.”

Many neuropathies are acute in onset, but most are more insidious and chronic. Certain subtypes

of neuropathy may intermittently relapse, while others are only short-lived. These differences suggest that screening most be an ongoing process and people must be alert to potential signs and symptoms at all times.

“The most exciting aspects of research for peripheral neuropathy are focused on these long-term issues, and trails of human nerve growth factor have already been published.”

Although the pathology involved is peripheral in location, the discomfort and pain of peripheral neuropathy is mediated at a central level as well. Management of the process then, is multifactorial and generally relies upon more than one intervention at a time. Peripheral and central pain receptors may respond to certain medications, but unfortunately, those medications are rarely specific for any one set of pain receptors. When the medications target alternate receptors, adverse effects and toxicities may result. This may limit the use of certain agents, particularly in people taking multiple agents for a variety of ills. Topical interventions seek to circumvent these problems, but have the disadvantage of being cumbersome. Direct intervention to the neural tissue, as in a “nerve block” is not

always technically feasible, and has decidedly mixed results. Adjunctive therapies such as acupuncture, massage, and manipulation may be of help. For the functional deficits of gait and balance, orthotics and physiotherapy are indicated. However, the most important long-term solutions must focus on neural reparation and regeneration.

The most exciting aspects of research for peripheral neuropathy are focused on these long-term issues, and trails of human nerve growth factor have already been published. The early work is encouraging, but much more refined and effective agents will need to be developed. The search for such agents is underway and there is hope that the diagnosis of HIV-related peripheral neuropathy will be made early in its course so that regenerative therapy will be one of the mainstays of treatment.



Peripheral Neuropathy: Symptoms and Treatment

(www.aidsmeds.com)

Symptoms of Peripheral Neuropathy

The symptoms of peripheral neuropathy usually occur in the feet and/or hands:

- Numbness/insensitivity to pain or temperature
- Extreme sensitivity to touch
- Tingling, prickling, or burning sensation
- Sharp pain/cramping
- Loss of balance/coordination
- Loss of reflexes (your doctor can check these)

- Muscle weakness
- Noticeable changes in the way you walk

Other symptoms of nerve damage:

- Noticeable increase in the number of times you need to urinate during the day and at night
- Difficulty walking up and down stairs
- Frequent stumbling or falls
- Erectile dysfunction

Treatment Options

Topical medications: 5% Lidocaine gel (Lidoderm®), an anesthetic gel applied directly to the skin, has been shown in clinical trials to be safe and effective for HIV-positive patients dealing with painful neuropathy.

Non-narcotic pain relievers: These include aspirin, acetaminophen (e.g., Tylenol®), ibuprofen (e.g., Advil®), and naproxen (e.g., Aleve®). All of these are available over-the-counter at pharmacies and grocery stores. These medicines are often quite effective in handling mild pain associated with peripheral neuropathy. Prescription versions of these are available for pain that is slightly more severe.

Tricyclic antidepressants (e.g., Elavil®): These drugs work by reducing certain chemicals in the brain, called “neurotransmitters,” that are associated with pain and emotional distress. They are often combined with non-narcotic pain relievers (see above) and are usually recommended for the treatment of mild-to-moderate pain. They are also prescribed, in combination with narcotic painkillers, to help manage severe pain.

Anticonvulsants (e.g., Epitol®, Tegretol®, Dilantin®): Anticonvulsants are normally used to treat epilepsy, another neurological disorder. These drugs help calm the central nervous system, including the part of the nervous system

responsible for processing pain. Data from clinical trials are either limited or have not shown that these drugs are, in fact, effective.

Narcotic pain relievers (e.g., morphine, oxycodone, codeine, and meperidine): When the symptoms of peripheral neuropathy get to be too much and don’t subside with the use of the medications discussed above, it might be necessary to use some of the more powerful narcotic drugs to manage the pain. These drugs are usually used in combination with non-narcotic pain relievers, along with tricyclic antidepressants or anticonvulsants. While it’s certainly safe to use narcotic pain relievers to manage pain over the short term—even for HIV-positive people with a history of drug addiction—they can become addictive if used on a long-term basis. Narcotic medications can also cause nausea, vomiting, and sleepiness.

Complementary therapies: Some of the complementary, or “alternative” therapies that have been used to help manage peripheral neuropathy symptoms include peptide T, alpha-lipoic acid, L-carnitine supplement combination (see *Searchlight* Spring 2003 issue regarding our new clinical trial of micronutrient supplementation), and acupuncture. Unfortunately, there isn’t much data from clinical trials to support their use—either they have not been adequately studied, or clinical trials have failed to find these treatments to be of significant benefit.

A New Study for Protease Inhibitors (PIs)-Experienced Patients Bristol-Meyers Squibb

Title

A phase IIIB, open-label, randomized, multi-center study evaluating the effect on serum lipids following a switch to the protease inhibitor (PI) Atazanavir in HIV-1 infected volunteers evidencing virologic suppression on their first PI-based antiretroviral therapy.

Background

Currently 6 protease inhibitors (PIs) are available to HIV-infected patients for use as part of the Highly Active Antiretroviral Therapy (HAART). However, their usefulness is limited by high pill burden and severe toxicities (lipid disorder and fat-redistribution syndrome). There is a clear need for potent PIs with convenient dosing, adequate drug exposure and less toxicities including improved blood lipid parameters. In addition many treatment-experienced patients may benefit from a new PI with a different resistance profile, which is non-overlapping with current PIs. Atazanavir (ATV) is a new protease inhibitor showing high activity against current PI-resistant strains of HIV-1. Its advantage include once daily dosing (2 capsules per day) and efficacy in both treatment-naïve and treatment experienced volunteers, as well as reduced effects on the lipid profile seen with other protease inhibitors.

Study Design

Volunteers will be randomly assigned to one of the 2 treatment groups:

Primary Objective & Endpoints

The primary objective of this study is to determine the percent change from baseline in fasting LDL cholesterol (at week 12) between volunteers on an atazanavir-containing regimen and those on a regular PI regimen without atazanavir. Secondary objectives include time to virologic rebound (increase in HIV viral load in blood), change in CD4 cell counts, changes in serum level of fasting glucose and safety and tolerability of atazanavir.

Dosing

HIV-positive volunteers, who meet the inclusion criteria, will be randomly assigned to group 1 and 2.

Inclusion Criteria (*partial list*)

1. Qualifying plasma HIV RNA < 50 copies/ml
2. ≥ 18 years old
3. Fasting LDL cholesterol >140 mg/dl (3.36 mmol/L)
4. On HAART over 6 months period prior to study entry, and must include a PI or HAART-boosted PI plus 2 NRTIs. The PI regimen must be the first regimen the patient ever received.

Number of Volunteers Slots/estimated at ARA
6-10

Principal Investigator

Stephen J. Brown, M.D.

GROUPS	1	2
DURATION	48 Weeks	48 Weeks
PATIENT NUMBER	3-5	3-5
DOSES	Atazanavir (ATV, 400 mg) + 2 NRTIs Switch PI to ATV at day 1	Current HAART regimen Switch PI to ATV (400 mg) at day 42

Lipid panel and HIV viral RNA will be determined throughout the study. All volunteers will have their medications switched to Atazanavir; however, volunteers in group 1 will be changed immediately, those in group 2 will be switched after 42 days.

A Study of the Safety, Tolerability, and Immunogenicity of a New HIV Vaccine in Healthy Volunteers

Merck & Co., Inc.

Title

A phase I dose-ranging study of the safety, tolerability, and immunogenicity of the Merck trivalent adenovirus serotype 5 HIV-1 gag/pol/nef vaccine (MRKAd5 HIV-1 gag/pol/nef) in a prime-boost regimen in healthy adults.

Background

The human immunodeficiency virus (HIV) continues to spread around the world, touching communities previously little troubled by the epidemic. While HIV treatment has continued to allow substantial improvements in quality of life and life expectancy for HIV-infected individuals, these therapies are out of reach for most HIV-infected patients around the world. Therefore, the biomedical community is redirecting efforts towards development of an effective AIDS vaccine.

The Merck HIV vaccine program is designed to investigate whether potential vaccine candidates are capable of inducing potent and broad cellular

Study Design

Volunteers* will be randomly assigned to the first group, receiving the lower dose of the vaccine (6 volunteers) or placebo (2 volunteers). If the clinical and laboratory safety data are acceptable, additional volunteers will be randomized to group 2 (higher dose) or placebo. The study will continue by stage until volunteers are randomized for group 4. After data for safety has been evaluated following the second dose of vaccine, remaining volunteers will be randomly enrolled in one of the 4 groups*.

Primary Objective & Endpoints

The primary objective of this study is to determine the safety, tolerability, and immunogenicity of different doses of a 3-dose prime-boost regimen of the MRKAd5 HIV-1 gag/pol/nef vaccine. Secondary objective of this study is to characterize the breadth of the immune response and to estimate the impact of preexisting Ad5 immunity on the immunogenicity of the vaccine.

Dosing

HIV-negative volunteers who meet the inclusion criteria will be randomly assigned to group 1 to 4 or placebo.

Inclusion Criteria (partial list)

1. ≥ 18 years old
2. Must meet pre-specified low-risk behavioral criteria for HIV infection
3. Volunteer has negative serologic tests up to 45 days prior to the first vaccination for:
 - HIV
 - Hepatitis B (HbsAg)
 - Hepatitis C (HCV)

Number of Volunteers Slots/estimated at ARA

10-15

Principal Investigator

Stephen J. Brown, M.D.

* No health care service plan, disability insurer, nonprofit hospital service plan, self-insured employee welfare benefit plan, or life insurer may withhold any settlement or coverage of an individual solely because of his or her participation in an AIDS/HIV vaccine clinical trial studied under an investigational new drug application effective pursuant to Section 312 of Title 21 of the Code of Federal Regulations, or Section 111595.

* As this article was being written, Merck was planning to study additional lower dose groups.

GROUPS	REGIMEN (WEEKS)	MRKAd5 dose (Viral particles/dose)
1	0, 4, 26	3 x 10 ⁹ or placebo
2	0, 26	3 x 10 ¹⁰ or placebo
3	0, 4, 26	3 x 10 ¹⁰ or placebo
4	0, 4, 26	1 x 10 ¹¹ or placebo

immune responses against HIV-1 in humans. The basic delivery system used in the present study is a replication defective adenovirus serotype-5 vector system that carries HIV-1 genes (gag, pol, and nef). Adenovirus is a common cause of cold and respiratory infections. After intramuscular injection, adenovirus vector (MRKAd5 HIV-1 gag/pol/nef) enter cells and translate the HIV-1 genes into proteins. Protein fragments are then transported to major histocompatibility complex class I (MHC-I) molecules and are expressed at the cell surface for recognition by CD8 and CD4 positive T cells. Following recognition by specific T cells, both effector and memory T cells are induced, which can be measured using specific cellular immune assays.


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PROSTRATIN UPDATE

The phorbol ester, prostratin, used in Western Samoa as an ethnobotanical treatment for viral hepatitis, was isolated at NCI in 1992. Prostratin up-regulates expression of viral products from latently infected cells such as U1 and ACH-2 cell lines. It also inhibits the replication of HIV-1 and prevents viral spread. Prostratin represents a distinct subclass of Protein Kinase C (PKC) activators based on the fact that it is non-tumor promoting. Prostratin's lack of tumor promotion, coupled with its ability to up-regulate latent HIV-1 provirus expression, are important features that could be exploited as an effective therapy to target latent reservoirs for patients on Highly Activate Antiretroviral Therapy (HAART). In March 2001, AIDS ReSearch Alliance in-licensed prostratin from the National Institute of Health (NIH) and is aggressively moving prostratin through the drug development pipeline. Considering the critical issue of latent virus in HIV chemotherapy, it is vital to enter prostratin into clinical trials as soon as possible.

The following progress has been made since the last issue of *Searchlight* to advance the development of prostratin as an adjunctive therapy targeting the elimination of the HIV reservoir:

- Dr. Ivan Hirsch (INSERM, France) submitted a paper to the *Journal of Virology* in June 2003. They showed that in purified CD4 T lymphocytes and lymphocyte tissue prostratin inhibits HIV infection and at the same time reactivate virus from latency.
- Dr. Michelangelo Foti (University of Geneva, Switzerland) demonstrated that prostratin, similarly to PMA, rapidly reduces cell surface expression of CD4 and CXCR4, but not CCR5, by inducing their endocytosis. Internalization of CD4 and CXCR4 is mediated by the activation of conventional and novel Protein Kinase C (PKC) in response to prostratin or PMA. A manuscript has been submitted to the *Journal of Virology*.
- A grant application, in collaboration with Dr. Michelangelo Foti, was submitted in July to Glaxo-Smith-Kline, to identify the specific PKC isomer involved in prostratin's activity, by using RNA interference technique.



News & Views

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eties. In addition sCD4-17b was highly potent compared to previously known broadly neutralizing antibodies IgG1b12, 2G12, and 2F5. They reported also that several primary isolates were insensitive despite the presence of binding sites for CD4 and 17b. The authors suggested the potential utility of sCD4-17b for passive immunization against HIV-1 infection in various contexts, including mother to child transmission, post exposure prophylaxis, and topical microbicides.

Sexual transmission of HIV is the dominant contributor to African's HIV pandemic⁵.

In sub-Saharan Africa, 3.5 million new HIV infections were reported in 2002. A recent study suggested that heterosexual transmission accounts for only 35% of HIV incidence in this region, and parenteral transmission such as unsterile medical practice is the main route of infection. To further elucidate this suggestion, Walker and colleagues compared prevalence estimates of HIV with those of hepatitis C virus (HCV), which has a greater rate of parenteral transmission than that of sexual transmission. This comparison study demonstrated different epidemic histories of HIV and HCV in sub-Saharan Africa, indicating that parenteral transmission is unlikely to be the main source of HIV infection. While it is important to highlight the issue of transmission by unsafe injection, continued efforts to encourage safe sex are urgently required to decrease the spread of the HIV virus in the African continent.

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