

SEARCHLIGHT

QUARTERLY NEWS FROM AIDS RESEARCH ALLIANCE OF AMERICA

The National Leader in Fast-Track AIDS Research

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What's News—

* * *

Clinical Research

Bristol-Myers Squibb has selected AIDS Research Alliance of America to participate in a multicenter, randomized study to evaluate an easier dosing, **extended release** formulation of **Zerit**[®] (stavudine) when used in combination with **Epivir**[®] (lamivudine) and **Sustiva**[®] (efavirenz). By reducing the number of doses per day of antiretroviral medication, clinicians expect that compliance should be improved.

(Article on page 3)

* * *

Agouron Pharmaceuticals, Inc. has selected AIDS Research Alliance of America to participate in a Phase III, multicenter study to determine whether the therapeutic HIV vaccine **REMUNE**[™] can improve the response to antiviral therapy in HIV-infected people. By training the immune system to react against HIV, it is hoped that the immune system can participate in suppressing the virus.

(Article on page 5)

* * *

Science Newswatch: For at least some treated successfully with antiviral therapy, HIV continues to actively replicate, which accounts for the rapid return of virus in people who withdraw from therapy. This emphasizes the need for assays to monitor viral dynamics in infected people who have undetectable viral loads, one objective of an ARAA collaboration with **Dr. Peter Anton** and colleagues at **UCLA**.

(Articles on page 9, 15)

Introducing Spotlight

Development news at **AIDS Research Alliance of America** will now be reported in our new newsletter, **Spotlight**. **Spotlight** will appear concurrently with **Searchlight** and will be received by our donors.

* * *

Hydroxychloroquine Study Launched

FDA grants exemption from IND requirement for ARAA independent research project

LOS ANGELES, SEPTEMBER 15—AIDS Research Alliance of America (ARAA) announced the launch of a Phase I/II study of the combination of hydroxychloroquine (HQ), hydroxyurea and didanosine in the treatment of HIV infection. The last hurdle in the regulatory approval process was cleared on August 6, when ARAA received notice from the FDA that the study can proceed.

On July 2, ARAA had formally submitted an Investigational New Drug (IND) application. By law, an IND submission must be filed with the FDA before any new drug or new combination of drugs can be tested in humans for the first time. Although all three drugs to be used in this study have received FDA approval for their individual use, the proposed combination of the three is novel.

However, the FDA determined that the three-drug combination to be investigated can be studied without the need for an IND. In making this determination, the FDA cited four conditions that applied, the primary one being that "the investigation does not involve a route of administration, a dosage level, or a patient population that significantly increases the risks of the drug," for any of the drugs in this trial.

This study is an independent research project sponsored by ARAA, and is intended to address several of the difficulties associated with conventional HIV "cocktail" therapies. The components of the cocktail therapies are expensive, and many treated individuals develop problematic side effects as a result of the long-term use of these drugs.

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SEARCHLIGHT

QUARTERLY NEWS FROM AIDS RESEARCH ALLIANCE OF AMERICA

A National Leader in Fast-Track AIDS Research

ARAA envisions a future in which HIV and its effects are eliminated from infected individuals, and a vaccine preventing new cases eradicates the virus.

ARAA'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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Another Y2K Dilemma—

Despite Treatment Setbacks, Complacency Ravages On

Media headlines about the AIDS epidemic have been devastatingly glum lately. They include: "Reduction in AIDS Deaths Falls Sharply" (*Chicago Tribune*, 8/31/99), "AIDS Emergency Declared Among County's Minorities" (*LA Times*, 9/29/99); "Decline Slows In Rate of AIDS Deaths - Impact of Drug Therapies Wearing Off, Scientists Say" (*SF Chronicle*, 8/31/99); "Unsafe Sex Practices Traced to Confidence in AIDS Drugs" (*LA Times*, 9/1/99); "When It Comes To AIDS, Lots of People Are Thinking, Yeah, Whatever" (*Chicago Tribune*, 9/7/99)

These stories tell a tale of significant setbacks and onerous challenges facing the HIV/AIDS medical and scientific communities. No one could have predicted that the honeymoon of enthusiasm for treatment advances heralded by multi-drug treatment cocktails would be over so dramatically and so quickly.

However, virtually every time I tell someone that I run an AIDS research organization, I get a highly consistent response: "Oh that's really wonderful, but isn't the AIDS problem pretty much handled with the new treatments?" And 20 minutes into my passionate response to their question, they're sorry that they ever asked.

I am baffled by the fact that the message isn't sinking in to the broader community that AIDS is a bigger threat than ever, particularly with the transmission of viral strains that are already highly resistant to current treatments. Aren't people reading the headlines? We are facing some very significant challenges in the fight against HIV/AIDS that will not have any easy solutions. If the virus had a brain, I'd say that it planned it all in an effort to restore the complacency of the early '80s that allowed the epidemic to reach such dramatic proportions.

I liken the newfound complacency about the epidemic to the Y2K computer glitch—we were all mis-programmed by hype several years ago and it's going to take a massive coordinated effort to avert the ravages of its impact. And just like the Y2K fix, perhaps the only true solution will be to fix the glitch one by one (one person at a time) with a long-term methodical process.

Part of the message needs to be that despite the discovery of dramatic shortcomings of current treatment regimens, there are a lot of reasons to be hopeful about continued advances in the treatment of HIV/AIDS. There are massive international resources being devoted to the search for more effective treatments (and a vaccine to prevent future infections); the anti-HIV drug development pipeline is full of promising new pharmaceutical compounds; there are 14 FDA approved anti-HIV drugs on the market and more to come in the near future.

However, if complacency results in donations and capital drying up to fund the development of promising new treatments and individuals become less willing to participate in clinical trials, further progress will not be possible.

I am calling upon you to do your part in fixing the AIDS Y2K glitch of complacency—shine some light in your community of friends and associates that AIDS continues to be the greatest worldwide public health problem of our time. I remain optimistic that AIDS will be conquered with aggressive science in the new Millennium, but that won't be possible unless we all regain our sense of urgency about the crisis.

Yours truly in search for the cure,

Gregory S. Britt
Chief Executive Officer

Easier dosing formulation for anti-HIV regimens—

Bristol-Myers Squibb's Stavudine (d4T)

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.

LOS ANGELES, September 15—AIDS Research Alliance of America has been selected by Bristol-Myers Squibb to participate in a Phase II study of an extended release (ER) formulation of stavudine (d4T) as a component of a highly active antiretroviral therapy (HAART) regimen.

Stavudine, which was developed and is marketed by Bristol-Myers Squibb under the trade name Zerit[®], has been approved by the FDA for the treatment of HIV infection. Zerit[®] is provided in an immediate release (IR) formulation, and requires twice-daily dosing to maintain adequate plasma levels of drug. The new ER formulation to be studied in the present trial will theoretically require only once-daily dosing, simplifying the dosing schedules of HAART regimens in which it is used.

The objective of the trial is to determine whether the ER formulation of stavudine provides equivalent antiviral activity and safety profile as the IR formulation through 48 weeks.

HAART regimens require strict adherence to maintain potent suppression of viral replication. When doses of medication are missed, HIV is allowed to

replicate faster. Although missing an individual dose may in itself not cause harm, ultimately each round of viral replication and infection that occurs in the presence of sub-optimal amounts of antiretroviral drugs increases the chance that drug resistance will develop. A regimen with a simplified dosing regimen is likely to improve a patient's ability to maintain excellent adherence, which in turn might be expected to improve the durability of the response to the drugs.

The new formulation of d4T will theoretically require only once-daily dosing, simplifying the dosing schedules of HAART regimens in which it is used.

All participants will receive a HAART regimen consisting of the three drugs stavudine (d4T), lamivudine (3TC) and efavirenz (Sustiva[™]). However, all participants will be randomly assigned to one of two groups that will only differ in whether they will receive stavudine in the IR or ER formulations. Neither participants nor investigators will know who has been assigned to which group, because a placebo will also be administered to each participant (see the section on "Medications and Dose" below).

Additionally, the pharmacokinetic parameters of stavudine in the two formulations will be assessed. These data describe the rate at which stavudine is absorbed, and its half-life in the blood. An essential question to be answered by the pharmacokinetic evaluation is whether the ER formulation of stavudine provides sufficient levels of drug in the blood long enough to allow once-daily dosing.

Medications and Dose

All participants will receive antiretroviral treatment comprised of three drugs: stavudine (d4T), lamivudine (3TC) and efavirenz (Sustiva[™]). In addition, all participants will receive a placebo. The purpose of the placebo in this study is to keep both participants and investigators from knowing who received which formulation of stavudine. Thus, each participant will



Bristol-Myers Squibb

Founded in 1887, the Bristol-Myers Squibb Company has since diversified beyond medicine and medical products, although these still account for the majority of the company's sales. Among the long roster of medicines sold by Bristol-Myers Squibb are Videx[®] (also known as didanosine or ddI), the second antiretroviral drug approved by the FDA for treating HIV infection, and Zerit[®] (also known as stavudine or d4T), also approved for treating HIV infection. In May, the company announced a \$100 million commitment to improve HIV/AIDS research and community outreach in several African nations.

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Bristol-Myers Squibb's Stavudine (d4T)—

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Participants are randomized to one of two treatment groups. The dose of d4T (stavudine) is adjusted to body weight. All participants also receive 3TC and efavirenz.

	GROUP I	GROUP II
Weight \geq 60 kg (132 lbs.)	d4T ER 100 mg once daily Placebo IR twice daily	Placebo ER once daily d4T IR 40 mg twice daily
Weight < 60 kg (132 lbs.)	d4T ER 75 mg once daily Placebo IR twice daily	Placebo ER once daily d4T IR 30 mg twice daily

receive stavudine in one of the two formulations (ER or IR), and the placebo in the other formulation.

Stavudine and lamivudine are nucleoside reverse transcriptase inhibitors, and efavirenz is a non-nucleoside reverse transcriptase inhibitor. Lamivudine (150 mg taken twice daily) and efavirenz (600 mg once daily) will be administered open-labeled to all participants.

Participants who are intolerant to efavirenz will be allowed to substitute the protease inhibitor nelfinavir (Viracept®).

Participants will be randomized into one of two groups. The dose and formulation of stavudine received by each participant is determined by which group they are in, as well as by participant's body weight, as listed in the table above.

Side Effects

The most commonly reported side effect of stavudine (d4T) is peripheral neuropathy (numbness, tingling or pain in the hands or feet). Other side effects have been reported, including (but not limited to) headaches, fever, diarrhea and neutropenia (reduced number of white blood cells that help fight infection).

Potential side effects of lamivudine (3TC) include anemia (low red blood cell count), neutropenia, peripheral neuropathy, nausea, diarrhea, and headaches.

Side effects associated with efavirenz (Sustiva™) include fatigue, dizziness, headache, nausea, vomiting, diarrhea, rash, inability to sleep and abnormal dreams. It is recommended that efavirenz be taken at bedtime during the first two to four weeks of therapy to improve the tolerability of nervous system side effects.

Testing

One screening and one baseline visit is required before starting study medications. Once on medica-

tion, visits are required at weeks 2, 4, 8, 12, and 16. Blood will be drawn at each visit, which will also include a physical exam.

This study also has a pharmacokinetic component. For each participant, this will entail a second blood drawing (6 hours apart) at week 2. An extra tube of blood will also be taken at random from participants during the usual study visit at weeks 4, 8 and 12.

After week 16, participants will visit every 8 weeks until the last randomized subject completes 48 weeks of therapy.

Inclusion Criteria (partial list)

- 1) HIV RNA viral load > 5,000 copies/mL (Roche Amplicor® assay).
- 2) CD4 T cell count > 100 cells/ μ L.
- 3) Naïve to antiretroviral medication.
- 4) Subjects should be available for follow-up for a period of at least 48 weeks.

Exclusion Criteria (partial list)

- 1) Suspected primary (acute) HIV infection (i.e., the first weeks following initial infection).
- 2) Infection or condition requiring acute therapy at time of enrollment.
- 3) Women who are pregnant or breast-feeding.
- 4) History of acute or chronic pancreatitis, or of bilateral peripheral neuropathy.
- 5) Proven or suspected acute hepatitis within 30 days prior to study entry.

Patient Slots

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Status

Soon to enroll.

Principal Investigator

Stephen J. Brown, M.D.

For information about participation in this study, contact Corigan Castro at (310) 358-2429.

Adding an immune boost to antiviral therapy—

Agouron's REMUNE™

A randomized, double-blind, adjuvant-controlled, multicenter study to compare the virologic and immunologic effect of Highly Active Antiretroviral Therapy (HAART) plus REMUNE™ versus HAART plus Incomplete Freund's Adjuvant (IFA) on antiretroviral-naïve patients infected with HIV-1.

LOS ANGELES, September 15—AIDS Research Alliance of America has been selected by Agouron Pharmaceuticals, Inc. as a site for a Phase III study to determine whether the experimental therapeutic HIV vaccine REMUNE™ extends the duration of viral suppression when added to a highly active antiretroviral therapy (HAART) regimen of Viracept® and Combivir® in previously untreated HIV-infected individuals.

Like other vaccines, REMUNE™ is designed to promote immunologic memory and immune responses to specific antigens—in this case, to HIV proteins. Unlike vaccines that are used to prevent infections, however, REMUNE™ is meant to stimulate such responses in individuals who have already been infected with HIV. In theory, such stimulation could benefit patients by providing them with a measure of immune control of HIV replication.

The immune system mounts a potent response to HIV within weeks of infection, involving both antibodies, and cells known as cytolytic T lymphocytes (CTLs). In particular, the CTL activity against HIV is thought to exert an initially substantial control over HIV. In untreated individuals over time, however, HIV manages to escape from the control of the so-called “cellular” component of the HIV immune response, leading inexorably to progression to AIDS.

Successful suppression of viral replication with HAART also leads to reduced incidence of opportunistic infections, in part because the cellular component of the immune system is somewhat restored. However, the cellular responses against HIV itself are not reconstituted by HAART. Moreover, recent reports suggest that the remaining anti-HIV CTL activity is reduced further by effective HAART. The reasons for this loss is not certain; however, it has been suggested that in people whose viral loads have become undetectable, the amount of HIV antigens is insufficient to maintain CTL memory for the virus. If this is the case, then an HIV vaccine might address this deficit.

Previous clinical studies of REMUNE™ indicate that this vaccine candidate can boost responses against HIV in CTLs taken from infected individuals. Examination of a subset of participants in a recently concluded study of REMUNE™ revealed improvements in viral loads in the vaccinated subjects. However, the clinical benefit of REMUNE™ has yet to be determined.

The lack of immune control of HIV in HAART-treated patients leaves these individuals indefinitely dependent on antiretroviral medications to maintain viral suppression. Compounding this problem, viral replication may be continuing at very low levels despite HAART, which sometimes leads to the “failure” of treatment in some individuals. The amount of virus that would be encountered as viral breakthrough occurs is initially relatively small. The question to be tested in this Phase III study is whether a therapeutic vaccine might induce immune responses sufficient to control this viral breakthrough while on HAART, thus delaying or preventing treatment failure.

REMUNE™ consists of inactivated (killed) HIV in Incomplete Freund's Adjuvant (IFA). An adjuvant is a substance that boosts the immune response to a vaccine. As a control, the addition of REMUNE™ to a HAART regimen will be compared to IFA plus HAART.

Viracept® is the tradename for the protease inhibitor nelfinavir, and Combivir® is the tradename for a tablet containing both AZT (zidovudine) and 3TC

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Agouron Pharmaceuticals, Inc.

Since 1984, Agouron Pharmaceuticals, Inc. has been applying knowledge of the molecular structures of target proteins to develop drugs to fight cancer, AIDS and other diseases. This approach led to the development of Viracept® (nelfinavir), a highly prescribed inhibitor of HIV protease.

Agouron and the Immune Response Corporation entered into a collaboration in 1998 for the final development and commercialization of REMUNE™, an immune-based therapy for the treatment of HIV infection. Agouron is a subsidiary of the Warner-Lambert Company.

Agouron's REMUNE™ —

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(lamivudine). AZT and 3TC belong to the nucleoside analogue class of reverse transcriptase inhibitors.

In addition to the primary study objective of determining whether REMUNE™ delays the time to viral breakthrough when added to a HAART regimen, the effects of REMUNE™ on the immune responses of participants' CTLs will be assessed. These measurements will be performed in test tube experiments of cells collected during blood draws at study visits.

Medications and Dose

All participants will be placed on a HAART regimen that consists of twice-daily oral dosing of Viracept® (five 250-mg tablets per dose for a total daily dose of 2500 mg), and twice-daily oral dosing of Combivir® (1 tablet per dose; each tablet consists of 150 mg of zidovudine (AZT) and 300 mg of lamivudine (3TC)). These medications should be taken with food.

After 8 weeks of HAART therapy, those participants whose blood HIV-1 RNA (viral load) levels have dropped below 2,000 copies/mL will be randomized to receive either REMUNE™ or IFA (which serves as the control for the vaccine). REMUNE™ or IFA will be administered via intramuscular injection at a dosage of 1 mL approximately every 12 weeks starting at week 9.

All participants whose plasma HIV-1 RNA levels (viral load) exceed 2,000 copies/mL while receiving protocol-specified HAART will be eligible to receive salvage therapy (changes in the specific antiretroviral drugs comprising the HAART regimen) while continuing to receive REMUNE™ or IFA.

Side effects

Viracept® and Combivir® have both been approved by the FDA for the treatment of HIV infection. In general, the use of a HAART regimen (which commonly includes a protease inhibitor) is associated with abnormal distribution of body fat, elevated triglycerides (fatty acid in the blood) and/or elevated cholesterol. The most common side effects of the components of Combivir® are decreased blood cell counts, neuropathy (numbness in the hands or feet, possibly involving severe sensitivity to pain), inflammation of the pancreas, headache, fatigue, nausea and diarrhea. The most common side effects of Viracept® are diarrhea, lack of energy, decreased numbers of white blood cells that help fight infections, and elevated liver enzymes.

REMUNE™ or IFA injections can produce bruising or pain at the injection site, or fever and flu-like symptoms. In addition, since REMUNE™ consists of inactivated HIV, there is a very small possibility that some of the material could contain some live virus.

Testing

One screening visit is required prior to enrollment. The first visit following enrollment will include a complete physical examination, at which time participants will be placed on a HAART regimen. Visits will then be required for blood draws (1-5 tablespoons) at weeks 4, 8, 9, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 (and every 4 weeks thereafter until the last patient enrolled in this study has completed 48 weeks). REMUNE™ or IFA injections will be given at weeks 9, 20, 32 and 44 (with continued injections every 12 weeks thereafter until the last patient enrolled in this study has completed 48 weeks).

Inclusion Criteria (partial list)

- 1) HIV-1 seropositive individuals with plasma HIV-1 RNA (viral load) \geq 10,000 copies/mL at screening.
- 2) No prior use of antiretroviral therapy.
- 3) CD4 T cell count \geq 250 cells/ μ L at screening.

Exclusion Criteria (partial list)

- 1) Prior use of investigational drugs or immune-based therapies within 30 days of screening.
- 2) Immunizations within 6 weeks of screening.
- 3) Previous participation in a study with REMUNE™.
- 4) Pregnant or nursing women, or women of child-bearing potential that do not practice single-barrier contraception.

Patient Slots

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Status

Soon to enroll.

Principal Investigator

Stephen J. Brown, M.D.

For information about participation in this study, contact Corigan Castro at (310) 358-2429.

In the wake of the study closure—

Immune Response Corp. to provide “rollover” study for REMUNE™ participants

Despite the early conclusion of a large-scale study of the immune-based therapy REMUNE™, some promising results were obtained, and the participants of that study will have the opportunity to participate in a “rollover” study of REMUNE™.

In May, the 2,500-patient, placebo-controlled, Phase III clinical trial to evaluate REMUNE™ was concluded at the recommendation of an independent Data Safety Monitoring Board (DSMB). AIDS Research Alliance had been one of the Los Angeles sites for this trial.

The objective of the trial had been to assess whether REMUNE™ could significantly improve the duration of infected individuals’ survival without progression to AIDS. Subsequent to the initiation of this trial, the introduction of highly active anti-retroviral therapy (HAART, which usually includes a protease inhibitor) revolutionized the routine clinical management of HIV infection. The dramatic decline in progression to AIDS amongst study participants as a result of being treated with HAART made it very unlikely that any additional benefit from REMUNE™ on AIDS-free survival could be detected. It was on this basis that the DSMB recommended that the study be concluded.

REMUNE™ is a therapeutic vaccine. It consists of inactivated HIV, and is intended to be used in infected individuals to train immune cells to recognize and respond to viral proteins. The

immune systems of the majority of infected persons lack the ability to control viral replication, leaving HAART-treated individuals indefinitely dependent on medication to maintain viral suppression.

Although the objective of

*“We thank the patients and clinical investigators who participated in this trial, a trial that has yielded findings significant to the design of future studies.”—
Dennis J. Carlo, Ph.D., president and chief executive officer of The Immune Response Corporation*

demonstrating improved clinical outcomes for participants receiving REMUNE™ was not attained, the study did indicate that the vaccine succeeded in inducing immune responses likely to be important in bringing about immune control of viral replication. Furthermore, analysis of a pre-selected subgroup from this study indicated significantly improved viral load measurements in REMUNE™-treated individuals.

The DSMB is an independent board responsible for reviewing safety and efficacy data on a regular basis. The board had been provided regular reports on the progress of the trial, which was run collaboratively by the Immune Response Corporation and Agouron Pharmaceuticals, Inc. Their recommendations were in turn considered by the Immune Response Corporation and Agouron in conjunction with the FDA before the decision to terminate the study was rendered.

In a press release to announce the closure of that study, Dennis J.

Carlo, Ph.D., president and chief executive officer of The Immune Response Corporation explained, “We thank the patients and clinical investigators who participated in this trial, a trial that has yielded findings significant to the design of future studies. While HAART, which became the standard of care after we initiated this trial, has been an enormous benefit to HIV patients, it has made it exceedingly difficult to conduct a trial based upon reaching clinical endpoints. The significant improvements in viral

load and in lymphocyte proliferation observed in the REMUNE™ arm of the 250 patient cohort confirm previous results and provide support for a proposed rollover study for patients currently enrolled in the clinical endpoint study. This rollover study, which is planned to be initiated in the next 2-3 months after FDA clearance, is intended to evaluate the ability of patients to maintain viral load suppression after discontinuation of anti-retroviral drugs.”

The protocol for this rollover study has been submitted to AIDS Research Alliance of America’s Institutional Review Board (IRB) for consideration. The IRB is an independent group responsible for ensuring the rights of participants in all clinical trials conducted at AIDS Research Alliance of America. This study is solely for those individuals who had participated in the closed trial, and is distinct from the REMUNE™ study in antiretroviral naïve individuals announced in this issue of *Searchlight*.

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Hydroxychloroquine Study Launched—

continued from page 1

If proven effective, an HQ-containing regimen might be an attractive alternative to current cocktail therapies in several select HIV-infected populations. In particular, HQ has been extensively used in the long-term treatment of rheumatoid arthritis, and has an excellent safety profile, even when used for a number of years. This contrasts sharply with the toxicities that develop over time with many components of conventional HIV cocktail therapies.

The majority of the world's HIV infected people live in underdeveloped areas, especially sub-Saharan Africa. An effective regimen that is affordable as well would therefore have a substantial impact on HIV/AIDS treatment worldwide. Both HQ and hydroxyurea cost considerably less than drugs currently approved for treating HIV infection, making the three-drug combination in the ARAA study potentially available to large numbers of people who currently cannot afford treatment at all.

This study is referred to as a "Phase I/II" study because, although it is intended primarily to assess the safety of the HQ-combination therapy, efficacy data will also be collected. A Phase I study is conducted the first time a treatment is tested in humans, and is intended primarily to assess the safety of the treatment. The first tests of a treatment's efficacy usually occur in Phase II trials. Sometimes, as is the case with the HQ trial, efficacy data can be easily obtained during the initial safety tests, and the two types of trials are combined in one.

The Institutional Review Board of ARAA, charged with ensuring the protection of participants in clinical trials at this site, had already approved the protocol and informed consent forms for the HQ combination study. Enrollment will begin immediately.

HQ study in brief—

Study design

This is an open-label study in which all participants will receive all 3 drugs (HQ, hydroxyurea and didanosine) in combination for 8 weeks. Patients who have

received some clinical benefit (as indicated by a reduction in viral load or an increase in CD4+ T cell counts) from the study medication will be permitted to enter an extension phase for an additional 24 weeks.

Cohorts

Three populations of volunteers will be studied.

Cohort A: Those with less than 6 months experience with antiretroviral therapy. CD4+ T cell count > 200. Viral load between 5,000 and 80,000.

Cohort B: Those who have experienced significant viral rebound on previous antiretroviral therapy and gave discontinued their medication. CD4+ T cell count > 100. Viral load between 5,000 and 1,000,000.

Cohort C: Those who for personal reasons have discontinued antiretroviral therapy. CD4+ T cell count > 200. Viral load between 5,000 and 250,000.

Other inclusion and exclusion criteria will apply.

Doses

HQ: 400 mg twice daily; didanosine: 200 mg twice daily; hydroxyurea 500 mg twice daily.

Visits and Testing

One screening and one baseline visit; at both, blood will be drawn for laboratory tests including CD4 counts and viral loads. Once on study, visits will be scheduled every 4 weeks for blood draws and safety evaluations. A complete ophthalmological examination will be scheduled following the screening visit, at the end of 8 weeks of study, and following the extension phase (at 32 weeks, if applicable).

Principal Investigator:

Stephen J. Brown, M.D.

For information about participation in this study, contact Corigan Castro at (310) 358-2429.



Study update—

Measuring HIV within tissue specimens

An ARAA Collaboration with Peter Anton

Physicians use T cell and viral load measurements taken from blood samples to manage their patients' HIV infection. But to understand the biology of HIV disease progression, which will ultimately be necessary to improve treatment options for infected individuals, scientists must look within the body's solid tissues.

The vast majority of the body's immune cells reside within the solid tissue of the lymphoid system, and this is where the dynamic processes that underlie HIV/AIDS take place. HIV infection is initially established first within solid tissues. Throughout the course of infection, most viral replication occurs there, and the percentage of cells that are infected at any one time is much higher within lymphoid tissue than in the blood of infected individuals. Furthermore, the tissues most responsible for maintaining the immune system—lymph nodes and the thymus—become structurally disorganized over time as HIV infection progresses.

Gut biopsies can help us understand how HIV causes disease, plan vaccine strategies, and assess exciting new avenues of treatment, such as the use of anti-inflammatory medication.

CD4 T cell counts and plasma viral loads reliably predict a patient's prognosis and response to treatment, but changes in these measures are secondary to the disease processes occurring within the tissues.

As reported in last winter's *Searchlight*, ARAA has been engaged in a collaborative effort with Dr. Peter Anton and his associates at UCLA to study HIV infection within the lymphoid tissue of the gut. For participants, the procedure involves the extraction of a small amount of tissue from 30 cm within the rectum. Biopsies can be performed multiple times on the same individual, and involve minimal discomfort. This work addresses a number of questions at the forefront of today's HIV/AIDS research.

Critical questions

Current treatment strategies cannot cure HIV infection. These therapies can, however, suppress viral loads to below detectable levels. When HIV cannot be measured in the blood, any added benefit from further therapeutic interventions cannot be assessed without quantitative assays of HIV within tissues.

One aspect of the collaboration with Dr. Anton is to clinically validate a procedure to measure HIV within the gut-associated lymph tissue (GALT). This work is a prerequisite for the exploration of more advanced therapies, since the measures themselves must be shown to adequately represent viral activity.

Many kinds of tests are applied to the sample, yielding a variety of information. RNA and DNA is chemically extracted and used to measure the amount of HIV (the "tissue viral load"). An analysis of viral genetic sequences ("genotyping") provides drug resistance information. Furthermore, the extent of inflammation within lymphoid tissue is assessed. Each of these measures clarifies the processes that support the progression of HIV disease.

Update—Results to date






So far, this project has yielded significant information. Here is a summary of the progress to date:

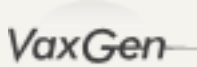





- ❖ One year of observations has already been completed, yielding novel findings on the nature of the tissue viral population. This type of study called a longitudinal study because data are obtained repeatedly from each participant in the study's the only means of learning how complicated processes such as the interaction of HIV with the immune system develop over time. At present, GALT represents the optimal site for conducting longitudinal studies on tissue viral load, since taking multiple lymph node biopsies from the same individual is not practical.

- ❖ Reliable measurements of viral RNA and DNA have been shown to be possible within these tissues. These measurements assess two different aspects of viral dynamics within GALT tissue. Viral DNA is found only within infected cells, usually

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C L I N I C A L T R I A L S

STUDY	SPONSOR	DESCRIPTION	STATUS
Remune™	Agouron Pharmaceuticals 	A randomized, double-blind, adjuvant-controlled, multicenter study to compare the virologic and immunologic effect of Highly Active Antiretroviral Therapy (HAART) plus REMUNE™ versus HAART plus Incomplete Freund's Adjuvant (IFA) on antiretroviral-naïve patients infected with HIV-1.	Soon to enroll
Zerit® (Stavudine)	Bristol-Myers Squibb 	Evaluation of the safety and antiviral activity of stavudine <u>extended release</u> formulation as compared to stavudine <u>immediate release</u> formulation, each as part of potent antiretroviral combination therapy.	Currently enrolling
Neurontin® (gabapentin)	Parke-Davis 	A randomized, double-blind study assessing "low dose" versus "high dose" gabapentin for the treatment of painful HIV polyneuropathy.	Currently enrolling
Anticort™	Steroidogenesis Inhibitors, Inc. 	A pharmacokinetic and safety study of Anticort™ (an oral procaine formulation) in HIV-infected patients.	Currently enrolling
Hydroxy- chloroquine (in combination with hydroxyurea and didanosine)	AIDS Research Alliance of America 	An open-label, Phase I/II study of the safety and antiviral efficacy of hydroxychloroquine in combination with hydroxyurea and Videx® (ddl or didanosine) in HIV-1 infected patients.	Currently enrolling
PMPA Prodrug	Gilead Sciences, Inc. GILEAD S C I E N C E S	A Phase II, randomized, double-blind, placebo-controlled study of the safety and antiviral activity of the addition of PMPA Prodrug to combination antiretroviral regimens in treatment-experienced HIV-infected patients.	Enrollment complete, study ongoing

STUDY	SPONSOR	DESCRIPTION	STATUS
AIDSVAX™ B/B	VaxGen, Inc. 	A double-blinded, placebo-controlled, Phase III trial to evaluate the efficacy of the AIDSVAX™ B/B vaccine in adults at risk of sexuality transmitted HIV-1 infection.	Enrollment complete, study ongoing
Antivirogram™ —treatment experienced	Virco, N.V. 	An open-label, randomized trial to determine whether immediate phenotyping with the Antivirogram™ can lead to improved treatment choices.	Currently enrolling
Antivirogram™ —treatment naive	Virco, N.V. 	A prospective study to assess the prevalence of drug resistance in antiretroviral-naïve HIV-1 infected individuals.	Enrollment complete, study ongoing
Ziagen™ (abacavir): Cognitive impairment	Glaxo Wellcome 	A Phase III, randomized, double-blind study to evaluate the safety and efficacy of Ziagen™ in patients with HIV-associated neurocognitive impairment.	Enrollment complete, study ongoing
Ziagen™ (abacavir): combination	Glaxo Wellcome 	A Phase III, randomized, double-blind study to evaluate the safety and efficacy of 3TC/AZT/1592U89 vs. 3TC/AZT/Crixivan in HIV-infected antiretroviral-naïve subjects.	Enrollment complete, study ongoing
Nelfinavir™ (viracept)	Agouron Pharmaceuticals 	A Phase II/III placebo-controlled study of Nelfinavir™ in combination with AZT+3TC versus AZT+3TC alone.	Long-term extension phase continuing

For information about enrolling in any of our studies, contact Corie Castro at (310) 358-2429. Transportation to our clinical research facility is available upon request. For priority notification of new/enrolling clinical trials, sign-up for our Priority Notification Program.

Natural Immunity to HIV—

In recent years, tantalizing reports have been circulating regarding the possibility that some individuals who have been exposed to HIV were only transiently infected with HIV. Understanding the reasons why these people remain uninfected should shed light on the nature of protective immunity against HIV.

All infected people exhibit immune responses against HIV. One such response, production of antibodies against HIV, is diagnostic of infection. The problem is, these immune responses fail to provide protection against the virus, and people become sick despite being sero-positive (that is, having antibodies in their blood (serum) against HIV).

Some researchers have studied sero-negative persons who have been repeatedly exposed to HIV, because of the possibility that such people had successfully managed to fend off infection with an appropriate immune response. Had HIV established an infection, antibodies against HIV would have been present in their blood, yet the immune cells of some sero-negative people respond to HIV in test tube experiments as though the cells had encountered the virus before.

The antibodies made against HIV that are detected in the standard HIV test, belong to a class of proteins called immunoglobulin G (IgG). Antibodies are also produced at mucosal surfaces where transmission of HIV usually occurs, but unlike the IgG species of antibody present in blood, mucosal antibodies belong to a different class of protein called immunoglobulin A (IgA). IgA against HIV would not be detected in an HIV test. Some researchers believe that the immune responses most likely to

protect against transmission of HIV are those that occur at mucosal surfaces. Could repeatedly exposed, yet uninfected, people have IgA against HIV?

Recently, a group of researchers in Italy headed by Dr. Mario Clerici examined a group of sero-positive individuals and their sero-negative partners for IgA against HIV. As expected, all sero-positive people had both IgG and IgA against HIV. The sero-negative partners had no IgG of course. The key finding is that these individuals expressed IgA antibodies against HIV. Furthermore, when several of the sero-negative partners were followed up one year following the cessation of "at-risk" sex, they remained sero-negative and their IgA levels were reduced.

One obvious conclusion is that these individuals were protected from HIV infection by virtue of high levels of IgA antibodies at their mucosal linings. In this model, one might imagine that those who remained sero-negative responded to HIV with a sufficiently potent IgA response. Those who become infected had an initially ineffectual or absent IgA response, and expressed copious amounts of IgA later (because HIV infection is active and chronic).

Remember that the individuals in this study were pre-selected, so that any genetic or biological attributes responsible for the pro-

TECTIVE immunity had also been pre-selected. In other words, the odds are very low that protective immunity would occur in any one individual; the researchers had defined a cohort that selected for the lucky minority.

However, one cannot jump to conclusions regarding cause and effect. It is possible that some other attribute or immune response conferred protective immunity on these sero-negative individuals. It is also possible that these individuals had been infected and that if one followed them long enough they would eventually exhibit signs of the infection (this possibility is less likely, but still plausible).

If mechanisms that protect people from HIV infection can be determined, this information might inform strategies for the development of a preventative HIV vaccine, and for controlling HIV in infected individuals.



HIV drug resistance profiles in tissues—

Study results presented at Treatment Strategies Workshop

Dr. Peter Anton and colleagues at UCLA, along with researchers from Virco, have compared the drug resistance profiles of HIV from gut with that of HIV from plasma. This work is an extension of the collaboration between Dr. Anton and AIDS Research Alliance of America. The following abstract was presented at the 3rd International Workshop on HIV Drug Resistance and Treatment Strategies (held in San Diego, CA, June, 1999), and is reprinted with permission from Antiviral Therapy, Volume 4, Supplement 1.

Comparative patterns of HIV-1 genotypic and phenotypic resistance profiles in gut and plasma.

PA Anton¹, L Michiels², J Vingerhoets², A Scholliers², M Poles¹, J Elliott¹, D Mark¹, DP Shi¹, P Stoffels², B Larder², K Hertogs². UCLA AIDS Institute¹, Los Angeles, CA; VIRCO², Mechelen, Belgium.

Purpose: Antiretroviral medications are known to have varying degrees of penetration into certain compartments. The gastrointestinal tract is the body's largest immune organ and is a main site of HIV replication and spread. Incomplete drug penetration in this compartment would favor emergence of resistant viral quasi-species.

Methods: 8 sets of blood and endoscopic rectal biopsies were obtained from 7 subjects with plasma viral load >1000 copies/ml. Tissue and plasma RNA was extracted sent for resistance testing. Genotypic analysis was performed by full sequence analysis and interpretational software (VircoGEN¹). Phenotype testing was assessed by recombinant virus assay methodology (Antivirogram).

Results: Genotypic and phenotypic resistance profiles for 14 drugs were obtained in plasma and tissue from all subjects. Profiles of genotypic resistance showed a high correlation between plasma and gut (R=1.0 in 7/8). Phenotypic profiles between the 2

compartments were also highly correlated (R>0.85 in 7/8; R=0.149 in 1 subject). Within compartments, there was high concordance between genotypic and phenotypic profiles and resistance correlated very highly with therapy. In both analyses, most observed differences between gut and plasma were at the level of mutant/WT mixtures. Interestingly, these mixtures were always found in gut samples. Corresponding plasma samples were always found to harbor a completely mutant quasispecies. As expected, profiles from the ART-naive subject were pan-sensitive in both compartments at 2 different time points; the subject off therapy showed resistance only to AZT (not used in over 6 months).

Conclusions: Suitable HIV-1 RNA for resistance testing can be obtained from rectal biopsy samples. There is a high concordance of resistance profiles from blood and gut compartments in this population of subjects. Sequential sampling is now required to determine if limited drug penetration into tissue contributes to the evolution of viral resistance.

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integrated within the cell's chromosomes. The more viral DNA within a specimen, the greater the number of infected cells. This is important because some of these infected cells are long-lived "memory" cells, and as such are a stable reservoir of HIV. Viral RNA can be found either within virus particles themselves, within newly infected cells (before the viral genetic material is converted into DNA), or within cells that also, are preparing new virus particles. The greater the amount of viral RNA in a tissue, the greater the amount of viral replication that is occurring at the time the biopsy was performed.

The vast majority of the body's immune cells reside within the solid tissue of the lymphoid system, and this is where the dynamic processes that underlie HIV/AIDS take place.

When considered together, these measurements provide broad information about the dynamic nature of HIV infection within lymphoid tissues.

Much of these data were presented in abstract form at the 6th Conference on Retroviruses and Opportunistic Infections this past February in Chicago (the abstract was reprinted in the Spring issue of *Searchlight*).

❖ Drug resistance and drug sensitivity profiles of virus found within GALT specimens can be determined. These data have been presented in abstract form at a recent conference (the abstract is reprinted on page 13, this issue).

The issue of drug resistance in tissue compartments is critical. Not all anti-HIV drugs penetrate equally well into tissues. In other words, although an individual takes multi-drug cocktails, the tissues (where the majority of viral replication takes place) may not always be bathed in effective amounts of drugs. Since viral replication in the presence of sub-optimal levels of drug favors the development of drug resistance, the analysis of where such resistance develops can be useful in making treatment decisions. In theory, drug resistant virus might be detectable in tissues before becoming the predominant virus in the blood.

Because of the potential for drug resistance to develop within tissue compartments, it is important for individuals on therapy to adhere faithfully to the dosing schedule.

In addition to the above issues of making quantifiable observations on the tissue viral load, this effort comprises two further elements—the role of inflammation within the gut on the pathogenesis of HIV infection, and the development of a preventative HIV vaccine that takes advantage of what is known about the transmission of HIV through mucosal membranes (such as are found in the gastrointestinal tract).

Taking the next step— Assessing anti-inflammatory HIV therapies

Inflammation promotes viral replication within solid tissues. GALT is often inflamed in HIV-infected people; this represents a normal compensatory response to the chronically active infection. In this sense, anti-HIV therapies fight an uphill battle, in attempting to suppress HIV in an environment that is optimal for increasing it. A whole new approach to reducing viral suppression is to use anti-inflammatory agents as adjunctive therapies to anti-HIV therapies.

GALT biopsies are ideal for assessing the effectiveness of such therapies. They provide specimens from which further reductions in viral replication below that achieved by anti-HIV therapies can be evaluated. They can also be used to evaluate whether an experimental adjunctive therapy actually reduces inflammation within the gut. Data taken from these biopsies have already indicated that markers of inflammation are easily recorded.

Dr. Anton and associates, in collaboration with ARAA, hope to pursue clinical trials in the near future of anti-inflammatory medication as adjuncts to "cocktail" therapies.

From the front lines— Vaccine development

The vast majority of new HIV infections occur at a mucosal surface. In this regard, immune responses that occur at mucosal surfaces represent the first line

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Obstacle to a cure—

Active virus despite effective therapy

The persistence of HIV despite effective treatment with cocktail therapies has been recognized as a major obstacle to a cure for HIV/AIDS. It has been known for several years that HIV persists in a latent form for years despite therapy. Now, it has become clear that even when therapy is highly effective (i.e., suppressing virus below detectable levels in blood), HIV may continue to actively replicate. These new findings force us to reconsider the nature of the persistence of latent virus that has thus far blocked a cure for the disease.

When protease inhibitor-containing regimens became available, they so dramatically improved the prospects for treating HIV infection that some scientists thought that it might provide the basis for a cure. It became apparent soon thereafter that these new highly active antiretroviral therapies (HAART) do not cure HIV infection.

Three reports came out almost simultaneously in 1997 that showed quite clearly that HIV was still present and recoverable in HAART-treated individuals, even when the virus was no longer detectable in the blood. HIV was shown to exist in latent form with-

in immune cells known as resting CD4+ T cells, and activation of these quiescent cells causes viral replication (see box on "latent virus"). Since this latent virus has the capacity to re-ignite a full-blown infection upon withdrawal of antiretroviral medication, this virus represents a *reservoir*.

The vast majority of individuals who withdraw from HAART following successful viral suppression experience the return of virus (viral "rebound") within days of withdrawing from treatment.

If this rebound were due to viral production from latently infected cells, it would mean that some stimulus routinely activates

those cells almost immediately upon cessation of therapy. Since these cells can exist for years without being activated, it is difficult to imagine that they would be activated just by chance in so many people within days of withdrawing from HAART. What, then, could account for viral rebound when HAART is stopped?

The paradigm— Ongoing replication in "undetectable" patients

Studies done in Dr. Anthony Fauci's lab at NIAID (a branch of the National Institutes of Health) showed that viral replication occurs predominantly within cells

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Latent virus

When HIV infects a new cell, it converts its genetic information into DNA, which is then integrated into the DNA of the "host" cell. Once this integration process has occurred, the viral DNA remains within the cell until that cell dies. If the cell enters a state of immune activation, it will produce new HIV from that DNA—the process known as viral replication. However, if the cell remains quiescent—meaning that the cell receives no signal to perform immune functions, and does not

become activated—then HIV remains latent; in this case, replication can occur at any future time when the cell does become activated.

Some cells of the immune system are called "memory" cells; they are meant to survive for many years, carrying the memory of a microbe it has seen previously. For all these years, they can remain in a quiescent state. If HIV DNA is integrated into such a cell, then the viral DNA will also survive for many years. In this way, HIV can persist in a latent form for a very long time.

Active virus despite effective therapy—

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in lymphoid organs, not in the blood. Asymptomatic, untreated, HIV-infected individuals could have little or no virus in their blood even as HIV continues to reproduce and infect new cells within various body tissues.

This concept has now been extended to patients with undetectable viral loads while being treated with HAART. A number of studies published recently have emphasized the role of ongoing replication despite HAART on the course of HIV infection. This low-level replication appears to occur within tissues, where antiretroviral drugs may not fully penetrate.

The evidence— Circumstantial evidence for ongoing replication

For a number of reasons, HAART-treated individuals may choose to discontinue therapy. As mentioned above, usually this leads to the return of detectable viral loads, and the subsequent exponential increase in blood viral load. Two groups of researchers have analyzed the viral rebound in detail, and published their results almost simultaneously.*

In both studies, individuals were selected who had been successfully treated with HAART and who had volunteered to cease treatment. Both studies obtained fairly similar data on viral rebound, emphasizing the reliability of the observation that viral rebound can occur rapidly upon discontinuing apparently effective therapy.

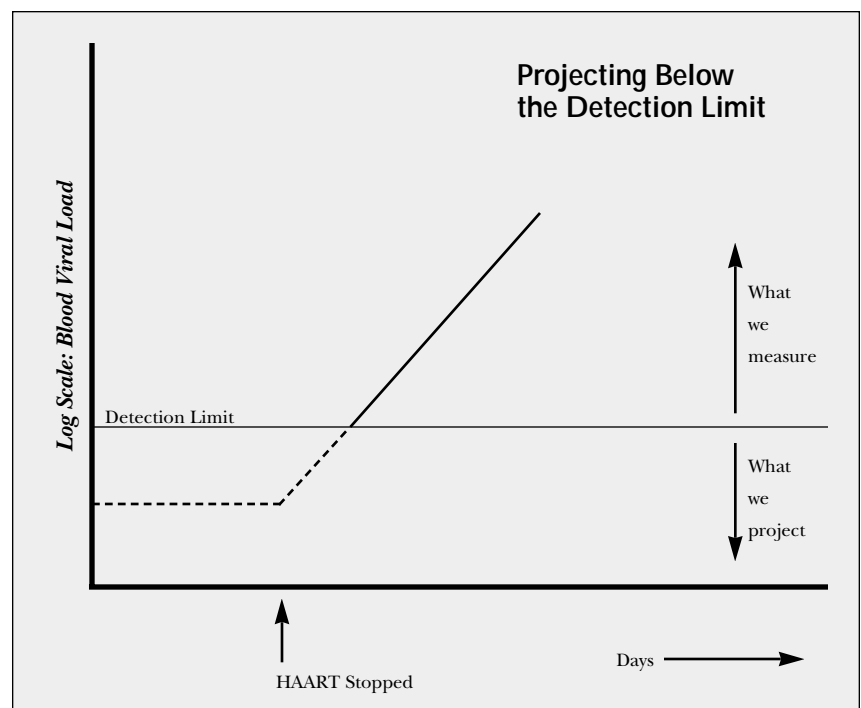
Clearly it is important to ascertain what the processes are that occur during the first few days following withdrawal from HAART, that lead to the viral rebound. Unfortunately, in that time viral loads remain undetectable, so changes in HIV are not directly observable. (This point underscores again the need for assays to monitor changes in HIV at times when the blood viral load is below the detection limit. For more on this, see the study update on the ARAA collaboration with Dr. Anton, page 9, this issue). However, these changes can be inferred indirectly from the measurable data once viral loads become detectable. One of the two groups attempted exactly this.

This group plotted the viral loads they could measure on a logarithmic scale, as a function of

time. Since the viral loads rise exponentially, they can be plotted as a straight line on this “semi-log” graph (see the graph, “projecting below the detection limit”).

If we assume that the processes that cause the viral load to increase exponentially were also operating before the viral load became detectable (not unreasonable, since the detection limit is a limitation of the viral load assay and has nothing to do with the cause of the viral rebound), then it is fair to extend the graph backwards in time for an estimate of the real blood viral load at the moment treatment was stopped (dotted line on the graph).

This method leads to the conclusion that HAART produces a steady viral load several orders of magnitude (several logs) below the level of detection. If these



minute levels are being maintained over time while on HAART, it is probably due to a steady level of ongoing replication. Although this represents indirect evidence for persistently active virus, it does suggest a mechanism to account for the rapid viral rebound, without having to postulate special activation of latently infected T cells.

At about the same time that these results were published, other groups provided more direct evidence for ongoing viral replication within tissues from patients treated effectively with HAART.

The evidence— Direct observation of ongoing replication

More direct evidence for viral replication requires more detailed investigation, but such measurements are feasible and have now yielded important findings.

One way to search for viral replication is to look for muta-

tions in the genetic material of virus recovered from cells within tissues. Mutations readily occur following the entry of HIV into cells, when the viral enzyme reverse transcriptase converts the viral genes from RNA into a DNA form. This process requires the enzyme to “read” the genetic information encoded in RNA, and to convert this information into DNA. However, reverse transcriptase has no “proof-reading” ability, and frequently makes errors. Any new HIV produced from these cells will contain any mutations that had been produced during reverse transcription. Genetic changes observed in HIV recovered from an individual become a record of viral replication that had been occurring within that person’s body.

Dr. David Ho’s group at the Aaron Diamond Institute in New York City has found such evidence of genetic evolution in infected cells from two HAART-treated patients with undetectable viral

loads. Importantly, the mutations found in their virus are not those that confer drug resistance. Normally, drug resistance mutations would be expected when HIV was replicating despite the presence of antiretroviral drugs. The conclusion is that, in these patients—for whom HAART was effectively suppressing virus—HIV was continuing to replicate (at low levels) in tissue compartments where antiretroviral drugs were not present in quantities sufficient to exert pressure on the virus.

Another approach to detecting low-level ongoing replication in HAART-treated patients is to observe it in action. There are two steps in the process of viral replication when HIV genes exist in a short-lasting (or labile) intermediate state. Detecting these labile forms of HIV indicates that viral replication had been taking place in the recent past.

Dr. Manohar Furtado and colleagues at Northwestern University Medical School in Chicago examined blood cells

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Logs of viral loads

Often, viral load measures are reported as the logarithm of the viral load. Though this may seem unnecessarily obscure (a viral load of 3.0 log could also be expressed as 1,000 copies/mL. $1,000=10 \times 10 \times 10$, or 10^3 . A “log” is a factor of 10), it is a useful means of relating two viral load results to each other.

For example, if one’s viral load is checked at two time points close to each other, and if the results differ by no more than 0.3 log, then that difference falls within the variability that is expect-

ed from the tests. In other words, the amount of virus in the blood may not actually have changed, as long as the two results are within 0.3 log of each other. This relationship holds no matter what the absolute values are of the test results: an increase in viral load from 3,000 copies/mL to 3,400 copies/mL represents the same change logarithmically as an increase from 300,000 to 340,000, and both fall within the test-retest variability of viral loads. (An individual who experiences such an increase in viral load results would require another measurement in order to determine if a real change has occurred).

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from 5 HAART-treated patients with plasma viral loads below 50 copies/mL. They were able to detect these labile forms of HIV in these patients. These measures decreased over time with treatment, yet never disappeared, providing direct evidence for ongoing replication despite at least 20 months of HAART therapy.

What does this tell us about the reservoir?

Since the reservoir of HIV within resting CD4+ T cells was first described, it has received a great deal of attention as an obstacle to a cure for HIV/AIDS. In part, this attention has been bestowed these cells because this reservoir has been well described. Other cells also contain replication-competent HIV, including seminal cells of the testes as well as cells within the central nervous system. Their roles have received far less attention from researchers.

However, one practical reason for the concern about the resting T cells is their long lifetime. These cells function as memory banks for the immune system, retaining information about microbes seen previously, so that an effective immune response can be mounted against them if encountered again. These cells are meant to survive for decades.

Consistent with their role in immunological memory, Dr. Robert Siliciano of Johns Hopkins University recently estimated that, under conditions of “maximal” suppression of viral replication, it would take on the order of 60 years for the resting T cell reservoir to become extinguished.

Patients would have to remain on medication at least that long before HIV is eradicated from their bodies.

This number represents the net rate of loss of latently-infected resting T cells. It would only represent the rate at which this population of cells dies if no new cells are added to the reservoir. In the absence of any ongoing replication, this seems like a safe assumption. If, however, new virus is being constantly produced, then it is possible that the latently-infected resting T cell reservoir appears more stable than it actually is. Newly produced virus can go on to infect new T cells, thereby replenishing the reservoir.

The new findings indicating such ongoing replication have this as a silver lining: truly complete suppressive anti-HIV therapy might reduce considerably the length of time needed to extinguish the persistent reservoirs. Unfortunately, we still do not know how to achieve “full” suppression, and we do not know just how much the estimates of the reservoir lifetime are affected by ongoing replication.

It must be emphasized that the real clinical implications of these new findings have yet to be worked out. Another important caveat is that the findings discussed above do not necessarily apply with equal weight to all cases of HIV infection. These were studies of selected. Clearly, the imperfect suppression of viral replication by HAART must be addressed. Adjunctive therapies

that aim to create an environment of immune control of HIV might, in principle, fill this gap.

The several examples of individuals—most notably the “Berlin” patient—who suspended treatment and maintained undetectable viral loads, indicate that conditions may exist to allow for a broader population of HIV-infected people to safely suspend treatment. These conditions have yet to be worked out.

One further note of emphasis: although HIV might be continuing to replicate at low levels, successful viral suppression with HAART has been widely shown to improve the health and extend the lives of HIV-infected people. Certainly, the results discussed above are not meant to impugn the standard of care for HIV/AIDS, but to point out the challenges that remain in treating affected individuals.

*Two nearly simultaneous reports have provided circumstantial evidence for ongoing viral replication despite HAART, based on analysis of viral “rebound” following cessation of therapy. These are:

Harrigan et al., *AIDS* (1999) Volume **13**, pages F59-F62.

Garcia et al., *AIDS* (1999) Volume **13**, pages F79-F86.



Immune Response Corp. to provide “rollover” study for REMUNE™ participants—

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“We believe the improved control of viral load observed in the clinical endpoint study provides strong support for new pivotal clinical trials of REMUNE™ to be based on virologic markers,” said Peter Johnson, Agouron’s president and chief executive officer. “Concluding the clinical endpoint trial at this time also presents a

unique opportunity to address a very contemporary question: can immune-based therapy extend the duration of the anti-HIV response induced by HAART under the most challenging conditions? The potential to produce this effect remains one of REMUNE™’s most important attributes.”

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of defense against the transmission of HIV.

Mucosae are moist membranous surfaces that line the entire gastrointestinal tract, the nasal sinuses, and the uro-genital tracts in both men and women. Mucosal tissues have the largest surface area of any tissue in the human body, far more than skin. As such, mucosal surfaces represent the largest points of contact between the human body and the external world. Because of this special attribute of mucosae, specialized immune responses have evolved to protect them from infection. Many researchers feel that a vaccine to elicit such “mucosal” immunity offers exceptional promise in the prevention of HIV transmission.

The mucosal lining of the gut provides an excellent route of administration for vaccines. Immunity can be stimulated there through oral or rectal routes, and immune responses can be elicited (at least in animal models) that

also protect mucosal linings in the genital tracts. But with regular assessment of GALT biopsies now a reality, human mucosal vaccine subjects can be monitored directly for the early development of immunity within the immunized tissues.

Studies such as the one described on page 12 of this issue although not conclusive—support the concept that inducing anti-HIV immune responses at mucosal linings might provide protective immunity against infection.

For more information

In the fall, Dr. Anton’s group will have a website up to provide a description of the center, educational information for patients or interested individuals, and descriptions of the ongoing research at the center. The website is: www.hivgut.com.



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❖ Remune™: A study of standard antiviral therapy in combination with immunotherapy.

❖ Antivirogram™: A study to determine whether drug resistance testing leads to improved treatment choices.

❖ Hydroxychloroquine (in combination with hydroxyurea and didanosine): A study to determine the antiviral activity & safety of hydroxychloroquine in combination with hydroxyurea and Videx® (ddl or didanosine).



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Para información en español, llame al 310/360.3876.

*ICCAC, abstract 1-179, 1997.