LAMS / MACS Newsletter

Harbor - UCLA - LAGLC

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- Harbor: (310) 222-3773
  Carlos Aquino
- LAGLC: (323) 993-7534
  Eduardo Mercado
- Wilshire: (310) 479-6691
  Dennis Miles

Inside this Issue

Letter from the Principal Investigator

We are pleased to publish this newsletter which highlights the contributions that you, the men of the Los Angeles Men's Study (part of the Multicenter AIDS Cohort Study - MACS), have made over the last several years. Because of your devotion to the study and the outstanding investigators at UCLA and all over the United States who have analyzed the data and specimens which we have collected from you, we have been able to advance our understanding of the natural history of HIV infection, AIDS and AIDS treatment and of the factors needed to produce a successful vaccine. This issue presents the results of several of the studies which have been completed and also tells you about some of the studies that are on-going and that we plan to do in the future.

Certainly the studies which we have conducted as part of the MACS have advanced the field of HIV/AIDS and treatment of HIV/AIDS tremendously. But the basic research that we have been doing as part of the HIV/AIDS field has also greatly advanced our understanding of how the human immune system responds to viral challenge and the inherent characteristics of viruses that allows them to infect us and to evade our immune defenses. Now, thanks to you, we are also learning about how cells and the immune system age and the factors that accelerate that aging. Two of the following articles deal with this issue. This research will benefit not just those with HIV but all of us who grow older!

I am pleased that our research represents the cutting edge of the HIV/AIDS field, a testimony to your persistence and the creativity of the many investigators. We and our collaborators will continue to strive to be on the cutting edge of HIV/AIDS research. That is the least that we can do to pay back all of you for well over twenty years of devotion to the LAMS/MACS.

Sincerely,

Roger Detels

Carta del Investigador Principal

Nos complacemos en publicar este boletín informativo que da a conocer las contribuciones que ustedes, los hombres de Los Angeles Men's Study (Estudio de Hombres en Los Angeles, parte del Estudio Multicéntrico Cohorte sobre el SIDA – MACS) han aportado durante los últimos años. A razón de la devoción que le han tenido al estudio y de los excelentes investigadores en UCLA y a lo largo de los Estados Unidos que han analizado los datos y muestras que hemos recopilado de ustedes, nos ha sido posible profundizar nuestro entendimiento de la historia natural de la infección del VIH, el SIDA y tratamientos del SIDA, y todos los factores necesarios para producir una vacuna exitosa. Este ejemplar presenta los resultados de varios estudios que ya han concluido y además les informa sobre algunos de los estudios en marcha y que tenemos programados para el futuro.

Indudablemente los estudios que hemos conducido como parte de MACS han avanzado enormemente el campo del VIH/SIDA y el tratamiento del VIH/SIDA, aunque las investigaciones básicas que hemos practicado como parte del campo del VIH/SIDA también han profundizado pronunciadamente nuestro entendimiento sobre cómo el sistema inmunológico humano responde a los retos virales y características inherentes de los virus que les permite infectarnos y evadir nuestras defensas inmunológicas. Gracias a todos ustedes también estamos aprendiendo cómo las células y el sistema inmunológico envejece y los factores que aceleran dicho envejecimiento. Dos de los siguientes artículos abordan este asunto. Estas investigaciones beneficiarán no sólo a aquellos con el VIH, ¡sino también a todos los que envejecemos!

Me complace que nuestras investigaciones representen la vanguardia de la tecnología en el campo del VIH/SIDA, un testimonio tanto a la persistencia de ustedes como a la creatividad de muchos investigadores. Nosotros, al igual que nuestros colaboradores, continuaremos afanándonos por mantenernos a la vanguardia de la tecnología en las investigaciones sobre el VIH/SIDA; esto es lo mínimo que podemos hacer para agradecerles a todos ustedes más de veinte años de devoción a LAMS/MACS.

Sinceramente,

Roger Detels

Preventing Immune Exhaustion in HIV Disease

Rita B. Effros, Steven Fauce and Stanley Parish

Our transition into the HIV field actually occurred unexpectedly. In earlier studies on how the immune system changes during aging, we had identified a certain innate property of white blood cells that limits the number of times those cells can divide. As it happens, the process we had been studying with respect to aging was highly applicable to HIV disease. Indeed, it is now increasingly recognized that the immune system in persons infected with HIV-1 undergoes what can be considered "accelerated aging." Here we describe the specific aspect of aging that takes place at the level of the individual cell and how our research is seeking to reverse or retard this process – research that would have been impossible without the assistance of LAMS donors.

The ultimate goal is to identify methods that can enhance and prolong the immune response against HIV-1.

When a virus invades our body, it cannot reproduce itself unless it enters a cell. Once inside a cell, the virus is able to hijack the cell's 'machinery' and make more of itself. However, the infected cell displays a small sample of the virus on its surface, tagging it for recognition by the immune system. One of the major players in combating viral infections of any kind, including HIV, is the so-called **cytotoxic (killer) T cell** or **CD8 T cell**. In addition to killing infected cells, these CD8 T cells also produce substances that slow down the ability of HIV to spread and infect other cells.

We have millions of killer T cells, each with a specific **receptor** or "recognizer". Only a small fraction of all our killer T cells is able to recognize any one virus. Therefore, in order to perform their protective functions efficiently, the HIV-specific cytotoxic T cells must constantly replicate themselves to make sure their numbers are sufficient to "patrol" all the tissues of the body. For many years these cells do a fine job and the viral load is kept in check, particularly in cases where drug therapy is also controlling the growth of HIV-1. But even

Immune Exhaustion, pg 7

GBV-C Virus: Protective Role in HIV Infection?

Douglas Morier and Georgina Castle

Have you wondered what is being done with all the specimens collected by the MACS? Here's a good example.

What is now called GBV-C virus was discovered about 12 years ago, though it has probably been around for a very long time. About 10-15% of healthy blood donors are either actively infected with GBV-C or have antibodies indicating past infection. The virus can be transmitted sexually, through blood and blood products, and from mother to infant at birth. At first, GBV-C was thought to cause hepatitis because it is a genetic relative of the hepatitis C virus. However, it does not infect liver cells and studies have failed to find any link between GBV-C and liver, or any other, disease.

GBV-C does not prevent infection by HIV, but it may slow the replication of HIV.

While most researchers were losing interest in GBV-C, HIV researchers were interested in its role as a co-infection in HIV patients. Everyone assumed the virus would behave like other opportunistic infections and worsen HIV infection and disease. But a few researchers began reporting that GBV-C seemed to

GBV-C, pg 8

The MACS and an Understanding of AIDS-Associated Lymphoma

Elizabeth Crabb Breen,Ph.D., for the Martínez-Maza Laboratory

I. The Beginning

It was twenty-five years ago last summer, in June of 1981, when five cases of *Pneumocystis carinii* pneumonia were reported in young gay men in Los Angeles. This was the first hint that a new medical condition was emerging, characterized by a weakened immune system. Additional reports of *Pneumocystis*, Kaposi's sarcoma (KS), and other unusual opportunistic infections (OIs) soon followed. These conditions defined what were, in retrospect, the earliest recognized cases of AIDS.

Over the next year (1981-82), four gay men in San Francisco were diagnosed with a rare cancer involving one of the white blood cells of the immune system. Known as B cell lymphoma, or non-Hodgkin's lymphoma (NHL), no cases of this cancer had been reported in the Bay Area for the previous four years. It was speculated

The unique design of the MACS and the remarkable repository of specimens available made this groundbreaking research possible.

Lymphoma, pg 8

More than 20 Years of HIV Pathogenesis Research

Charlie Price, Beth Jamieson Ph.D. and the MACSPathogenesis Research Laboratory

Twenty years! We can not thank you enough for your participation in the MACS and the many research sub-studies conducted over the years. Thank you for coming in for your regular 6-month visits. And a double thank you to those who have participated in the many extra visits needed for the research studies of Drs. Jamieson, Giorgi, Ferbas and many others at UCLA. We also want to welcome the many new participants in the study. All of you are the backbone of our achievements and we appreciate your commitment more than we can say.

It is also a time to remember those who are no longer with us. It sometimes seems so far away, other times it seems like yesterday that we were losing so many friends, lovers and family to AIDS. Sometimes it seemed so bleak. Sometimes it seemed so hopeful. Slowly over the years with your help we have made progress. Protease inhibitors/combination therapy against HIV has certainly been the biggest success of the past twenty years. But if you remember, there was not even an antibody test available when the MACS first began. Back then we were still trying to figure out exactly how HIV was transmitted. Methods of measuring T-cells were just being developed and viral load tests were many years in the future. There were many unanswered and even unasked questions.

...understanding why these highly exposed men do not become infected may lead to an HIV vaccine or more effective treatments.

LOOKING BACK

Below are brief summaries of some of the research from the MACS Pathogenesis Research Laboratory since the mid 1980's. The research has focused on how the human immunodeficiency virus acts in the body to cause harmful changes (pathogenesis) to the immune system. Without highly active antiretroviral therapy (HAART), these changes can result in a diagnosis of AIDS.

Pathogenesis, pg 11

Studies of Brain Functioning

Eric Miller, Ph.D.

Over the past 20+ years, more than 95% of the participants in the MACS have contributed their time and support to the neuropsychological studies. Information collected from this area of research has proven invaluable for looking at risk factors, disease progression and treatment response for a variety of brain disorders. We have studied extensively the occurrence of HIV-associated dementia, and data from the MACS played a pivotal role in convincing the scientific community and politicians that most symptoms of HIV infection in the brain are relatively mild until later stage illness. Investigators from the MACS also discovered that most patients with AIDS show normal *cognitive function* (thinking or knowing), even over several years of follow-up.

Recently, some investigators have suggested that the onset of cognitive disorders may be associated with duration of HIV infection, independent of immune system functioning. We looked at this possibility by examining neuropsychological data from HIV-positive participants who had maintained normal immunological functioning over a long period of time. The first group

Brain Functioning, pg 13

HIV, Heart Disease, Stroke and Diabetes

Barbara Visscher, M.D. Dr.P.H.

Heart disease and general hardening of the arteries (arteriosclerosis) as well as type 2 diabetes are important worries as we get older. In the last few years, we have found that people with treated HIV infection tend to develop arteriosclerosis and diabetes more rapidly than uninfected people – leading to earlier heart disease, stroke and other diabetic complications.

Because the MACS cohort already has collected many years of data on participants before, after and without becoming infected with HIV, and with and without antiretroviral treatment, we have added a new substudy to look at what is happening in some aspects of the cardiovascular system among our participants. We chose a group of men who were asked to undergo some special testing over a four year period. The special tests include additional blood chemistry tests and two "imaging" tests. One of these is to detect calcium deposits in

HIV Heart Disease, pg 14

Wilshire Study Site

Left to right:
Daniel Cheng
Alan Ernst
Eric Abril
May Htike
Dennis Miles

Fasting and Your Blood Draw

You have probably been reminded to fast, if possible, for your MACS blood draw. For the study this means not eating or drinking anything other than water, black coffee, plain tea, or a 1 calorie diet drink for a period of eight to 16 hours prior to your blood draw. Some of the tests performed for the study can only be run on fasting blood. These tests include triglyceride, plasma glucose, and insulin levels.

While you are fasting it is important to maintain proper hydration. Remember, fasting does not restrict water so drink plenty of water during the hours prior to your visit. In addition to being good for you, there are advantages to being well hydrated when you come to the clinic: your blood draw will likely be easier, and so will the collection of your urine sample.

HIV-Negative Men

Dear Seronegative Participants,

We need you. We really need you. You might think that your contribution is insignificant but you couldn't be more wrong. It isn't. Your participation is crucial to this project. Researchers need negatives as controls in most research that is done. Sometimes negatives are age-matched with positive participants to contrast the effects of medications, let's say. You are an invaluable part of our program. And because this is a longitudinal study, with every year that passes, you become more and more valuable to our research efforts.

Alan E is back

Saturdays as usual

Smile when you see him

Hollywood or Torrance

If you have dropped out of the project because our original location in West Los Angeles is too far for you to come to, you can be seen at Harbor UCLA in Torrance or at the GLC in Hollywood. If you'd like more information, call Dennis Miles at 310 479 6691.

Harbor-UCLA

Harbor-UCLA has been through some exciting times during the past year. A pilot sub-study was conducted during the final months of 2006 to understand better the "down low" phenomenon, a term referring to those who identify as heterosexual, but who covertly engage in same sex activities. Focus groups and individual interviews were conducted on topics such as gender identity, sexual behavior, and development of the *down low* experience. The pilot sub-study is currently being conducted at MACS sites in each of the cities with a MACS cohort, and should be finished this year. One of the goals of the pilot study is to develop a set of questions that could be administered to the MACS cohort to investigate the *down low* from the MSM point of view, as well as that of the individuals on the *down low*.

The MACS at Harbor-UCLA is still active in getting many of our missing guys back! In the next few months, fliers will be posted at HIV clinics and other community centers and shelters reaching out to these missing participants. Even if you have had just one visit to a MACS clinic, we would like to see you again – your participation is still important to our research efforts.

Harbor-UCLA ha pasado por unas etapas muy excitantes este pasado año. Un subestudio piloto que se condujo durante los meses finales de 2006 para entender más a fondo el fenómeno *"down low,"* término que se refiere a aquellos que se identifican ser heterosexuales pero que secretamente practican actividades del mismo género. Se condujeron grupos focales y entrevistas individuales en temas tales como identidad de género, comportamiento sexual y el desarrollo de la experiencia *down low*. El subestudio piloto se conduce actualmente en ubicaciones MACS en cada una de las ciudades con un cohorte MACS y ha de concluir este año. Una de las metas del estudio piloto es desarrollar una serie de preguntas que se le puedan administrar al cohorte MACS para investigar el *down low* del punto de vista MSM, al igual que el del individuo en *down low*.

¡El MACS de Harbor-UCLA aún se afana activamente en encontrar a nuestros muchachos extraviados! En los próximos meses se fijarán volantes en clínicas del VIH y otros centros y albergues comunitarios para ofrecerle alcance a estos participantes extraviados. Aún si sólo se presentó a una sola visita a la clínica MACS, nos gustaría volverlo a ver – su participación sigue siendo importante para

LAGLC

Left to Right:

Raymundo Mercado, Coordinator

Cynthia Harrison FNP-C, Clinician

Robert Bolan MD, Principal Investigator

Eduardo Mercado, Coordinator.

We would like to extend our gratitude to all of you who participate in the MACS at the LA Gay & Lesbian Center. We look forward to seeing all of you at your appointments. We enjoy working with you and we hope you find satisfaction in knowing that your participation in the study is a valuable contribution to the effort to fight AIDS.

Quisiéramos darles las gracias a todos ustedes que participan en el estudio MACS aquí en El Centro Gay y Lésbico de Los Ángeles. Esperamos con entusiasmo verlos a todos en sus citas. Disfrutamos el trabajar con ustedes y queremos que ustedes sientan satisfacción al saber que su participación en el estudio significa una contribución valiosa a la lucha contra el SIDA.

Immune Exhaustion
(from page 3)

in the presence of the most effective medications, the virus is never totally eliminated. Thus, T cells that recognize HIV are never allowed to totally rest and they must continue to undergo cell division indefinitely.

Cell division, even for a good cause, is not without its negative consequences. It happens that all the cells in our body, including these protective cytotoxic T cells, have an intrinsic limit in the total number of times they are able to divide. This number is actually quite large, and in most situations is more than sufficient to allow for an effective immune response. However, in cases of chronic infection, such as HIV, this limit in cell divisions is reached in certain T cells.

How does a cell know to stop dividing? It seems that there is a counting mechanism within the cell that registers the number of cell divisions that have been completed. Once the limit is reached, the cell is stopped in its tracks. This cell division "clock" is believed to be a structure at the end of each chromosome called a **telomere**. Telomeres are very important to the cell because they protect the DNA from getting damaged, much like the plastic cap at the end of our shoelaces prevent unraveling. However, because of a particular quirk in the way DNA copies itself, telomeres get a little bit shorter each time a cell divides. Eventually, the telomeres get so short that further shortening might damage important genes, compromising the ability of the cell to function properly. At this point, a brake is activated and the cell is no longer able to divide.

These so-called **senescent** T cells, which have used up their allotted number of cell divisions, also lose some of their protective functions and acquire activities that may hinder other aspects of the immune system in the fight against viral infection. Furthermore, senescent cells, once generated, seem to persist so that over time, as in the case of chronic viral infections, they actually occupy a progressively increasing proportion of the total population of white blood cells. As a result, they not only function suboptimally themselves, but they may crowd out other more functional cells.

During our studies on aging, we had shown that senescent CD8 T cells can actually be distinguished from other T cells by the absence of an important molecule on their surface known as CD28. In the 1990's, we began a collaboration with the late Janis Giorgi in which we showed that persons chronically infected with HIV-1 have high proportions of killer T cells that lack CD28. We also showed that these cells had much shorter telomeres than other killer T cells from that same person. This suggested, and was later confirmed by other laboratories, that one component of the immune exhaustion that is characteristic of HIV disease is the accumulation of senescent killer T cells.

Based on these studies, our current research is focused on developing strategies to prevent or retard the generation of senescent killer T cells. The ultimate goal is to identify methods that can enhance and prolong the immune response against HIV-1. We are using two approaches. One is based on telomeres, and the other is directed at the CD28 molecule. In the first approach, we are trying to increase the activity of a certain enzyme in the cell known as **telomerase**. This enzyme has the ability to lengthen telomeres each time a cell divides so that the telomere length remains stable and does not shorten as it otherwise would during cell division. Telomerase is actually turned on in cytotoxic T cells during the initial stage of acute viral infections, but with increasing rounds of exposure to the virus, the telomerase shuts down and is no longer active. In the absence of telomerase, the telomeres undergo progressive shortening and eventually the cell is unable to divide and perform its protective functions.

In recent studies, we were able to keep the enzyme telomerase turned on permanently by inserting an extra gene in the cytotoxic T cells. Those experiments demonstrated that cytotoxic T cells from persons infected with HIV can be altered, at least in the lab, to allow them to divide many more times and not lose telomere length. The genetically-altered cells were also able to kill infected cells better and to produce certain anti-viral factors that slow down the growth of HIV. Based on these "proof-of-principle" experiments, our current work involves testing certain chemical telomerase activators for their ability to allow the HIV-specific cytotoxic T cells to produce telomerase for longer periods of time and in greater amounts. Our preliminary studies suggest that cells that are exposed to these chemicals may also have improved anti-viral functions. Similarly, our studies on CD28 are using both a gene therapy approach as well as testing certain chemicals for their effect on CD28 expressed on the T cell surface. In both cases, the goal is to prevent or retard the generation of senescent killer T cells.

All of these studies have thus far been performed in the lab, *in vitro*, or "under glass." Hopefully, the research will lead to immunotherapy that can enhance the ability of cytotoxic T cells to maintain control over HIV in real patients. But no matter how hard we work in our laboratory research, there is no way that our studies could have been performed without the ability to obtain blood samples through the LAMS and the UCLA MACS. We are immensely grateful to all the volunteers who participated in this research by donating blood. Your commitment to this program is ensuring that both the clinical

research and a myriad of basic science studies on HIV disease will continue providing a more comprehensive understanding of this very complex viral infection.

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GBV-C (from pg 3)

protect some patients from disease. The results were so unexpected, few researchers believed them. This was partly because most of the reports were on small numbers of people, or because a few of them reported no benefit from GBV-C.

This is where the stored MACS specimens enter the story.

To more carefully examine the effect of GBV-C on survival of HIV patients, researchers used stored samples collected from MACS participants. The researchers tested serum samples from men who became HIV-positive *after* joining the study. The samples tested were those collected within 18 months of the patient's first HIV-positive antibody test. GBV-C was found in 39% of these "early" samples.

At first, researchers looked at survival of the HIV-positive men by comparing those who had GBV-C infection in their *early* blood sample to those who did not. Using only the early blood sample data, the researchers found that men who had GBV-C did not survive any longer than those who did not. This finding is consistent with previous studies mentioned above that did not find a survival advantage for HIV-positive individuals with early GBV-C co-infection.

Then, blood samples drawn five to six years later were examined. The researchers used only blood samples collected before 1996, to avoid the effects on survival of newer AIDS drugs in highly active antiretroviral therapy (HAART).

Investigators then evaluated survival based on whether the men were still infected with GBV-C in their later blood sample. The men who had GBV-C infection in the two blood samples taken at least five years apart lived the longest. Eleven years after contracting HIV, 75 percent of the men who had GBV-C in both blood samples were alive. Of the men who did not have GBV-C in either blood sample, 39 percent survived for 11 years. The men who had GBV-C in their first blood sample but not in the second had the greatest risk of dying. Only 16 percent of them were still living after 11 years.

These MACS findings suggest that the survival advantage associated with GBV-C is evident only for HIV-positive men who have long-term infection with GBV-C. They also suggest that the previous studies did not find this advantage because they did not consider the duration of the GBV-C infection.

GBV-C does not prevent infection by HIV, but it may slow the replication of HIV. Jack Stapleton, M.D., one of the senior researchers collaborating with the MACS group, has studied the virus in the test tube (*in vitro)* to understand how it works. He has reported that the virus binds to the CCR-5 receptor on the surface of T-cells. This is the same receptor that is used by HIV to enter the white blood cells. This competition for binding sites may limit the amount of HIV that can enter the cell. This type of phenomenon is known as *competitive inhibition.* Here GBV-C may act as a competitive inhibitor of HIV.

The GBV-C infection also increases the production of various chemokines, proteins that mobilize and activate white blood cells to fight infections. One of these proteins, called RANTES, also competes with HIV for the CCR-5 receptor. Dr. Stapleton concludes that there are multiple mechanisms by which GBV-C could help the HIV-positive.

Dr. Stapleton's team and the MACS are continuing this work to help understand why and how GBV-C gives HIV-positive men a survival advantage. Questions remain as to why some of the men cleared the GBV-C virus from their systems and why this was associated with an earlier death. Additional studies could answer these questions and suggest new ways to fight HIV infections.

Reference: *New England Journal of Medicine*, 2004; vol 350, p 981

Note: Researchers that have not found a survival advantage for HIV-positive individuals co-infected with GBV-C, have come to a different conclusion. Rather than the loss of active GBV-C infection leading to HIV disease progression, the counter hypothesis is that the CD4+ cell decrease associated with HIV-disease progression causes the loss of GBV-C. (Reference: *Journal of Infectious Diseases*, 2005; vol 191, p 678) The controversy and the research continue.

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Lymphoma (from pg 3)

that these B cell cancers might be related to the newly-recognized immunodeficiency syndrome. Physicians were urged to report cases of B cell lymphoma among persons at risk for AIDS to public health authorities.

By 1984, HIV-1 had been isolated but was still known as LAV, HTLV-III, or ARV. More than 7000 cases of AIDS had been reported but these were defined almost exclusively by KS or OIs. Meanwhile, a study of 90 cases of NHL in gay men from 1980-83 demonstrated that this cancer of the immune system was "... a serious manifestation of AIDS and the AIDS-related complex" (Ziegler *et al*, NEJM 1984 311:565). The MACS was in its early stages, but already setting the course that would make it an incredibly valuable resource for examining the interactions among HIV, the immune system, and B cell cancer. Within another year (1985), HIV antibody testing was available, and the definition of AIDS had been updated and expanded. B cell

lymphoma/NHL in an HIV-seropositive person was included as an AIDS-defining condition (AIDS-NHL).

Around this time, Dr. Otoniel Martínez-Maza, in collaboration with Dr. John Fahey, became very interested in the effect of HIV infection on B cells. It had been observed that, while T helper cells were becoming deficient in persons with AIDS, B cells were becoming hyperactive. Dr. Martínez and others in the laboratory began to wonder if overactive B cells might have something to do with the B cell cancers that were becoming increasingly common in persons with AIDS. With the invaluable assistance of Dr. Janis Giorgi and the flow cytometry lab at UCLA, we found evidence that men with AIDS did have increased numbers of B cells that appeared to have been stimulated or activated. What was stimulating the B cells, and how was this related to HIV infection?

Through a series of studies using culture dishes in the laboratory as well as blood samples from HIV-infected and uninfected persons, we showed that a newly-discovered immune system protein which stimulates B cells, known as interleukin-6 (IL6), was being over-produced in those people who were HIV-infected. This led us to wonder if overactive B cells in HIV infection were due to the overproduction of one or more immune system protein(s) that are supposed to stimulate B cells under normal circumstances. There was evidence in other cancer systems that prolonged stimulation or activation of normal B cells might lead to the development of cancerous B cells. Perhaps B cell stimulatory proteins were the link between HIV infection and B cell lymphoma.

As of 1990, statistics from all U.S. cases of AIDS, as well as from cases within the MACS, showed that persons with HIV/AIDS were about sixty times more likely to develop B cell lymphoma than the U.S. population in general. As the second-most common AIDS-associated cancer (KS being the most common), the number of cases of B cell lymphoma was increasing by about 20% every year within the MACS.

At this time we recognized that the MACS provided a truly unique opportunity to look for the link between B cell stimulatory proteins and the development of B cell AIDS-NHL. Throughout the history of cancer research, most studies of people with cancer have begun at the point in time when an individual was diagnosed with cancer. Any changes that might have preceded the cancer diagnosis had to be inferred from observations made at the time the cancer was first recognized and in follow-up as the cancer patient was treated. In the MACS, however, blood samples were being collected on a regular basis over many years and frozen for future studies. This meant that when a man participating in the MACS was diagnosed with B cell lymphoma, it was possible to then go backwards in time and look for changes in his blood *before* he was diagnosed with cancer. This unprecedented opportunity to look for increases in B cell stimulatory proteins ***preceding*** the development of B cell lymphoma provided the framework for multiple studies in our laboratory.

II. The UCLA 50

Since the 1990s, we have studied extensively a group of AIDS-NHL cases from the Los Angeles MACS known in our laboratory as the "UCLA 50." We have examined pre-lymphoma blood samples from these fifty HIV-infected men who developed lymphoma, and compared those results to results from blood samples from HIV-infected men with or without AIDS as well as HIV-seronegative men. Our goals were to describe pre-lymphoma changes in the immune system that might shed light on how and why B cells become cancerous in the context of HIV infection, and to identify immune system proteins that might be useful as a screening test for HIV-infected men at high risk of developing AIDS-NHL.

We have identified seven different immune system proteins that are increased in the blood up to 2-3 years **prior to** the diagnosis of B cell lymphoma. Of these, three are known to stimulate B cells (soluble CD23 [sCD23], IL6, CXCL-13) and four are indicators of B cell stimulation (sCD27, sCD30, sCD44, IgE). In collaboration with the other three MACS study sites and the National Cancer Institute, we combined the UCLA 50 AIDS-NHL cases with more than fifty additional MACS AIDS-NHL cases to examine levels in the blood of another B cell stimulatory protein, IL10. We also wanted to characterize the IL10 gene in DNA samples. Not only were we able to add IL10 to the list of proteins in the blood that are elevated preceding AIDS-NHL, but we were able to show the first-ever association between a particular genetic type (one form of the IL10 gene) and the development of B cell lymphoma. The unique design of the MACS and the remarkable repository of specimens available made this groundbreaking research possible.

These studies showed that hyperactivation of B cells does indeed precede the development of AIDS-NHL, and that an underlying genetic type that favors B cell activation is found more often than expected in those HIV-infected men who are diagnosed with lymphoma. These results suggest that B cell hyperactivation may indeed be driving and/or supporting the development of malignant lymphoma tumors. Therefore, these immune proteins and/or genotypes may be good predictors of the risk of developing lymphoma. We are currently collaborating with Dr. John Boscardin to develop a preliminary "Lymphoma Risk Score" based on two or more of the individual immune system proteins

which might be appropriate for use as a screening test.

III. AIDS-NHL since HAART

The introduction of protease inhibitors in 1995 began the era of **highly active anti-retroviral therapy (HAART)**. Initially, HAART did not appear to have much impact on AIDS-NHL. In an ongoing analysis of cancer statistics within the MACS from 1984-2004 (courtesy of Dr. Eric Seaberg, CAMACS), the rate of NHL among HIV-infected participants remained high through 1999. However, as more persons have lived longer with HIV infection and HAART, AIDS-NHL rates among HIV-infected MACS participants have started to decline. For the time period 2000-2004, the rates of NHL among HIV-infected persons were clearly lower than earlier time periods, but they still remained 2-3 times higher than the rates among HIV-seronegative MACS participants.

In collaboration with Dr. Roger Detels and Ms. Debby Regidor, a study is underway examining blood levels of selected B cell stimulatory proteins before and after starting HAART. The hope is to obtain a better understanding how this kind of therapy might affect the link between B cell hyperactivation and the development of B cell lymphoma. As all of our earlier "UCLA 50" AIDS-NHL cases occurred prior to the HAART era, the results of this study will help direct us in future studies on newer AIDS-NHL cases with and without HAART experience. Once again, such studies would not be possible without the invaluable MACS repository materials that span the pre- and post-HAART eras, including the many samples yet to be collected in the months and years ahead.

In 2007, the MACS continues to contribute to our laboratory's research focusing on B cell activation and the development of B cell lymphoma in HIV infection. In work that is an extension of our earlier "UCLA 50" studies that included a chemokine that stimulates and attracts B cells (CXCL13), Dr. Daniel Widney is exploring possible roles of chemokines and chemokine receptors in AIDS- NHL.

Drs. Martínez and Breen have recently completed a greatly-expanded study of B cell stimulatory molecules in the blood preceding AIDS-NHL by utilizing the national MACS repository to which the Los Angeles and other centers contribute. This enabled us to examine almost 200 AIDS-NHL cases at multiple time points up to more than five years before a diagnosis of lymphoma. We demonstrated that at least three immune system molecules (IL6, sCD27, sCD30) are consistently elevated 3-5 years prior to NHL diagnosis. In addition, we discovered that evidence of B cell hyperactivation, (i.e., elevated blood levels of B cell stimulatory proteins) was seen only in the group of men who developed lymphoma in a location other than the brain or spinal cord. Men with brain or spinal cord lymphoma (which tends to occur when CD4 T cell counts are very low) had blood levels of B cell stimulatory proteins that were similar to other HIV-infected men who never developed lymphoma. This observation has helped us to refine our understanding of AIDS-associated B cell lymphoma, which clearly consists of at least two major subtypes that appear to be very different in the role played by B cell hyperactivation.

The results from this expanded study will also allow us to test our preliminary Lymphoma Risk Score, as well as to develop more sophisticated approaches for identifying HIV-infected men at high risk of lymphoma. We will do this by incorporating multiple measurements over time and a wider array of genotyping data. For example, in addition to looking at the level of IL6 in a blood sample from a particular point in time, we will be able to assess if participants' IL6 blood levels are increasing over time. If only the men who developed lymphoma have increasing IL6 levels and/or their levels are rising at a faster rate than in the men who did not, then such increases might be valuable as an indicator of developing lymphoma. Expanding this example to the genetic level, we will be able to examine whether different forms of the IL6 gene are related to the development of B cell lymphoma and/or to the IL6 levels seen in the blood. With the information obtained, we are searching for combinations of blood and/or genetic results that are most strongly associated with the development of AIDS-NHL.

It was hoped that we might be able to utilize the study results to pursue a clinical trial identifying HIV-infected persons at high risk for AIDS-NHL and offer a preventative treatment. The proposed treatment (Rituximab/Rituxan®, a monoclonal antibody routinely used to treat B cell lymphoma), has few side effects in HIV-uninfected persons. When used to treat AIDS-NHL patients, however, it has had unexpectedly high rates of serious bacterial infections, and so is no longer a good candidate for a preventative treatment in HIV-infected persons.

In a follow-up study led by Ms. Marta Epeldegui, we are investigating the possibility of combining B cell stimulatory protein testing in serum or plasma with another approach for evaluating B cell hyperactivation that focuses on the expression of a recently-described gene (activation-induced cytidine deaminase, or *AID)* that is essential to normal B cell function. Utilizing stored white blood cells from the UCLA-MACS repository for a small preliminary study, we have been able to demonstrate abnormally-high expression of this gene preceding NHL diagnosis; in many cases more than five years prior to lymphoma, with one case more than nine years prior. Such an observa-

tion is only possible due to the longevity of the MACS and the extraordinary commitment of participants over many, many years.

Our work in the MACS has laid the groundwork for additional studies in other groups of HIV-infected subjects. One such study, utilizing materials collected by the AIDS Malignancy Consortium from HIV-infected lymphoma patients from across the country, is examining serum protein levels and *AID* gene expression at the time of AIDS-NHL diagnosis and over the course of treatment. This may eventually lead to the use of *AID* gene expression along with other blood and genetic results as described above, not only to predict (and reduce?) the risk of AIDS-NHL *before* diagnosis, but to predict survival and/or success of treatment *after* diagnosis.

As researchers and citizens concerned about the impact of HIV/AIDS, we would like to continue to express our deepest gratitude to the men of the MACS, for your participation in and contributions to what is truly one of the most remarkable institutions in the world of HIV/AIDS research. We welcome this opportunity to share the scientific progress we have been able to make as a result of your participation in the MACS, and thank you in advance for all that you will continue to do in the years to come.

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Mind-boggling Statistic:

You have contributed to more than 1,000 scientific publications.

Pathogenesis (from pg 4)

Cellular immunity – Janis Giorgi, PhD came to UCLA in 1984 to join the MACS research team and to set up the project's flow cytometry lab. She immediately became interested in HIV and AIDS. She conducted numerous research studies on the role of CD4 and CD8 T-cells in HIV infection. She studied how CD4 T-cells became the primary target of HIV and how CD8 T-cells kill and clear HIV from the body. She became an internationally recognized expert in measuring the ability of Cytotoxic T-Lymphocytes (CTL) to control or not control HIV infection.

CD38 – In 1993 Dr. Giorgi published a paper reporting elevated levels of CD38 expression on CD8 (*killer*) T-cells in HIV-positive MACS participants. This research demonstrated the ability of CD38 levels to predict the likelihood of developing AIDS: the higher the level of CD38, the greater the likelihood of developing AIDS. Today, all LA MACS participants get a report on their CD38 levels along with their other T-cell counts (CD4, CD8).

Resistance to HIV – In 1994 Roger Detels, MD, MS and Dr. Giorgi published a paper comparing men who had been repeatedly exposed to HIV but remained HIV-negative to men who had similar exposure and became infected. The research suggested that CD8 T-cells may play a role in preventing HIV infection. Later studies showed a small percentage (1-2% of Caucasian men) had a genetic mutation of their T-cells, a deletion of the CCR5 receptor that made them almost completely unable to become HIV infected. Studies of resistance continued for many years and with the exception of the CCR5 deleted group, there are still no strong conclusions as to exactly why some people continue to resist HIV infection. Many people believe that understanding why these highly exposed men do not become infected may lead to an HIV vaccine or more effective treatments.

Immune reconstitution – In the mid 90's with the introduction of protease inhibitors and other effective therapies (HAART), Dr. Giorgi and Marty Majchrowicz began looking at the effects of these therapies on restoring the immune system. After measuring a variety of factors they found a slow increase in the CD4 T-cells and some decrease in CD8 T-cells. These changes brought immune function closer to its pre-HIV infection state. While it may not seem very surprising today, it was not clear at the time what the therapies would do to the immune system.

The thymus and immune reconstitution – In 1997 Beth Jamieson, Ph.D. began looking at the role of the thymus in HIV infection. The thymus, located just above the heart, is the source of most human T-cells. It was known to decrease production rapidly after the age of 20 and thought to stop producing new ones altogether in middle age. Dr. Jamieson discovered that new T-cells can be produced as late as age 56. And though they are fewer in number, they are capable of producing responses to antigens similar to those produced in youth. This knowledge raises the hope that treatments might be found that can restore the T-cells lost to HIV, an important possibility in the age of HAART.

Reservoirs of HIV infection – After some initial hope that HAART might be a cure for HIV, it became apparent that there are reservoirs in the body where the virus "hides" from the drugs. If medication is stopped, the virus will usually rebound to some detectable level. In 2000, Drs. Giorgi and Jamieson began looking at subsets of T-cells that might contain virus and whether the virus in these reservoirs was capable of reproducing. Most recently we have identified

"double positive" T-cells, which have features of both CD4 and CD8 T-cells. While they are a very small percentage of all T-cells in the body – usually 0.5% or less – they do appear to be carrying virus. We are now conducting experiments to learn more about the virus in this reservoir. The identification of specific reservoirs may point to therapies that target HIV in these reservoirs making viral rebound less likely.

Mucosal immunology – Peter Anton, MD in collaboration with Dr. Giorgi, began examining the role of mucosal (oral, rectal and vaginal) tissue in transmission and continuing infection with HIV. They found that the mucosa is constantly *activated;* i.e. it is looking for pathogens to carry away in order to prevent infection or disease. Unfortunately, this activation makes the mucosal tissues an ideal target for HIV infection. It also appears that the mucosa is a reservoir of HIV. Recently Drs. Anton, Jamieson and Otto Yang, MD have been investigating whether the site of immunization makes a difference in stimulating the mucosal anti-HIV defenses. Results from these studies are pending.

LOOKING FORWARD

These are some of the studies involving MACS participants that are ongoing or have been proposed.

Gender differences in HIV infection – Several studies over the past few years have indicated some differences in the body's response to HIV based on gender. It appears that on average, women have lower viral loads for at least the first 4½ years of HIV infection when compared to men who are infected for the same duration. This study will look at a racially/ethnically, age-matched cohort of individuals infected for less than 3 years. The goal is to examine the differences in the impact of HIV on women and men and the different immune responses mounted by women and men.

Long-term non-progressors (LTNP) — There have been many studies by our lab, and others, of the phenomena of long-term HIV infection (10 years or more) with little or no impact on health status. Some of these individuals have normal T-cells and no viral load after 20+ years without treatment. Numerous factors have been examined. Recently Dr. Jamieson proposed that some individuals with a certain human leukocyte antigen (HLA) type (an immunological defense mechanism inherited genetically) that were exposed to non-HIV virus(es) soon before their primary HIV infection may have built up an immune defense that allowed their body to control HIV for extended periods of time without HAART. This study began recently and it relies on a unique feature of the MACS. We have samples collected from individuals before they were infected with HIV and who are now LTNP. This study would not be possible without the repository of cells you have provided.

CD31 – Age is thought to play a role in the rate of disease progression, with older individuals progressing more rapidly than younger individuals. Even in the absence of HIV-1 infection, people become more susceptible to infectious diseases and cancers and make poorer immune responses to vaccines as they age. The population of HIV-1 positive individuals is getting older. This is not only because of better survival in the era of HAART, but also because new infections among older adults are on the rise. Therefore, it is important to understand how age affects HIV-1 positive individuals. As CD4+ T-cells are important for mounting protective immune responses, we are studying the impact of aging on this **compartment** (population of cells).

Specifically, we have looked at the population of CD4+ T-cells that are **naïve**, which means they have never been involved in an immune response. We think of these cells as the reserve on which the immune response relies when a new pathogen is encountered. Even though the **thymus** (organ that produces T cells) gets smaller with age, we had previously shown that the overall number of naïve CD4+ T-cells does not decrease much over time. This suggested that either the adult thymus is more active than we thought, or that the naïve cells, once out in the peripheral blood, divide to make more copies of themselves. We set out to determine how these cells were maintained.

We examined the naïve CD4+ T-cell compartment of 12 seronegative MACS participants over a time frame of 15 years. We used **cryopreserved** (frozen) samples from men ranging from 20 to 70 years of age. We found evidence that naïve CD4+ T-cells do age as a result of cell division that occurs in the peripheral blood in an effort to maintain their cell numbers. This cell division results in shorter telomeres, caps found on the ends of chromosomes. These caps protect the genetic information in the chromosomes and they get shorter each time the cell replicates its DNA and divides. The cell cannot divide if the caps get too short. This means that once an aging, naïve CD4+ T-cell encounters a pathogen, it might not be able to divide as many times and make as many copies of itself as a naïve CD4+ T-cell from a younger person. This may contribute to the declining immune response of older individuals. *(See article on immune exhaustion, page 2)*

We also examined the naïve CD4+ T-cells for the presence of a newly described surface protein called CD31, or PECAM-1. This marker divides the naïve CD4+ T-cells into two subsets, those with CD31 and those without. The CD31+ subset is rich in cells that have not divided since leaving the thymus. At some

point, these cells divide enough to lose CD31 and become CD31-.

Using the frozen samples, we showed that with aging, the CD31+ subset declined significantly reflecting a decrease in the output of new cells from the thymus. In contrast, the CD31- subset remained stable up to 70 years of age demonstrating that this subset maintains the proportion of naïve cells largely through a high number of cell divisions. This is important because each cell has a limited number of divisions it can undergo before the cell is signaled to die.

Because HIV-1 infects and destroys CD4+ T-cells, we have begun preliminary experiments to determine how HIV-1 affects the aging of the naïve CD4+ T-cell compartment. Our preliminary studies show that HIV-1 may accelerate aging in the naïve CD4+ T-cells that do not become infected. These cells have telomeres that are as short as those found in naïve CD4+ T-cells from uninfected men 20 to 30 years older.

Dr. Jamieson has recently submitted a grant application to the NIH to fund studies with three specific questions in mind: 1) What is the mechanism by which HIV-1 shortens telomeres in naïve cells, 2) Do these shortened telomeres affect how well these cells can respond to HIV-1 and other pathogens, and 3) Does HAART restore telomere length and function in this population of cells. These experiments will give us a better understanding of how HIV-1 disables the CD4+ T-cell compartment, and may help explain the faster disease progression observed in older infected individuals.

Today most people with HIV in the MACS are thriving, but there are still many challenges ahead. What are the long-term effects of the treatments? Can we make effective treatment available worldwide? Can we find a vaccine? Can we stop HIV transmission in other ways? Can we find a cure? Each contribution you have made to the MACS brings us closer to answering these questions and many more. We thank you again and deeply appreciate your current and past support of this research. Without you none of it would be possible.

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Brain Functioning

(from pg 4)

consisted of participants who had remained AIDS-free for more than 15 years and had never received antiretroviral therapy (long-term nonprogressors). The second group consisted of participants receiving antiretroviral therapy who had maintained undetectable viral loads for more than 5 years since starting HAART. Five years of data from the Trail-Making and Symbol Digit tasks were analyzed. Contrary to what some other investigators have suggested, no differences were found between HIV-negative participants and those in the long-term nonprogresor and long-term undetectable viral load groups. Also, there was no evidence of decline in cognitive performance measured in the long-term asymptomatic groups over the 5 year period. It appears that long-term asymptomatic HIV-positive individuals with well-controlled viral loads do not show evidence of decline in **psychomotor measures** (tests of movement associated with thinking) over 5 years of follow-up. These findings suggest that cognitive decline is primarily associated with generalized immune system changes rather than duration of infection.

A number of investigators have proposed that HIV-infected individuals are at increased risk for **cognitive sequelae** (impaired thinking or knowing) as they become older. This risk would seem to be increased in the era of HAART since many medications are known to increase risk of **cardiovascular** (heart and blood vessel) disease, most likely including **cerebrovascular** (brain blood vessel) incidents. In addition, cognitive side effects of antiretroviral drugs are just beginning to be explored, with some indications that non-nucleoside reverse transcriptase inhibitors (NNRTI) may have unanticipated neuropsychiatric side-effects.

The MACS is currently in the process of adding a **neuroimaging** (brain scan) study to take a better look at changes in normal brain function among older study participants. This study will examine the effects of HAART, HIV, and aging on the brain. Participation in this study will be limited to MACS volunteers (HIV-positive and negative) 50 years and older who are also enrolled in the Cardiovascular Study and the Neuropsychological Study. Participants in the study will have a magnetic resonance (MRI) scan of their brain and will be asked to complete some additional neuropsychological tests that are similar to the testing already conducted as part of the MACS Neuropsychological Study. We will look for changes in brain structure as it may be related to aging, use of HAART, and performance on cognitive tests. Additional information about this study will be circulated to eligible participants.

Even though many HIV-infected individuals never show any serious signs of cognitive problems, our studies have established that subtle signs of cognitive deterioration can begin appearing as long as two years before an individual meets clinical diagnostic criteria for HIV dementia. It is important, therefore, to monitor changes in brain functioning so that medication regimens can be re-evaluated as soon as there is evidence of some sort of decline in normal thought processes. The Neuropsychological study will continue to ask all participants in the MACS to complete the Trail-Making and Symbol Digit tests at every visit so that we can pick up subtle changes in psychomotor slowing that may indicate early signs of more serious cognitive problems. In addition, we will be asking all participants to

complete our 45-minute set of neuropsychological tasks at least every two years so that we can keep track of any changes that may occur in other areas of functioning such as memory, fine motor skills, and abstract reasoning. Participants who have difficulty with the neuropsychological tests may be asked to complete the testing more often.

Thanks to you, for more than two decades the MACS has proved to be a unique and invaluable resource for neurological and neuropsychological studies. These ongoing longitudinal studies have allowed the MACS to make significant contributions in a broad range of studies of nervous system functioning. With your support, we anticipate that the MACS will continue to be a leader in studying the effects of HIV on the nervous system, so that ultimately we can reduce these effects.

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HIV, Heart Disease
(from pg 4)

the arteries supplying the heart; the other is an **ultrasound** test to detect thickening of the carotid arteries, which supply blood to the brain.

Since we already follow all participants for major disease outcomes, we will be able to study the relationships among HIV disease, anti-HIV treatments, and the imaging tests and blood chemistry tests like cholesterol, triglycerides, inflammatory markers, blood glucose, and insulin levels. We don't expect very many people will be unlucky enough to have disease outcomes, but we will be able to watch intermediate outcomes, like changes in the imaging tests and changes in glucose and insulin levels. These studies will help reduce the likelihood that people treated over long periods of time for HIV/AIDS will develop diabetes and heart disease prematurely.

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Notes

Ayunas y extracciones de sangre

Probablemente le hayan recordado presentarse en ayunas, si fuera posible, para las extracciones de sangre en MACS. Para el estudio, esto significa no comer ni beber nada excepto agua, café sencillo, té sencillo, o una bebida de dieta de 1 caloría por un período de 8 a 16 horas antes de la extracción de sangre. Algunas de las pruebas que se practican para el estudio sólo pueden practicarse en sangre bajo ayunas. Estas pruebas incluyen triglicéridos, glucosa del plasma, y niveles de insulina.

Durante la ayuna es importante que mantenga una hidratación adecuada. Recuerde que estar en ayunas no significa restricción de toma de agua; por lo tanto, beba suficiente agua durante las horas antes de su visita. Además de que esto le es beneficioso, existen las ventajas de estar debidamente hidratado al presentarse a la clínica: la extracción de sangre con toda probabilidad será más fácil, al igual que la obtención de la muestra de orina.

Peripatetic Participants

If we haven't seen you in awhile because this newsletter has found you somewhere outside of the LA Metro area, please consider participating in one of the following cities where there are alternative MACS clinics: San Francisco, San Diego, Palm Springs, Baltimore, Chicago, and Pittsburgh. If you would like more information about participating at a clinic in any of these cities, please call the MACS clinic where you enrolled in the study. The contacts and their telephone numbers are on the front page.

Participantes Peripatéticos

Si no lo hemos visto por algún tiempo porque este boletín lo ha encontrado en un sitio fuera de la zona metropolitana de Los Angeles, por favor considere participar en una de las siguientes ciudades que cuentan con clínicas alternativas MACS: San Francisco, San Diego, Palm Springs, Baltimore, Chicago y Pittsburgh. Si desea más información sobre cómo participar en la clínica de una de estas ciudades, favor de llamar a la clínica MACS donde se inscribió en el estudio. Los contactos y números de teléfono se encuentran en la primera página.

The Importance of the Medical Records Review

Why does the MACS review medical records after being told about an illness?

For the MACS, diagnoses have three levels of reliability – from highest to lowest: 1) **Definite**, based on complete records of appropriate testing and well documented clinical observation; 2) **Presumptive**, based on documented clinical observation, but supported by incomplete records or less than definitive testing; and 3) **Probable**, based only on limited clinical observations or testing. As you can see, a self-report of illness has no bearing on the reliability rating.

For whatever reason, many of us typically do not remember exactly or entirely what we are told by our doctors. So,

Medical Records Review, pg 15

Medical Records Review (from page 14)

when the study is fortunate enough to receive medical records about a self-reported illness, the diagnosis is not always confirmed by the medical records.

Misinformation is worse than missing information; so, if a reasonable level of certainty about a diagnosis is not possible, that diagnosis can't be used in analyses. The ability of researchers to form valid conclusions is improved by omitting misinformation and minimizing missing information. This is why medical records reviews are so important to the research.

Unfortunately, it can be difficult for the study to acquire the medical records necessary to rank reported diagnoses as definitive, or even presumptive. In many cases, the only way we will be able to acquire sufficient medical records will be with your help.

"*How can I help?*" you ask. Your help begins with providing the full name, address, and telephone number of each health care provider (HCP) that diagnosed and/or treated you (since your last study visit). Your HCP could be an individual physician, a medical practice, clinic or hospital. If you have business cards, letterhead with contact information, or a list you prepared of your HCPs, please bring them with you to your study visit.

Most HCPs are responsive to our requests, some are not. In case your HCP is not responsive, your participation would be most helpful. Some of you already have copies of your medical records that document the illness(es) you will be telling us about. It would be helpful to bring them with you when you come in for your study visit. As a last resort, we might ask you to request relevant medical records from your HCP on behalf of the study. In that case, you would be reimbursed for your costs. Working together, we can minimize missing clinical information, and, at the same time, strengthen the study.

Importancia del repaso de los registros médicos

¿Por qué es necesario que MACS repase los registros médicos después de que se les informe de una enfermedad?

Para MACS, las diagnosis cuentan con tres niveles de confiabilidad – del más alto al más bajo: 1) **Definitivo**, basado en registros completos de pruebas correspondientes y observación clínica debidamente documentada; 2) **Presunto**, basado en observación clínica documentada aunque respaldada por registros incompletos o pruebas no del todo definitivas; 3) **Probable**, basado únicamente en observaciones o pruebas clínicas limitadas. Como podrá ver, un autoreporte de enfermedad no podría integrarse en las clasificaciones de confiabilidad.

Por alguna razón muchos de nosotros típicamente no recordamos exactamente o completamente lo que nos informan los doctores; por lo tanto, cuando el estudio tiene la suerte de recibir los registros médicos de una enfermedad autoreportada, la diagnosis no es siempre reconfirmada por los registros médicos.

La desinformación es peor que la falta de información; por lo tanto, si no es posible establecer un nivel razonable de certeza referente a una diagnosis, dicha diagnosis no puede usarse para análisis. La capacidad del investigador de poder lograr una conclusión válida mejora al poder descartar desinformación y minimizar la falta de información. Es por esto que un repaso de los registros médicos es tan importante a la investigación.

Lamentablemente, al estudio le podría ser difícil poder adquirir los registros médicos necesarios para clasificar una diagnosis reportada ser definitiva o hasta presunta. En muchos casos la única manera que nos es posible adquirir suficiente información procedente de registros médicos es con su ayuda.

"¿Cómo puedo ayudar?" podría preguntar usted. Su ayuda comienza al proporcionarnos el nombre completo, dirección y número de teléfono de cada proveedor de atención de salud (HCP, por sus siglas en inglés) que lo haya diagnosticado y/o tratado (desde su última visita de estudio). Su HCP podría ser un médico individual, una práctica médica, clínica u hospital. Si usted tiene tarjetas de negocio, membrete con información de contacto, o una lista que usted haya preparado de sus HCPs, favor de traerlos con usted a su próxima visita de estudio.

La mayoría de HCPs contestan nuestras solicitudes, aunque otros no. En caso de que su HCP no conteste una solicitud, la participación suya seria de gran utilidad. Algunos de ustedes cuentan con copias de registros médicos que documentan la(s) enfermedad(es) que nos han indicado. Nos seria útil si los trajera con usted cuando se presente para su visita de estudio. Como último recurso podríamos pedirle que le solicitara los registros médicos pertinentes a su HCP de parte del estudio; en dicho caso, le reembolsaríamos los costos. Si colaboramos podemos minimizar la falta de información clínica y a la misma vez fortalecer el estudio.

Follow-up Status of the LA MACS Cohort

The following tables show the level of follow-up for the original LAMS cohort of 1637 men, enrolled between 1984 and 1985.

PARTICIPANTS WITH KNOWN VITAL STATUS or CONTACT SINCE 01/01/2006

HIV Status	Visit	Contact w/o Visit	Deceased AIDS	Deceased Non-AIDS	Total
Negative	317	27	0	34	378
Positive	212	8	614	46	880
Total	529	35	614	80	1258

PARTICIPANTS WITH UNKNOWN VITAL STATUS

HIV Status	Refused	No Response	Total
Negative	52	234	286
Positive	34	60	94
Total	86	294	380

826 of the participants that entered the study in 1984-85 were HIV seronegative. Since then, 164 (20%) of these men have been infected with HIV. The last seroconversion (change from negative to positive antibody test) occurred in August 2005, and two occurred that year. 89 (54%) of the 164 men have been diagnosed with AIDS; and of the 89 men, 24 (27%) are living with AIDS.

Of the 974 HIV seropositive men (those who entered the study HIV seropositive and seroconverters), 691 have been diagnosed with AIDS (71%). 78 (11%) of the men are living with AIDS.

The following tables show the level of follow-up for the cohort of men enrolled between 2001 and 2003.

PARTICIPANTS WITH KNOWN VITAL STATUS or CONTACT SINCE 01/01/2006

HIV Status	Visit	Contact w/o Visit	Deceased AIDS	Deceased Non-AIDS	Total
Negative	100	7	0	0	107
Positive	158	10	2	7	177
Total	258	17	2	7	284

PARTICIPANTS WITH UNKNOWN VITAL STATUS

HIV Status	Refused	No Response	Total
Negative	0	41	41
Positive	4	41	45
Total	4	82	86

370 men enrolled and completed a baseline (first) visit. 311 of the 370 participants have contributed at least one additional, follow up visit. 154 of the participants that entered the study in 2001- 03 were HIV seronegative. Since then, six (3.9%) of these men have been infected with HIV. The last seroconversion occurred in October 2006, and three occurred that year. None of these six men have been diagnosed with AIDS.

Of the 222 HIV seropositive men (those who entered the study HIV seropositive and seroconverters), five have been diagnosed with AIDS (2.3%). Three of the men are living with AIDS.