MACS/LAMS
Newsletter
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Harbor-UCLA · LAGLC · UCLA Wilshire

FROM THE PRINCIPAL INVESTIGATOR

Roger Detels, M.D., M.S.
UNIVERSITY OF CALIFORNIA LOS ANGELES

It is with great sadness that we report the death of Dennis Miles. Dennis was with the study from the very beginning and embodied the spirit and soul of the Los Angeles MACS. His positive attitude and genuine concern for the men of the MACS and his fellow staff infused the spirit of our center and was key to our success. We will deeply miss Dennis' wit and fellowship but are grateful for all that he has given us. He has made a major contribution to the success of the MACS and to confronting the worst epidemic of the 20th century.

In this issue we report a few of the exciting recent advances that we have made thanks to your continuing commitment and loyalty to the MACS. Many of you have been with us for over 30 years and are now entering into the age when many chronic diseases including heart disease are more likely to occur. In this newsletter we present the results of studies that have looked at the issue of aging with HIV. We have discovered that aging appears to be more rapid in individuals who are HIV-infected. Learning about the factors that contribute to premature aging and increased risk of chronic diseases will help us to find ways to halt this premature aging.

One of the intriguing aspects of the HIV epidemic is that some individuals appear to be resistant to infection by HIV. We have learned that some of these individuals lack the receptor that HIV uses to attach to CD4+ cells. However, there are very few of these individuals and the majority of "resistant" individuals have other mechanisms for avoiding becoming infected. In this newsletter we report exciting work that suggests another mechanism by which these individuals are protected. Helping to understand the mechanisms of resistance will help to identify ways in which we may confer resistance to individuals who do not have this "natural" resistance.

One of the most disturbing aspects of HIV infection is that long-term infection can be associated with cognitive loss. We report on some of these factors that are associated with decline in cognitive function. Fortunately, we have the ability to address some of the factors described in this report and thus, presumably, to slow the cognitive decline associated with these factors.

One of the diseases that appears to occur more frequently among men who have sex with men and who are HIV-infected is anal cancer. Our studies have revealed that HIV infected men are more likely to harbor human papilloma virus (HPV) strains associated with malignancies in their anal canal. Fortunately our studies reveal that men who take HAART consistently are less likely to harbor these malignant HPV strains.

Finally we report that physical exercise, which has been shown to promote good health in uninfected individuals, also benefits HIV-infected men, particularly in terms of retaining their cognitive ability.

As we commence our 4th decade of follow-up, it is particularly important that we continue to make important observations regarding the impact of aging on cognitive, physical and biologic/immunologic function in uninfected gay men as well as in HIV-infected men. You, the men of the MACS, have been extraordinary in your loyalty. We hope that you will continue to do so as we explore the impact of HIV on aging and the aging process itself. We cannot do it without you!!!

ARTICLES

Studies on Aging

Investigating the Dual Impact of Aging and HIV-1 Infection on the Immune System

Tammy Rickabaugh, PhD
UNIVERSITY OF CALIFORNIA LOS ANGELES

We can't thank you enough for all you have done. Your participation in the MACS and in the subsequent research studies conducted over the years has helped us all make strides in the fight against HIV/AIDS. We especially want to thank all those who have participated in the research studies conducted by Dr. Beth Jamieson and her lab. Your participation has made it possible for us to conduct studies to investigate the effects of age on HIV/AIDS disease progression. We currently have a grant to investigate how advancing age and HIV-1 infection work together to destroy the CD4+ T-cell compartment. Our prior publication in February of 2011 in PLoS ONE showed that in many ways, both HIV and age have similar effects on this important T-cell compartment. Therefore, when someone over the age of fifty becomes infected, the dual impact of age and HIV infection quickly limits the ability of their CD4+ T-cell compartment to respond, not only to HIV, but to other infections as well. Our results may help explain why individuals who become infected after the age of 50 years are more likely to progress to AIDS than someone in their 20's or 30's.

In addition, the aim of our research is to develop an in depth understanding of the immune system and the development of better drug therapies that not only help suppress the progression to AIDS, but also help all of us respond better to vaccines and infectious diseases during the normal course of aging. One area in which we are expanding this research is examining epigenetic changes in gene expression, caused by HIV and ART on the immune system and how they are associated with aging-related conditions and clinical manifestations seen in HIV-infected people. An epigenetic change to DNA is not a mutation, but it changes which proteins are made and the amount of those proteins. We are in the process of submitting a manuscript on this work. We are particularly interested in understanding how age impacts the ability of HAART to restore both T-cell numbers and clinical health. We are submitting a manuscript that indicates that HAART treatment cannot fully restore the CD4+ T-cells that are necessary for maintaining the ability to fight new infections as we age. These studies will hopefully lead to better treatments and a better quality of life for people living long-term with HIV/AIDS.

Words cannot express how much we appreciate your commitment and altruism for future generations; without your help, and the help of those that we have lost, none of these advances could have been possible.

Studies on Brain Functioning

Effective antiretroviral treatments continue to keep rates of neurologic disease at very low levels in the MACS. Currently, HIV-positive participants are only 14% more likely to show signs of cognitive problems as compared with HIV-negative participants. There are a number of factors, however, that modify risk for HIV-associated neurocognitive disorders. During the past year the MACS has looked specifically at ways in which lung function and physical activity impact cognitive functioning. We also looked at changes in the frequency of HIV-associated neurocognitive disorders over the period from 2007-2012.

Lung Function and Brain Structure in HIV

Alison Morris, MD, MS
UNIVERSITY OF PITTSBURGH

Both cognitive impairment and chronic obstructive pulmonary disease are non-AIDS-associated co-morbidities that are increased in HIV-infected individuals. The purpose of our study was to determine the relationships among lung function, brain structure, and cognitive function and to determine whether these relationships are altered in HIV infection. 65 men participating in the Multicenter AIDS Cohort Study (55% HIV infected) underwent measurement of lung function, brain magnetic resonance imaging, and neuropsychological functioning. We found significant

associations between diffusion lung capacity and grey matter in the brain. Lower diffusing capacity was associated with worse cognitive functioning. There was no significant change in risk as a function of whether or not the participants were HIV-infected.

[Morris A, Kingsley L, Gingo M, Fitzpatrick M, Detels R, Martinez-Maza O, Miller E, Alger JR, Kleerup E, Becker JT. *Smoking and abnormal lung function alter brain structure and function in HIV*. To be presented at the Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 2015.]

The Impact of Physical Activity on Cognition in HIV

Anne Monroe, MD
JOHNS HOPKINS UNIVERSITY

Several studies have shown the frequent benefit of aerobic exercise in reducing CNS inflammation, Alzheimer-type pathology and cerebrovascular disease, the main mechanisms by which patients are thought to develop HIV-associated Neurocognitive Disorders (HAND). Aerobic exercise intervention studies have frequently shown benefit in cognitive measures in HIV-uninfected populations, however, the data in HIV-infected populations are sparse. Our objective with this study was to determine the association between physical activity and cognitive function in an HIV-infected population. The International Physical Activity Questionnaire was administered to 622 men (44% HIV-infected). Metabolic Equivalents (METs) were calculated by summing the MET-minutes per week for walking, moderate and vigorous intensity activity. Assessment of psychomotor and executive functioning was performed at a baseline visit and at up to eight subsequent MACS visits. The high physical activity category was associated with better cognitive test scores compared with low activity among all men and was associated with better psychomotor test scores when HIV-infected men were examined separately. Results suggest that physical activity may have protective effects against HIV-associated neurocognitive disorders.

[Monroe A, Zhang L, Jacobson L, Plankey M, Brown T, Munro C, Miller E, Martin E, Becker J, Li Y, Sacktor N. *The impact of physical activity on cognition in men with and without HIV*. To be presented at the Conference on Retroviruses and Opportunistic Infections, Seattle, WA, February 2015.]

Frequency of HIV-Associated Neurocognitive Disorders over Four Years of Follow-up

Ned Sacktor, MD
JOHNS HOPKINS UNIVERSITY

Prior to the introduction of combination antiretroviral therapy (cART) in 1996, HIV-associated neurocognitive disorders were both common and seriously debilitating with a predictable pattern of progressive cognitive decline. The current study examined cognitive functioning in 197 HIV+ individuals in the MACS who were receiving current standard-of-care cART therapy. All participants had completed neuropsychological testing on at least three occasions between 2007 and 2012. The overall frequency of HIV-associated neurocognitive disorders (HAND) during the 2007-2008, 2009-2010, and 2011-2012 periods were 25%, 25%, and 31% respectively. The overall frequency of HAND increased slightly over this four year period due to an increase in the frequency of asymptomatic (detectable only on neuropsychological tests) impairment from 12% in 2007-2008, and 8% in 2009-2010, to 19% in 2011-2012. Frequencies of mild neurocognitive disorder (10-15% in the three time periods) and dementia (2-3% in the three time periods) were unchanged. Between the first and last time periods, 77% of the HIV+ individuals remained at their same HAND stage, with 13% showing deterioration in HAND stage and 10% showing an improvement in HAND stage. HAND is still common in HIV+ individuals in the cART era. However, for the majority of HIV+ individuals on cART with systemic virological suppression, the diagnosis of HAND is not a progressive clinical condition over four years of follow-up.

[Sacktor N, Reynolds S, Skolasky R, Munro C, Becker J, Martin E, Ragin A, Levine A, Miller E. *Frequency of HIV-associated neurological disorders over four years of follow-up: results from the Multicenter AIDS Cohort Study*. To be presented at American Academy of Neurology, Washington, DC, April 2015]

For more information on any of the above brain functioning studies, contact Eric Miller, Ph.D., at: emiller@ucla.edu

Transcriptome (RNA) Analysis of HIV-infected Peripheral Blood Monocytes

Andrew Levine, PhD
UNIVERSITY OF CALIFORNIA, LOS ANGELES

Immunologic dysfunction mediated by monocyte activity has been implicated in the development of HIV-associated neurocognitive disorders (HAND). We hypothesized that changes in peripheral blood monocytes (a type of white blood cell) might relate to neurocognitive functioning in HIV+ individuals, and that such alterations could be useful as biomarkers of worsening HAND. RNA was isolated from the monocytes of 86 HIV+ adults. Neurocognitive functioning was correlated with multiple gene transcripts, most notably those involved in neurologic dysfunction and oxidative stress. While the associations were not strong enough to justify their use as biomarkers of HAND, they provided potential for prevention and treatment of HAND, targeting a specific anti-oxidant pathway.

Between October 2013 and March 2014, several of the original blood donors returned and gave another sample. In addition new participants were recruited including HIV- individuals. We are currently analyzing those data to determine if gene expression at baseline is able to predict neurocognitive change two years later.

[Levine, A.J., Horvath, S., Miller, E.N., Singer, E.J., Shapshak, P., Baldwin, G.C., Martinez-Maza, O., Witt, M.D., & Langfelder, P. (2013). *Transcriptome analysis of HIV-infected peripheral blood monocytes: gene transcripts and networks associated with neurocognitive functioning*. Journal of Neuroimmunology. 265, 96–105.]

For more information contact Andrew Levine at:
AJLevine@mednet.ucla.edu

Studies on Human Papillomavirus (HPV) Infection

HPV Infection and Anal Cancer Screening

Dorothy Wiley, PhD, MSN, RN
UNIVERSITY OF CALIFORNIA, LOS ANGELES

We thank the MACS participants for their dedication and contribution to better understanding oral and anal HPV infection and the value of anal cancer screening. One of our studies, the Persistence of Oral Papillomavirus Study (POPS), has been analyzing mouthwash samples for HPV for the past two years. So far, we've found that nearly 28% of the men enrolled in the study have tested positive for new HPV infections. However, after 12 months, 83% of the men with the new HPV infections tested negative, having cleared their infections. And, nearly 51% of the men whose first mouthwash sample tested positive for HPV, also tested negative after 12 months. HIV-infected (HIV+) men were twice as likely to acquire new HPV infections as HIV-uninfected (HIV-) men, and those with fewer than 200 CD4+ T cells/mm^3 were 6-times more likely to test positive for HPV. These results suggest we can detect HPVs in the mouth often but that these HPVs are cleared quickly, on average.

Additionally, findings from the MACS Anal Health Study (AHS) were recently published. This study reported that anal infections with the types of HPV that are most often associated with anal cancer (high-risk HPV) occur at a higher rate in older, HIV+ men than in older, HIV- men. Important to HIV+ men, the analysis showed tangible benefits of adherence to HIV-treatment: men who reported complete adherence to their HAART regimen had a significantly lower risk of infection with high-risk HPVs.

And finally, our recently reported findings on anal swab sample collection suggest that the efficacy of the anal Pap test could be improved simply by using a nylon-flocked swab, instead of the standard Dacron swab. More specifically, in men with biopsy-confirmed, high-grade (higher-risk) anal pre-cancers, Pap testing samples collected with a nylon-flocked swab were found to be about 29% more likely to reveal cellular abnormalities than Pap testing samples collected with a Dacron swab (81% with the nylon-flocked swab, 52% with the Dacron swab).

There are ongoing debates on the value of anal cancer screening, and on when high resolution anoscopy should be done as a follow up to an abnormal Pap test. What you are contributing to these studies is helping to answer that important question. We are grateful for all that you have contributed and

for the effort that it takes for you to participate in the MACS.

[Wiley DJ, Li X, Hsu H, Seaberg EC, Cranston RD, et al. (2013) *Factors Affecting the Prevalence of Strongly and Weakly Carcinogenic and Lower-Risk Human Papillomaviruses in Anal Specimens in a Cohort of Men Who Have Sex with Men (MSM)*. PLoS ONE 8(11): e79492.]

MACS participants interested in additional studies comparing the Pap test to other types of viral tests may contact Dr. Wiley's team via telephone or email at:
(310) 825-0540 or hrastudy@sonnet.ucla.edu

Study on Cardiovascular Health

Update on the MACS Heart Health Substudy

Carlos Aquino, MACS Coordinator
LA BIOMEDICAL RESEARCH INSTITUTE AT HARBOR-UCLA MEDICAL CENTER

During the past few years, many of you participated in the MACS Heart Health Substudy at the LA BioMedical Research Institute at Harbor-UCLA Medical Center in Torrance, CA. Specifically, 261 participants enrolled in the study at our MACS site and 1001 men enrolled across all the MACS sites (Chicago, Pittsburgh, Baltimore/Washington DC, and Los Angeles). The goal of the Heart Health Substudy led by Dr. Wendy Post, with help from the MACS Cardiovascular Working Group (including local investigator, Mallory Witt, MD), was to clarify whether an association exists between HIV disease and atherosclerosis. Atherosclerosis, or hardening of the arteries, is a chronic disease in which fat, cholesterol, and other substances build up in the walls of the arteries and form hard structures called "plaque". Previous studies have shown some association between HIV and atherosclerosis, but have reached inconsistent conclusions.

The Heart Health Study asked participants to attend two visits. The first involved performing a Computed Tomography (CT) scan of the heart, with or without contrast dye, to look for blockages and plaque. While the second study involved performing a carotid ultrasound on the right side of the neck to look for narrowing of the carotid artery.

After detailed analysis, the results were published in the Annals of Internal Medicine journal in April 2014. Researchers found that "noncalcified [soft] coronary artery plaque was more prevalent and extensive in HIV-infected men, suggesting increased risk for cardiovascular events;" such as heart attacks and strokes. Additionally, it was found that those with advanced HIV infection, identified as those with a lower T-cell count and a greater number of years receiving anti-retroviral treatment, have a higher risk of coronary artery blockage.

The importance of these findings was highlighted by the National Institutes of Health in a March 2014 press release. "[The] findings from the largest study of its kind tell us that men with HIV infection are at increased risk for the development of coronary artery disease and should discuss with a care provider the potential need for cardiovascular risk factor screening and appropriate risk reduction strategies," stated Gary H. Gibbons, MD, director of the National Heart, Lung, and Blood Institute (NHLBI), part of NIH.

However, continued research is still needed to better understand the relationship between HIV and heart disease. Additional studies may help determine whether noncalcified, soft plaques build up at a slower rates in HIV-infected men or whether it is the incidence of new noncalcified plaques that increases. Investigators would also like to explore associations of coronary atherosclerosis with specific antiretroviral therapy regimens and measures of inflammation and immune activation. The MACS Cardiovascular Working Group is in the process of developing further studies to address these issues.

Copies of the article and press release will be available at your respective MACS center or online at:
http://annals.org/article.aspx?articleid=1852867
and
http://www.nih.gov/news/health/mar2014/niaid-31.htm

Study on Immunology of HIV Transmission

Exploring Why Some People Seem Resistant to Becoming HIV Infected

Otto Yang, MD
UNIVERSITY OF CALIFORNIA, LOS ANGELES
AIDS INSTITUTE

Why some people have remained uninfected despite dozens or hundreds of exposures to HIV remains a key mystery. Researchers at UCLA have started studies on MACS participants who were highly sexually exposed in the mid-1980s when HIV was rampant in the gay community, yet never became infected. Exciting, preliminary work suggests that the immune cells in their rectal tissue appear to be different from those of men in general. Their cells seem to produce less "cytokines" (immune messenger molecules) that cause immune activation. Because HIV infects activated (not resting) CD4 T cells, it may be that this difference contributes to making individuals less susceptible to infection, because they have fewer activated CD4 T cells in their rectal tissues. These exciting results need to be confirmed and expanded, so more volunteers who were highly exposed but uninfected in the 1980s are needed.

To find out more about this study, please contact Dr. Yang by email at: oyang@mednet.ucla.edu

ANNOUNCEMENTS

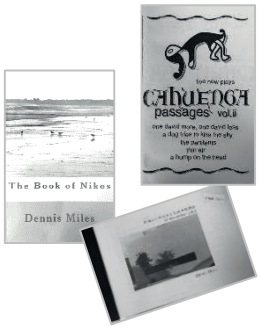
· The National Institute of Allergy and Infectious Diseases (NIAID), with co-funding from the National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), and National Institute of Mental Health (NIMH), have renewed their support of the MACS through March 2019.

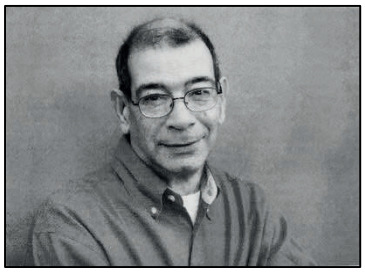
·New Wilshire Clinic email address available for general contact purposes: lams@ph.ucla.edu

Cuban-American playwright and author Dennis Miles was
Born in Santiago de Cuba on November 28, 1952.
He passed away in Los Angeles on August 10, 2014 surrounded
by his loving sister and friends. At age fourteen he was sent by his parents to live in Spain,
from there he went on to Chicago and lived with relatives until his parents and sister
arrived in the USA. He graduated from Mount St. Mary's College,
served in the Army during Vietnam, and was the Site Manager at the LAMS for over 30 years.

It is in his honor that we dedicate this edition of our newsletter –
to "the heart and soul of the LAMS":

Mr. Dennis Miles





Your smile and wit will be missed.

For additional information related to MACS history, publications, contributions, etc.
Please visit the MACS website at:
http://www.statepi.jhsph.edu/macs/macs.html