Welcome to the July 2019 ACTG Newsletter

In Remembrance

The ACTG is deeply saddened to have lost two invaluable colleagues this month:

Kevin Robertson, PhD, Professor of Neurology and the director of the AIDS Neurological Center at the University of North Carolina (UNC), Chapel Hill, was a dedicated investigator and passionate mentor in the ACTG, past chair of the Neurology Collaborative Science Group, and protocol team chair and member for several important studies. Kevin led global research initiatives in neurological complications of HIV and trained clinicians and researchers all over the world to establish research capacity in neuropsychological testing in Uganda, South Africa, Malawi, Nigeria, India, Thailand, Peru, and Zimbabwe. He was passionate about studying the relationships among HIV cognitive disorders, ART and inflammation, and HIV persistence in the CNS. Most recently, he was the co-first author on “Persistent HIV-infected cells in cerebrospinal fluid are associated with poorer neurocognitive performance,” a *Journal of Clinical Investigation* paper highlighted below. We will miss Kevin’s brilliant mind and sharp wit, his thoughtfulness, respect for colleagues, and enduring commitment to mentoring young investigators around the world.

Dr. Charles (Charlie) van der Horst led the University of North Carolina (UNC) ACTG site until 2002 and served in multiple leadership roles in the network until his retirement in 2014. Charlie was a dedicated clinician and activist investigator who made important contributions to studies to improve treatment and prevention for opportunistic infections, most notably cryptococcal meningitis and PCP. He was committed to the expansion of ART to underserved populations from rural North Carolina to southern Africa. He led one of the largest single-center studies of prevention of vertical transmission (in Malawi), and he and his trainees improved treatments for cryptococcal infection around the globe. Charlie was a driving force in the efforts to establish an international component of the ACTG network in 2000. Charlie will be remembered for his compassion and commitment and for his unrelenting desire to make the world a better place for all.

ACTG Annual Network Meeting

The ACTG annual meeting took place June 17-21 in Arlington, VA and drew more than 850 attendees. Highlights included robust discussions about the ACTG research agenda among international investigators, a workshop

introducing new investigators to the ACTG, and plenary sessions providing a sneak preview of new ACTG data that will be presented at the 10th IAS Conference on HIV Science, taking place in Mexico City in July. We are also excited to announce the winners of the three ACTG excellence awards this year:

- **Constance B. Wofsy Women's Health Award:** Kimberly Scarsi, PharmD, Northwestern University CRS, University of Nebraska Medical Center
- **John Carey Young Investigator Award:** Trevor Crowell, MD, Kenya Medical Research Institute/Walter Reed Project Clinical Research Center (KEMRI/WRP) CRS
- **Donna Davis Community Award:** Catherine Godfrey, MD, PEPFAR/Office of the Global AIDS Coordinator Department of State

Thank you to all who were able to attend for making it such a productive meeting and congratulations to our honorees!

Awardees shown clockwise from top left: Kimberly Scarsi, Trevor Crowell, and Catherine Godfrey)

MINMON Study Fully Enrolled

In November 2018, the ACTG launched enrollment for A5360: A Single-arm Study to Evaluate the Feasibility and Efficacy of a Minimal Monitoring Strategy to Deliver Pan-genotypic Ribavirin-free HCV Therapy to HCV Infected Populations who are HCV Treatment Naïve with Evidence of Active HCV Infection or The MINMON Study. Globally, nearly 71 million people have chronic HCV, of whom an estimated 4-5 million also have HIV. In this context, there is an urgent need for advances in treatment delivery. In some parts of the world, the healthcare system itself - through requiring frequent visits and laboratory monitoring during HCV treatment - can lead to barriers to HCV treatment with the new easy-to-take once a day treatments for HCV cure. The basic premise of the study is to eradicate all of these healthcare system barriers. In A5360, patients (n=400) will be provided HCV treatment with sofosbuvir/velpatasvir (Epclusa) for 12 weeks without any traditional laboratory or clinical monitoring or planned visits.

We would like to announce now that MINMON is fully enrolled! Enrolling sites are in Africa, Brazil, India, Thailand, and the United States. Following HCV treatment, participants will be followed for an additional 72 weeks to assess the long-term outcomes related to HCV and liver disease, including the incidence of HCV reinfection. Study investigators hypothesize that this “minimal monitoring” for HCV treatment outcomes will result in more cost-efficient and effective

paradigms in HCV treatment management, expanding the number of people who can achieve HCV cure worldwide.

Publications

PERSISTENCE OF HIV DNA IN CEREBROSPINAL FLUID AND NEUROLOGICAL IMPLICATIONS

The persistence of HIV in sanctuary sites in the human body even in the presence of antiretroviral therapy (ART) is a potential barrier to HIV remission and cure. The central nervous system is one of those sanctuary sites and it has unique properties, in terms of cell composition and antiretroviral penetration. Because neurocognitive function can be compromised even in individuals whose HIV is well treated, it is important to understand HIV persistence in the nervous system. In the ACTG HIV Reservoirs Cohort Study (A5321), virally suppressed individuals with HIV taking long-term ART were tested for persistent HIV in their cerebrospinal fluid.

The study included 69 participants with well-treated HIV who had their cerebrospinal fluid and blood collected and underwent neurocognitive assessments, which included tests of memory, learning, motor function, and more. Participants were mostly male (97%) and had been on HIV treatment for a long time (median almost 9 years), with a good response to medications (HIV viral loads all <100, and median CD4 count in the normal range). The team examined genetic material of HIV in the cells from the cerebrospinal fluid, as well as from the portion of the fluid without cells. The study revealed that HIV DNA was detected in almost half of participants and was associated with poorer neurological and cognitive function. This persisted even after adjusting for participants' age and the severity of immune suppression they had experienced in the past.

The association between HIV genetic material in cerebrospinal fluid with poorer performance on cognitive tests suggests that there may be a link between HIV persistence in the brain compartment and the neurological complications that some people living with HIV experience. Further studies will help determine

strategies to reverse this persistence and improve neurological functioning in patients with long-standing HIV.

A5321

Spudich S*, Robertson K*, Bosch R, Gandhi RT, Cyktor J, Mar H, Macatangay B, Lalama C, Rinaldo C, Collier A, Godfrey C, Eron J, McMahon D, Jacobs J, Koontz D, Hogg E, Vecchio A, Mellors J. Persistent HIV-infected cells in cerebrospinal fluid are associated with poorer neurocognitive performance. Journal of Clinical Investigation 2019, in press.
*Authors contributed equally

DO ELITE CONTROLLERS REQUIRE ART FOR SECONDARY BENEFITS?

There is an ongoing debate in the literature about whether elite controllers require antiretroviral therapy (ART) for secondary benefits, including control for low-level viral replication and reduction of inflammation. ACTG A5308 attempted to resolve this debate by looking at the effect of ART on virologic suppression, the viral reservoir, immune activation, and quality of life in a group of elite controllers enrolled in the ACTG.

A5308 study was a prospective, open-label study of rilpivirine, emtricitabine and tenofovir disoproxil fumarate provided to ART-naïve HIV controllers (n=35) defined as having HIV RNA levels of <500 copies/mL off of therapy. The study found that ART was effective in increasing the proportion of individuals with undetectable residual viremia and decreasing the proportion of CD38+HLA-DR+CD8+ T cells (a marker of immune activation). Researchers also identified a modest but statistically significant improvement in self-reported quality of life. A5308 resolves the question around the value of ART for elite controllers, by demonstrating the clinical benefits of ART in this population.

A5308

Li J, Segal FP, Bosch RJ, Lalama CM, Roberts-Toler C, Delagreverie H, Getz R, Garcia-Broncano P, Kinslow J, Tressler R, Van Dam CN, Keefer M, Carrington M,9, Lichterfeld M, Kuritzkes D, Yu XG, Landay 5, Sax PE; ART reduces T cell activation and immune exhaustion markers in HIV controllers. Clin Infect Dis. 2019 May 25. [Epub ahead of print]

Investigator Highlight:

Rajesh Gandhi, MD, Harvard Medical School, Massachusetts General Hospital

Rajesh Gandhi, MD is Professor of Medicine at Harvard Medical School and leader of the Massachusetts General Hospital ACTG Clinical Research Site in the Harvard/Boston/Providence Clinical Trials Unit. He has been involved with the ACTG for almost 20 years. Dr. Gandhi has led or been involved with multiple ACTG trials evaluating the impact of interventions on the HIV reservoir, including the effect on the latent reservoir of initiating intensive therapy in treatment-naïve participants, antiretroviral intensification, latency reversal with an HDAC inhibitor, and modulation of latency reversal with estrogen blockade in women with HIV. Given the need to answer critical questions regarding HIV persistence to inform the development of novel interventions aimed at curing HIV, Dr. Gandhi serves as protocol co-chair of ACTG A5321, a longitudinal cohort study examining a number of immunologic, pharmacologic, and virologic contributors to HIV reservoirs among participants on long-term ART. Dr. Gandhi is a former chair of the HIV-1 Reservoirs and Eradication Transformative Science Group, or Cure TSG, and is now on the ACTG Executive Committee. In addition to his work on HIV reservoirs, Dr. Gandhi has been involved in ACTG studies of therapeutic vaccines, interventions designed to decrease immune activation, and optimal treatment of people with drug-resistant HIV.

The ACTG values Dr. Rajesh Gandhi's team-based and mission-based approach to clinical research, which exemplifies the general ethos of the ACTG. Dr. Gandhi looks forward to many more years of productive interactions in the ACTG as it continues to advance our knowledge in improving the lives of people with HIV.

CAB Member Highlight:

Morenike Giwa Onaiwu, Houston, TX

Morenike Giwa Onaiwu approaches her role as a CAB member through a social justice lens. Since joining the CAB 10 years ago, she has worked to address the issues of particular concern to her local community of Houston, TX, including the role that stigma plays in limiting testing. "We need to have more acceptance, we need to have better policies, we need to have better treatments, we need to eradicate stigma because stigma kills," she says.

Morenike argues that HIV research needs to better address the multitude of the factors that result in disparities and suboptimal outcomes among people with multiple marginalizations - especially related to the intersections of various identities, including gender, race, age, ability, and mental health. "We've made progress in this area, but there is still a great need," she notes.

Morenike hopes that she has demonstrated that there's a place in HIV advocacy for everyone. "I came into this work as a 20-something year old working-class Black woman living in the South; I had a baby on one hip and another on the way - yet I have helped to make lasting changes that have had

an impact on the HIV community on a global scale."

Ultimately, she looks forward to the day when the ACTG is no longer needed because society will have addressed the systemic inequalities that drive the epidemic and researchers will have found a cure.

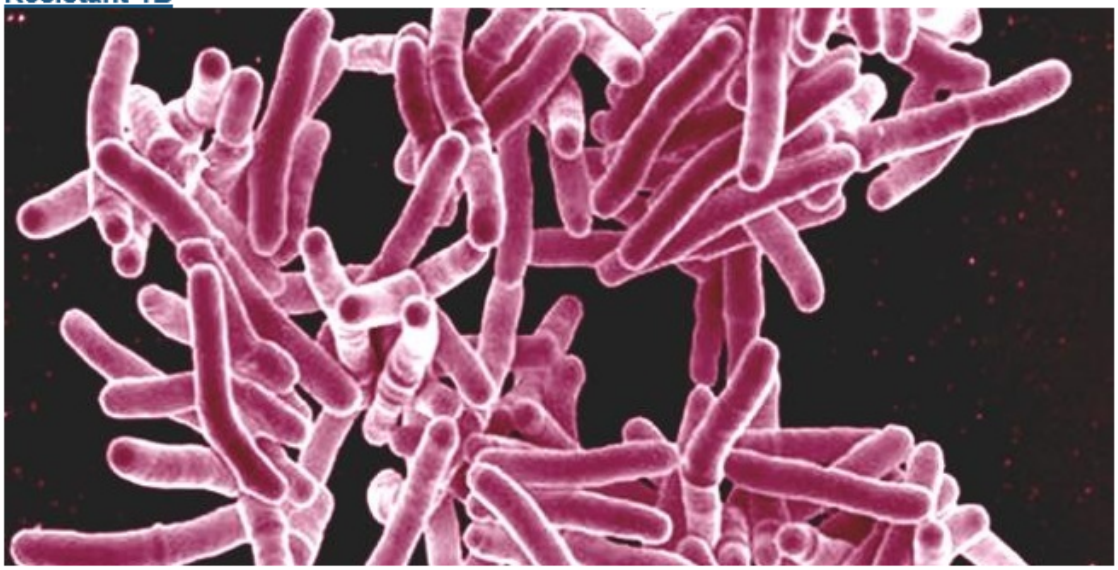
MEDIA SPOTLIGHT ON PHOENIX TRIAL

In our last newsletter, we highlighted the opening of the historic PHOENIx **(**Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/) trial. Last week, NIAID/NIH featured the news in its media spotlight. Read their coverage of the study here.

National Institute of Allergy and Infectious Diseases

Tuesday, June 25, 2019

NIAID Launches Large TB Prevention Trial for People Exposed to Multidrug-Resistant TB



A large clinical trial to assess treatments for preventing people at high risk from developing multidrug-resistant tuberculosis (MDR-TB) has begun. The study is comparing the safety and efficacy of a new MDR-TB drug, delamanid, with the decades-old TB drug isoniazid for preventing active MDR-TB disease in children, adolescents and adults at high risk who are exposed to adult household members with MDR-TB.

Read more

National Institute of Allergy and Infectious Diseases | National Institutes of Health

Do you have news or information about an ACTG study or site you'd like to share for our next newsletter? Send it to ACTG Leadership & Operations Center Executive Director Alexis Sexton.

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