ACTG
AIDS CLINICAL TRIALS GROUP
Update
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Statisticians Share Their Role in ACTG Studies

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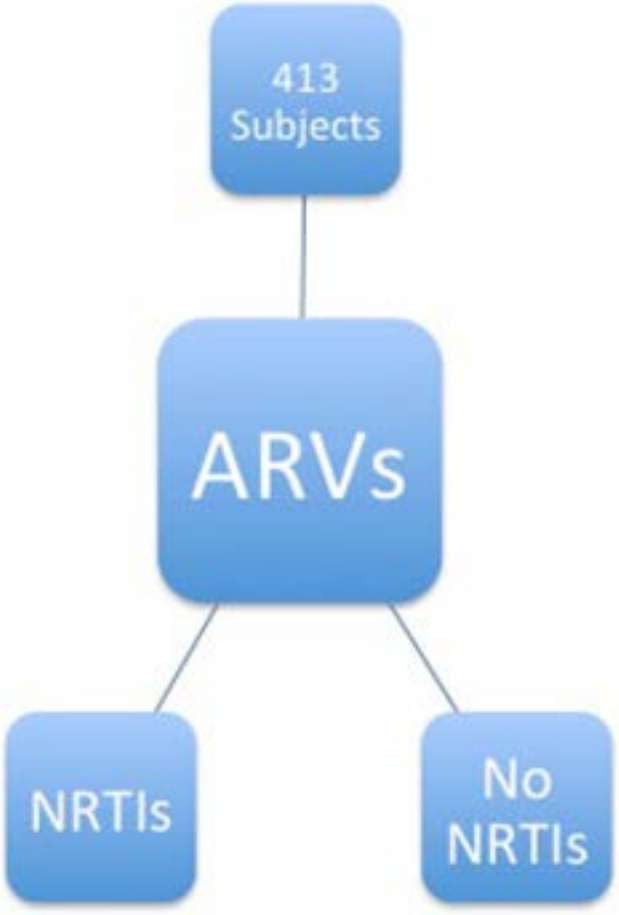

Also Inside This Issue:

Making Data Meaningful:

A Profile of the ACTG's Biostatisticians

Summer Zheng, PhD, knows how to keep a secret. The Research Scientist at the Statistics and Data Analysis Center (SDAC) in Boston, Mass., USA, works with the AIDS Clinical Trials Group Network's study investigators to translate their raw data into research results. When she drafts a trial's interim report, she can usually tell which treatment arm is producing the best results.

"You have to be able to keep a secret and mask the treatment arms when writing the interim report," Zheng says. "After the study is complete, you can tell the team which treatment arm worked."

Holding a doctorate in biostatistics, Zheng has spent the past eight years at SDAC working with ACTG researchers from around the world. She acknowledges that her background could have led to a career in a variety of other fields, but she was passionate about bringing her skillset to clinical research.

"With clinical research, you can help make data useful," Zheng says. "For example, you can help identify a new drug therapy or determine which treatment has less toxicity."

Summer Zheng, PhD, enjoys working on studies to benefit global health.

Zheng is one of 35 statisticians overseen by the ACTG's Principal Investigator at SDAC Michael Hughes, PhD. He and his team have offices at the Harvard School of Public Health's Center for Biostatistics and AIDS Research (CBAR), where he serves as the Director. CBAR is home to statisticians who work on studies from many Harvard-affiliated HIV/AIDS research networks. The ACTG's SDAC is CBAR's largest project. Hughes says two statisticians sit on each ACTG protocol. And like Zheng, he decided to use his mathematical mind in a medical setting in order to impact global health.

"Most statisticians are framed in math and many people pursue careers in finance and the like," Hughes says. "I liked the opportunity to be a mathematician in an environment where the work had important implications for humanity."

A British ex-pat, Hughes joined the ACTG more than 20 years ago. And his passion for the work remains strong two decades later.

"What is fascinating to me as a statistician is how successful we have been over the years," Hughes says. "In the 1990s, getting the virus under control and clinical outcomes were the focus. There were efforts to evaluate biomarkers such as CD4 count and

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Spotlight on Service: Dr. Kimberly Smith Comes Full Circle

Before she finished high school, Kimberly Smith, MD, MPH, knew she wanted to pursue a career as a physician. And before she finished medical school, she knew Infectious Diseases, specifically HIV/AIDS research, would become her professional focus.

Kimberly Smith, MD, MPH, is the CRS Leader at the ACTG's site at Rush as well as Chair of the UPC.

"I was a political rabble rouser in college," Smith says with a laugh from her office at Rush University Medical Center in Chicago, where she is the leader of AIDS Clinical Trials Group's (ACTG) Clinical Research Site (CRS) as well as an Associate Professor of Medicine. "I worked on anti-apartheid and anti-racism movements. I was drawn to HIV research because it was clear to me early on that this disease was disproportionately impacting people who were already shunned by society, including the GLBT (Gay, Lesbian, Bisexual and Transgender) community and IV drug users in New York City, Detroit and Chicago."

The year before she graduated medical school, Smith remembers sitting on her couch watching basketball legend Magic Johnson announce that he was HIV positive.

"He was publically showing the world how HIV was impacting the black community," Smith says. "I graduated med school and then went on to complete my residency in the early 1990s during the height of the worst part of the HIV epidemic when lots of people where dying. When I was doing my Infectious Diseases fellowship in 1996, combination antiretroviral drugs (ARVs) were first being introduced."

This was also the year that Smith began her relationship with the ACTG, becoming one of the first two recipients of the Network's Minority HIV Investigator Mentoring Program (MHIMP). This program allows a site within the ACTG Network to offer a mentorship to a junior minority investigator with an interest in virology, immunology, pharmacology or another aspect of HIV/AIDS research. Smith immediately became involved at Rush with protocols ACTG 315/375, which were designed to examine the effects of highly active antiretroviral therapy (HAART) in certain HIV-infected patients.

"The MHIMP program is designed to integrate you into every aspect of a protocol right away," Smith says. "It exposed me to everything from IRB (Institutional Review Board) approval to writing a manuscript. It is a great trial by fire."

Currently part of the MHIMP program includes serving on the ACTG's Underrepresented Populations Committee (UPC). Flash forward 17 years and Smith is marking her fourth year as Chair of the UPC.

"The UPC has three primary goals," Smith says. "First, we want to increase the representation of minorities in the ACTG's clinical trials, specifically African-Americans, Latinos and other people of color. We also focus on increasing women in ACTG clinical trials since they are also underrepresented. Second, we want to ensure that we are asking research questions that are relevant to these populations. And finally, we want to find ways to increase the numbers of minority investigators involved in HIV research at ACTG sites.

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HIV-Therapy Just got Easier:

Fewer Drugs may be needed for Treatment-Experienced Patients

One of the reasons Karen Tashima, MD, enjoys being a part of the AIDS Clinical Trials Group is the opportunity for collaboration the Network provides her and her counterparts at sites around the world. It was at an ACTG working group meeting several years ago that Tashima first proposed the idea to study a new group of HIV medications from several new classifications of drugs in patients who were treatment-experienced.

"There were a few new drugs coming out at the same time and we decided to turn the question around. Instead of having patients take their current medications from the NRTI (nucleoside reverse transcriptase inhibitors) class as well as these new drugs from different classes, we asked half of our study participants to add NRTIs and half of them to leave NRTIs out from their new treatment plan," says Tashima, Leader of the ACTG's Clinical Research Site (CRS) at The Miriam Hospital in Providence, RI, USA. "The cool thing about the ACTG is that you have the smartest scientists who get together at retreats and talk about the next study they want to work on. Working together, we were able to take the usual study paradigm and turn it around."

Karen Tashima, MD, Study Chair for A5241, presented the protocol's groundbreaking results at CROI.

From these ACTG meetings grew the A5241 OPTIONS Trial or The Optimized Treatment that Includes or Omits NRTIs Trial: A Randomized Strategy Study for HIV-1-Infected Treatment-Experienced Subjects Using the cPSS to Select an Effective Regimen. Tashima, the study's chair, says that after 48 weeks on study, treatment-experienced HIV study participants, who had previously taken NRTIs or shown resistance to at least one NRTI, did show viral suppression when taking new drugs from new classes.

"It is so exciting to have your hypothesis come true," says Tashima. "There is no question that the results show what we had set out to prove. A treatment-experienced patient does not need the old class of NRTIs to achieve viral suppression. We are so excited to show this data."

Tashima presented A5241 and a poster about baseline resistance at the Conference on Retroviruses and Opportunistic Infections (CROI) in Atlanta in early March. A5241's results were the ACTG's biggest news to come out of CROI this year. Study Co-Chair Richard Haubrich, MD, an Investigator and Professor of Medicine at the ACTG's site at University of California at San Diego, shares Tashima's sense of pride in working together to change the scope of medication options for treatment-experienced patients.

"There are several options for treatment naïve patients, but not as many for treatment-experienced. The HIV research field accepted that nucleosides would be an important component for multiple class-experienced patients," Haubrich says. "However, our results were very clear. We can safely exclude NRTIs, giving physicians a new paradigm for ART prescription in clinic and potentially changing treatment guidelines."

Sixty-four US-based sites from the ACTG Network, the International Maternal Pediatric Adolescent AIDS Clinical Trials Group and the Adolescent Medicine Trials Network participated in A5241. Study volunteers needed to be at least 16 years old and show treatment experience or resistance to their current HIV medications. Most of the A5241 participants had been on ART for 10 years or more. The new medications studied included darunavir and tipranavir from the protease inhibitor class of HIV medications, maraviroc from the CCR5 antagonist class, raltegravir from the integrase inhibitor class, etravirine from the non-nucleoside reverse transcriptase inhibitors class and enfuvirtide an injectable drug from the fusion inhibitors class.

Traditional antiretroviral therapy consists of medications from the nucleoside reverse transcriptase inhibitor

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Enrolling Study A5294 Seeks to Change the Standard of Care for HIV/HCV Co-Infections

Kenneth Sherman, MD, PhD

The Hepatitis C virus (HCV) infection is a curable disease. Yet many people do not know whether they are infected, or do know and wait until it is too late to begin treatment. Those people living with both HIV and HCV are at a greater risk of rapidly reaching end-stage liver disease due to the co-infection.

"In the United States about 25 percent of all people living with HIV also have HCV," says Kenneth Sherman, MD, PhD, a Hepatologist and Professor of Medicine in the Division of Digestive Diseases at the AIDS Clinical Trials Group's (ACTG's) University of Cincinnati Clinical Research Site. "And the timeline of HCV progression is compressed when you are co-infected with HIV."

HCV causes liver scarring, progression to cirrhosis and, ultimately, end-stage liver disease. The timeline for a person mono-infected with HCV and not on treatment is 30 to 35 years until the development of end-stage liver disease. However, a person living with HCV and HIV will see these symptoms in 10 to 15 years, Sherman says.

"It is very important for all HIV patients to be tested for HCV because many people living with HIV do not know that they are also co-infected with HCV," he adds. "There is this fallacy out there that you don't need to be on treatment for HCV until you become sick from liver disease and that is absolutely incorrect. By the time you start showing symptoms of liver disease, it may be too late to help you beat HCV."

In an effort to provide the most effective treatment to people co-infected with HIV and HCV, Sherman and Adeel Butt, MD, MS, an Infectious Diseases Investigator at the ACTG's University of Pittsburgh Clinical Trials Unit, developed study A5294, which is currently enrolling. The protocol's official name is A5294/BIRTH: A Prospective, Phase III, Open-Label Study of Boceprevir, Pegylated-Interferon Alfa 2b and Ribavirin (PEG-IFN/RBV) in HCV/HIV Co-infected.

"The primary aim of A5294 is to determine the HCV sustained virologic response (SVR) rate to combination therapy with PEG-IFN/RBV and Boceprevir in HCV/HIV co-infected persons with genotype 1 HCV infection," says Butt. "This regimen will be tested in those persons who have never been treated for HCV infection, as well those who have previously been treated, but did not respond to treatment or relapsed."

Previously, mono-infected HCV patients and co-infected people living with HIV and HCV were treated using PEG-IFN/RBV. Sherman says this drug combination has been the standard of care from 2001 to 2011 and led to a 50 percent chance of HCV clearance in mono-infected individuals and 27 percent HCV clearance in co-infected patients. In 2011, a series of Phase III trials looked at adding either Telaprevir or Boceprevir to the PEG-IFN/RBV regimen for mono-infected HCV patients. Sherman was the lead principal investigator of one of these trials.

"Both drugs when paired with PEG-IFN/RBV increased the rates of SVR and in a shorter amount of time," Sherman says. "We learned that adding these medications made HCV treatment more efficacious and shorter. This shorter duration of treatment also led to patients not experiencing side effects as long."

Phase II trials using Boceprevir with PEG-IFN/RBV for co-infected HIV/HCV patients have been successful, which has led to Sherman and Butt's currently enrolling Phase III trial. Sherman says the goal is to begin seeing co-infected HIV and HCV patients reach suppression as early as 24 weeks instead of the traditional 48-week course of treatment.

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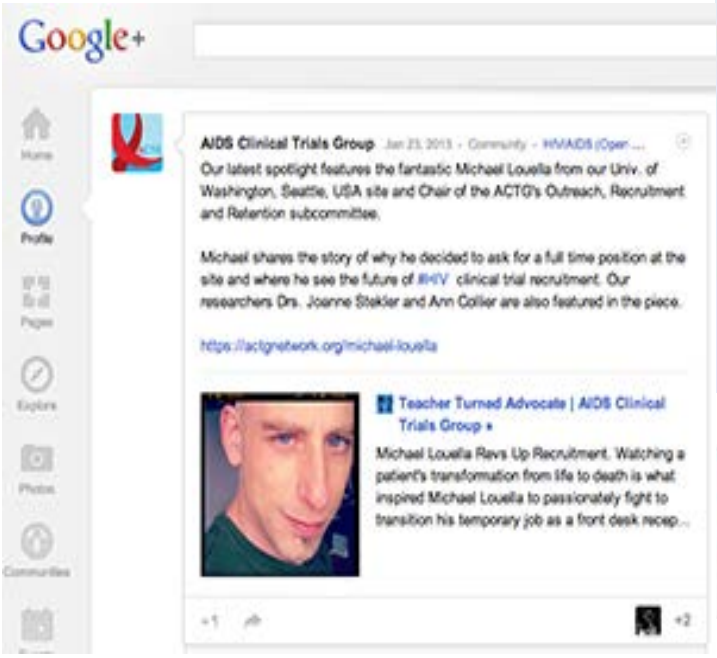
Don’t Miss the Conversation Online

The ACTG has embraced social media and if you have a Facebook, Twitter or Google Plus account, we invite you to interact with us online! You can also always watch our 14 videos on our YouTube channel without having any sort of personal social media presence. Here are some of the conversations you might have missed if you are not a fan on Facebook, a follower on Twitter or in our circles on Google Plus: a photo of ACTG Executive Director Lauren Robertson presenting in Boston on Facebook, a video of Michael Hughes, PhD, PI at SDAC, talking about his favorite ACTG study on YouTube, our tweets about our California sites on Twitter and a spotlight article about OR&R Chair Michael Louella on Goolge Plus!



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Dr. Kimberly Smith Comes Full Circle

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Smith looks forward to ushering in a new pair of junior minority investigators into the MHIMP. Click here for further eligibility requirements and to apply by March 29, 2013.

“Kim has had a tremendous impact on the field as an investigator, educator and tireless advocate for under-represented populations in clinical research,” says Daniel Kuritzkes, MD, Chair of the ACTG Network.

Once she had the MHIMP under her belt, Smith stayed on at Rush writing her first protocols in immunology and immune reconstitution. She still remembers her first K23 grant that allowed her to study growth hormones and if they could boost the immune system of people living with HIV. This study also gave her the opportunity to explore securing funding from multiple sources including the ACTG and other NIH grants. She now sits on an NIH study section for K grant approval as well as serving on the Center for Disease Control and Prevention (CDC) Board of Scientific Directors, an external advisory committee that provides input to the CDC.

Yet, her main focus is her patients and the research site she runs at Rush, the place she got her start back in 1996. When asked what study has meant the most to her over recent years, she only hesitates a moment before recalling A5202 a treatment naïve trial.

“African American patients living with HIV are not getting the same rates of virologic suppression as whites and this study really gave us important data to help us begin to have a better understanding of this issue,” Smith says. “Now we can say, ‘what’s next? How can we change this pattern?’ I am proud to be a part of the ACTG and have the ability to conduct research and be a part of findings answers to these questions.”

Enrolling Study A5294 Seeks to Change Standard of Care for HIV/HCV

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Adeel Butt, MD, MS

If their study is successful and Boceprevir is approved by the Food and Drug Administration (FDA) for co-infected patients, this will mean a change in the previously practiced standard of care for people living with HIV and HCV.

“When the preliminary results of Directly Acting Antiviral Agents for HCV (DAA) were announced for HCV mono-infected persons, there was immediate enthusiasm and hope that these agents could also be used for co-infected persons,” Butt says. “There has been a tremendous need for better therapeutic agents for HCV in the co-infected population, since treatment response with the current regimen are much lower. So, developing a treatment trial of the new agent was a natural progression.”

“Traditionally, mono-infected women respond better to HCV drugs than men. In men and women who are co-infected with HIV and HCV, African Americans do not respond as well to HIV/HCV treatment as other races,” Sherman says. “However, these gaps are lessened when the newer treatments we are testing are added. Our goal is to cure as many people of HCV as possible and change the currently accepted FDA-approved course of treatment.”

Butt and Sherman’s trial is currently enrolling at ACTG sites in the United States only. Men and women co-infected with HIV and HCV who are treatment naïve and treatment experienced are eligible. All study volunteers must have their HIV fully suppressed. For more information about A5294, visit https://actgnetwork.org/study/a5294birth-prospective-phase-iii-open-label-study-boceprevir-pegylated-interferon-alfa-2b-and-.

Fewer Drugs May be needed for Treatment Experienced Patients

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class, including tenofovir, azidothymidine and lamivudine. However, many people living with HIV who have been taking ART long term may develop a resistance to the drugs in this NRTI class due to changes in the virus as a result of the patient's poor adherence to his or her prescribed treatment plan, says Haubrich.

This motivated Haubrich, Tashima and their team to try different treatment options from new drugs from new classes of HIV medications. Tashima says the goal was also to eliminate treatment failure due to drug resistance and to tackle the problem of patient adherence to medications prescribed.

"We are so comfortable clinically with the NRTI class. When we design a study, we think we must always use at least one drug from the NRTI class in the treatment," Tashima says. "For this study, we carefully reviewed each study participant's test results and medication history and recommended new treatments directed at treating their HIV virus. We also recommended which NRTIs to take. Half of the study population then took NRTIs and half did not. This study was a randomized prospective study, which is the best study design in the clinical research world."

Richard Haubrich, MD, Study Co-Chair for A5241, says the results give physicians a new paradigm for ART prescription in clinic and potentially change treatment guidelines.

This individualized approach to developing a treatment plan for each of the research study's 413 participants mimicked the type of care the patient would receive in a clinic, Tashima says. She, Haubrich and their team were able to look at each subject's study labs and study collected medical history at the same time thanks to a web utility created by the ACTG's data management center at the Frontier Science & Technology Research Foundation (FSTRF). Tashima also praises the statisticians from the ACTG's Statistical and Data Analysis Center (SDAC) for their input.

After 48 weeks on study, Tashima, Haubrich and the A5241 team were confident that treatment-experienced patients who were solely on new drugs from the new classes and not any NRTI medications showed viral suppression. They will continue to follow the participants until 96-weeks, or this April, to ensure the response to this new treatment is sustained.

"We now know that it is okay to exclude this old class of HIV medications for treatment-experienced patients and that these patients will not lose virologic suppression because they are omitting this traditional therapy," Tashima says. "Physicians in the clinic can safely prescribe this new regimen of medications without including the NRTI class."

Haubrich and Tashima are grateful for the work of all of the investigators and site staff involved with the A5241 study team, including Laura Smeaton, MS, SDAC in Boston, Mass.; Adriana Andrade, MD, MPH, Johns Hopkins Adult AIDS CRS in Baltimore, Md.; Joseph Eron, MD, University of North Carolina AIDS Clinical Trials Unit in Chapel Hill, N.C.; Carl Fichtenbaum, MD, University of Cincinnati CRS in Cincinnati, Ohio; Rajesh Gandhi, MD, Massachusetts General Hospital ACTG CRS in Boston; Victoria Johnson, MD, Alabama Therapeutics CRS in Birmingham, Ala.; Karin Klingman, MD, DAIDS in Bethesda, Md.; Kim Hollabaugh, MS, SDAC; Katie Mollan, MS, SDAC; Lumine Na, MS, SDAC; Evelyn Hogg, BA, Social & Scientific Systems, Inc. (SSS) in Silver Spring, Md.; Dave Rusin, MT, ASCP, FSTRF in Amherst, N.Y.; and Adam Manzella, MA, FSTRF.

A Profile of the ACTG's Biostatisticians

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viral load as surrogate endpoints for these clinical outcomes. Now that HIV infection is a potentially manageable chronic disease, evaluating biomarkers remains incredibly important but the emphasis has shifted markedly: we're now trying to understand numerous biomarkers in the context of HIV-associated end organ disease, HIV eradication, and viral hepatitis and tuberculosis co-infections. This diversity of research brings new and exciting challenges in study design and analysis for statisticians."

Initially, ACTG investigators meet with Hughes, Zheng or one of their statistician colleagues to determine a study design based on a research hypothesis.

Michael Hughes, PhD, admires the international ACTG site staff for working through unique circumstances, such as civil unrest, to conduct research.

"Recently, I created a study design with a researcher working on an agent to stimulate dormant HIV in the body," Zheng says. "It is really exciting work and makes me feel like I am on the cutting edge of science, getting right in front of new research areas."

Hughes says the proper study design is critical not only for the study to yield meaningful results, but also for future sub-studies or cross-studies. "If a study is designed well, the analysis is easy," he says. "But statistical analysis can never resolve bad design. So the study design needs to be done well and the primary analysis should be the main focus. The secondary objective is to design a study that may yield a database of information for future studies to answer further questions."

After the study design and creation of a concept proposal are complete, protocol development begins. Zheng and Hughes enjoy working with every member of the research team including clinicians, "-ologists," data managers, and site research nurses. Once the protocol is approved, the study will enroll participants and the trial will begin.

"In my role, I monitor the study to ensure it fits with the approved protocol and that the data is being collected as outlined in the protocol," Zheng says.

The health and wellbeing of study participants also fall under Zheng and Hughes' purview. "It is our job to prepare interim analysis reports that are reviewed by the Data and Safety Monitoring Board (DSMB)," Hughes says. "The safety of patients is protected and a study will be modified or terminated if safety issues arise. A study may also be terminated if the results are already conclusive at the interim reporting stage."

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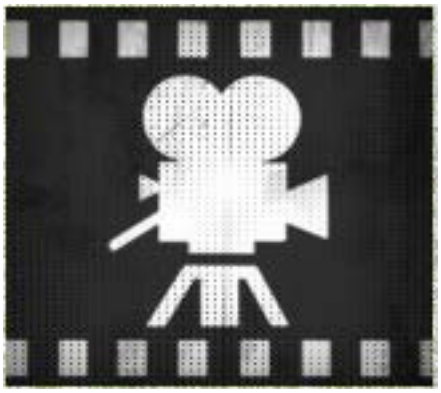

WATCH: Hughes talks about his favorite study to work on during his more than 20 years with the Network on the ACTG YouTube Channel.

In addition to producing the interim report, Zheng and Hughes write an analysis report upon a study's completion. This information is then used for the study's authors to produce their manuscript detailing the trial's results.

"I am always impressed with how well all the sites work together on a particular study," Hughes says. "I especially admire the international sites because they have to contend with factors we do not face in the United States. Some sites have had to deal with earthquakes and civil unrest, but they managed to keep conducting studies extremely well and kept study volunteers on treatment apparently without missing a dose."

Through the ACTG, Hughes has led a four- to six-month SDAC International Internship Program annually for two site staff based at the Network's international sites. In the spring of 2012, an epidemiologist from Brazil and a statistician from Malawi came to Boston to work alongside Hughes' team on the ACTG's international antiretroviral treatment studies, evaluating tuberculosis as a risk factor for treatment outcome and renal toxicities respectively. In January of this year, two new interns arrived in Boston from the ACTG's sites in Thailand and Malawi.

"This was a program developed by the ACTG leadership. We used this as an opportunity to involve statisticians at the international sites and get their staff involved in analysis of data from ACTG studies," Hughes says. "While they are here in the US, they work and develop these skills to then bring back to their sites abroad and share with their colleagues."

Applicants to the ACTG SDAC International Internship Program typically should hold an advanced degree (PhD, MD or equivalent; or MS, MPH or equivalent in biostatistics or epidemiology, or a similar quantitative science). They should also be engaged in HIV/AIDS and related research activities with the ACTG, and should return to these research activities upon completion of their time at SDAC. Check the ACTG public website at https://actgnetwork.org/ for a future story on the deadline and materials needed to apply.

Like Hughes, Zheng finds the interaction with ACTG staff from sites around the globe a fascinating part of her role within the Network.

"I enjoy working with everyone within the ACTG Network," Zheng says of the research process. "It's challenging work and I like having an intelligent group of colleagues from around the world."

Questions, Comments and Story Ideas

This is the third edition of the ACTG Update. If you would like your enrolling study featured or results from your completed trial highlighted, please contact Morag MacLachlan at mamaclachlan@partners.org. Any questions, comments and story ideas are also welcomed!