ACTG
AIDS CLINICAL TRIALS GROUP
Update
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Women and HIV: Their Crucial Role in Studies

(Page2)

Also Inside This Issue:

Women and HIV:

Women Play Crucial Role in HIV Research

Sharon Maxwell became involved with the AIDS Clinical Trials Group (ACTG) Network at its site in St. Louis, Missouri, USA, in 1995 after being diagnosed with HIV. She wanted to find women who she could relate to, but she's remained involved with the Network for nearly two decades because she knows she's making a difference in women's health.

"I was a married woman. There were a lot of men to talk to, but finding women was what was important to me because the virus affects us differently," says Maxwell. "I wanted to talk to other women about side effects of the medications that were available at the time."

Sharon Maxwell, GCAB Co-Chair, has been involved with the ACTG since 1995.

She enrolled in ACTG studies in addition to joining the St. Louis site's Community Advisory Board (CAB). In 1996, Maxwell applied for and was elected to the ACTG's Community Scientific Subcommittee (CSS) as one of 29 members globally who offer investigators insight into the Network's clinical trials. Maxwell became a CSS representative to the ACTG's Women's Health Committee. She and the other female CSS rep. on the committee provided feedback from the community's perspective about the two studies the ACTG had at the time for women.

"One protocol was about HIV and pregnancy and the other was about HIV and genital secretions," says Maxwell. "The other female CSS rep and I had no plans to become pregnant and I remember her saying, 'I'm more than genital secretions.' Neither of these studies applied to us and we wanted other studies about women and HIV to be researched as well. We were concerned about the long-term effects of the antiretroviral (ARV) drugs. We wanted to know about HIV and menopause. ACTG leadership asked for our feedback and listened, which was very important."

Because they spoke up, the number of studies enrolling women jumped from two to 11 by the end of Maxwell's term. She is currently finishing up her term as Co-Chair of the Network's Global Community Advisory Board (GCAB), which is now made up of representatives from each of the ACTG's more than 70 research sites around the world. She along other CAB members, site staff and investigators continue to work tirelessly to ensure the ACTG's research agenda includes women, that women are aware of the Network's many volunteer community advisory opportunities and that women enroll in studies open to them. In fact, a symposium about women and HIV will be held during the ACTG annual meeting in July in Washington, DC, highlighting the importance of enrolling women in ACTG trials and reviewing several sex differences that have been found in recent Network studies.

HIV Affects Women Differently

Worldwide, HIV is the leading cause of death among women of reproductive age according to UNAIDS. In the United States, 1.1 million people are living with HIV and one in four of them is a

Women Play Crucial Role in HIV Research

woman, according to the Centers for Disease Control and Prevention (CDC). In 2011, UNAIDS estimated that 34 million people in the world are living with HIV infection, about half of whom are women. In sub-Sahara Africa, up to 60 percent of people living with HIV are women. Heterosexual sex is a dominant mode of HIV acquisition in women globally.

The inclusion of women in HIV research is critical as the virus affects them differently than men. For example, ACTG's researchers recently discovered that even when taking antiretroviral therapy (ART) successfully, 16 percent of women and 4 percent of men living with HIV experienced a persistent viral load in their genital secretions. These results of the Network's A5185s study published in the journal of Clinical Infectious Diseases in April 2013 suggest the female genital tract may be a reservoir for the virus. The study of 158 men and 170 women from seven countries, including the US, Brazil, India, Malawi, Peru, Zimbabwe and South Africa, clearly shows the need for further trials focused on how the virus uniquely impacts a woman's health and her likelihood of transmission to her partner.

"Some people think science is science and research results can be generalized to all populations," says Liz Barr, BA, MS, a doctoral student at the University of Wisconsin Madison and an ACTG CSS rep. "But research is showing that sex differences appear at a cellular level. Not all results can be applied to all populations."

Susan Cohn, MD, MPH, and Cindy Firnhaber, MD, are Co-Chair and Co-Vice Chair of the Women's Health Inter-Network Scientific Committee (WHISC).

In an effort to make women's enrollment in clinical trials a priority, the ACTG's GCAB and CSS drafted a letter to the Network's leadership. In the letter, they request sex-based comparisons as primary and secondary objectives for each ACTG study; the collection of female-specific data in all studies such as gynecological and menopausal information and fertility concerns; support for research across all science groups that addresses women's health; and the release of summaries of published study results quarterly.

"It is so crucial to understand what the community thinks is important and what kinds of studies women are interested in participating in," says Susan Cohn, MD, MPH, an Investigator at the ACTG's Northwestern University Clinical Research Site (CRS) in Chicago, Illinois, USA. "Liz has done a fabulous job articulating the concerns of the CAB."

Cohn is the ACTG Co-Chair of the Women's Health Inter-Network Scientific Committee (WHISC), which has members from both the ACTG as well as the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group. Cindy Firnhaber, MD, Technical Director of the ACTG's Clinical

Women Play Crucial Role in HIV Research

HIV Research Unit in Johannesburg, South Africa, is the group's ACTG Co-Vice Chair. WHISC's mission includes overseeing studies of interest for HIV-infected women and their safety as well as helping to enhance the enrollment of women in US protocols. The ACTG and IMPAACT, through the WHISC, are soliciting input from women and other successful research networks domestically to increase enrollment of women into their network's protocols.

"The reality is that enrolling five women in a research study in the United States is much harder than enrolling five men," says Cohn. "We appreciate that it often takes more effort and the ACTG supports increasing the enrollment of women in its protocols."

Getting Women to the Table

Cohn and Firnhaber believe posting study results in laymen's terms to the ACTG website will show women how their participation moves HIV research forward.

"We know that women are not feeling appreciated. They need to understand what role they play in a clinical trial," Cohn says. "Each study summary needs to devote a section to gender analysis whether or not anything was found, so women can see how their participation is appreciated and important. Women need to be able to understand study results to know what's being done, what we plan to do in the future and why they should participate."

Pamela Tshandu and Liz Barr are CSS reps and CAB members from the ACTG's sites in South Africa and the United States respectively.

In Africa, Firnhaber says more women are infected by the virus than in the US, thus attracting them to research studies is a bit easier, but retention can be a challenge. "They have other concerns besides their own health," Firnhaber says. "We will see women who test positive for HIV during pregnancy take their medications to keep their baby healthy, but then they will stop taking their medications after they give birth."

Pamela Tshandu, a CAB and CSS member at Firnhaber's ACTG site in Johannesburg, says she and other CAB members have made community outreach a priority to educate women about not only the work being done by the ACTG, but also about the virus itself.

"In South Africa, not everyone is exposed to HIV/AIDS education," Tshandu says. "When we approach women, we need to be sensitive to cultural differences. It is not a one size fits all approach. We come from different ethnic backgrounds and that counts a lot. When we do our outreach, we tell people about our clinic and the services we offer there. Unless women understand the services

Women Play Crucial Role in HIV Research

offered and the research being conducted at our site, they will never come. I have also worked to translate the ACTG's study flyers into laymen's terms to help everyone understand the work being done."

In addition to making women a research priority and publicizing the ACTG's studies, Tshandu, Barr and Maxwell encourage women who are infected or affected by HIV to take an active role in the Network's many volunteer advisory opportunities.

"When I see researchers nodding and taking notes when I share my thoughts, I feel listened to," says Barr. "Community members and researchers are a team and they come to research from different perspectives."

For Maxwell, her participation not only connected her with other women living with HIV, but led to lifelong friendships and the opportunity to be at the table with researchers who were testing medications to help treat opportunistic infections that directly affected her.

"When I was living with cytomegalovirus (a condition that can lead to blindness) in the 1990s and realized the researchers really cared about me and didn't think I was some lowly person in the community with HIV, that's when I really began to love my work with the ACTG," Maxwell says. "It is one of my most memorable moments. They really wanted me to be there so they could understand what people living with HIV were going through. It was really inspiring and I remember thinking 'I'm going to be a part of every study I can.'"

The ACTG's annual meeting will feature several discussions about women and HIV research. The WHISC is also hosting a Think Tank with the Network's End Organ Disease/Inflammation Transformative Science Group within the WHISC meeting on Wed., July 31, from 8-10 a.m. The symposium on women and HIV research will be held on Friday, Aug. 2, between 8 - 10 a.m. The meeting takes place at the Grand Hyatt Hotel in Washington, DC. For more information about the annual meeting, completed and enrolling ACTG studies for women and joining one of the Network's Community Advisory Boards, visit https://actgnetwork.org/.

Complete OR&R's Survey at the July Meeting

The ACTG's Outreach, Recruitment and Retention (OR&R) Subcommittee wants to hear from you! Did you know OR&R created a Library of Recruitment Materials on the ACTG member website? Does your site use the recruitment flyers available on the protocol specific web pages? Has the ACTG Facebook page been useful for outreach efforts?

These questions and a few others will be included in a quick survey available for completion by all Network members in between sessions at the annual meeting in Washington, DC, in July. Let OR&R know how they can be of service to you!

Don’t Miss the Conversation Online

Do you know the many ways to connect with the ACTG online?

Check us out on Facebook, Twitter, YouTube and Google Plus as well as our newest accounts on blogging site Tumblr (below) and photosharing app Instagram (right). There you can check out the ACTG’s latest news and catch up with site staff from the US to Malawi!

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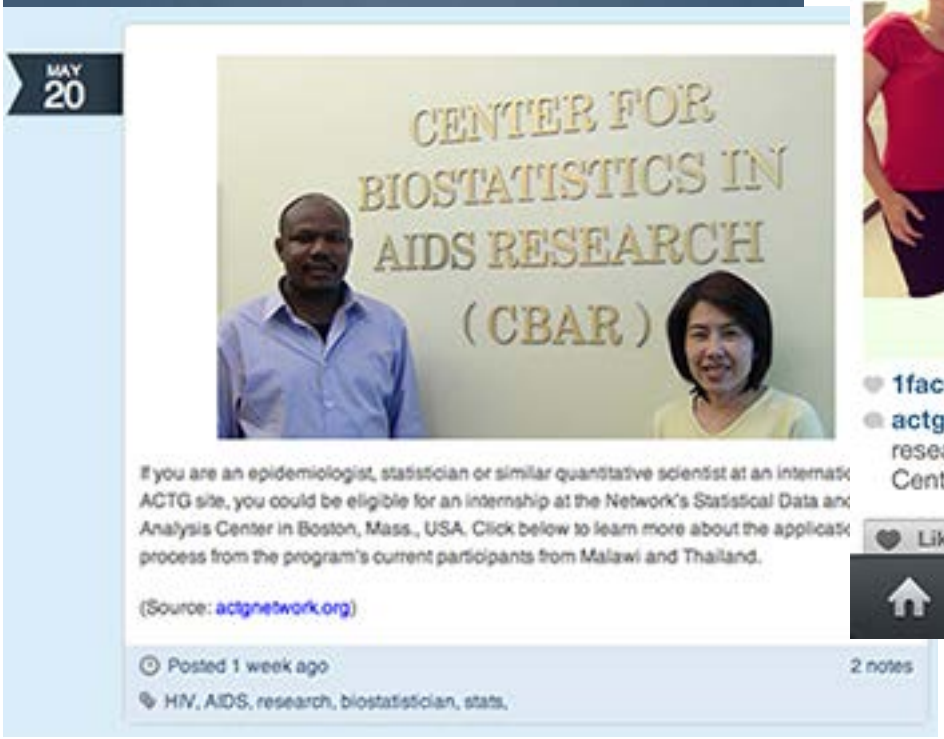

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Spotlight on Service with Dr. Jackson Orem:

Uganda Native Returns Home to Treat HIV and Cancer

Until recently, Jackson Orem, MB, ChB, MMED, was the only oncologist in Uganda, a country home to 33 million people. It was this very lack of clinicians that inspired his career path.

“From an early age I noticed that there were fewer doctors in our country, that motivated me to go into medicine so that I can contribute to the workforce in health,” says Orem, who is the AIDS Clinical Trials Group (ACTG) Network’s Clinical Research Site (CRS) Leader at the Uganda Cancer Institute (UCI) in Kampala.

Jackson Orem, MB, ChB, MMED, left, gives researchers from Uganda and the United Kingdom a tour of the Uganda Cancer Institute (UCI).

Orem completed his medical oncology training at Case Western Reserve University (CWRU) in Cleveland, Ohio, USA, before returning to his homeland in 2004. Bob Salata, MD, is an investigator at the ACTG’s site at Case Western.

“It was evident when Jackson was at CWRU, that he was destined to become an outstanding leader and researcher in Uganda,” says Salata. “The training he received at CWRU gave him the perspective and tool set to be successful when he returned to his country. He is dynamic, highly collaborative and demonstrates terrific vision about the spectrum of oncology research at the UCI especially as related to underlying HIV infection. He is a great friend and collaborator and we at CWRU are thrilled to be working with him again on ACTG protocols.”

Once back in Uganda, Orem became Director of the UCI in 2005. It is the only dedicated cancer treatment center in the country.

“On specializing in oncology, again, I noticed that contrary to the prevailing opinion, cancer was common enough in Africa to warrant emphasis,” Orem says. “What, however, surprised me most was the lack of importance accorded to cancers among HIV patients in Africa, despite being the most visible face of the epidemic in Africa from the onset. This partly influenced my decision to train in oncology and to focus on treating patients with a compromised immune system.”

In Uganda alone, Orem says between 50 and 60 percent of cancers in adults are related to HIV. There are two kinds of cancers people with HIV can develop – HIV-related cancers and non-AIDS

Uganda Native Returns Home to Treat HIV and Cancer

defining cancers.

"Some cancers are indicator conditions of HIV/AIDS, hence, called HIV-related cancers. There is, therefore, a vicious cycle with HIV influencing cancer disease and vice versa. Early cancer diagnosis and effective treatment is needed as a starting point in breaking this cycle of disease," Orem says. "The other group of cancers develops due to improved management of HIV. These are called non-AIDS defining cancers. Their development usually compromises gains resulting from prompt effective treatment of HIV. Early diagnosis and effective treatment of these cancers are important in improving the overall outcome for patients already on effective treatment for HIV. In both scenarios, HIV/AIDS, if not effectively treated, will lead to poor outcomes for these patients compared to those people living with HIV without cancer."

Dr. Orem returned to Uganda after studying in the US. At one time, he was the only oncologist in Uganda.

Thus early diagnosis and treatment remain two of the biggest hurdles Orem is striving to overcome. "Few specialists have adequate knowledge for the treatment of both diseases," he says. "HIV awareness in Uganda is very high and testing facilities are available. So there is widespread knowledge of HIV prevention. At best HIV awareness is higher than cancer awareness, and stigma to cancer is probably higher than that of HIV."

Orem hopes a partnership with the Fred Hutchinson Cancer Research Center in Seattle, Washington, USA, will eradicate the barriers to early diagnosis and treatment for HIV and cancer in Uganda. The two centers joined forces in 2004, forming the Uganda Program on Cancer and Infectious Disease (UPCID). Orem is the Co-Scientific Director. The collaboration has brought more clinicians into Uganda and led to the expansion of the existing UCI.

"The Uganda Cancer Institute and the Fred Hutchinson Cancer Research Center have partnered under the UCI-Hutchinson Center Alliance to fight infection-related cancer through research training and provision of high quality care," Orem says. "Together we are putting up a new facility with cutting edge research laboratories specializing in molecular diagnostics, immunology, pathology and clinical chemistry/hematology. There will also be an outpatient clinic capable of accommodating more than 20,000 visits annually and a training center. This will upgrade the level, the range and the quality of services offered at the UCI. The investment in this will be up to $9 million."

The government of Uganda is also building a new inpatient facility, which will increase the current center's capacity from 120 to 200 beds. This investment is critical as Orem says it is difficult to secure monies for cancer treatment in Uganda when compared to receiving funding for other diseases.

Uganda Native Returns Home to Treat HIV and Cancer

“This is partly because cancer treatment is more expensive. Secondly, there is a perception, not only in Uganda but globally, that investment in communicable disease control is more cost effective than investing in cancer control in developing countries,” Orem says. “In Uganda, we believe that developing a long term infrastructure for management of cancer will pay off handsomely in the future by providing a system that will make current efforts in creating cancer awareness and early detection more meaningful and focused.”

In addition to the clinical benefits, Orem will continue conducting important research at the upgraded site. His lab investigates novel oral chemotherapy combinations to improve cancer delivery in resource-poor settings, treatment of viral-associated malignancies and infections in cancer patients with compromised immune systems.

“HIV infection clearly increases the incidence of cancer by a large magnitude, although little is known about the specific role HIV infection plays in the natural history of cancer,” Orem says. “Studies in both the US and Uganda clearly document that survival is markedly lower in persons with HIV infection and cancer. Reasons for this may include the immunosuppression accompanying HIV infection leading to less immune control of cancer, the inability to tolerate aggressive chemotherapy regimens or persistent low-level HIV replication, which in itself may lead to the production of pro-inflammatory angiogenic and tumorigenic cytokines.”

In 2009, Orem led the first clinical trial in Africa to explore a modified dosage of oral chemotherapy for AIDS-related non-Hodgkin lymphoma patients. This work is especially critical in Uganda as many Ugandans living with HIV die from cancerous conditions including non-Hodgkin lymphoma or Kaposi sarcoma (KS).

“We are expanding our observation that oral combination chemotherapy for treating lymphoma works in low-resource settings by conducting similar studies in other African countries,” Orem says. “We are doing this under the auspices of the AIDS Malignancy Consortium (AMC) and the National Cancer Institute (NCI). We are hopeful that this idea will develop eventually into one that ACTG would be interested in for the future.”

Orem is part of the ACTG A5264 study team, which is enrolling patients in a protocol designed to understand the best way to treat HIV/AIDS-related KS in resource-limited areas of the world. Read more about that study on page 10.

While conditions for him to treat patients and conduct studies keep improving in Uganda, Orem never forgets the foe he is up against as more people die of cancer in low and middle income countries than AIDS, malaria and tuberculosis combined. He is grateful for the partnerships he has with Fred Hutchinson Cancer Research Center and the ACTG as he continues to tackle cancer and HIV in his homeland.

“Running the Uganda Cancer Institute is very challenging, but at the same time, very exciting given we are at a turning point in the fight against cancer in general, and in particular, in the HIV population in Africa,” Orem says. “Being part of the ACTG Network at this point is very opportune. I'm looking forward to networking more with colleagues in the ACTG to bring to the forefront some of the questions in cancer research that previously didn't have opportunities to be explored in resource-limited settings such as in Africa.”

A5264 Seeks Treatment Regimen for Early Stage Kaposi's Sarcoma

Kaposi's sarcoma (KS) is a common cancer in many African countries. In some African countries KS is the most commonly reported cancer in men, and in women ranks second after cervical cancer. In an effort to find an effective treatment for early stage KS in people living with HIV, the AIDS Clinical Trials Group (ACTG) Network is enrolling patients in a study testing antiretroviral therapy (ART) alone or in combination with chemotherapy.

Thomas Campbell, MD, conducts KS research in Zimbabwe.

"There is a high incidence of KS in Africa and it is difficult to treat in a limited-resource setting," says Thomas Campbell, MD, Principal Investigator at the University of Colorado Hospital in Denver ACTG site. "Even with ART, patients do not always do well. So it is important to look at ART in combination with chemotherapy."

The study, A5264, is formally called "A Randomized Evaluation of Antiretroviral Therapy Alone or with Delayed Chemotherapy versus Antiretroviral Therapy with Immediate Adjunctive Chemotherapy for Treatment of Limited Stage AIDS-KS in Resource-Limited Settings" or REACT-KS. Campbell, who also conducts KS research in Zimbabwe, is Co-Chair of this study along with Mina Hosseinipour, MD, Clinical Research Coordinator at the ACTG's site in Lilongwe, Malawi.

"Our early work demonstrated that patients who receive some treatment – ART, chemotherapy or both, stay alive and in care longer than those without any treatment," says Hosseinipour. "A5264 is focused on those people living with early stage KS disease. For this population, the goal is to see if ART alone versus ART plus immediate chemotherapy is better. For people taking ART alone, if their KS progresses, they will be given chemotherapy."

The cancer drug being used in A5264 is etoposide. This drug and the HIV medications in this study will be taken orally. Men and women over the age of 18, living with HIV, who have early stage KS and have never been treated for their KS nor have they taken ART in the past six months are eligible. The study will be conducted at ACTG's sites in South Africa, Zimbabwe, Kenya, Malawi, Uganda, Brazil, Peru and Tanzania. The study will run for 96 weeks and then an additional 144 weeks for those patients who receive ART and chemotherapy. Click here for further information on eligibility and enrollment.

"There is very little data on treating people with KS and HIV in Africa and other resource-limited settings," Campbell says. "There's a great void in the literature and we are hopeful our study can provide information on the best course of treatment."

Mina Hosseinipour, MD, works at the ACTG's site in Lilongwe, Malawi.

Early Initiation of Antiretroviral Therapy Prevents Death in HIV/TB Co-Infected

Tuberculosis (TB) is the leading cause of death for people living with HIV. In South Africa alone, 65 percent of TB cases are people living with the TB-HIV co-infection, says Diane Havlir, MD, Principal Investigator at the AIDS Clinical Trials Group (ACTG) Network site at the University of California San Francisco. Havlir led the Network's study A5221 to determine the best time to initiate antiretroviral therapy (ART) in people living domestically and abroad with the TB-HIV co-infection. The results showed the earlier people living with the co-infection begin ART, the less likely they are to develop AIDS or die.

Diane Havlir, MD, says that early ART reduces the chance of AIDS and death in people living with HIV and TB.

"We found that 27 percent of patients with a CD4 count less than 50 developed AIDS or died within a year if they waited to start ART compared to 16 percent among those who started ART within two weeks of TB treatment initiation," Havlir says. "This is an example of an ACTG study which had a direct and high impact on patients and policy."

The A5221 study or "STRIDE: A Strategy Study of Immediate Versus Deferred Initiation of Antiretroviral Therapy for AIDS Disease-Free Survival in HIV-Infected Persons Treated for Tuberculosis with CD4" grew out of a debate about the best time to start ART. Havlir says many people in the medical community thought it made more sense to wait to start ART in a person newly diagnosed with TB because it would be too difficult for the patients to take so many pills, that there would be more side effects, and that drug interactions between HIV and TB drugs posed a risk. People also feared that TB-associated immune reconstitution inflammatory syndrome (TB IRIS) would be worse if ART was started early.

"Others, myself included, thought that delaying ART in a person with TB would put them at risk for complications of HIV," says Havlir. "The point is that a patient coming in with TB and HIV was a very common scenario. The stakes were very high for the patient in terms of initiating ART, and we did not have data to guide this decision."

The study led to major findings in preventing the progression of HIV to AIDS and death in people living with HIV and TB.

"For all the patients in the study, 16 percent who started ART late compared with 13 percent who started ART early devleoped AIDS or died. This difference was highly statistically significant," Havlir says. "Equally as important, we discovered starting ART at two weeks for all the patients was not associated with greater side effects, more drug interactions, or more cases where HIV RNA was not suppressed. We did see more TB IRIS in the cases with early versus later ART start, but these were not fatal. These are important observations because it reassures clinicians that ART can be safely started early in patients with a new TB diagnosis, and that it is critical that ART is started within

Early Initiation of Antiretroviral Therapy Prevents Death in HIV/TB Co-Infected

two weeks in patients with low CD4 counts."

Study volunteers enrolled at the ACTG's sites on four continents including Africa, South America, Asia and North America. Havlir says the majority of patients participated at the Network's international locations.

"Enrollment of the study generally reflected the disease burden globally, but the question of optimal time to start ART was as relevant for patients in San Francisco as it was in Cape Town, South Africa," says Havlir.

And the results have implications for treatment guidelines worldwide.

"We now know that starting ART at an optimal time can reduce AIDS and death in patients," Havlir says. "From a policy perspective, this study, along with two others, provides the evidence and foundation for the World Health Organization's (WHO) HIV and TB treatment guidelines as well as the U.S. HIV treatment guidelines. Now that we know when to start ART in patients with TB, we need to implement these results globally."

Communications & Web Drop-In Hours during July Meeting

Communications Specialist Morag MacLachlan and Web Content Specialist Larry Lawrence will be on hand to answer your communications and web questions during the ACTG's annual meeting in Washington, DC, in July.

Stop by and learn about the ACTG's social media channels, newsletter, web spotlight articles, press releases, videos, portal login and more. Interested in creating social media channels for your site? Do you want to learn how to customize the ACTG Portal to your user experience? Morag and Larry can help!

Look for the commuication drop-in hours location and times in your meeting registration packet in July. If you have questions before then, email actg.communications@fstrf.org.

Questions, Comments and Story Ideas

This is the fourth 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!