Welcome to the June 2019 ACTG Newsletter

PHOENIx Study Chairs (left to right): Drs. Anneke Hesseling (inset), Susan Swindells, Gavin Churchyard, and Amita Gupta; along with study team (May 2017)

PHOENIx MDR-TB Study Prepares to Open

PHOENIx **(**Protecting Households On Exposure to Newly Diagnosed Index Multidrug-Resistant Tuberculosis Patients (A5300B/I2003B/) is a Phase III, open-label, multicenter trial to compare the efficacy and safety of 26 weeks of delamanid (DLM) versus 26 weeks of isoniazid (INH) for preventing confirmed or probable active TB among high-risk household contacts (HHCs) of adults (index case) with multidrug-resistant tuberculosis (MDR-TB). This

ACTG/IMPAACT cross-network collaboration expects to follow 5610 participants (~2158 index cases and 3452 HHCs) for 96 weeks.

Twenty-seven potential participating sites from 12 countries (Botswana, Brazil, Haiti, India, Kenya, Peru, Philippines, South Africa, Tanzania, Thailand, Uganda, Zimbabwe) are eligible to apply to participate in PHOENIx. Each participating site will have a run-in phase, where the site will demonstrate its capacity to identify adults with MDR-TB (index cases), access their HHs, screen HHCs, and enroll and follow eligible HHCs. While the study opening has been delayed for a number of requested protocol changes, we now anticipate two sites (Botswana: Gabarone/12701 and Brazil: Chagas/12101) opening for enrollment this month, with others to follow.

Congratulations to the PHOENIx's team persistence and resilience as the study prepares to get underway! PHOENIx is critical to define the best way to prevent TB in contacts of those with MDR-TB and will have profound implications for preventative TB care worldwide.

LATITUDE Study (A5359) Garners Widespread Media Attention

The LATITUDE (Long-Acting Therapy to Improve Treatment Success in Daily Life trial (ACTG A5359) study received extensive media attention on its recent opening. LATITUDE is evaluating long-acting ART (monthly injections of injections of rilpivirine and cabotegravir) in individuals who have difficulty adhering to daily oral ART. The study, which opened in May at several U.S. sites, garnered significant media attention in outlets including *POZ*, *Bloomberg*, *Pharmafile*, and many others. Read the study news release here. Congratulations to the LATITUDE team on the successful launch of this important new trial!

7500 Volunteers Enrolled in REPRIEVE Study (A5322) of

HIV and Heart Health

Full enrollment of the REPRIEVE study (Randomized Trial to Prevent Vascular Events in HIV, ACTG A5322) was commemorated in May with a NIAID Now blog and video. REPRIEVE opened in 2015 with support from NIAID and NHLBI. This ambitious trial is testing whether a statin medication can reduce the risk of heart disease in men and women with HIV who have low to moderate traditional risk factors for CVD. Participants are randomized to receive pitavastatin 4mg daily or placebo and will be followed for up to 8 years. Researchers completed the enrollment phase of the trial earlier this year, with more than 7,500 participants in eleven countries enrolled.

REPRIEVE investigators and NIAID collaborators also discussed the study design and goals in the June issue of the *American Heart Journal* (Grinspoon S et al. Rationale and Design of the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE). American Heart Journal. June 2019; 212: 23-35). Congratulations to the REPRIEVE team on the successful enrollment of this important study!

Publications: OPTIONS Study (A5241) Asks Whether NRTIs are Essential in Salvage Regimens

When people with HIV develop resistance to antiretroviral medications, their clinicians often prescribe previously-used nucleoside reverse transcriptase inhibitors (NRTIs), along with other drugs, in the new “salvage” regimen, reasoning that the NRTIs may improve the chances of treatment response. These extra drugs may result in side effects, however, and it is not certain if they’re necessary if other active medicines are included in the salvage regimen. In the OPTIONS trial (ACTG A5241), the AIDS Clinical Trials Group asked whether NRTIs are an essential component of salvage regimens if the regimen has other active medications.

The OPTIONS trial included more than 350 people with HIV who had received many different treatment regimens and developed resistance to a variety of medications before entering. The trial, which lasted almost 2 years, showed that clinicians do not need to add NRTIs to salvage regimens, as long as the new regimen has a cumulative activity of 2 or more active medicines from other drug classes. Salvage regimens that did not include NRTIs gave similar rates of durable virologic suppression as those that included NRTIs. This means that clinicians and people with HIV can be confident that they don’t need to add NRTIs as long as the rest of the regimen is strong enough. Fortunately, with newer and better antiretroviral medications, most people with HIV will have treatment options that result in successful control of the virus. By avoiding NRTIs when we don’t need them, we reduce the pill burden, side effects and the expense of extra medicines.

There were other important findings from the trial. The study found that younger people and those starting fewer new medications were less likely to achieve HIV suppression with salvage therapy. This means that we need to make extra efforts to make sure younger people and those who receive fewer new medicines are able to achieve successful control of their HIV. The study also used a questionnaire to assess participants’ quality of life scores before and during the study: participants in the trial had significant improvement in their scores, demonstrating the strong link between effective treatment and quality of life.

The participation of hundreds of people with HIV who took part in the OPTIONS trial, many of whom had received treatment for more than a decade before they joined, has already made a difference: treatment guidelines have changed

thanks to the contribution of the study participants and the staff at the many ACTG sites in the OPTIONS trial.

Gandhi RT, Tashima KT, Smeaton LM, Vu V, Ritz J, Andrade A, Eron JJ, Hogg E, Fichtenbaum C. Long-term Outcomes in a Large Randomized Trial of HIV-1 Salvage Therapy: 96-week Results of AIDS Clinical Trials Group A5241 (OPTIONS). *Journal of Infectious Diseases* 2019 May 28
(Accompanying editorial: Hoenig M, Little S. Salvage Antiretroviral Therapy: Time for "DeNUKElearization"?)

Publications: Can Text Messaging Support Adherence for People Failing Secong-Line Therapy in Low- and Middle-Income Countries (MULTI-OCTAVE Study [A5288])

(ACTG) A5288 (MULTI-OCTAVE) is one of the first studies to look at interventions for medication adherence in lower-income and middle-income countries (LMICs) for individuals failing second line therapy. All participants in this unprecedented prospective interventional study were failing 2nd line ART, with the majority on lopinavir/ritonavir-based ART. Participants were either kept on that regimen or randomized to receiving third line ART regimens based on the results of viral genotyping on enrollment, and followed for a median of 72 weeks.

A randomized cell phone-based adherence support intervention was conducted among most of the study participants. In the intervention, field staff would text participants to see how they were doing in terms of taking the ART and participants would text back, first daily and then tapering down to once a week. The study showed a small (but not significant) benefit of a mobile phone-based intervention for ART adherence on the primary outcome of achieving virological suppression at 48 weeks, and a small (and statistically significant) effect on the outcome of time to virological failure.

The authors conclude that adherence behavior is challenging and that two-way text messaging might help a bit, but does not seem to be as fruitful as hoped.

Therefore, more research on this and other adherence support strategies are needed.

Gross R, Ritz J, Hughes MD, Salata R, Mugyenyi P, Hogg E, Wieclaw L, Godrey C, Wallis CL, Mellors JW, Mudhune VO, Badal-Faesen S, Grinsztejn B, Collier AC. Two-way mobile phone intervention compared with standard-of-care adherence support after second-line antiretroviral therapy failure: a multinational, randomized controlled trial. Lancet Digital Health 2019; 1: e26–34

Investigator highlight:

Dr. Aadia Rana, University of Alabama-Birmingham, School of Medicine

ACTG researcher Dr. Aadia Rana is Associate Professor of Medicine at the University of Alabama-Birmingham and an Investigator with the Alabama CRS. Aadia's ACTG career began in 2010 when she started working as a site investigator at The Miriam Hospital CRS under Dr. Karen Tashima. Concurrent with her NIH-funded research, which addressed the need to improve care for and treatment adherence among people living with HIV, Aadia focused on developing strategies to promote recruitment, retention, and adherence in populations poorly represented in research studies as a member of the ACTG Underrepresented Populations Committee (2012-2016). In 2015, she also joined the Long-Acting Therapy Working Group of the ARTS and the Hard-to-Reach Populations Working Group.

Through these groups, Dr. Rana and Dr. Jose Castillo-Mancilla submitted a proposal in 2016 to compare the use of long-acting injectable antiretroviral

therapy versus standard of care in individuals with a history of non-adherence to care and treatment. This proposal developed into A5359, Long-Acting Therapy to Improve Treatment SUccess in Daily LifE, A Phase III Study to Evaluate Long-Acting Antiretroviral Therapy in Non-adherent HIV-Infected Individuals (LATITUDE), which started enrolling participants in May 2019. LATITUDE tests a combination novel therapeutic strategy of injectable ART supported by short-term conditional economic incentives to improve outcomes in a challenging population. In 2017, Aadia Rana moved to UAB, where she co-directs the Ending HIV in Alabama Scientific Working group at the UAB Center for AIDS Research and became an Investigator with the ARTS.

CAB member highlight:

Angel Hernandez, University of Puerto Rico

University of Puerto Rico CAB member Angel Hernández is committed to ensuring that clinical research is translated to his largely rural community in ways that are not only understandable, but also culturally appropriate. A CAB member since 2010, Hernandez is concerned about an aging population in which 72% of PLWH are 45 years or older, research is often misunderstood, and services can be irregular.

“While the PLWH in our community receive adequate health services,” he notes, “we still lack enough clinics with extended service hours; consistent availability of ART for inpatients at hospitals; availability of integrated primary care; and provision of support services. Our community also faces ageism, stigmas, and discrimination.”

Hernandez responds with an impressive commitment to bridging those gaps. Since joining the ACTG, he has served on the AEC, SASC, CSC, and ITSG, as the CSS co-chair, and as part of the Forum for Collaborative HIV Research, as well as on several protocol development teams. He is also proud to have been part of the team that developed the *Feedback to CAB Protocol Draft Feedback* procedure, and has also collaborated on the development of the CSS scientific agenda priorities.

What he has seen has instilled a number of priorities in Angel, which he and his colleagues are working to move forward. “My hopes for the ACTG and HIV research are to continue studies on new formulations with less toxicities that are easier to take,” he says. “A high priority should be the focus on aging issues, and increased efforts to include underrepresented populations in clinical trials. Of upmost importance is to conduct research on the long-term effects of HIV and ART in long-term survivors.”

As for his personal legacy, Angel adds: “I want to be remembered as an active advocate who brought the concerns of participants in clinical trials to the table.”

Open Positions

The Baltimore-Washington-India (BWI) Clinical Trials Unit, which conducts ACTG trials in the US and in India, is seeking candidates for an IRB and Regulatory Specialist position. The BWI Clinical Trials Unit comprises Johns Hopkins University, Byramjee Jeejeebhoy Government Medical College, and Whitman Walker Health. Candidates can learn more about the position and apply at the Johns Hopkins University Jobs website.

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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