ANNOUNCEMENTS

After much hard work by the ACTG Chair and Vice-Chairs, Leadership and Operations Center, investigators, and community members, The ACTG renewal application has been submitted to the NIH! Congratulations to all!

PUBLICATIONS

We have had a number of high-impact ACTG publications recently. Two important publications are featured below, and a full list of publications is available on PubMed:

The Impact of ART on the Efficacy of Vaginally Delivered Hormonal Contraception

ACTG Changes Guidelines

Effective family planning, which often involves the use of hormonal contraception, is an important component of care for women living with HIV. Unfortunately, some hormones have drug interactions with some

antiretrovirals that may jeopardize hormone effectiveness or tolerability. Non-orally administered hormones may reduce the risk of these drug-drug interactions. The A5316 team sought to determine whether estrogen and progestin administered by a vaginal ring would be affected by oral ART containing either efavirenz or atazanavir/ritonavir.

Overall, 84 women participated in A5316 across 21 ACTG and IMPAACT sites in Asia, South America, sub-Saharan Africa, and the United States. The woman were either not yet on ART or were receiving ART containing efavirenz- or atazanavir/ritonavir, and agreed to use a vaginal ring containing ethinyl estradiol and etonogestrel continuously over 3 weeks. The results showed that hormone concentrations were significantly changed by both types of ART. Efavirenz-based ART decreased both ethinyl estradiol and etonogestrel hormones, raising concerns for lack of efficacy and the risk of unintended pregnancies. While the atazanavir/ritonavir-based ART increased progestin exposure (providing reassurance that the contraceptive effectiveness would be maintained), it decreased estrogen exposure, which may increase the risk of mid-cycle bleeding.

While the findings are directionally similar to what we've seen with ART and oral hormones to date, the vaginal ring ART-hormone interaction often resulted in even larger changes in hormone exposure. A5316 further identified the influence of participant pharmacogenetics on the extent of the drug interaction. The study finding that efavirenz-based ART may jeopardize the effectiveness of hormonal contraception delivered by a vaginal ring has already been included in both the Adult and Adolescent as well as the Perinatal DHHS HIV treatment guidelines, highlighting the influence of this study. The importance of understanding the pharmacology of vaginally administered drugs has particular relevance as vaginal rings are being developed for multipurpose prevention of both HIV and pregnancy.

Scarsi KK, Cramer YS, Rosenkranz SL, Aweeka F, Berzins B, Coombs RW, Coughlin K, Moran LE, Zorrilla CD, Akelo V, Aziz M, Friedman RK, Gingrich D, Swaminathan S, Godfrey C, Cohn SE, for the AIDS Clinical Trials Group A5316 Study Team. Antiretroviral therapy and vaginally administered contraceptive hormones: a three-arm, pharmacokinetic study. *Lancet HIV*.

2019; 6:e601-12.

Comment in: Chappell CA and Achilles SL. Drug interactions: not just for orally administered drugs. *Lancet HIV*. 2019; 6:e563.

A Landmark ACTG Study Evaluating Second-Line ART Failure in Low- and Middle-Income Countries: "A Major Step Forward"

Prolonging the success of ART regimens in light of earlier starts and therapy over a lifetime requires innovative monitoring and treatment strategies. The Management Using the Latest Technologies in Resource-Limited Settings to Optimize Combination Therapy After Viral Failure (MULTI-OCTAVE) A5288 study was an open-label phase IV strategy study conducted in 19 sites in 10 lower- and middle-income countries (in Africa, Asia, South America, and the Caribbean) for patients failing second-line ART. This study used newer antiretroviral therapies (ART) and contemporary management approaches, including population-based sequencing to select appropriate antiretrovirals, to evaluate virologic outcomes and emergence of resistance.

All patients enrolled into A5288 were failing second-line ART. The majority of these were on lopinavir/ritonavir (LPV/r)-based ART. Real-time standard genotyping at enrollment was performed and participants were placed into one of four cohorts with third-line ART tailored to the viral resistance results. The largest cohort (Cohort A) had the least amount of resistance and stayed on LPV/r-based therapy. Of the 545 participants enrolled from January 2013 to September 2015, 287 (53%) were assigned to Cohort A, 154 (28%) to B, 70 (13%) to C, and 34 (6%) to D, with increasing levels of resistance in each cohort. Overall, 64% (95% CI 60, 68%) of participants achieved viral loads = 200 copies/mL at week 48 with proportions of virologic suppression for Cohorts A, B, C, and D varying from 44%, 88%, 90%, and 74% respectively.

This important trial showed that most individuals had no resistance to the most commonly used second-line protease inhibitor (lopinavir) and little resistance to nucleoside or nucleotide reverse transcriptase inhibitors, suggesting that poor adherence is likely a major contributor to second-line ART failure. This finding points to the need to develop novel methods to

both measure adherence and boost adherence. Those with virologic resistance achieved excellent rates of virologic suppression on third-line ART, pointing to the need for targeted HIV resistance testing when indicated.

A5288 is an unprecedented cohort of second-line ART failure in lower- and middle-income countries, incorporating rigorous metrics of adherence measurement (via hair levels) and resistance testing into its design. In an accompanying editorial, A5288 was hailed as “a major step forward in clinical research methods serving a rarely studied population.” More to come from A5288 in the ensuing months but in the meantime, please take the opportunity to read this primary outcome paper!

Grinsztejn B, Hughes MD, Ritz J, Salata R, Mugyenyi P, Hogg E, Wieclaw L, Gross R, Godfrey C, Cardoso SW, Bukuru A,, Makanga M, Faesen S, Mave V, Wangari Ndege B, Nerette Fontain S, Samaneka W, Secours R, van Schalkwyk M, Mngqibisa R, Mohapi L Valencia J, Sugandhavesa P, Montalban E, Avihingsanon A, Santos BR, Kumarasamy N, Kanyama C, Schooley RT, Mellors JW, Wallis CL, Collier AC; and the A5288 Team. Third-line antiretroviral therapy in low-income and middle-income countries (ACTG A5288): a prospective strategy study. Lancet HIV. 2019 Jul 29. pii: S2352-3018(19)30146-8.

Comment in Mills EJ and Nsanzimana S. Have clinical trials in HIV finally matured? Lancet HIV. 2019 Jul 29. pii: S2352-3018(19)30240-1

SEPTEMBER 18TH IS NATIONAL HIV/AIDS AND AGING AWARENESS DAY

To honor this important day, E. Turner Overton MD from the University of Alabama, Birmingham (UAB) summarizes ACTG’s HIV and aging research agenda

Despite advances in effective HIV treatments, new challenges have arisen as people live with HIV into their 60s, 70s, 80s, and beyond. An increased incidence of diseases linked to aging appears to occur at higher rates in people living with HIV compared to the general population. These diseases include

cardiovascular disease (CVD), diabetes, hypertension, dyslipidemia, chronic kidney disease (CKD), obesity, liver disease, cognitive impairment, and impaired physical function. In addition, as populations living with HIV age globally, the burden of morbidity due to chronic disease will continue to rise and threatens to offset the improvements observed in the first few decades of effective ART. Current data from the U.S. predict that, by 2035, the average age of people living with HIV in the U.S. will rise to 58 years and that 90% will have one or more chronic aging-related diseases. The excess morbidity and rising healthcare costs associated with these trends make interventions to prevent and treat comorbidities in high-risk populations of people living with HIV a critical priority for the ACTG.

The ACTG is a leader in addressing aging-related comorbidities. In response to the advocacy of the Global Community Advisory Board, the network created A5322 (also known as HIV Infection, Aging & Inflammation Longitudinal Observational Study, or HAILO), a cohort study of aging people living with HIV that seeks to characterize the changes seen in those with controlled HIV. That research confirmed that multimorbidity (the presence of two or more diseases) and polypharmacy are common among people living with HIV. The study highlighted that frailty is a common comorbidity among older people living with HIV and is associated with other diseases of relevance, including CVD, diabetes, and cognitive impairment. Frailty also increases the risk for falls and overall mortality. In addition. the study demonstrated that excess inflammation in the setting of controlled HIV contributes to the aging-related diseases that people living with HIV are experiencing.

The network is committed to improving the health of people living with HIV beyond suppressive ART. Several ongoing studies focus on the comorbidities described above, including:

- InMIND: testing whether certain HIV medications can prevent decline in cognitive function
- REPRIEVE: assessing whether pitavastatin can prevent heart attacks and strokes in people living with HIV who have a low to moderate risk for these diseases
- SLIM LIVER: will determine whether we can reverse the excess deposition of fat in the liver and other tissues associated with HIV

These are just three examples of how the ACTG is working to meet the new

challenges that people face in their daily lives as they age with HIV. We hope to continue to collaborate with the HIV community to make a difference in both the duration and quality of the lives of people living with HIV.

INVESTIGATOR HIGHLIGHT

Igho Ofotokun, MD, MSc, Emory University, Atlanta, GA

Dr. Igho Ofotokun, Professor of Medicine and Behavioral Sciences and Health Education at Emory University School of Medicine and Rollins School of Public Health, describes the high point of his work with the ACTG as the proposal (in collaboration with Dr. Jeffrey Lennox and others) of the idea that led to the ACTG 5257 study. That study tested the efficacy of three initial ARV regimens that did not contain efavirenz, and thus (at the time) would be preferable for women living with HIV who are of childbearing age. A5257 recruited 1809 subjects at 52 U.S. sites, including 435 women. At 24% of study participants, this was one of the highest proportion of women in an ACTG study. The findings from this ground-breaking study contributed to the revision of the U.S. HIV treatment guidelines in 2015 to prioritize ARV regimens that are better tolerated by women and all populations.

Dr. Ofotokun has been a member of the ACTG since 2004 and was a recipient of the ACTG Minority Fellowship early in his career. He has been part of the membership and leadership of close to 20 different committees within the network and currently serves as the Study Monitoring Committee (SMC) Chair

for the Antiretroviral Therapy Strategies Transformative Science Group (ARTS TSG). Dr. Ofotokun was also the co-chair of ACTG 5299, a protocol aimed at studying the safety, tolerability, and efficacy of ibalizumab, a long-acting humanized CD4 monoclonal antibody with potent anti-HIV activity and a protocol member of ACTG 5303, a trial that studied the bone effects of a maraviroc-containing and tenofovir-sparing antiretroviral regimen. Among his other roles, Igho Ofotokun is Principal Investigator of the MAC/WIHS Combined Cohort Study (CSS) at Emory, PI of the Building Interdisciplinary Research Careers in Women's Health (BIRCWH) K12, and PI of a recent Nigeria-Emory D43 award.

He describes his work with the ACTG as giving him national exposure, "opening doors for me to serve on high-profile committees, including the FDA Antimicrobial Drugs Advisory Committee, several NIH study sections, and on the boards of the IDSA and the HIVMA." He says that he has leveraged his experience with the ACTG to contribute to the scientific missions of other research consortia, which in turn has significantly boosted the number of women investigators engaged with the ACTG at Emory University and the enrollment of women in ACTG studies at that site. We applaud Dr. Ofokotun for a career focused on enrolling women and minority participants in HIV research and thank him for his long and ongoing career in the ACTG.

CAB MEMBER HIGHLIGHT

Belinda Ameterra, South Africa

Belinda Ameterra is proud of the role she has played in combatting HIV and TB in her community and describes working with the ACTG as playing an important part in that service. She has worked in a variety of capacities since joining ACTG in 2014, currently serving as the co-chair of the Community Scientific Subcommittee. She also serves as a member of the Community Partners Group in the ACTG, which strives to promote effective representation of and timely communication among the many communities involved in ACTG studies.

Belinda describes her community as facing a number of concurrent challenges. Worcester, which is in the Western Cape of South Africa, has a large proportion of people living with HIV, TB, and poverty. Many in her community are not able to consistently take their medications. Other challenges include securing quality housing, insufficient public accommodations for people with disabilities, unemployment, crime, and a lack of youth activities.

“Because we are also a rural area, people in our community do not have access to all the needed resources,” she said. “Stigma also remains a large issue and impacts the way patients are treated.”

Belinda looks forward to continued engagement with the ACTG. One of her biggest hopes is that the ACTG will continue to work to help empower people to understand their health conditions.

A CALL FOR ACTG MILESTONES

The ACTG is putting together a timeline that highlights the contributions our network has made to the history of the global HIV/AIDS response. We would love to hear your thoughts on the network's most important milestones. When you think about the difference that the ACTG has made in the epidemic, what moments come to mind? What high points were you part of? What do you see as our most important achievements? Please share your thoughts with us by emailing *ACTG Leadership & Operations Center Executive Director,* Alexis

Sexton.

NEWS TO SHARE?

Do you have interesting ACTG-related news to share? Has your site done something exceptional? What's the latest news about your study? Do you have job postings or any other ACTG-related information? We want to know! Please submit your news to *ACTG Leadership & Operations Center Executive Director* Alexis Sexton.

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