Treatment Action Group

TAG HIV Research Network Statements: Advancing Clinical Therapeutics Globally (ACTG) for HIV/AIDS and Other Infections Network

Background and Achievements

The ACTG has a long history dating back to 1987 and the initial assessments of the efficacy of nucleoside analog antiretrovirals in people with HIV (research spurred in part by the known effectiveness of the nucleoside analog acyclovir against herpesvirus). At a time when opportunistic infections (OIs) were a widely prevalent threat to people with HIV, the network led the research and development of OI prevention strategies that have since become broadly beneficial for people with non-HIV-related immunodeficiency.

In the early 1990s, the ACTG 076 trial demonstrated that the risk of transmission from mothers to newborns could be dramatically reduced by zidovudine, a finding that averted the lifelong burden of HIV for vast numbers of children and their families.

It's no overstatement to say that network investigators subsequently transformed the prognosis of people living with HIV, with the results of the first study of a triple drug antiretroviral therapy (ART) regimen containing the protease inhibitor indinavir, zidovudine, and lamivudine. When the initial results were presented at a conference in early 1996, the audience was astounded: after years of seeing presentations about single and dual ART regimens that led to only transient increases to CD4 T cell counts (a key measure of immune system integrity) and temporary drops in HIV levels, a graph on screen showed CD4 counts progressing consistently upward while HIV viral load plummeted to levels below detection and stayed there over months of follow up. The ACTG subsequently confirmed the profound health benefits of the regimen in the larger ACTG 320 protocol.

As a direct result of this work, new combination ART regimens were approved and morbidity and mortality from HIV plummeted in the United States and elsewhere (as activism drove costs down and increased access).

ACTG research has continued to support the development and implementation of ever safer and more convenient ART options, including long-acting regimens for people who face challenges to adhering to oral drugs.

The network and affiliated researchers have played key roles in identifying health issues not fully addressed by HIV viral load suppression and the contributory factors, such cardiovascular disease, dyslipidemia, and persistent inflammation. The ACTG's work in

the international REPRIEVE trial demonstrated clear cardiovascular health benefits of statin therapy in people with HIV considered at relatively low risk by traditional measures.

A related agenda aims to address aging-related morbidity and mortality that can be accelerated in people with HIV despite control of viral load. A new frontier in this portfolio is the assessment of therapeutic candidates known as senolytics, which has the potential to be applicable to all people at risk of aging-associated ill health, independent of HIV status.

The ACTG has led research that has dramatically improved the standard of prevention and care for tuberculosis (the leading cause of death for people with HIV globally) for the first time in decades. This work has included demonstrating that just one month of rifapentine plus isoniazid is noninferior to nine months of isoniazid for preventing TB in people with HIV, and that a four-month rifapentine-based regimen containing moxifloxacin has equivalent efficacy to the standard six-month regimen in the treatment of TB. These advances benefit people with, and at risk for, TB everywhere but international study sites were essential for the conduct of the trials.

The ACTG is currently finishing the largest clinical trial in history of preventive treatment for people exposed to drug-resistant TB and is partnering with the HIV Vaccine Trials Network (HVTN) on trials of new TB vaccines. Addressing additional co-infections, a recent ACTG study showed that an improved hepatitis B vaccine candidate is superior to the standard vaccine in people with HIV who hadn't previously responded to vaccination. Trials are also being conducted with the aim of improving hepatitis C treatment options for people both with and without HIV.

A major focus now for the ACTG is the discovery and development of interventions that can lead to long term suppression of HIV viral load without the need for continuous ART (sometimes referred to as remission) and ultimately a broadly applicable and scalable HIV cure for all people with HIV. The goal of this research is to reduce — and eventually dispense with — the need for the costs, monitoring, and inconvenience of ongoing HIV treatment and care. Currently this portfolio includes unique, large cohorts of people on long term ART (in some cases decades) that have, and continue to provide, vital insights into how the virus persists, along with interventional protocols such as those involving broadly neutralizing antibodies (bNAbs) which are showing increasing promise for inducing extended control of HIV after ART interruption.

In essence, the ACTG is working both domestically and internationally on a daily basis to try to create a future in which the network is no longer needed.

TAG Recommendations on Research Priorities

- Continued focus on the development of an HIV cure including the potential intermediate step of inducing long-term suppression of HIV replication in the

absence of ongoing antiretroviral therapy (ART). The cure research agenda should encompass assessments of user-friendly technologies for self-monitoring of HIV viral load to allow individuals to determine if ART reinitiation is required. Funding support should be provided for long-term monitoring of participants in HIV cure-related protocols that include analytical treatment interruptions (ATIs) to gather information on long-term safety.

- Continue to study mechanisms of HIV persistence in people on ART and correlates of post-treatment control to inform the design of therapeutic strategies. Curative and remission strategies have the potential to benefit individuals, reduce onward transmission, and greatly reduce the costs of HIV treatment.

- Improving antiretroviral therapy (ART) options for all people living with HIV, including: investigating long-acting options in novel combinations that individual manufacturers are reluctant to evaluate together, studying novel antiretrovirals with the potential to address HIV resistance to available ART, and optimizing implementation of available ART to maximize uptake and persistence of viral load suppression.

- Investigation of approaches for ameliorating the increased risk of accelerated aging and co-morbidities in people with HIV to improve individual health and reduce the need for additional interventions and need for healthcare resources. Potential approaches include those targeted toward specific co-morbidities (e.g. cardiovascular disease, frailty, cognitive impairment) and interventions with the potential to have broadly beneficial effects in reducing aging-related conditions such as senolytics (which aim to reduce or reverse significant negative biological effects of aging) and therapies targeting chronic cytomegalovirus infection. Investigations of these approaches in people with HIV can contribute significantly to evaluating their potential for all aging populations both in the United States and globally.

- Continued study of improved approaches to treating significant co-infections including tuberculosis (still the leading killer of people with HIV globally), hepatitis B, and hepatitis C.

- Conduct clinical trials to improve the treatment of drug-resistant and drug-sensitive TB by studying regimens composed of new and/or existing drugs in line with the following priority considerations:

- TB treatment trials should aim to do more than shorten the duration of TB treatment by focusing on objectives that matter to patients and communities, including optimizing regimens for safety, tolerability, compatibility with other medications (including ART), durability of cure (i.e., low risk of relapse), “forgiveness” (i.e.,

adherence), and intensity of required monitoring and frequency of health system interactions. To achieve these objectives, the ACTG should incorporate person-centered outcome measures in TB treatment trials and social science informed evaluations of acceptability and feasibility.

- Where TB treatment shortening is the objective, the ACTG should seek to reduce treatment duration by looking beyond a "one size fits all" paradigm to test the application of stratified medicine approaches (applied, for example, to the four-month rifapentine-based regimen containing moxifloxacin [HPMZ] for drug-sensitive TB or the 6-month regimen of bedaquiline, pretomanid, linezolid, and moxifloxacin [BPaLM] for drug-resistant TB).

- It is imperative that ACTG retains its commitment to generating evidence in priority populations, including PLHIV, and others that bear a high risk of TB but have faced historic exclusion from TB research. These groups include adolescents, people over 55 years, people who use drugs, and people with diabetes.

- Trials to address bedaquiline-resistant TB and to expand treatment options for people with XDR-TB will grow in importance over the next funding period. TB researchers must urgently address the problem of bedaquiline resistance and answer the high unmet medical need of people with XDR-TB (current treatment is 18+ months containing older injectable and IV agents).

- The first long-acting formulation of a TB drug (bedaquiline) to enter clinical development began a phase I trial in 2025 (TMC207TBC1006) and long-acting formulations of other TB medicines (e.g., rifapentine, isoniazid, macozinone, pretomanid, sorfequiline [TBAJ-876], TBAJ-587, and telacebec) are in preclinical development. The ACTG should consider testing long-acting formulations of TB drugs for both TB prevention and treatment indications.

- Continued collaborative research with the HVTN and external stakeholders to advance clinical development of new TB vaccines that can prevent TB disease. This should include research to generate the evidence required to include PLHIV (of all ages) in TB vaccine prevention-of-disease efficacy trials.

- Respond to emerging infections and pandemic threats such as mpox and COVID-19 by investigating potential therapeutics.

- Support laboratory research to identify new therapeutic leads and improve the scientific understanding of infectious disease pathogenesis and immunology.

- Incorporate and conduct implementation science to maximize uptake of interventions in diverse populations with the goal of ending the HIV epidemic in the US and globally.