Treatment Action Group

TAG HIV Research Network Statements: International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT) Network

Background and Achievements

The IMPAACT network is the only research enterprise focused on clinical studies to improve maternal, pediatric, and adolescent health in people with (or at risk for) HIV, tuberculosis (TB), and related conditions. The development of interventions for these populations has a longstanding and damaging history of lagging behind those for nonpregnant adults.

IMPAACT has played an essential role in addressing this lag, conducting studies supporting the licensure of pediatric formulations of new treatments for HIV such as dolutegravir, abacavir, and lamivudine. Recently, IMPAACT 2017 provided results supporting the use of new long-acting antiretroviral therapy (ART) with cabotegravir and rilpivirine in adolescents aged 12 years and older.

The network has also facilitated the licensure of the new TB drug bedaquiline for children; for example, the IMPAACT P1108 bedaquiline trial led to updated global guidelines for the provision of TB care to children and adolescents. IMPAACT is now conducting essential research on pediatric formulations of pretonamid, which are necessary to allow children with drug-resistant TB to benefit from the standard-of-care regimen that adults receive.

The continuation of a dedicated network for addressing pediatric, adolescent, and maternal TB is important given the lack of market incentives for industry to study new medicines in these populations. For example, there were 6–13-year gaps observed between when TB drugs such as delamanid, rifapentine, bedaquiline, and pretomanid were licensed for adults versus when they were (or will be) licensed for children. In the end, studies of these compounds in children were led by IMPAACT and other public-sector research initiatives rather than by pharmaceutical companies. Children represent around 12% of the global burden of TB (1.2 million of the 10 million people who develop TB each year are children) and around 16% of TB deaths (>200,000 each year) but pediatric research makes up less than 10% of all money spent on TB research. The U.S. NIH is the largest funder of pediatric TB research in the world, contributing around one-fourth of total expenditures in this area with the IMPAACT Network being the centerpiece of this investment.

The international distribution of IMPAACT network sites is critical to this work because the successful reduction of HIV transmission from mothers to newborns (made possible by past studies by both ACTG and IMPAACT) means that global research is necessary to recruit enough participants to produce statistically robust findings. The same is true for TB treatment trials among children, which must operate internationally in order to enroll enough children to study new treatment regimens with sufficient precision. Although global in its reach, the IMPAACT network benefits children and families everywhere, including in the United States.

A key current priority for IMPAACT is the pursuit of HIV remission and cure strategies to reduce and hopefully eventually eliminate the need for continuous ART in infants, children, and adolescents living with HIV — populations for which adherence can be particularly challenging. IMPAACT investigators have led the way in pediatric HIV cure research, from involvement in studying the first reported case of extended HIV viral load suppression in an infant after ART interruption (the "Mississippi baby") to the development and conduct of the large ongoing international P1115 study evaluating whether this type of outcome might be replicable more broadly. At the time of the last report, four infants in the trial have experienced a long period of HIV remission after ART interruption and three have yet to restart.

IMPAACT network research to establish the safety of important therapeutics in pregnancy and postpartum remains ongoing and includes antiretrovirals, TB drugs, long-acting ART, ceftriaxone, benzathine Penicillin G, and glecaprevir/pibrentasvir for hepatitis C.

The network's prevention agenda includes assessments of the potential of broadly neutralizing antibodies (bNAbs) as an alternative to ART-based prophylaxis against HIV and shortened regimens to prevent TB.

The unique role of the IMPAACT network and its exemplary track record underscores that continued funding support is vital.

TAG Recommendations on Research Priorities

- Continued focus on the development of curative, immunotherapy and remission strategies for infants, children, and adolescents with HIV to benefit individual health, reduce the burden of adherence to antiretroviral therapy (ART), reduce costs, and reduce the complexities of healthcare provision by caregivers and families.

- Development of improved, more convenient, and easier to implement therapeutics for use during pregnancy and postpartum, and for infants, children, and adolescents with HIV.

- Development of improved, more convenient, and easier to implement therapeutics for related diseases and conditions, with a primary focus on tuberculosis (TB) (both with and without HIV coinfection) in infants, children, adolescents, and during pregnancy and postpartum.

- For TB trials, the focus should be on supporting studies necessary for children to benefit from access to the full suite of short-course regimens recommended for the treatment of drug-sensitive and drug-resistant TB in adults and adolescents. This includes completing IMPAACT 2034, a single-dose pediatric pharmacokinetic (PK) and safety study of pretomanid, a step toward ensuring children can benefit from shorter regimens that include the drug. If supported by the results, next steps will need to include multi-dose evaluations of pretomanid.

- Conduct studies and coordinate stakeholders to pursue research to address TB during pregnancy and lactation in pursuit of the objectives of the *Consensus Statement: Optimal and Early Inclusion of Pregnant and Lactating Women in Tuberculosis Research*.

- Continued research to develop and optimize methods for understanding and addressing mental health complications associated with HIV and related conditions in infants, children, adolescents, and during pregnancy and postpartum.

- Collaborative research with the HVTN, ACTG, and external stakeholders to advance clinical development of new TB vaccines that can prevent TB disease among infants, children, adolescents, and during pregnancy and postpartum (in populations both with and without HIV). Adolescents, pre-adolescents, and younger children remain under-represented in TB vaccine clinical trials (typically justified by low incidence of TB disease in these age groups, which belies the fact that young people get TB and are not always well served by existing preventive and treatment options). Currently, the TB vaccine pipeline contains only one candidate in an active trial among infants (a phase III study of MTBVAC compared to BCG funded by the European Commission).