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tagline

NEWS ON THE FIGHT TO END HIV/AIDS, HEPATITIS C, AND TUBERCULOSIS

NOTHING ABOUT US WITHOUT US



NOTHING ABOUT US WITHOUT US:

Community Engagement in Research to End the Epidemics

By Erica Lessem

On May 21, 1990, HIV activists from ACT UP—including several members who would go on to form Treatment Action Group in 1992—occupied the U.S. National Institutes of Health (NIH) campus. Protesters at the “Storm the NIH” demonstration and “die-in” depicted on this TAGline edition’s cover demanded political will and funding for research and equitable access to treatment for HIV and its related opportunistic infections and cancers. Their bold and informed action resulted in a massive increase to investment in HIV research and sweeping changes to how AIDS clinical trials were conducted.



ACT UP “Storm the NIH” occupation of the National Institutes of Health Building 1, May 21, 1990. From the Office of NIH History and Stetten Museum.

These activist advances paved the way for the accelerated development of highly effective combination antiretroviral therapy in 1996, and ultimately for the range of prevention and treatment options we have today, which have ushered in the possibility of ending the HIV epidemic. This process proved the need to meaningfully involve affected communities in each step in the planning and conduct of research itself, to reach the goal of “Nothing about us without us.”

Elizabeth Lovinger and Suraj Madoori’s [“Act Up. Fight Back. Fight TB”](#) (page 3) explores how this powerful legacy of engagement of HIV-affected communities in research activism has advanced and can further inspire advocacy for research into HIV’s leading deadly coinfection, tuberculosis (TB).

Jeremiah Johnson explains in [“From Engagement to Leadership”](#) (page 6) how community engagement has grown toward stronger leadership in HIV prevention research, as the field’s exciting and essential developments come with ethical and scientific challenges.

In [“Sound Off: Three Activists Reflect on Community Victories and Priorities in TB Research,”](#) (page 9), Mike Frick and Lindsay McKenna interview TB community leaders, who share their unique perspectives on the evolution of engagement in TB research, from successes to challenges to future needs.

In the aptly named [“Scientific Complexity and Ethical Uncertainties: The Importance of Community Engagement in HIV Cure Research”](#) (page 12), Richard Jefferys illustrates progress in and the need for thoughtful involvement of affected communities in the complex pathways toward a cure, which offer hope and risk in equal measure.

[“The Final Frontier: Breaking Down Barriers to Community Engagement in Diagnostics Research”](#) by Erica Lessem and Stacey Hannah (page 15) highlights the need for thoughtful approaches to community engagement in diagnostics research: Across diseases, communities have long been left out, to the detriment of development and access.

ACT UP. FIGHT BACK. FIGHT TB: POTENTIAL PATHWAYS TO R&D FUNDING ADVOCACY FOR THE U.S. TB COMMUNITY

By Elizabeth Lovinger and Suraj Madoori

Since the beginning of the HIV epidemic in the United States—before HIV even had a name—those most affected have been vocal activists, and better access to treatment and prevention innovations have long been among their concerns. In many ways, TB-affected communities face similar challenges as people living with HIV (PLHIV) did in the early days of the epidemic. TB is also a communicable disease that ravages marginalized populations. As with HIV in the 1980s and early 1990s, TB receives very little political and private attention, despite being a public health crisis with limited tools to stop it. TB today has surpassed HIV as the world’s leading infectious killer and is the most common cause of death among PLHIV globally. Like HIV, TB is concentrated among low-income communities and disproportionately affects people of color, people who are homeless, and immigrants.

TB keeps its grip on these communities in part because research funding, which increasingly comes from publicly funded institutions, has been stagnant. Underinvestment in research and development (R&D) has led to the use of arcane TB treatments with multiple pills and daily injections, which produce debilitating side effects such as hearing loss and mental health issues. As Mike Frick notes, limited resources for TB R&D limits equity from the outset: Scant funding forces researchers to compromise on conducting research that truly reflects the needs and characteristics of key populations. For example, to get the biggest results with the smallest, least expensive trials, researchers may prioritize patients with the “easiest to treat” profile, e.g., those with very little cavitation in the lungs, or PLHIV with high CD4 counts. Very few TB studies include those most vulnerable to TB, including children, pregnant and lactating people, and people who use drugs.

Limited funding for TB R&D thus excludes the particular needs of these populations from the beginning, leading to data and policy decisions that exclude the very people we should prioritize for treatment.¹

There are many lessons to be learned from the successes of HIV activism. In the HIV movement, activists brought attention to the dearth of research on HIV, contributing to a dramatic increase in R&D funding, as well as influencing research design.² For example, the U.S. Food and Drug Administration (FDA) licensed zidovudine (AZT) in 1987 based on data from a placebo-controlled study that was stopped early because of a disproportionate death rate in the placebo arm. After that, activists and PLHIV worked to minimize the use of placebo arms.

Over the next 10 years, activists and scientists worked to evolve and improve both clinical trials and the underlying standards of HIV care. These came to allow the use of concomitant medications, including prophylaxis for opportunistic infections such as *Pneumocystis pneumonia*, cytomegalovirus, toxoplasmosis, and *Mycobacterium avium* complex. Through activists’ pressure, scientists created new regulatory pathways: expanded access and parallel track programs to allow preapproval access to experimental therapies when people were ineligible for controlled clinical trials, and accelerated approval, through which the FDA could offer preliminary approval for a drug based on favorable changes in surrogate markers (requiring that these be confirmed later in controlled clinical trials).

These initiatives both broadened access to and sped up approval of experimental therapies for HIV, thus significantly increasing the speed of innovation.³ These and many other successes forever changed the landscape of HIV science. The current level of HIV research funding at the National Institutes of Health amounts to nearly \$3 billion, having doubled from \$1.5 billion in 1995 to its current level in 2004.⁴

Research on TB is ripe for similar changes, and global communities of TB survivors are better poised than ever to mobilize and call for these changes. They are finding connections through partner organizations and social media, and they have demonstrated solidarity in advocating for the R&D funding necessary to defeat the aforementioned treatment toxicities, inaccessibility, and inequities.

As Mike Frick notes, limited resources for TB R&D limits equity from the outset: scant funding forces researchers to compromise on conducting research that truly reflects the needs and characteristics of key populations.¹

There's a global annual TB R&D funding gap of \$1.3 billion, with only \$772 million in total research funding committed worldwide in 2017. At the United Nations, the September 2018 UN High-Level Meeting on TB signaled the need for action, including scaling up contributions to TB R&D—but member states made little in the way of concrete commitments. So how can the TB advocacy community in the U.S. catalyze much-needed investments in TB R&D?

The role of TB survivors and community advocates in the U.S. is particularly important. With 40 percent of total TB R&D funding coming from U.S. government agencies, the U.S. TB advocacy community is well-positioned to influence these institutions to advance R&D for new TB tools that will have an impact in the U.S. and globally. In part, this will mean messaging the successes and global implications of U.S. investment to policymakers as reasons to continue momentum and strengthen

TB research investments. These successes include: 4-week and 12-week regimens to treat latent TB infection (which are shorter than, and just as effective as, previous regimens); bedaquiline; and potential future therapeutics for TB such as pretomanid, the latest TB drug to be submitted to the FDA for evaluation. As the administration continues to vocalize the need for other countries to “pay their fair share,” U.S. TB advocates are well-positioned to advance a globally accepted, TAG-developed fair share target for TB R&D in Congress and among agencies. This target, for U.S. and other member states to each devote 0.1% of existing gross domestic expenditure on R&D overall toward TB-specific research, would bring the world to a funding amount that could end TB by 2030. For the U.S., this amounts to a manageable \$131 million in additional funding from the government, split across several institutions.⁵

Lastly, mirroring the HIV activist legacy, the U.S. TB community should deepen its involvement in TB research conducted by U.S. institutions to ensure that studies continue to answer critical questions and engage communities in research. Doing so requires investment in building the capacity and leadership of members in nascent constituency-based advocacy networks such as We Are TB (see textbox)—including increased funding for advocacy trainings and participation in policy conversations at the regional and national levels, as well as connecting them to other TB advocacy groups with a strong research orientation, such as the Global TB Community Advisory Board (see [Sound Off](#)). This, in turn, would change many of the benefits from U.S. research institutions and ensure that funding is never the reason why critical TB R&D is compromised.

Endnotes

- 1 Frick M. Using human rights to strengthen TB research and access [transcript of TB2016 plenary address]. TAGline. 2016 Fall. <http://www.treatmentactiongroup.org/tagline/2016/fall/science-and-solidarity>.
- 2 Colvin CJ. Evidence and AIDS activism: HIV scale-up and the contemporary politics of knowledge in global public health. *Glob Public Health*. 2014;9(1-2):57-72. doi: 10.1080/17441692.2014.881519.
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- 4 Summers T, Kates J. Trends in U.S. Government Funding for HIV/AIDS Fiscal Years 1981 to 2004. Henry J. Kaiser Family Foundation. 2004 March. <https://kaiserfamilyfoundation.files.wordpress.com/2013/01/issue-brief-trends-in-u-s-government-funding-for-hiv-aids-fiscal-years-1981-to-2004.pdf>
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We Are TB

We Are TB is a national patient-survivor community with about 40 members across the United States. We Are TB connects TB survivors with each other and with local and state departments of health to share information about the issues that have directly affected them, including TB R&D. Members can access capacity-building and advocacy opportunities to educate elected officials about their experiences and explain how increased R&D funding would have made a difference for them. There are members across the country in almost 30 cities, from Los Angeles to Birmingham and Denver to Burlington. Members of this group have proven to be effective in advocacy: They've contributed to a slew of victories to support TB R&D funding, from protecting the Centers for Disease Control and Prevention's domestic TB program from budget cuts in FY17 through FY19, to increasing funding for the U.S. Agency for International Development's global TB program to its highest level at \$306 million in FY19, to influencing policies on the inclusion of pregnant people with TB in clinical trials by testifying before the Task Force on Research Specific to Pregnant and Lactating Women.

FROM ENGAGEMENT TO LEADERSHIP: PLACING COMMUNITY PRIORITIES AT THE HEART OF HIV PREVENTION RESEARCH

by Jeremiah Johnson

Highly Effective PrEP Requires Rethinking HIV Prevention Trial Design

The advent of effective biomedical prevention options has introduced a number of ethical tensions in the field of HIV prevention research. While the development of a safe, highly effective pre-exposure prophylaxis (PrEP) using the drug combination TDF/FTC (tenofovir disoproxil fumarate and emtricitabine) is welcome, we need more biomedical prevention tools. As we've learned from the field of contraception, options are important, and we are unlikely to achieve a sustainable end to HIV without a vaccine.

In any field of clinical research, ethics can become more complicated once one or more highly effective interventions are developed. The use of a placebo in the control arm is only acceptable if we can reasonably say that nothing better exists, otherwise the ethical obligation is to provide the standard of care or, in this case, the standard of prevention (SoP). The principle of equipoise in research ethics requires the investigator to be genuinely unsure as to whether participants in the experimental arm will see as much benefit as those in the control; the better the control intervention is, the harder that bar is to clear. And if the SoP is extremely effective and safe, ethics may suggest it should be given in both arms, with the new intervention added on top of the background SoP in the experimental arm. But because clinical trials must be powered to detect differences in events (e.g., HIV infections) in the control and experimental arms, the stronger the SoP is, the larger or longer the trial must be to pick up enough endpoints to detect a difference in efficacy. Larger trials are more expensive and can greatly slow down research.

While the pre-PrEP prevention toolbox did contain effective interventions, low adherence to control arm options such

as condoms and behavioral counseling effectively ensured that researchers would see a difference in HIV infections if a new prevention modality was effective at averting infections. But PrEP changed the game: It is both highly efficacious and easier for more people to adhere to. As such, the ethical

...the way forward must be just as focused on finding the right process for resolving ethical tensions as finding the right answers – and that community leadership must always be at the heart of that “right process.”

obligation to offer trial participants the current best biomedical prevention option, TDF/FTC PrEP, now stands in conflict with the traditional pathway for developing new technologies. As additional effective tools are approved, such as long-acting injectable PrEP and vaginal rings, these challenges will be even more pronounced.

Seeking Community Input on a Way Forward

In November 2018, the major HIV prevention trial networks funded by the National Institutes of Health invited community advocates, including TAG, to take part in a symposium on future HIV prevention trial designs in the post-PrEP era.

The stakeholders in the room weighed several ethical considerations: What is the most ethical control arm or background SoP for new prevention trials? Can we develop trial designs that allow us to enroll participants who are not using other forms of biomedical prevention as part of a control arm? Are there alternative ways to demonstrate efficacy, in addition to measuring new HIV infections?

While input at the gathering helped to advance the dialogue, there were few definitive answers to these questions. In many ways, the discussion highlighted that the way forward must be just as focused on finding the right process for resolving ethical tensions as finding the right answers—and that community leadership must always be at the heart of that “right process.”

Community Priorities for Future Prevention Clinical Trials

As discussions advance regarding novel approaches to establish efficacy for new HIV prevention tools, major community concerns are likely to fall into at least three “buckets”:

Bucket One: Providing Quality Access to Existing Prevention Tools

A major concern for community research advocates going forward will be the SoP offered to participants as part of future clinical trials. TAG took a deep dive into this topic in 2017 by surveying community research advocates and members of community advisory boards, finding a clear preference for easy access to PrEP for participants whenever possible and that all trial participants should receive comprehensive education on PrEP and referrals to PrEP services, if interested (see: [HIV Research in the Era of PrEP: The Implications of TDF/FTC for Biomedical Prevention Trials](#)).¹ But many respondents noted that these aren’t easy questions. Ultimately, advocates from communities hosting HIV prevention research need to be involved by providing guidance on how to choose an acceptable background level of prevention support in a trial while advancing vaccine, microbicide, and other essential research.

Bucket Two: Clearly Establishing the Risks and Benefits of Novel Statistical Approaches or the Use of Correlates to Estimate Efficacy

Researchers are investigating alternative ways of establishing efficacy in cases where participants receive a highly effective

SoP package and are unlikely to have new HIV infections. In one approach under exploration, bacterial sexually transmitted infections (STIs) are being viewed as a proxy to estimate the number of HIV infections averted in a clinical trial. Another method might be to use historical incidence data to create an external control arm. The idea behind both is to estimate how many participants would have gotten HIV in the absence of effective prevention options, to sidestep the ethical issues around SoP provision. At this year’s Conference on Retroviruses and Opportunistic Infections, investigators from the Discover trial—which was designed to determine if F/TAF (emtricitabine and tenofovir alafenamide) is non-inferior (as opposed to superior) to TDF/FTC as PrEP—in partnership with the Centers for Disease Control and Prevention gave a glimpse into what this might look like, revealing a model using background incidence in the communities where research took place to estimate what percentage of infections had been averted.²

But the issue with these methodologies is that bacterial STIs and incidence estimates are highly variable in different contexts and within different populations. Given that STI infections are rising around the globe and HIV incidence is in fluctuation, we’re basing our estimates on a moving, inconsistent target. Community advocates will understandably be concerned with the risks of overestimating or underestimating efficacy with these approaches. As novel ways of proving efficacy are developed, it will be essential for researchers and statisticians to clearly explain the dangers (and benefits) of these new approaches to community advocates and to solicit explicit guidance on when these new methodologies are appropriate to use.

Bucket Three: Ensuring Ethical Enrollment

Researchers are also evaluating whether there are novel recruitment methods that could allow for a placebo-controlled randomized controlled trial (RCT) in which participants include people who cannot or will not use PrEP. One such way to do this would be to recruit individuals and establish their level of interest in PrEP use. Those who are already on PrEP or who would like assistance in getting on PrEP would be placed within an observational cohort, while those who are not interested in PrEP would be randomized into an experimental or control arm. If individuals in the observational cohort go off of PrEP, they too could become part of the RCT; similarly, individuals in the RCT who want to go on PrEP would switch into the observational cohort.

Proposals to Modify Population Enrolled: Addressing the Remaining Unmet Need

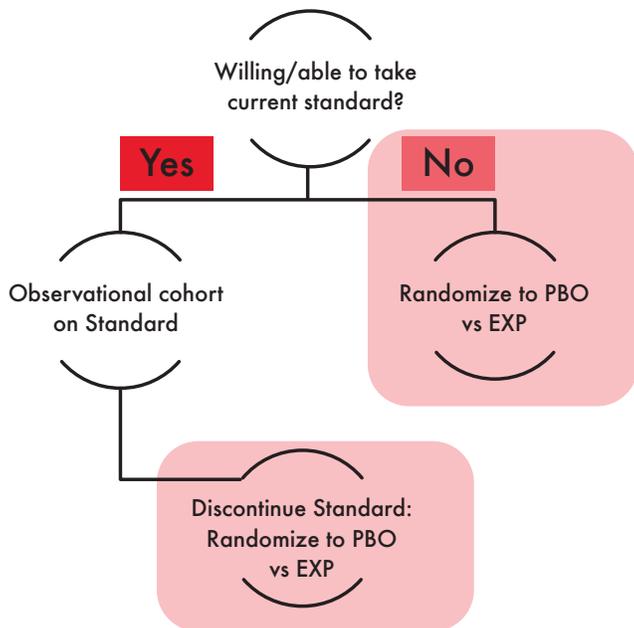


Image adapted from: Donnell D. Novel trial design in the era of successful HIV prevention interventions. Presented at: 3rd HIV Research for Prevention conference; 2018 October 21-25; Madrid, Spain.

On the surface, the approach is appealing; it provides for participant autonomy while allowing for a placebo-controlled RCT. And many community advocates, including those of us at TAG, are interested in pursuing this option in order to facilitate development of future prevention tools. However, many challenges exist in this approach. What are the risks of selection bias between the observational and RCT cohorts, and how would researchers minimize incorrect conclusions? How would researchers ensure that the trial wouldn't disrupt successful PrEP use by potential participants? How would

we monitor that researchers are appropriately offering PrEP, including adherence and access support, to those in the observational cohort?

As such, it becomes once again imperative that the dangers and benefits of this approach are clearly presented to community advocates in order to draw from their expertise on what will and will not be acceptable for future research.

With all three "buckets," concrete answers are few; however, one consistent conclusion stands out: Community leadership in navigating these ethical minefields will be essential. Given the highly technical aspects of these discussions, establishing that sort of community leadership will require dedication from researchers and trial networks; simple attempts at "engagement" will fall short. Community research advocates will need funding to develop and share their expertise, while researchers and trial networks will have to provide education and regularly solicit feedback from community advisory boards and the communities where research takes place. Additionally, researchers may need to make difficult decisions in order to meet the needs of community members, both with regard to the challenges outlined in this article and many other priorities that are of concern to community advocates, such as greater inclusion of vulnerable populations in research and real-world access to the products that result from the hard work of research communities.

Endnotes

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SOUND OFF: THREE ACTIVISTS REFLECT ON COMMUNITY VICTORIES AND PRIORITIES IN TB RESEARCH

By Mike Frick and Lindsay McKenna

An interview with Sarah Mulera, Ezio Távora, and Wim Vandeveld

TAG's TB Project co-directors interviewed Sarah Mulera, Ezio Távora Dos Santos Filho, and Wim Vandeveld, three activists from three continents who have led efforts to promote community engagement in TB research. Sarah, Ezio, and Wim's experiences span decades, and their expertise stretches from engaging communities at specific clinical trial sites to working with community advisory boards (CABs) on the national, regional, and global levels. We asked each to reflect on notable victories won by communities as well as unresolved challenges in TB research.

Sarah began community engagement work 10 years ago after losing a relative and friends to TB. Today, she coordinates two CABs in Kenya that are affiliated with the Kenya Medical Research Institute. She has also served as the community representative to the TB Alliance Stakeholders Association.

Ezio started doing AIDS advocacy in the 1980s and CAB work in the 1990s. He coordinates the Brazilian National TB CAB (CCAP) and directs the community engagement program for the STREAM study—one of the largest multidrug-resistant TB treatment trials in history. He is a member of the Global TB Community Advisory Board (Global TB CAB).

Wim Vandeveld became involved with CABs about 18 years ago, first working with the European Community Advisory Board at the European AIDS Treatment Group. He was a founding member and has served as chair of the Global TB CAB, where he remains an active member. He works at GNP+ as the liaison officer for the Unitaids board Communities Delegation.

TAG: What are some of the big victories that TB CABs have won over the past 5–10 years?

Ezio: Progress has been immense since we started, specifically for the establishment of CABs. I started helping the TB Alliance with their first sites in Africa back in 2004 and 2005. We also had a CAB in Rio de Janeiro related to the CREATE consortium. [CREATE was an \$80 million project in Brazil, Zambia, and South Africa that studied the impact of novel TB-HIV interventions.] The work I do now on STREAM is totally related to what I did previously with other TB studies.

The simple existence of a CAB has a symbolic power that already makes researchers and institutions think twice about what they are doing. This is very difficult, almost impossible, to measure. This accountability that the CABs bring is crucial."

— Ezio Távora Dos Santos Filho

It would be unethical to have a clinical trial in TB nowadays if there is not a community eye supervising, overseeing the process, and making sure there is a feedback [mechanism] to society. We are going towards my ideal scenario, where every study has to have a CAB.

Sarah: To me, the role of CABs has been very significant in gaining community buy-in for research. When I started coordinating CABs in Kenya, there was a lot of resistance to research. Community members thought that they were being used as guinea pigs. As much as researchers tried, the community resisted—until the CAB was formed. When we formed CABs is when we started getting to the grassroots and getting information about why there was resistance to research.

We came to realize that results were not disseminated, so due to this the resistance began. We started making sure that after every clinical trial, we disseminate the results, beginning with very core stakeholders, like the patients themselves. Through CABs involving different stakeholders, we have been able to gain trust. Communities look at research and they see that this is our own thing; it is something that is going to benefit all of us. Everybody is able to give their views, which get absorbed into the research system. By doing this, every stakeholder sees how research is going to benefit us.

Wim: From working with national, regional, and global CABs, I can definitely say that there's been huge progress. When we started, we really had to fight to be heard. That has changed amazingly—I believe NIH [U.S. National Institutes of Health] made CABs mandatory for all of their AIDS clinical trial sites. We also see that in Unitaid, which is a large funder of TB studies: Civil society engagement is now required in every grant. That made a big change in the acceptance of CABs by the research community as an equal partner.

We can measure progress by how we've influenced research through protocol reviews, seeing how our comments are taken on, and how studies are changed for the better. We know we've been effective because even before we start looking at protocols, researchers already have in mind what comments we might give.

TAG: You've spoken about progress not only in terms of the acceptability of research within communities, but also acceptance of community views by researchers themselves. Are there examples where CABs have changed the direction of a study?

Ezio: I think the Global TB CAB has done a good job trying to shape the research agenda. Although sometimes we knock our faces against the wall when we ask for changes that are not implemented.

For the implementation of studies, there is huge progress with the existence of CABs. A good example is the PROVE-IT study in Brazil, where there was a lot of criticism about the way the study was designed by the communities right before the study was approved. [PROVE-IT assessed the rollout of new TB diagnostics in Brazil.] Two years later, the researchers were proceeding with partnerships exactly like the CAB members had suggested at the beginning.

On the PROVE-IT study, one thing that I was really proud of was the fact that the CABs had time to revise the protocol and almost completely rewrite the informed consent form. My boss at the time was furious, thinking that I was going to delay his study. On the contrary, the fact that the CABs revised those instruments accelerated approval at the ethics committee and at other committees.

TAG: Ezio, you said that sometimes in trying to influence research, we end up banging our heads against the wall. Why is there a wall in the first place?

Ezio: Many researchers are very close colleagues and are usually keen on community engagement. But when it comes to influencing study design, I think we have a long way to go.

Wim: But we've been quite successful with some studies. We [Global TB CAB] managed to tweak the STREAM protocol because of reaching out to the donor, USAID [the U.S. Agency for International Development]. We also have a watchdog role that has a preemptive influence even before we see the protocol. I'm thinking of the inclusion and exclusion criteria regarding age restrictions, pregnant women.

Sarah: Initially for us in Kenya, it wasn't easy for the CAB to be allowed to review protocols and informed consent forms. But something has changed, because usually we are called on to review both. We have gotten somewhere, but we are still hoping to see improvements. For example, we are usually given protocols to review just after they [researchers]

have already printed them. Our response was that the CAB is supposed to be given the informed consent and the protocol to review before the final draft.

TAG: What role have CABs played in implementing research findings?

Sarah: This was evident when we had to roll out the new pediatric formulations [of first-line TB drugs]. The role of CABs was to reach out to the government and the community to create awareness that this product is good. For pediatric tuberculosis, the old treatment was very difficult—administering the drugs was not very accurate. We went door to door informing community members and handing out materials, passing on the information to the community and the government that a new drug has come. Through this, Kenya was the first country that rolled out the new pediatric formulations.

Wim: I've seen great examples of CABs distributing study results to grassroots communities. I remember some TB vaccine work where community town hall meetings gathered as many participants as possible to explain the trial results. Especially for prevention, it can be hard to explain negative results. That's hugely important.

Ezio: We [CCAP] did a couple of surveys and found that there were about 1,400 studies on TB going on in Brazil. But very little is being implemented and turning into policy. That is exactly why we want to do a better job.

I think the best example of engaging communities in implementing policies would be the CREATE Consortium THRio study in Brazil. [The THRio trial studied TB preventive therapy for people with HIV.] There was community engagement since the beginning, and TB activists helped to spread information on TB prophylaxis for people living with HIV. There was an immense impact at the study sites. Then the study finished, the CAB was dismantled, and that initiative went down the drain. Physicians no longer were doing prophylaxis. Activists were no longer advocating for it.

Wim: To add: we have been relatively successful placing research-literate community members on national and

international guideline panels. It is almost standard now that civil society representatives, whether or not they come from CABs, are members of guideline committees.

TAG: Looking forward, what are one or two issues you think TB CABs will need to address in the next five years?

Sarah: It's very important to sustain CABs, even during the period after research dissemination, when we are waiting to see what is yet to come up in the pipeline. Because we are not yet there. We need more, better products. Community is paramount in the fight to end TB. It's very important to sustain this link.

Wim: First, I think CABs should reach out more to generic manufacturers, which are at some point necessary in the access work. Also more engagement with regulators. Second is measuring the impact of our work. I wouldn't call it cost-effectiveness of CABs, but at least some evaluation of our work and publishing these achievements. And third, we'll have to continue to build the capacity of our CAB members on fields that we haven't looked at much, like diagnostics or regulatory work.

Ezio: We still have to convince the scientific community that CABs are not there to jeopardize the interest of the studies, but actually to help implement and get the best results. The role of CABs is far from being understood yet. I agree with Sarah about the sustainability issue—that's absolutely fundamental. Wim is absolutely right: We have to understand our impact. I am a qualitative methods person, and it's very hard for me to work with my Anglo-Saxon colleagues on this concept of measurement. The simple existence of a CAB has a symbolic power that already makes researchers and institutions think twice about what they are doing. This is very difficult, almost impossible, to measure. This accountability that the CABs bring is crucial, but it's still not understood.

This interview, which was conducted by phone, has been edited for clarity and length.

SCIENTIFIC COMPLEXITY AND ETHICAL UNCERTAINTIES: THE IMPORTANCE OF COMMUNITY ENGAGEMENT IN HIV CURE RESEARCH

by Richard Jefferys

Introduction

The past decade has seen a major expansion of the research effort to develop a cure for HIV infection. The U.S. National Institutes of Health (NIH), the world's largest biomedical research funder, has identified the pursuit of a cure as one of five primary priorities for HIV.¹ Total global financial support increased substantially in the period 2012–2017, from \$88 million to \$288.8 million.² In 2014, TAG launched an online listing of cure-related clinical research drawn from registries (primarily ClinicalTrials.gov). The list initially contained less than 50 entries; it currently includes 98 clinical trials and 34 observational studies that are ongoing.³ Over 7,000 people are expected to enroll in these studies.

As with other areas of HIV research, engagement of the community of people living with HIV and their advocates is vital for ensuring that the conduct of cure-related studies is ethical, appropriate, and responsive to community priorities. Dissemination of clear, understandable information is also essential for imbuing participants with knowledge about what they are getting into, so that their consent is truly informed.

Seeds of Hope

The seed for the blossoming of HIV cure research was Timothy Ray Brown, the first person considered cured of HIV. Brown's case was first described in 2008 in a little-noticed poster presentation at the Conference on Retroviruses and Opportunistic Infections (CROI). Notably, one of the only people to draw attention to the report at the time was community activist Martin Delaney, founder of Project Inform.⁴

Brown was cured of HIV after receiving stem cell transplants as part of a series of treatments for a life-threatening cancer diagnosis.⁵ He has now been off antiretroviral therapy (ART) for 12 years without any sign of a return of the virus.

Recent presentations at the March 2019 CROI indicate that two additional people may have joined Brown,^{6,7} but follow-up is far shorter: One of the individuals has been off ART without evidence of HIV rebound for 18 months, while the other is at about four months.

Translating to a Wider Community

These additional cases of possible cures are encouraging, but the method used to achieve this outcome cannot be used in most people with HIV, who do not require stem cell transplants for cancer (the high mortality risk associated with transplantation precludes its use outside of this setting).

In the absence of any known safe alternatives for obtaining similarly robust depletion of HIV from the body, investigators are evaluating a broad array of interventions. In some cases, the aim is to ascertain if the immune system can be manipulated to control HIV replication in the absence of ART, as opposed to eliminating the virus entirely.

The early, exploratory nature of the HIV cure research field raises difficult issues for study participation and community engagement.

Understanding Risks and Benefits

The current early stage of the research means that there is little to no prospect of any health benefits to participants, and risks can be significant. Sources of risk include side effects of experimental interventions, invasive study procedures (e.g., tissue sampling), and the conduct of analytical treatment interruptions (ATIs—a temporary stoppage of ART). In the case of ATIs, the potential risk applies to not only study participants but also sexual partners, because HIV viral load rebound is

associated with increased infectiousness (one case has been documented in which a study participant transmitted HIV to a partner during an ATI⁸).

The invocation of the term “cure research” may complicate attempts to accurately communicate the uneven risk/benefit equation to potential participants. The mere use of the word “cure” can mislead people into expecting that there is some prospect of being cured when there is typically none, a problem known as therapeutic misconception. The tendency of the mainstream media to overhype preliminary HIV cure research results is an additional factor that may skew perceptions of risks and benefits.

The difficult ethical terrain that HIV cure research must negotiate has spurred social science studies aiming to shed light on the knowledge and attitudes of potential participants (as well as the broader community). The first online survey to probe these issues was conducted by two longtime community activists, David Evans and Nelson Vergel, with social scientist Michael Arnold leading the analysis.⁹ Several academic and community-based groups have since been funded to expand the social science knowledge base, such as the searchHIV collaboration.¹⁰ A key theme emerging from this work is the central importance of altruism as a motivator to engage with the research, with the goal of benefiting science and future generations.

The Need for Representation

Against this complex backdrop, efforts are also underway to broaden appropriately informed participation in HIV cure research. The goal is to better reflect the demographics of the HIV epidemic, because otherwise the generalizability of results can be limited. There is evidence of important biological sex differences relevant to HIV cure research, and variation based on ethnicity or geography is also a possibility.^{11,12,13} So far, reports indicate that the diversity of cure research participation is far from optimal, with a particular underrepresentation of women.^{14,15}

A Glimpse at the Engagement Landscape

Multiple organizations and collaborations are undertaking cure-related community engagement activities.

The primary NIH-supported HIV cure research bodies are named after Martin Delaney, who died in 2009. Three Martin Delaney Collaboratories (MDCs) were founded in 2011, and this was expanded to six in 2016. Each has a community advisory board (CAB), and two representatives from each CAB participate in conference calls intended to enable cross-CAB communication and collaboration.



Sylla L et al. What would an HIV cure mean to you? Ascribing meaning through an HIV cure tree. Poster abstract WEPEC1047, IAS 2017.

In addition to providing community input into collaborative research, MDC CABs have sponsored educational outreach initiatives including webinars, in-person meetings, and written educational materials. At the International AIDS Conference in Durban in 2016 MDC CABs jointly sponsored a booth in the Global Village to provide educational materials and to solicit feedback from attendees on what an HIV cure would mean to them.

The amfAR Institute for HIV Cure Research at the University of California, San Francisco, also has a CAB and sponsors a free annual summit to update the local community on the status of its work. A program to support HIV cure research was launched at amfAR soon after Timothy Ray Brown’s case was reported and has included substantial community input as well as the generation of accessible educational literature.

The AIDS Clinical Trials Group (ACTG), which has been the primary clinical research network in the U.S. for decades, formed an HIV Reservoirs and Viral Eradication Transformative Science Group (Cure TSG) in 2011. The Cure TSG includes representatives from ACTG community advisory boards.

The International AIDS Society (IAS) launched its Towards an HIV Cure Initiative in 2010, and several community advocates are on the advisory board. Activities targeted toward the community include workshops held immediately before annual

IAS scientific conferences and the recently initiated Advocacy-for-Cure Academy, a three-day training and development course for people in resource-limited settings. The first was held in May 2018 in Uganda, and the second is taking place at the end of April 2019 in Botswana. Moses “Supercharger” Nsubuga, a Ugandan activist involved in the initiation of these academies, has set up one of the first advocacy coalitions on the African continent, the Cure Research Advocacy Group (CRAG).

The National Association of People with HIV Australia has long been involved in cure research advocacy and collaborates closely with researchers at the Doherty Institute on the community-oriented website hivcure.com.au.

Many other community-based organizations with a history of working to increase research literacy, including (but not limited to) AVAC, the European AIDS Treatment Group, HIV i-Base, NAM, Project Inform, TAG, and the Well Project, have expanded their coverage to include the cure field. The Well Project’s Women’s Research Initiative on HIV/AIDS is addressing the issue of the involvement of women by hosting discussions and publishing an issue brief on the topic.¹⁶

Conclusion

The dauntingly complex science underpinning the search for an HIV cure makes it challenging to develop accessible strategies for educating and engaging community stakeholders. But many individuals, organizations, and advisory bodies have begun to address the need. Compared to the longer history with HIV treatment and prevention research, we’re in relatively early days, and there is room for advocates in these different silos to share information and learn from each other.

As HIV cure research expands globally, the need for international information-sharing mechanisms will grow. The listing of community engagement mechanisms and activities in this article is far from exhaustive, and this speaks to an information gap: It could be beneficial to have a central resource listing from which to work as advocates strive to expand and improve the extant landscape.

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THE FINAL FRONTIER

Breaking Down Barriers to Community Engagement in Diagnostics Research

by Erica Lessem and Stacey Hannah

Throughout this *TAGline* edition, we've seen the power of community engagement to positively influence prevention and treatment research, and how the HIV and TB research fields have evolved—albeit at different paces—from a default policy of exclusion of communities from decision-making to an acceptance, appreciation, and normalization of community engagement and even leadership in research. Yet these advances have largely been absent from diagnostics research.

We're seeing progress toward engaging communities in the development of diagnostics. For example, developers of TB diagnostic products in late-stage development have consulted with the Global TB Community Advisory Board (TB CAB, see [Sound Off](#)) on pathways to developing their tests and on getting them recommended and supported through donor funding mechanisms. Manufacturers who have inappropriately marketed TB tests in India have had to respond to TB CAB concerns.^{1, 2} The Stop TB Partnership's New Diagnostics Working Group, housed at FIND, includes community representation and thoughtfully liaises with civil society organizations such as TAG in many of their efforts. A TB survivor participated in the World Health Organization's process to develop target product profiles for new TB diagnostics.³ A Unitaid grant to FIND for hepatitis C diagnostics scale-up includes a community engagement component.

But the little community engagement in diagnostics development so far has often been tokenized, or has come rather late in the process. This exclusion is likely in part due to: (i) lack of awareness of the need to involve communities and the mechanisms for doing so, (ii) presumptions around communities' ability to engage in the more technical nature of diagnostic development, and (iii) the fact that diagnostic research does not follow the same clinical development pathway with human participants as development for drugs, vaccines, and other prevention interventions.

Increasing the involvement of communities, from concept development to the post-implementation review stage, would help ensure that tests are responding to patient needs and are acceptably designed (e.g., with regard to the type of sample

collected and the route of collection, and with affordability and simplicity in mind). This could include organizing community surveys or consultations, interviewing community leaders during the design stage about applicability, and having developers meet with community advisory boards or community steering committees before approving or launching a diagnostics development or implementation project. At later stages of the development lifecycle, engaging communities in planning in-country validation studies—which are often required for national use—would ensure selection of sites that are appropriate, geared to key populations, and community-friendly. This includes potentially involving members of key populations as screening/testing peer educators, to ultimately inform national guidance.

These communities can include people who are at risk for or have the disease, as well as those who care for them, including community health workers and clinicians. For example, for hepatitis C diagnostic research, including community representatives who use drugs or engage in sex work might be critically important to ensure that tests meet their needs and are being implemented in places where they seek care. For TB, key community members to engage might include parents of children with TB, and people with HIV, for whom sensitive diagnostics with easy sample collection are still lacking.

Empowering communities to engage in diagnostics research is essential. Investing in expanded opportunities to increase diagnostics literacy would sensitize communities to new tools coming down the pipeline, building their technical capacity to advocate for sound research and uptake of appropriate tools. Such advocacy could include calls to streamline regulatory processes and normative guidance development at the national and global levels.

Given that existing community engagement principles have largely been developed for a distinct scope—clinical trials that involve putting an intervention directly into bodies—a targeted effort to guide community engagement in diagnostics research would be useful for community members, developers, and donors alike. Key recommendations and tools for Good

Participatory Practice Guidelines—which were originally developed for biomedical HIV prevention trials, and have since been adapted to TB drug, TB vaccine, and emerging pathogens trials⁴—should be developed to guide engagement in diagnostics development across diseases. The GPP guidelines provide a systematic framework that could be adapted to the processes, stakeholders, and decision points critical to diagnostic research. Over a decades' worth of GPP implementation and lessons learned will provide a solid foundation for making ethical and appropriate community engagement a cornerstone of diagnostic research and development.

Stacey Hannah is the Director of Research Engagement from AVAC.

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