THE FORUM FOR COLLABORATIVE RESEARCH

EXPANDING INCLUSION FOR LONG-ACTING HIV TRIALS

Executive Summary

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THE FORUM
For Collaborative Research℠

Berkeley Public Health

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ABSTRACT

The Forum for Collaborative Research convened the "Expanding Inclusion for Long-Acting HIV Trials" workshop to address a broad set of challenges and possible solutions for people who could benefit from long-acting HIV Treatment. Participants discussed the need for, approaches to, and regulatory considerations for expanding inclusion in clinical trials to all people living with HIV, especially those with difficulties adhering to oral therapy. The goal was to clarify the types of future clinical trials researchers should focus on to show efficacy in specific population groups for FDA approval and treatment guidelines. The workshop brought together representatives from the Food and Drug Administration (FDA), National Institute of Health (NIH) Office of AIDS Research, National Institute on Drug Abuse (NIDA), National Institute of Mental Health (NIMH), Health Resources and Services Administration (HRSA), AIDS Clinical Trial Group (ACTG), various academic institutions, governmental agencies, and industry sponsors like Merck, ViiV, and Gilead.

LESSONS LEARNED FROM OTHER FIELDS AND OPPORTUNITIES

The workshop began with lessons learned from other fields and disease areas, such as Hepatitis C Virus (HCV) and psychiatry and examined case studies of clinical trials that included populations who historically have been unrepresented in clinical trials. For example, Dr. Gregory Dore from the Kirby Institute, described his experience working with people who inject drugs in a clinical trial testing Directly Acting Antiviral (DAA) medication for HCV efficacy and virulency. The key populations in HCV include people who are drug users (within the past six months), people in prison, and people on opioid treatment, such as methadone. One study described was the CO-STAR Study, the first major trial on DAA safety and efficacy, that included people who inject drugs with 53 sites in North America, Europe, and Australia. Dr. Dore's studies highlighted that efficacy and safety outcomes among people who inject drugs were comparable to the wider population.

In another example, Dr. Sally Hodder from the University of West Virginia discussed the lack of clinical trials in rural communities across the United States and Puerto Rico. For many reasons, including inadequate HIV prevention and treatment infrastructure, there have been rising trends in HIV prevalence and incidence alongside the rise in drug overdose mortalities in communities across West Virginia. West Virginia is heavily burdened with two major HIV outbreaks and 300 cases to date, yet there are zero HIV clinical trials in the state. Dr. Hodder described two approaches to increase trial participation including tapping into the IDeA States Consortium for Clinical Research (ISCORE) network that focuses on including underserved populations in clinical trials and has proven to be highly instrumental during COVID-19. Another network is the West Virginia Practice-Based Research Network that includes 129 sites, mostly Federally Qualified Health Centers where researchers originally from West

Virginia, approach the community and ask what kind of research would be most beneficial. This approach resulted in greater participation and follow-up among all the clinical trial sites. Dr. Hodder demonstrated that there is a lack of clinical trials being conducted in the most burdened places in the country. Only a small percentage of NIH clinical trials are conducted in 46% of US States and Puerto Rico and there is a great need for novel trial networks to alleviate these disparities. Dr. Hodder also emphasized the importance of being transparent around the implications of clinical trials to increase engagement and "buy-in" to the science.

Jonathan Liu, a Resident Physician at George Washington University Department of Psychiatry and Behavioral Sciences, bridged the conversation into the field of psychiatry. There is an overlap between people living with HIV and those experiencing psychosis, such as a subgroup of injection drug users, in which long-acting psychiatric medications have been shown to be greatly beneficial. Similar to the projections of implementing HIV long-acting treatment, psychiatric long-acting medications are the most cost-effective approach in terms of reduced risk for hospitalization among psychosis patients. A widely used implementation model in psychiatry, the Assertive Community Treatment (ACT) model, uses mobile teams to conduct home visits and individualized treatment plans to meet the patient in the community. This model has proven to be effective in increasing treatment adherence and could be used in implementing long-acting HIV treatments for similar population groups.

Circling back to the HIV field, physicians and people living with HIV shared success stories and challenges from the real-world. Consensus among physicians present was that long-acting injectables have saved the lives of those who otherwise could not be virologically suppressed on oral HIV treatment. Patient adherence to long-acting injectables is a bit more forgiving and there are fewer patients who had virologic failure. Physicians described that even their most stigmatized and disenfranchised patients who could not be suppressed using oral antivirals were finally virologically suppressed with long-acting injectables. People living with HIV and on long-acting injectables described how life-changing it is to not experience pill burden, stigma, or the daily reminders of carrying around a pill bottle. They described long-acting injectables as more convenient and allowing greater freedom to travel. There is a real hunger in the community to have access to long-acting injectables, but people living with HIV and physicians both felt that there are still some challenges and concerns. Physicians described some of the difficulties with rolling out programs for long-acting injectables including how to engage people, especially those who are marginalized, to come back to clinic every two months for their injections. People living with HIV felt a real concern around missed injections and the fear of resistance. Both physicians and people living with HIV discussed the difficult process of switching from pill to injectable treatment in terms of access, cost, and insurance coverage. The key takeaway from this conversation was that the benefits of long-acting injectables outweighed the risks. Moving forward, all participants agree that it is essential to include populations from a full spectrum of backgrounds in order to understand the safety and efficacy of long-acting injectables and the necessary implementation strategies.

ENSURING ACCESS TO LONG-ACTING ARVS IN THE PRE-APPROVAL SETTING

Timothy Jancel, a Clinical Reviewer from the FDA Division of Antivirals, spoke on the FDA's role in expanding inclusion in clinical trials for long-acting ARVs, as well as regulatory considerations and various examples of clinical trials in HIV-1 drug development. The FDA acknowledges the desire of investigators to expand the use of long-acting ARVs in populations not evaluated in clinical trials. FDA guidance recommends approaches that industry sponsors can take to increase enrollment of underrepresented populations in their clinical trials but can only encourage (not mandate) clinical trials for specific indications and patient populations. As safety, efficacy, and general benefit-risk assessment is better understood for a drug, additional populations may be included in later stages of development, like post-approval. Post-approval clinical trials may focus on drug-drug interactions or patients with renal or hepatic impairments. The final indication is reflective of the overall benefit-risk assessment for various populations studied. To further elaborate through a recent example in HIV drug development, the GRACE study was used to show outcomes in women after starting on an ARV regimen. This study focused on a specific population. Whereas the results are not included in labeling they do influence the practice in medicine and treatment guidelines. Another example is the DRIVE-SHIFT model that was used in doravirine studies in treatment-naïve and treatment experienced patients. Participants were randomly assigned to the immediate switch group or delayed switch group to compare primary efficacy. This immediate vs delayed approach has also been used in HCV trial designs, as well. In summary, not every premarket or post market trial is included in labeling but can make important contributions in practice and in treatment guidelines. The FDA emphasized that the agency is not involved in the policies that state formularies or insurance companies require for coverage.

Present FDA representatives made it clear that the highest standard for clinical trials in any population group is randomization but there are ways to incorporate other study designs, such as immediate and delayed treatment, for populations who have challenges adhering to treatment. For example, the PrEP/Truvada placebo-controlled clinical trial included nonadherent patients and the overall efficacy was less than what had been hoped. To address this, the study team did a detailed reclassification on drug levels that correlated with efficacy. Alongside reporting the primary results, they also reported the pharmacology to determine dose ranging type. This type of study is less limiting than a single-arm study for non-adherent and non-suppressed patients. Representatives from the FDA made it clear that the agency is always open to new ideas and willing to work with industry sponsors to be able to include various populations in labeling.

Industry sponsors from Merck, ViiV, and Gilead spoke on drug development priorities, challenges, and opportunities during pre-approval research. It is critical early in drug development that trial participants are adherent to the drug to determine safety and efficacy but there could be more done to include those who are hardly reached and close the gap where HIV exists the most. The primary objective for drug companies is to get the drug approved, but following approval, the FDA has opened the door for

creativity. For example, the FDA has created a series of guidance on the use of real-world evidence in the post-marketing space, such as pragmatic trials, as support for label extension. Third-party data, such as pregnancy data, could also be used for indication and safety. Another way to increase inclusion in clinical trials is through investigator studies or collaborative programs with external groups. Collaborations with social and behavioral scientists could be beneficial in finding ways to make clinical trials more human-centered and empowering for participants. There is also potential for public-private partnerships in which industry sponsors partner with institutions or networks, like the AIDS Clinical Trials Group, to study the drug in specific target populations parallel to Phase 3 clinical trials. Industry sponsors, researchers, and physicians should challenge the assumption that expanding inclusion to those who are hardly reached will slow down the approval process. In contrast, it has been shown that people who are included in trials are more likely to be adherent.

Another approach to expanding inclusion in the pre-approval setting is creating more specific exclusion and inclusion criteria. For instance, viral load criteria, biomedical markers of drug levels, or future risk of virologic failure could be used as criteria. It is more useful to use objective measures of non-adherence instead of categorizing a person as non-adherent. The term “non-adherent” puts the blame on the patient and does not center the whole person.

In thinking creatively in how to engage more people who are hardly reached to participate in trials, one size does not fit all. For example, to engage rural communities it may require the use of mobile units or retail pharmacies to expand access, enrollment, and services. For other communities, decentralized or remote options could help with inclusion and expansion. Incorporating co-principal investigators from the communities can increase trust and help ~~to~~ address regional concerns. It is also important to consider existing organizations such as the Department of Veterans Affairs (VA), representing the aging HIV population, who already have established facilities and resources.

ENSURING ACCESS TO LONG-ACTING ARVS IN THE POST-APPROVAL SETTING

Once safety and efficacy are established, there are ways in which post-approval clinical trials can prioritize hardly reached populations. Two examples highlighted were the ongoing LATITUDE Study (ACTG 5359) and the Ward 86 Pilot Study. Co-principal investigators Dr. Aadia Rana and Dr. Jose Castillo-Mancilla discussed their experience working with “non-adherent” patients to determine the durability of long-acting injectable HIV treatment. Long-acting ART has the potential to improve virologic suppression in non-adherent patients because it requires infrequent dosing and allows for directly observed therapy. The researchers hypothesized that after achieving suppression during a 24-week period of incentivized standard of care (SOC), long-acting ART will be successful (achieve virologic suppression) compared to SOC in previously non-adherent patients. The study included 350 participants that were randomized to receive either oral ART or long-acting ART, with some participants crossing over from oral ART

to long-acting ART at 48 weeks. Adherence support strategies, such as travel vouchers and graduation diplomas for step completion, were used during the study and proved to be very motivating. Every site also had A5359 study coordinators that would do outreach work like calling people, arranging transportation, and finding participants. There were some challenges in recruitment, screening, and randomization but the protocol has evolved over time to address these challenges.

Dr. Monica Gandhi from the University of California, San Francisco described her ongoing work at Ward 86. Ward 86 caters to some of the most vulnerable populations who experience mental illness, poverty, addiction, and lack of housing. The initial 100 participants (now 122) included in the pilot study did not need to be virologically suppressed but had to express verbal commitment. The study participants could not adhere to daily pills due to a variety of reasons and directly started on injectable treatment without an oral lead-in. Key elements that contribute to the study's success include the multidisciplinary team with a Pharm. D., pharmacy technician, clinic leadership, and POP-UP program leader who could help review each patient and refine the protocol based on observations. In the clinic, there are designated social workers, a registered nurse, a pharmacist, and a provider present every day to provide injections and on-site medical services. The clinic also provides life services such as food resources, social services, emergency housing, and treatment program referrals. Results of the first 100 participants show that between June 2021 and August 2022, 100% (59 participants) of participants who were suppressed at baseline remained suppressed and 98% (41 participants) of participants who started unsuppressed at baseline became suppressed after two injections. Implementation and incentive strategies, such as gift cards, were used to ensure patients made it back to the clinic and, in some cases, participants were located to provide mobile injections or bring them back to the clinic.

A panel consisting of representatives from HRSA, NIH, industry, researchers, and participants discussed post-marketing trials and treatment guideline necessities. Messaging and marketing need to be different to engage hardly reached populations and researchers should try to address the concerns of these participants when designing post-marketing trials. In terms of trial design, a randomized clinical trial is the gold-standard with randomization into immediate and delayed arms. It could also be possible to have different clinical trial sites in rural areas that could study both efficacy and implementation with the necessary support system to achieve suppression. This data can be translated into the real-world by establishing a road map to achieve suppression over time. A representative from industry clarified that for sponsors the type of post-marketing clinical trial is dependent on the end goal. The end goal may be a label change or expanding the body of data for treatment guidelines. If the pharmaceutical company wants the label to read that drug X can be used in patients who are treatment naïve or switch patients that are intravenous drug users, it is more expensive and complex because it needs to go through a phase 3 trial. This type of study is resource intensive with respect to study size and time. Alternatively, data to change clinical guideline recommendationsmay come from less resource intensive type of studies.

The HIV treatment guidelines panel consists of about 50 people representing major agencies like the NIH, HRSA, CDC, and other academics, experts, and

community members. The panel's mission is to synthesize all currently available information and make practical recommendations that providers can refer to on how to manage their patients. The panel also consults established subgroups that look at all available data for specific populations. Once all the data has been considered, the panel votes and grades the data. The data is ranked in two different ways: by letter (A is strongly recommended, B is moderately recommended, C is weak recommendation) and by number (1 is randomized control trial, 2 is observational, 3 is expert opinion). The score reflects the strength of the data for that recommendation. While the FDA looks at drug safety and efficacy, the guidelines panel looks at different recommendations based on safety, efficacy, and whether there are high barriers to resistance. The panel also compares the different treatment strategies and determines the optimal strategy for providers to take the best care of their patients. The panel's willingness to make recommendation outside perfect score (A1) would be based on knowledge gap, such as in the case of treating unsuppressed populations where there are not as many treatment options.

Guidelines are important in determining insurance coverage and reimbursement, especially when the physician decides to use a treatment off-label. State AIDS Drug Assistance Programs (ADAP) only require including one drug from each category/class on their formulary. Additionally, HRSA cannot require ADAPs to have specific drugs on their formularies. Once long-acting injectables are written in the guidelines, ADAP formularies usually follow through. For example, in Massachusetts, where guidelines hold weight, the Massachusetts ADAP formulary includes long-acting injectable treatment as the standard of care. Price and cost are the biggest factors ADAPs consider. If there is more data on the drug that is targeting a specific population, it makes the option more attractive for payers. ADAPs do consider that long-acting injectables may be a slightly risky investment if the state procures the treatment in bulk but patients don't show up for injections. So far, only 29 state ADAPs have long-acting injectables on their formularies.

ALL OPTIONS ON THE TABLE

Researchers, physicians, and people living with HIV all agree that long-acting injectables have potential to vastly improve quality of life for all people living with HIV, especially those who find the healthcare system complicated and have not succeeded with oral therapy. Long-acting injectables allow for longer intervals between medication, meaning those living with HIV do not need to think about HIV on the daily basis. Through examples from other fields and disease areas, the HIV field knows it is possible to successfully include populations who are hardly reached in clinical trials. It is important to include community members in HIV scientific efforts because by addressing their concerns, people who are hardly reached are more likely to engage in clinical trials and adhere to treatment. In future pre-approval clinical trials, industry sponsors should create a balance between designing a clinical trial for quick drug approval that also includes the people who could benefit most from the drug. Alternate models for clinical trials, such as immediate and delayed switch trials, could be the

avenue to include populations that are hardly reached earlier in the process of drug approval. There are several examples of post-marketing trials in these populations, such as ACTG 5359 and the Ward 86 pilot study, that prove long-acting injectable treatments in conjunction with adherence support can be extremely successful in achieving viral suppression. These studies have shown that it requires an extraordinary amount of work, resources, alongside political and medical will.

All participants have a shared goal of creating safe and effective treatment and making it accessible to all people living with HIV. Treatment guidelines provide useful information that help physicians, insurers, and people living with HIV make decisions about what treatment is best for them or their patients. It may be more feasible to design clinical trials tailored to inform treatment guidelines as opposed to drug label changes. These studies are easier, quicker, and less costly, allowing long-acting injectable treatments to be available to those who need it most at an accelerated rate.

The Forum for Collaborative Research recognizes the necessity of equitable HIV research that benefits everyone. The workshop on “Expanding Inclusion for Long-Acting HIV Trials” is only the beginning in a longer discussion on how to make HIV treatment more accessible and put an end to HIV. In the future, the Forum for Collaborative Research hopes to continue the conversation in addressing challenges and approaches to the real-world implementation of long-acting HIV treatment. These topics could include who pays for treatment (Medicaid, ADAP, private insurers, etc.), further exploring what it would take to get them to pay (such as treatment guidelines changes), and the broader public health benefit of long-acting treatment using cost effectiveness modeling.