

**U.S. Department of Health and Human Services
National Institutes of Health
Office of AIDS Research**

**Office of AIDS Research Advisory Council
Forty-Second Meeting**

**April 7, 2016
5601 Fishers Lane Conference Center
Rockville, Maryland**

Meeting Summary

Members Present: Dr. Roy M. Gulick (Chair), Dr. Robert W. Eisinger (Executive Secretary), Mr. Moisés Agosto-Rosario, Dr. Ralph J. DiClemente, Dr. Monica Gandhi, Dr. Priscilla Hsue, Dr. Daniel R. Kuritzkes, Dr. Ronald T. Mitsuyasu, Dr. Darrell P. Wheeler

Ex Officio Members Present: Dr. Emily Erbelding, Division of AIDS, National Institute of Allergy and Infectious Diseases (in place of Dr. Carl Dieffenbach); Dr. James E.K. Hildreth, Meharry Medical College; Dr. Paul T. Scott, Walter Reed Army Institute of Research (for Dr. Nelson Michael)

Ad Hoc Members Present: Dr. David Celentano, Dr. Elizabeth Connick, Ms. Dázon Dixon Diallo, Dr. Michael M. Lederman, Dr. Scott D. Rhodes, Dr. Charles Wira

Invited Speakers and Guests: Dr. Elizabeth R. Brown, Dr. Deborah J. Donnell, Dr. Charles W. Flexner, Dr. Monica Gandhi, Dr. Cynthia Grossman, Dr. Sharon L. Hillier, Dr. Jonathan E. Kaplan, Dr. Angela Kashuba, Dr. Lisa C. Rohan, Dr. James A. Turpin, Dr. Kimberly A. Woodrow

MICROBICIDES AND PREP: THE NEXT STEPS

Welcome and Meeting Overview

Roy M. Gulick, M.D., M.P.H., Weill Medical College of Cornell University

Dr. Roy Gulick welcomed the participants to the forty-second meeting of the National Institutes of Health (NIH) Office of AIDS Research Advisory Council (OARAC), invited members and speakers to introduce themselves, and reviewed the meeting materials. Meeting materials included the agenda, a conflict-of-interest form, dates for the two upcoming OARAC meetings, materials to frame the discussions, and minutes of the November 12, 2015 meeting. The OARAC members approved the minutes from the previous meeting as written.

Dr. Gulick then briefed the Council on the agenda for the day, noting the inclusion of time at the end of the meeting for public comment.

Report from the Office of AIDS Research (OAR) Acting Director

Robert W. Eisinger, Ph.D., OAR, NIH

Dr. Robert Eisinger welcomed all of the participants to the meeting. He reminded the OARAC members to complete their conflict-of-interest forms and submit them to an NIH staff member. NIH policy also requires all individuals appointed to serve as Council members to complete the appropriate financial disclosure forms prior to the OARAC meeting.

Dr. Eisinger detailed the portfolio review requested by the NIH Director, Dr. Francis Collins and conducted by OAR, in cooperation with the NIH Institutes and Centers (ICs), that was described during the November 2015 OARAC meeting. The purpose of the review is to assess the alignment of current NIH funded HIV/AIDS research with the new overarching HIV/AIDS research priorities released in August 2015. The review included extramural grants and contracts and intramural investigator-initiated projects supported HIV/AIDS funds during fiscal year (FY) 2014 and scheduled to re-compete for funding in FY 2016 were presented to the NIH Advisory Committee to the Director on December 11, 2015.

The results of the portfolio review were described. . Of the projects scheduled to re-compete for funding in 2016, there were 1,207 extramural projects. Sixty-nine percent of those, were rated as high priority; 11 percent were rated as medium priority; and 20 percent of the total, were rated as low priority. Low-priority projects included studies on basic virology and immunology, genomics, infectious pathogens outside of the context of HIV, and training projects with no clear indication of an AIDS component. There were 56 intramural projects reviewed. Thirty-two percent were rated as high priority; 21 percent were rated as medium priority; and 47 percent were rated as low priority. The low-priority projects included research on infectious pathogens not in the context of HIV; basic studies on tumor immunology and genetics, T cell development, autoimmunity, and cancer; and the evaluation of biological and behavioral effects of drug dependence and treatment with no HIV/AIDS component. Of the portfolio of contracts eligible to re-compete in FY 2016, one contract was deemed low priority.

Following the portfolio review, the approximately \$65 million that funded low-priority grants and contracts was reallocated to a Common Pool that will be used to fund high priority HIV/AIDS-projects. All ICs were eligible to submit funding proposals to the OAR for high-priority projects aligned with the new overarching HIV/AIDS research priorities. The proposals were reviewed, final determinations were made, and the funds now are being transferred from the Common Pool to the relevant ICs. This approach ensured that all HIV/AIDS research is in alignment with the overarching priorities identified by Dr. Collins.

The OAR is conducting the next portfolio review which focuses on projects that were supported by AIDS funding in FY 2015 and are eligible to re-compete in FY 2017. The results will be available in spring 2016. A similar annual review is planned for the next 3 to 4 years to ensure that the entire AIDS portfolio is aligned with the overarching HIV/AIDS research priorities.

Since the release of the new overarching HIV research priorities, the OAR has launched a number of new processes to ensure that future funding decisions align with the priorities. These include OAR review of:

- Funding opportunity announcements (FOAs), requests for applications (RFAs), and requests for proposals (RFPs) before they are issued
- New and competing grants, contracts, and intramural projects that are proposed for support by AIDS funding. Discussions are ongoing with the Center for Scientific Review (CSR) on referral guidelines and the potential restructuring of AIDS Integrated Review Group study sections.

In addition, the OAR discretionary fund will only be used to support peer-reviewed grants, contracts, and intramural projects. At the end of the third and fourth quarters of the current fiscal year, the OAR will examine all of the projects supported with HIV/AIDS funding to ensure that they are aligned with the new overarching priorities and appropriately coded to match NIH HIV/AIDS strategic plan codes. For the FY 2017 trans-NIH AIDS budget, developed in consultation with the NIH Director, the OAR provided guidance for the development of the ICs' AIDS budget submissions to ensure that each proposed new, re-competing, and expanded initiative was aligned with one or more of the overarching priorities.

The FY 2017 Trans-NIH Plan for HIV-Related Research (the Plan) was recently released. The Plan outlines the priorities for NIH HIV/AIDS research efforts to end the AIDS pandemic for the scientific community, the public, and HIV-affected populations. The overarching priorities include:

- Reducing the incidence of HIV and AIDS
- Developing and testing the next generation of HIV therapies
- Research toward a cure
- The prevention and treatment of HIV-associated comorbidities, co-infections, and other complications.

The Plan also includes crosscutting areas with a continued emphasis on basic research, research to address health disparities, and training. Although total FY 16 HIV/AIDS funding is estimated to remain constant at \$3 million compared with FY 2015, the AIDS funding allocation among the ICs has changed to ensure that resources address high-priority studies. The portfolio review process has been critical in identifying projects that are no longer aligned with the new overarching priorities and can no longer be supported with HIV/AIDS funding. Regarding the distribution of funding by scientific area, from FY 2015 to FY 2016, funding increased significantly for vaccine and microbicides research, behavioral and social science research, and research toward a cure.

Update on OARAC Working Groups for Treatment and Prevention Guidelines

Jonathan E. Kaplan, M.D., Centers for Disease Control and Prevention (CDC)

Dr. Jonathan Kaplan provided an update on the OARAC Working Groups on the treatment of HIV-infected adults and adolescents and on the prevention and treatment of opportunistic infections (OIs) in HIV-infected adults and adolescents. The Panel on Antiretroviral Guidelines for Adults and Adolescents meets via conference call monthly and in-person annually. Of note:

- Subgroups work to update the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* and the AIDSinfo website (<https://AIDSinfo.nih.gov>)

- A new *Guidelines* mobile app launched in December 2015 has generated significant activity and excitement
- The next update, to be released in July 2016, will reflect U.S. Food and Drug Administration (FDA) approval of products containing tenofovir alafenamide (TAF).
- The customer satisfaction survey on the usability of the guidelines, organized by Health Resources and Services Administration (HRSA), contained responses from more than 400 healthcare providers. Out of a maximum score of 100, the guidelines scored uniformly high—in the 80s and 90s—in customer satisfaction, usability, overall content, and accessibility. The only scores below 80 concerned document length and who to contact for assistance.

The guidelines are maintained online at the AIDSinfo (www.AIDSinfo.nih.gov) website. During the past 6 months, the guidelines have been updated multiple times. Demand for the guidelines continues despite the decrease in the incidence of OIs in the era of ART. There have been more than 250,000 page views and 25,000 downloads in the past 12 months. The guidelines will remain evidence-based to the extent possible but will include expert observation-based opinion due to the lack of trials to validate some new approaches.

Dr. Nahida Chakhtoura of NICHD reported on the Pediatric OI, Pediatric ART, and Perinatal Guidelines. The last full update by the Pediatric OI Panel was in November 2013. Pediatric topics are reviewed approximately every 2 years. Recently reviewed sections currently undergoing CDC clearance include influenza, microsporidiosis, and HHV-8. The CD4 threshold harmonization was a major focus for the panel.

The Pediatric ART Guidelines Panel published its most recent update of the *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* in March 2016. Major changes included simplification and streamlining of the recommendations; improved alignment with other guidelines; the recommendation of ART for all children regardless of age at diagnosis; an updated “What to Start” section with a new figure representing preferred and alternative regimens by age and drug class; and an update of pediatric and pharmacokinetic safety data, as well as updated dosing recommendations. A recommendation regarding the Odefsey® regimen will be added in the coming weeks.

The Perinatal Guidelines Panel last published an update in August 2015 and anticipates a full update in summer 2016. Drug section updates will be published as they are finalized. The two sections with the greatest number of page views from March 2015 through February 2016 are “Infant ART Prophylaxis” and “Initial Postnatal Management,” with more than 23,000 and 10,000 views, respectively.

Dr. Chakhtoura recognized the efforts of the chairs, co-chairs, executive secretaries, AIDSinfo website staff, and more than 200 volunteer members of the working groups in producing and updating the guidelines. Dr. Gulick added that 2016 marks the 20th anniversary of the HIV/AIDS guidelines, sponsored by the Department of Health and Human Services. He recognized Dr. Kaplan, who has served on the OI guidelines panel during its entire 20 years. Dr. Gulick commented that the high numbers of page views for the guidelines is an indication that

they have been successful in meeting their goal of providing cutting-edge information to individuals caring for people with HIV/AIDS.

Dr. Eisinger thanked Dr. Darrell Wheeler and Dr. Clemente Diaz, whose terms on the OARAC end prior to the next meeting, for their dedication and participation in the OARAC. In addition, he acknowledged staff members who recently joined the OAR, including Dr. Vanessa Elharrar, Dr. Shoshana Kahana, and Ms. Dominica Roth.

Introduction to OARAC Topic

Gina Brown, M.D., OAR, NIH

Dr. Gina M. Brown, the Coordinator for Microbicides and Women and Girls HIV Research in the OAR, introduced the topic for the OARAC discussion: *The Next Steps for Research on Pre-Exposure Prophylaxis (PrEP) and Microbicides*. She recognized the tremendous scientific advances have been made for HIV prevention including knowledge about the mechanisms of HIV acquisition, mucosal immunology, the microbiome; the development of surrogate models for prevention, including animal and tissue models; and new product development and delivery methods.

Dr. Brown described the current OARAC meeting as an effort to consider how to advance the science. She reviewed the topics for the day's discussion and reminded the audience that although a perfect product that solves all of the problems of HIV prevention likely never will exist, it is important to view the current status of HIV prevention as a "half-full glass" and to strive to fill the rest of the glass.

Dr. Gina Brown thanked the speakers for presenting the science at this meeting. She urged the participants to reflect on how their perspectives can be used to advance the science of HIV prevention.

Microbicides and PrEP Studies: What Have We Learned?

Sharon L. Hillier, Ph.D., University of Pittsburgh

Dr. Sharon Hillier addressed lessons learned from microbicides and PrEP research. She noted:

- There have been eight clinical trials of tenofovir-based oral PrEP -with six showing a reduction in HIV incidence
- There have been three trials of intravaginal tenofovir gel completed, with one positive result
- Two trials of the dapivirine ring have been completed. Both had positive results
- Maraviroc has been evaluated alone and in combination with tenofovir for PrEP
- A Phase 2 study of tenofovir gel as a rectal microbicide has been completed
- Early-phase studies of injectable integrase inhibitors and vaginal rings have been completed
- Phase 1 studies of combination rings containing contraceptives and antiretrovirals (ARVs) are underway

She noted that clinical trial evidence for effective HIV prevention options demonstrates diverse results. The reasons for this are poorly understood.

Dr. Hillier stated that testing the effectiveness of oral PrEP and microbicides is complicated. Ensuring effective HIV treatment has revealed gaps and inefficiencies in the health system, and attempts to achieve effective primary prevention has revealed many of the same gaps and inefficiencies in the health care system that interfere with effective HIV treatment. The effectiveness of the same drug under study can vary widely by population age, sex, geographic region, and study site. She provided examples of study differences testing the same drug by population including:

- Outcome differences in women in the Partner's PrEP, FemPrEP, and VOICE trials of oral PrEP. These differences were thought to be related to participant adherence
- Age-related differences in adherence and effectiveness in younger compared to older women in the dapivirine ring studies (ASPIRE and The Ring Study). Younger women were less adherent and the product was not effective. Older women were more adherent and the product was significantly more effective. Poor adherence was also present in younger men in the IPREX study of PrEP in MSM
- Sex differences in the Partner's PrEP study of oral tenofovir and oral Truvada demonstrated 84 percent effectiveness in heterosexual men and 65 percent effectiveness in heterosexual women. This difference was not statistically significant
- Post-effectiveness follow-up studies of PrEP use by MSM demonstrated that intermittent use (IPERGAY) reduced infection by 86%

Dr. Hillier discussed that the degree to which differences in prevention product effectiveness between women and men and among younger vs. older women can be explained by biology and pharmacokinetics versus behavior is not known. Other factors that may affect study success include:

- The tangible and intangible differences at the site level that create differences in protocol retention and missed visits including site leadership, team orientation, personal engagement between staff and participants, and non-study visit interactions. Developing best practices will improve efficacy results
- The location and route of dosing. Efficacy and effectiveness depend on drug delivery (local vs. systemic), drug concentrations in tissues, and route of infection (genital tract vs. colon). For systemic delivery, whether local tissue concentrations will be predictive of efficacy is not known, but for topical delivery, local tissue concentrations have been shown to be critical in estimates of effectiveness. Vaginal vs. rectal concentrations differ with oral dosing. Topical agents result in more drug in the vagina and cervix than systemic PrEP. This could lead to potential sex differences in adherence forgiveness for oral PrEP and lowered effectiveness ceilings for topical drugs
- Decision making among younger people is different than with adults, which presents a significant challenge for primary prevention of HIV. The solution is not to exclude youth from prevention studies but rather to consider different approaches to prevention in these populations

- When consent language emphasizes that the product might not protect against HIV and describes possible side effects, participants concerned about the toxicity and safety of the drug, may not be adherent. From the participant's perspective, continued participation in the study to receive free preventive services may be the motivating force for attending study visits. The ADAPT study which demonstrated product adherence when women knew that PrEP was effective, had consent language that was very different from the VOICE study. It explained the purpose of the study more clearly, assured product safety, and resulted in improved adherence. Feedback provided by women participating in the studies revealed that women highly value the reproductive health services that the studies provide; the youngest participants are least able to balance product risks versus benefits; and there is a stigma associated with use of ARVs even for prevention.

Dr. Hillier described new technologies (e.g., vaginal rings, injectables) to promote adherence, but stated that they are not the only solution. During the dapivirine ring studies, it was learned that although the ring delivers the drug effectively to the vagina and cervix, dapivirine disappears rapidly when the ring is removed. Most but not all women report that the ring is comfortable and cannot be felt during sex. However, some women (especially young women) removed the ring after leaving the clinic and reinserted it prior to returning for study visits.

In summary:

- Trials of microbicides and PrEP have revealed that ARVs work if people use them, but determining how well they work is complicated
- Ascertaining which products will work for different populations is challenging
- Providing products that meet people's needs, including on-demand, sustained delivery; topical delivery; and combination products with contraception will be the key to their uptake

Research opportunities and gaps include:

- The need to explore barriers and identify solutions for engaging youth in HIV prevention studies
- Critical pharmacodynamics and pharmacokinetics studies to determine why more drug is needed to prevent vaginal transmission compared to rectal transmission
- Understanding what makes some sites more successful in HIV prevention research
- The availability of more options for HIV prevention is important because people are more likely to use a treatment option that they select themselves
- Ethics research to help simplify the consent documents to help study participants accurately weigh risks and benefits

How Good Is Good Enough? Efficacy Versus Effectiveness

Elizabeth R. Brown, Sc.D., Fred Hutchinson Cancer Research Center, University of Washington

Dr. Elizabeth Brown discussed the concepts of efficacy and effectiveness, the application of these concepts to PrEP and microbicide clinical trials, the implications of the trial results for understanding efficacy and effectiveness, and improving predictions of how the interventions

tested will affect the epidemic. Differentiating between efficacy and effectiveness applies to prevention fields in addition to HIV.

- Efficacy is defined as “the performance of an intervention under ideal and controlled circumstances” (i.e., the biomedical impact of the product) and implies an upper limit to “real-world effectiveness”
- Efficacy trials are highly controlled and typically blinded (unless ethically or otherwise not possible), include stringent inclusion/exclusion criteria, are operated under ideal circumstances, and generally are of short duration (i.e., long enough to measure a product’s effect but not the durability of the effect).
- Effectiveness has varying definitions, including providing a real-world estimate vs. an estimate that would be obtained in a clinical trial. It is a population-level measure that summarizes the reduction of a primary endpoint, whereas efficacy is an individual-level measure.
- Effectiveness trials, which also are referred to as pragmatic trials and mimic real-world settings to varying degrees, may be blinded or unblinded, may be randomized, and are not as easily identified or defined as an efficacy trial.

Dr. Elizabeth Brown noted that Dr. Hillier’s presentation made it clear that clinical trials are not being conducted under the ideal circumstances that are characteristic of efficacy trials.

The concepts of efficacy and effectiveness have been applied to prevention trials.

- The terminology and interpretation of “efficacy trial” for prophylactic prevention trials derives from vaccine trials, which are characterized by strict inclusion/exclusion criteria, guaranteed compliance, and short duration: therefore, vaccine trials are best characterized as *efficacy trials*.
- In typical non-vaccine prevention trials, exclusion criteria are minimal, participants determine the level of intervention, and the population is heterogeneous across a variety of settings: therefore, non-vaccine prevention trials are best described as *effectiveness trials*.

The terminology used to describe clinical trials is important because the labeling of effectiveness versus efficacy affects the interpretation of a trial and its results. Efficacy often is taken to be the upper bound on real-world effectiveness, but the effect size from a non-vaccine prevention clinical trial may not accurately represent the upper bound on real-world effectiveness. Trial designs and interpretations exist on a continuum. Trials measuring efficacy traditionally are thought of as having large impact/effect size and limited inclusivity and generalizability. Clinical trials measuring public health impact have more limited impact/effect size and a large degree of inclusivity and generalizability. Effectiveness trials fall in between.

According to this paradigm, iPrEx, a randomized, double-blinded, placebo-controlled trial of TDF/FTC which showed a 45% reduction in HIV; IPERGAY, a double-blinded, randomized trial of on-demand TDF/FTC; and PROUD, an open-label randomization of immediate versus delayed provision of TDF/FTC) which demonstrated an 86% reduction in HIV, would be best characterized as effectiveness trials. The iPrEx trial tends toward the efficacy end of the continuum and PROUD toward a public health effect trial. Dr. Brown proposed limiting the use of the terms “efficacy” and “effectiveness” to prevention trials and using “public health impact”

to describe the effect of an intervention on the epidemic. From the TDF/FTC trials, it is evident that the results from initial effectiveness studies are not upper bounds on the public health effect of the intervention.

All of these trials are structured for intention-to-treat (ITT) analyses. What defines these as effectiveness studies and not efficacy analyses is adherence. Adherence is important because the primary analysis in a prevention effectiveness trial always is an ITT analysis, which can be different from determining whether a prevention strategy prevents HIV transmission. Effectiveness is the product of efficacy and adherence. The definition of adherence depends on the study and setting. It can include full use of the product as directed, use of a product as would be expected outside of a randomized controlled trial setting, adequate use for protection, and detection of a biomarker: all of which would yield different estimates of efficacy. It was noted that none of these adherence measures is achievable when a participant does not use the product, highlighting the importance of full study adherence to achieve full product adherence.

The various approaches used to estimate efficacy from the prevention trials include objective adherence measures (e.g., drug levels in plasma, residual drug levels in the product delivery device, hair drug levels) and statistical measures that link to HIV risk. Estimating efficacy from effectiveness trials is difficult because measuring actual use eliminates randomization and introduces selection biases such as differential risk in adherers versus non-adherers and self-reporting of confounders. In addition, not all objective measures are equal (e.g., varying measurement frequency). Translating efficacy estimates to public health effects is difficult because an understanding of such factors as cost, uptake, adherence, and unintended consequences (e.g., drug resistance, risk compensation) is needed.

Discussion

The discussion raised comments about:

- The adequacy of the dose being administered by the dapivirine ring was raised by several participants. Dr. Hillier responded that the best estimate of dapivirine ring effectiveness is approximately 70 percent, which is comparable to Truvada in the Partners PrEP trial. The amount of drug delivered via the ring to the tissue likely is the maximum feasible and very similar to gel or film application. Approximately 20 percent of the 25 mg of dapivirine loaded on the ring is released over the month, indicating that higher drug levels in the device will not be useful
- The need to streamline the approach to obtain informed consent with the understanding that when the efficacy of an intervention is less well known, the informed consent will need to be more complex. Dr. Hillier responded that the approximately 1,000 qualitative interview summaries from the VOICE trial led her to the conclusion that concerns about the content of the consent, including very remote risks, were very common and may influence the decision to not use the product among the youngest women. This has important public health implications for young women in some parts of Africa who have up to a 10 percent HIV annual incidence rate. She also pointed out the different influence on adherence between informed consents for first-generation studies (placebo-controlled), which must state that there is no proof of efficacy, and those for second-generation studies, which can state that efficacy is known.

- The difference in product effectiveness among younger women who are recognized to have a high incidence rate of HIV compared to older women
- The need to better understand female reproductive tract biology. This includes the biology of the adolescent reproductive tract, the effects of sexual violence, and the effects of genital tearing during consensual sex which may affect the tissue dose from the dapivirine ring. Approaches to understanding injury also were proposed
- The need to better understand the differences between younger women and older women, including different recruitment approaches
- Approaches to increasing adherence including the need in future trials to have strong monitoring of study adherence and to take action when it is not achieved. It also was suggested that to reach young people, peer education, engagement, navigation, and involvement need to be increased in trials. Rethinking the social relationships and settings in which trials can take place might be effective
- Community engagement was suggested as one of the intangible factors that might differentiate study sites. It was noted that all NIH-funded sites are required to have community advisory boards and develop a community plan, but community advisory boards might resist innovations, such as recruiting younger people to serve on the board. It was suggested that community-based organizations that deliver services to the same participant population being targeted in the trials should be engaged in the community advisory boards and the paradigm by which community engagement is developed in trials should be re-evaluated
- In addition to adherence variability, pharmacokinetic variability is inherent in populations and should be measured in trials
- The need for improved scientific communication among federal agencies such as the NIH OAR, HRSA, and CDC to foster translation of research into clinical practice was also discussed

Designing Products That People Will Use: If We Build It, Will They Come?

Cynthia Grossman, Ph.D., FasterCures

Dr. Cynthia Grossman spoke about designing products across diseases so that people will use them. She drew a parallel to the home-building design process, which involves teams of people with different areas of expertise, is not a linear process, and always is conducted with the end-user in mind. In contrast with other types of design, the process of design of medical research products is unique because:

- There are limited opportunities along the design pipeline for returning to the starting point and beginning again based on what has been learned from research
- Different teams of people are involved at different points along the product design pipeline
- The end-user has limited input into the prevention product design process.

Inherent in the question “If we build it, will they come?” are assumptions that have formed the basis of the medical product design process for microbicides and PrEP. These assumptions include designing a single product rather than multiple products, not gathering data in advance about what people want, and not involving the end-user in the design process.

Dr. Grossman proposed the following three ways to change the process:

- Allow for ways to iterate and work with end-user communities early in the process to determine their preferences, values, and priorities
- Build multidisciplinary teams comprised of individuals with the specific expertise needed for product design
- Strive to understand the nuances of differences among end-users' priorities and accommodate those priorities during product design.

Regarding engaging end-users early in the design process, Dr. Grossman discussed how the field of HIV prevention has been relatively proactive in community and stakeholder engagement, and the opportunities for improvement.

- The opportunity to involve end-users early in the design of injectables, during the basic and translational research phases of the pipeline, may have been missed. Early-phase opportunities could include engaging with prototypes, developing and validating measures, and conducting early discrete-choice experiments
- Most of the work and progress in end-user engagement in HIV product development has been in the middle phase (i.e., clinical development), including conducting in-depth interviews, testing different products, conducting experiments that test methods to increase participation, and collecting data that are actionable during the course of trials
- In the late phase (i.e., FDA review and approval of new drug applications), the two main challenges are (1) waiting until a packaged product is ready for sale before seeking end-user input and (2) a lack of connection between those who market the product and measure its public health effect and the researchers involved in the product's development

Current initiatives to determine how communities and individuals prefer to participate in medical research design include patient-focused drug development meetings being held by the FDA and inclusion of patient-focused efforts by pharmaceutical companies in their development pipelines.

- Compared with other diseases, the field of HIV research benefits from a worldwide community with a long history of engagement, as well as a cadre of expert social and behavioral scientists who can participate in multidisciplinary teams
- Rather than more funding, a culture shift that will reposition the investments of time and the perspective of teams is needed

Dr. Grossman offered two recommendations that would be effective in changing the system: (1) reposition the teams' time, money, and resources and (2) ask at every meeting, with every product, and with every activity: "What will the patient think"?

CURRENT CHALLENGES IN BIOMEDICAL PREVENTION RESEARCH

Pharmacokinetic–Pharmacodynamic Relationships in HIV Prevention: Where Does the Drug Need to Be?

Angela Kashuba, PharmD., University of North Carolina at Chapel Hill

Dr. Angela Kashuba discussed the effect of pharmacokinetic (PK) and pharmacodynamics (PD) relationships in HIV prevention. She discussed how drugs distribute to mucosal tissues, what

influences this drug distribution, whether mucosal tissue concentrations influence the effectiveness of prevention products, and whether we can understand PK/PD early enough in the development process to assist the design and interpretation of clinical study. Dr. Kashuba's research is particularly focused on the effect of drug distribution in mucosal tissue on HIV prevention and whether ARV target concentrations exist that could inhibit HIV infection early in pathogenesis when HIV crosses the epithelial border over the lamina propria into the stroma. Pre-clinical studies in macaques and clinical PrEP studies have demonstrated a dose-response relationship to levels of protection. High plasma concentrations of drug delivered whether vaginally, rectally, orally or parenterally resulted in full HIV protection. Low concentrations resulted in low or no protection.

- There is interest in defining how the tissue concentrations of drug also may play a role in protection, particularly in humans
- Antibiotics studies have shown heterogeneous tissue distribution, with variability found both within and between tissues, suggesting that target site concentrations may differ from plasma concentrations
- Infrared imaging in non-human primates also revealed heterogeneous distribution of ARV concentrations. Plasma concentrations of drug may not be reflective of specific tissue concentrations

Dr. Kashuba explained that although a study of ARV exposure at mucosal surfaces found that concentrations were normalized to blood plasma concentrations, heterogeneous distribution of drug within tissue across ARV therapeutic classes and within therapeutic classes was shown. Female genital tract concentrations were lower than colorectal concentrations.

- The factors that influence heterogeneous distribution of agents and predict how a drug penetrates mucosal tissue are unknown. Variability was significant, and drug transporters likely play a major role
- The relationship between specific ARVs and specific transporters and the effect on tissue concentration is a growing area of research. Tissue concentrations also were relevant based on data from the topical microbicides field. Dr. Kashuba detailed vaginal microbicide studies that demonstrated a 50 percent decrease in the probability of HIV infection between patients with higher versus lower amounts of tenofovir gel detectable at the mucosal surface in the vaginal lumen. Topical tenofovir products, which were dosed only on the surface of the mucosal tissue, experienced a sharp decline in stromal drug exposure. Plasma concentrations were also low for tenofovir. In similar studies of the dapivirine ring, plasma levels were low and the ring demonstrated 30 to 50 percent protection.

Different product formulations may protect differently, and it is unknown whether target tissues and drug concentrations vary for topical versus systemic delivery via oral, long acting injectable, or the subcutaneous route. .

- Topical products with high concentrations in the lumen also have high concentrations in the tissue, but regional lymph nodes and plasma concentrations are very low
- Systemic products may have a relatively high plasma concentrations, and lower tissue concentrations, or perhaps higher tissue levels if the drug is concentrating there, and also very higher concentrations in regional lymph nodes

- It is not clear what the contribution of exposure in regional lymph nodes provides. The lymph node effect may be different for different drugs. The location of most of the product activity may vary by product

Dr. Kashuba evaluated oral delivery of TRUVADA® and its efficacy in relation to mucosal tissue concentration.

- Tenofovir diphosphate concentrations began and remained high in rectal tissue but were low and dropped quickly in female genital tract tissue
- FTC-triphosphate had a greater concentration in female genital tract tissue compared to female colorectal tissue, but levels in the genital tract tissue dropped within 72 hours.
- The relevance of endogenous nucleotides which compete against the phosphorylated tenofovir and FTC metabolites in cervical, vaginal, and rectal tissue, may render tenofovir to be less protective of the genital tract when tenofovir diphosphate metabolite concentration is low but dATP concentration is high

Dr. Kashuba explained a model for Truvada that considered nucleotide interference to determine the target tissue differences for tenofovir and FTC and evaluate whether the drug effect is additive or synergistic. Results indicated that FTC achieved steady state concentration within 6 days and tenofovir within 9 days of beginning dosing. Efficacy was estimated using pharmacokinetic/ pharmacodynamic (PK/PD) modeling of “IPERGAY” dosing that required seven doses per week in the female genital tract compared to just two doses in the lower gastrointestinal (GI) tract. The target exposure was achieved, but differed in men and women. Some of these differences appear to be related to endogenous nucleotide concentrations in the two tissue types. Further study is needed to determine how long a drug exposure is needed to cover a viral exposure. Dr. Kashuba also described work conducted to understand dichotomies in clinical trial outcomes, some of which were from a lack of drug adherence.

Lastly, Dr. Kashuba described new strategies of the NIH Division of AIDS Best Practices Working Group for Pharmacology, including understanding exposure response in animal models to translate to people and defining pharmacokinetic targets that predict efficacy in humanized mice and non-human primates to better design optimal dosing strategies for humans.

Her brief summary stated:

- Drug distribution in mucosal tissues is heterogeneous and there is currently no way to predict how drugs are going to penetrate these areas
- Research indicated that drug transporters play an important role and that this field still needs to be developed. Protein binding and volume of distribution also may play a role
- There is not a lot of tissue PK data for vaginal and rectal tissue. General drug development has not been evaluating drug exposure in colorectal tissue and vaginal tissue
- A database of PK information about these tissues needs to be built to inform the development of models that are predictive of drug distribution
- One consistent marker of PrEP efficacy has not yet being defined. It is not clear whether looking at mucosal tissues is enough, or is it necessary to understand regional lymph node concentrations in order to best know how to dose these drugs.
- Early-phase PK/PD data can be used to enhance our understanding of how to design drug dosing for clinical studies. The FDA uses pharmacometrics approaches to not only inform study design, but to estimate the drug doses that result in organ impairment, drug

doses in pediatrics, and drug doses in pregnancy. These tools can be used to help advance drug development more quickly

Discussion included:

- Age should be considered as a continuous variable making the use of a strict cut-off to differentiate between younger and older participant groups difficult. Age is a surrogate marker for developmental status, which represents a cluster of variables, such as impulsivity and executive function that may be a marker for substance use and perceived risk for HIV. These and other traits are associated with adherence in young people. Understanding these factors could be used to screen study participants and identify appropriate interventions
- Differences in intracellular drug concentrations by cell type was discussed. In one study, drug concentrations in isolated mucosal cells in the gut were correlated with concentrations in tissue homogenates
- In women, it is difficult to obtain enough cells to detect intracellular metabolites, but the extent of phosphorylation of compounds in isolated epithelial cells and CD4+ T cells are similar
- There is a gradient of intracellular tenofovir diphosphate concentrations in the reproductive tract, with high concentrations in epithelial cells to lower concentration in the HIV-target cells
- Progesterone reduced tenofovir diphosphate in the cells by up to 50 percent, indicating that the hormonal milieu, as well as contraceptives, might affect the intracellular concentration
- Animal studies are underway to measure tenofovir alafenamide (TAF) concentrations including measurement in isolated regional lymph nodes
- It is difficult to extrapolate conditions in intact tissue from results in isolated cells: A participant asked about the effects of metabolism and cell transport on intracellular concentrations measured using biopsied tissue. Dr. Kashuba replied that for drugs that are metabolized inside cells, the advantage of measuring intracellular metabolites is that they do not leach out. For drugs that are not metabolized inside cells, isolating cells without losing a significant amount of drug is difficult. Infrared-matrix-assisted laser desorption electrospray ionization (IR-MALDESI) is a technique to measure intracellular levels for such drugs at close-to-biologic conditions. Tissue is manipulated as little as possible and snap-frozen to minimize leaching of drugs from cells. In an animal model dosed with efavirenz, the drug was found to be concentrating in areas where CD3⁺ cells were located.
- Gender differences in drug efficacy were discussed. Modeling results of the FEM-PrEP versus iPrEx studies showed differences in efficacy based on tissue penetration of different drugs. If drug distribution differs among areas of infection, systemic markers such as plasma or peripheral blood mononuclear cells (PBMCs) might not be predictive for particular infection areas
- Gender differences in drug adherence and effectiveness and the relationship with the drug administration route was discussed. Additional research to understand the dosing and adherence needed for tenofovir-based PrEP to be effective in women was suggested
- The mechanisms behind differences in tissue penetration of different drugs, which might reveal drugs that are more effective in women, are not well understood

- Protection from rectal exposure in women and the risks, vulnerabilities, uptake, and adherence to PrEP in transgender individuals also need to be considered
- While phosphorylation in colorectal tissue of women and men does not appear to differ significantly, but the effects of hormone therapy need to be studied
- In animal studies, vaginal administration of tenofovir gel resulted in rectal drug exposure, but at levels too low to be considered protective
- There was a proposition for thinking differently about discussing sexuality with participants and for incorporating discussions of sexual well-being, long-term sustainable sex, and prevention of disease.

MOVING FORWARD IN HIV PREVENTION

Non-ARV-Based Products for HIV Prevention

James A. Turpin, Ph.D., National Institute of Allergy and Infectious Diseases (NIAID), NIH

Dr. James Turpin presented on non-ARV-based products for HIV prevention. He provided an overview of the historical perspective of non-ARV prevention products; the barriers to their advancement to clinical testing; leading non-ARV candidates; and bacterial and viral vector delivery of non-ARV products. Dr. Turpin discussed:

- The historically, robust pipeline of non-ARV-based products available for testing as possible prevention. After 2010, when early non-ARV-based products failed in trials, attention focused on ARV-based prevention products
- Non-ARV drug developers began the measurement of candidate product antiviral activity and stability in semen, genital, and GI secretions in primary cells and tissues. From 2010 to the present, the emergence of broadly neutralizing antibodies (BNabs) as high-priority non-ARV prevention candidates and other protein-derived non-ARVs began to overcome biophysical and biological barriers and started to advance to clinical trials. This has led to an increased interest in non-ARV-based products for prevention
- While the non-ARV pipeline is rich with possibilities; the advancement of non-ARVs has been prevented by barriers that include the cost of production, overcoming biophysical and biological limitations, and overcoming negative perceptions about the value of non-ARVs in HIV prevention
- Animal studies may need small amounts of non-ARV-based products, but clinical studies need larger amounts. The ability to produce these large volumes of the products for clinical study needs to be considered early in the development process
- Plant production has been one approach to generating larger volumes of non-ARV-based prevention products. However, plant-based antibody production may have some immunogenicity differences compared to production in mammals
- Other concerns include: chemical instability, degradation in formulations, the need for cold chain storage, and biological limitations such as stability in semen, genital, and G.I. secretions; bioavailability, duration of action, and potency. Products may not be worth producing if they are highly unstable or not likely to have a long duration of action

Leading Non-ARV-based microbicide products include:

- Next-generation BNabs -These products are bioengineered for increased neutralization and potency. Products may be combinations of two or more antibodies. Pod intravaginal

ring (IVR) and pump IVR drug delivery systems for these products have been developed and provide 100 percent virus coverage. Issues of production, potency, and biological and biophysical limitations in next-generation BNabs are being addressed

- Griffithsin (GRFT), a gp120 entry inhibitor that was isolated from a red alga *Griffithia* species possesses antiviral activity, is synergistic with other agents, has a high barrier to resistance, is resistant to most bacterial proteases, and has no effect on genital or GI secretions. As a result of GRFT susceptibility to oxidation, it was initially considered not suitable for development. GRFT has since been modified to contain a mutation (Q-GRFT), which is resistant to oxidation. A Phase I three-stage clinical trial is planned for 2018
- 5p12-RANTES is a CCR5 entry inhibitor and a modified form of the naturally occurring product that is being explored for prevention
- A variety of viral vectors and bacteria and yeast species have been proposed as microbicide delivery systems, and lactobacilli delivery is a model system being used for HIV. The MucoCept technology platform leverages the lactobacilli colonization features of the natural microbiota. Anti-HIV-protein-expressing lactobacilli have not been approved for clinical testing, and many factors will need to be addressed, such as colonization, immune tolerance, the regulatory process, and environmental control

In conclusion, non-ARVs are a viable pathway to new HIV prevention products. The manufacturing, biological, and biophysical issues that prevented early advancement are being actively addressed. Advances in delivery devices are making it possible to envision longer-acting antibody and protein non-ARV prevention products that could compensate for pharmacokinetic limitations using sustained-release methodologies. Within the next decade, non-ARV prevention products could be key players in an effective HIV prevention package.

Long-Acting ARVs

Charles W. Flexner, M.D., Johns Hopkins University

Dr. Charles Flexner discussed long-acting injectable ARVs and how they could help to end the HIV epidemic. Long-acting injectable drugs for HIV are being developed because the technology is available to support the efforts. For example, the novel long-acting/extended release (LA/ER) drug cabotegravir is detectable for up to 6 months following a single 800 mg intramuscular injection when given to healthy volunteers; with 400 mg subcutaneous doses, the drug can be detected in plasma for up to 1 year.

LA/ER ARVs for prevention offer promising benefits also pose some risks.

- LA/ER drugs remains in the system for a long period of time, and adverse effects may not be unavoidable. Approaches have been introduced to manage adverse effects, such as the use of an oral “lead-in” period and increased efforts by developers to produce products that will minimize adverse effects
- Safety and efficacy data for use during pregnancy are needed
- The sub-therapeutic medication concentration “tail” and the risk for resistance when a dose is missed and an individual becomes HIV-infected should be considered. It is important to know how long the lower level systemic concentration of the drug in the “tail” provides protection

- Benefits of long-acting ARVs include infrequent dosing, lower drug dose requirements, protection from poor adherence, the possibility of directly observed therapy, use in patients with pill fatigue, better protection of health privacy, and avoidance of GI adverse effects.
- Issues that still need to be resolved include the potential need for more than one drug for full protection and the timing for dosing if the drugs have different half-lives and metabolism. The mechanism of dosing should also be considered including whether it is a single injection or multiple injections and how large is the injection volume
- Currently, two long-acting injectable drugs are undergoing clinical trials: cabotegravir and rilpivirine.

Implant delivery systems are another new, promising long-acting ARV technology. These products are placed under the skin and are designed for slow, sustained release of drug and a long-term effect. Two current implantable candidates are tenofovir alafenamide (TAF) and MK-8591.

- Animal studies of ARVs in implants have demonstrated systemic drug for as long as 180 days
- Implants may be advantageous compared to injectables because they are removable, have a consistent and predictable drug release, and may remain in place for years
- The pharmacokinetic profile is not dependent on the injection site
- Disadvantages include the need to use a specialized device for insertion, the need to perform a minor surgical procedure for removal, regulatory issues since the product is both a drug and a device, and difficulty moving to a generic marketplace

Dr. Flexner mentioned that nano-formulations of medications are to be discussed in a later talk.

Dr. Flexner commended the NIH for effectively promoting drug development in the form of the Resource-Related Research Projects (R24) funding mechanism. He stated that he is a principal investigator for the R24 award for a LA/ER ARV Program (LEAP) at Johns Hopkins University. LEAP's three specific aims are to:

- Support innovation related to the development of LA/ER ARV drugs through investigator access of broad-based scientific expertise
- Develop a communications and data hub to support investigators in the field
- Provide a modeling and simulation core service that helps investigators identify the most promising approaches to the development of new products

Next steps include:

- Nano-formulations of products
- Application of long-acting dosing formulations to other diseases such as Hepatitis C, Tuberculosis, Malaria, Ebola, etc.

Topical Formulations: Options and Challenges

Lisa C. Rohan, Ph.D., University of Pittsburgh

Dr. Lisa Rohan provided an update on topical formulations, which she described as critical for drug development. In topical formulations, the active pharmaceutical agent is housed in a vehicle

that has a specified route of administration to deliver the drug to the target in a solubilized state to induce the intended pharmacological effect. The formulation process can be divided into two parts: getting the drug into the formulation and delivery to the target.

- Several determining factors are involved in the process of packing the drug into the formulation: the environment where the drug is being introduced (fluid volume in the environment, etc.), drug solubility, passive diffusion, thermodynamics, product degradation and erosion, disintegration rate, and dissolution.
- Equally as important are the factors that affect the delivery of drug to the target including: drug diffusion, transporters, metabolizing enzymes, protein binding, ionization, lipophilicity, and concentration
- The formulation processes can be evaluated with dissolution testing, *in vitro* release testing, and *ex vivo* permeability testing.

Product development encompasses a larger scope and must take into consideration chemical and physical properties, desired release rate, drug target, product distribution, biological considerations, user preferences, cost and scale up, and dosage form.

- The product development process begins with the development of a quantitative assay to monitor the active pharmaceutical ingredient (API), which includes pre-formulation studies for solubility, stability, partitioning, and excipient compatibility.
- The physicochemical properties uncovered from the pre-formulation studies help understand the behavior of the API and identify the next course of action in the formulation process
- Once the basic information regarding the API has been ascertained, necessary steps can be taken to pursue formulation types, modify the assay development method, conduct formulation assessments, perform stability tests, and finally generate the prototype product.
- The prototype product can be in many forms, such as a cream, suppository, ring, or implant, to provide options for the user

Dr. Rohan described various topical products and lessons learned from clinical trials.

- Vaginal gels exhibited poor adherence and could not be used for rectal applications because of high osmolarity.
- Applicator issues were discovered with the use of rectal gels, which suggested that different formulation strategies were needed
- The size and shape of vaginal inserts are important
- A learning curve was associated with the use of vaginal rings and films

Options currently available for clinical study include rectal gels in Phase I and Phase II studies; vaginal inserts in Phase I studies; intravaginal rings in open-label extension Phase I and Phase II studies; and vaginal films in Phase I studies

Understanding the progression pathway for establishing suitable dosage forms for the various routes of administration is important.

- The first rectal-specific products used were the original vaginal formulations, which caused adverse effects due to the osmolality. Reducing the osmolarity removed these adverse effects

- The newer class of rectal-specific products have further reduced osmolarity, and pH has been adjusted to better mimic the environment of the rectal compartment
- Rectal formulations also are being designed based on user preference
 - With new rectal enemas, greater drug distribution is achieved, and hypotonic solutions take advantage of the normal features of GI absorption.
 - Alternative dosage forms include suppositories, which are semisolid dosage forms that can be used without an applicator for local and systemic drug delivery. A disadvantage of the suppository is the instability of absorption via the rectal route. Two separate types of suppository formulations can significantly vary the release profile and allow for optimizations of the two drug products

Other topical products being explored include tablets, vaginal rings, and vaginal films.

- Topical inserts currently being developed by CONRAD are solid dosage forms that incorporate both elvitegravir and tenofovir and have been used in clinical trials
- Another tablet formulation utilizes the osmotic system to release the drug from the tablet, which contains a coating that is responsive to pH changes
- Intravaginal rings-(IVRs) provide sustained release of the drug, whereas the vaginal ring with pod insert—a more advanced technology—provides flexibility for designing a formulation that meets specific drug delivery requirements. The pod ring consists of an API core coated with a dissolvable, biodegradable membrane that can be modified to control drug delivery. One disadvantage of this delivery method is the manufacturing required for the complicated design
- Vaginal films are inexpensive, easy to manufacture, discreet, and portable, and they offer decreased dilution of the endogenous antiviral properties of vaginal fluid. Two clinical trials using vaginal films have been completed. Areas of advancement in vaginal film product development will include extended drug release, combination drug release systems, combination with multipurpose prevention technologies, and new manufacturing methods

Dr. Rohan stated that challenges for topical PrEP formulation include drugs with low aqueous solubility, protein/peptide drugs, probiotics, combinations, and dual compartments. To overcome targeting and release issues, next-generation drugs will need next-generation drug delivery systems. Opportunities and research gaps include:

- Further evaluations of suppository and film dosage forms
- Studies that match product design with practical use considerations
- Establishment of better design targets for how much drug is need and for how long it must remain
- An improved toolbox for studying biologically relevant drug release formulations
- Cross-comparisons between types of dosage forms
- Expansion of dosage form types that can be utilized for multipurpose prevention technology product development

Nano-Formulations for Local and Injectable Use

Kimberly A. Woodrow, Ph.D., University of Washington

Dr. Kimberly Woodrow provided an overview of nano-formulations for local and injectable use. Her laboratory has been focused on the use of a diverse array of nano-formulations as topical microbicides, which can be categorized as particulate carriers, fibers, or composite materials.

Delivery of drugs locally provides opportunities to maximize drug concentrations in the tissue, and a positive correlation exists between protection and local tissue concentration of drug. Dr. Woodrow's group has focused on extending the protection window, overcoming adherence issues, and lowering dosages. She highlighted previous research that has shaped the ideas for designing biological efficacy, establishing a quantitative basis for efficacy known as the inhibitory potential and identifying the target value needed to completely suppress viral replication. These concepts can be applied to HIV treatment and provide strategies for repurposing existing compounds into new formulations to provide long-term ARV inhibitory activity that would lead to greater potential for HIV prevention.

- The first approach was to investigate nano-carriers for physiochemically diverse ARV microbicides. The nano-carriers are matrix-based systems and tend to have lower loading potential. A reduced-dosage nanoparticle-formulated system, when tested in vaginal explants in animals, was able to achieve a reduction in virus replication and was shown to be safe in the doses tested
- A second platform tested was the electrospinning technology, which produces nanofibers. Compared to other carrier systems, the nanofibers provide more versatility and can formulate ARV compounds, contraceptive-type compounds, and other types of antivirals for multipurpose use. The advantage of fibers is the ability to control the micro-architecture in order to deliver drug combinations in various configurations

Dr. Woodrow explained that fiber micro-architecture is amenable to sustained release. Sustained-release products can be further micro-ionized to be used for injectable, oral, and topical applications. The nanofiber electrospinning technology also can be used to develop nanostructures to control the release profiles of formulated compounds, and to deliver asynchronous release of drug, achieving a multiphase drug-release system capable of burst-release and sustained-release patterns. Production-scale electrospinning efforts are being developed. Also, preliminary studies to test the safety and efficacy of the nanofiber microbicides in a small-scale animal study suggest minimal adverse effects and effective drug activity. Dr. Woodrow closed by reaffirming that the role of nanotechnology is expanding the prevention portfolio against HIV.

Discussion

Discussion topics included:

- Strategies to overcome the risk of resistance of long-term injectables in patients that are to follow up. Dr. Flexner responded that it depended on whether one was addressing treatment or prevention applications. With respect to treatment, the risk is linked to the particular drug, and some drugs have lower genetic barriers to resistance than others. It also is dependent on the type of drug combination in the treatment regimen. Resistance

also is seen when individuals receiving oral formulations stop taking the medications, and the likelihood of resistance differs than that of low-level extended exposures. Potential solutions to the resistance problem exist; however, the logistical implementation is not straightforward

- The potential utility of the Small Business Innovation Research (SBIR) program supporting HIV efforts. Dr. Turpin agreed that the SBIR funding mechanism provides a good platform for bringing the HIV products to the clinic. Dr. Eisinger commented that the OAR did not specifically provide funding for SBIR contracts that was separate from the NIH budget. When asked how successful the SBIR contracts were in bringing a product to market, Dr. Turpin explained the recent changes to the SBIR program, which allowed investigators to move directly to Phase II trials
- Differences in and clinical significance of the observed pharmacokinetic profiles of the long-acting cabotegravir compared to the modeled profile. Dr. Flexner responded that the PK fluctuations depend heavily on the pharmacological mechanisms of action and the route of administration. Intramuscular injectable sustained-release products depend on the actual amount of drug delivered to the muscle versus the fat tissue at the site of injection.

The amount of drug that could be available was expected to be eluted over time from biomaterials such as the ring formulations. Dr. Woodrow responded that it depended on the ring polymer. Rapid-release formulations are limited by solubility, while some sustained-release products could elute at a rate of 5 percent per day

Novel Approaches to Measuring Adherence

Monica Gandhi, M.D., M.P.H., University of California, San Francisco (UCSF)

Dr. Monica Gandhi provided an update on novel approaches to measuring adherence. She noted that adherence is a problem in other illnesses: only 51 percent of Americans being treated for hypertension are adherent in their long-term therapies.

The importance of understanding adherence to HIV medications is evident in Phase III trials.

- A review of seven of the major efficacy PrEP trials suggests correlations of adherence to efficacy
- Adherence metrics are necessary for determining interventions to enhance effectiveness
- Measurements of adherence are separated into two categories:
 - Subjective measures, which include self-reporting, questionnaires, and pill counting, which may be inaccurate
 - Objective measures, which are based on pharmacy refills, pharmacologic measures, directly observed therapy (DOT), and medical event monitoring systems. DOT, the gold standard of adherence measurement is not always practical in a clinical trials setting

The use of pharmacologic measures of adherence is an integrated approach to assessing behavior (drug-taking) and biology (pharmacokinetics). Such measures include:

- The amount of drug in a biomatrix—such as plasma, PBMCs, dried blood spots, and hair

- Plasma levels are critical to the interpretation of various PrEP and microbicide trials in which participants with higher detectable drug plasma levels had significantly lower likelihoods of HIV acquisition compared to participants with lower detectable drug plasma levels
- Limitations to using plasma samples to measure adherence include a short window of exposure, intra-individual variability, subjective interpretations, and the “white coat” adherence phenomenon—instances when drug dosing is performed just prior to a clinical visit and timed measurements and therefore are not necessarily representative of typical adherence behavior

Dr. Gandhi explained that the use of single hair strands as a pharmacologic measure provides a long-term measure of cumulative drug exposure

- Hair is collected easily with no special skill requirements
- Studies are feasible in resource-limited settings
- Studies have demonstrated that hair is a strong predictor of virologic response
- Other applications that have used hair as a marker of drug-level monitoring include epilepsy, latent tuberculosis, environmental pollutants, forensic analysis, and stress
- Dr. Gandhi and the Hair Analytical Laboratory at UCSF have developed ARV hair assays for measuring adherence in HIV patients. Following multiple dose regimens (2, 4, or 7 doses) for 6 weeks with washout periods in between, hair samples from participants showed a strong linear dose-response relationship. This experimental design helps to identify the protective dose associated with ARVs

Dr. Gandhi noted that Dr. Kashuba and others have developed a novel method for analyzing ARVs in hair using IR-MALDESI mass spectrometry imaging technology. This methodology will provide an *in situ* longitudinal assessment of drug in a single strand of hair over time. Collaborations are ongoing between UCSF and the University of North Carolina at Chapel Hill to analyze maraviroc levels in hair samples for the HPTN 069/ACTG 5305 prevention study using the IR-MALDESI technology.

Another novel strategy in adherence monitoring is the use of taggants (chemical or physical markers). Drugs are labeled with an inert, detectable taggant, and adherence is measured through a breath test. Proof-of-concept studies for this methodology have been completed.

In summary, PrEP efficacy trials illustrated the limitations of self-reported adherence, and objective biomarkers are needed. Pharmacologic measures involve measuring drug in the biomatrix, with untimed plasma measures being the most common. Emerging and novel measures of exposure include dried blood spots, hair monitoring, and taggants. Low-cost, point-of-care measures of adherence are needed and being tested.

Trial Design in the Era of PrEP and Treatment as Prevention (TasP)

Deborah J. Donnell, Ph.D., Fred Hutchinson Cancer Research Center, University of Washington

As the final presenter, Dr. Deborah Donnell discussed prevention trial design in the era of PrEP and Treatment as Prevention (TasP). She provided two themes for the design of clinical trials: (1)

trials needed for developing new prevention products and (2) trials needed to evaluate proven prevention products as the basis for the presentation.

- In the design of clinical trials for new prevention products, the development of new products that are safe and more effective than current approaches is prioritized
- Adoption of the treatment model of comparison which combined an existing product with a new product in PrEP trials, providing prevention product to all participants as standard-of-care and randomizing use of another product (superiority trial)
- Conducting a direct head-to-head comparison of a new product with an existing product (superiority or non-inferiority trial).

The effect of PrEP and TasP on randomized controlled trials of new biomedical prevention interventions is analyzed using examples of superiority and non-inferiority clinical trial designs. The superiority trial for the VRC01 antibody has the primary objective of determining how well the broadly neutralizing monoclonal antibody can prevent HIV infection. In general, superiority trials can demonstrate lower incidences of disease in the study population, are more expensive to conduct, and are uncomplicated to analyze.

Dr. Donnell explained that the superiority and non-inferiority designs are fundamentally different.

- A superiority trial is designed to demonstrate that a new drug is more effective than the standard drug. The statistical test for a superiority trial will select for a difference that is a clinically important improvement and will require selection of a sample size large enough to demonstrate high probability of detecting the improvement
- A non-inferiority trial is designed to show that a new drug performs as well as the standard drug. The non-inferiority statistical test will select for a difference that is not clinically important and outcomes are at least as effective as the original product. The non-inferiority lower boundary is set based on the successful superiority trial results.

Dr. Donnell provided examples to further explain the statistical procedures for evaluating clinical trials and their applications to HIV prevention trials and shared her experiences with non-inferiority trials. To achieve an attainable sample size for a non-inferiority trial with PrEP as a standard arm, the non-inferiority lower boundary must be justifiable, and the potential for an efficacy advantage of the new product must exist.

- Clinical trials using existing prevention products—or pragmatic trials—are designed for the optimal use of a known preparation such as TasP to change the trajectory of HIV acquisition. These include population-based and demonstration studies. Four large population-based cluster TasP clinical trials currently are in progress.
- Another strategy that has high potential is the step-wedge cluster randomization trial. This type of trial is most suited to program interventions, requires rapid ascertainment to endpoint, and has added value for effect evaluation
- Population-based studies are able to provide a direct assessment of the total population, but challenges include being subject to secular trends and migration, less protection by randomization, a requirement for large expected intervention, practical issues associated with the delivery of a high-fidelity intervention at a population-level, high-quality assessments, value proposition, and added cost.

Additionally, in the context of using existing prevention products, two new strategies include the immediate versus deferred method trials and the sequential multiple assignment randomized trial. In brief, the demonstration projects provide opportunities for open-label extensions from clinical trials and typically target a specific risk group.

Public Comments

Dr. Gulick called for public comments. No public comments were offered.

Discussion

No new discussion points were raised.

Summary of Discussion and Next Steps

Roy M. Gulick, M.D., M.P.H., Weill Medical College of Cornell University

Dr. Gulick summarized the day's presentations and discussions. He stated that, in the last 5 years, significant scientific advances have been made and substantial progress has been realized in HIV prevention. He stated that the purpose of the meeting was to assess the current status of HIV prevention research and determine the next steps.

- An overarching message heard from multiple speakers was that multiple approaches are needed for effective HIV prevention. Like contraceptives, different people prefer different methods of HIV prevention, and these preferences may change over time
- The causes underlying the variability of the results from effectiveness trials are complex. Factors include participants' age, sex, race and ethnicity, education, concomitant medications, contraceptive use, behaviors, exposure types, and adherence
- Drug differences, including the route of administration (e.g., topical vs. systemic), drug target, pharmacokinetics, and tissue distribution, are important determinants of successful prevention. A better understanding of the tissues to which the drug should be delivered (e.g., regional lymph nodes, plasma, the lumen) is needed
- Potential sources of variability related to drug distribution that need more study include drug half-lives, binding by drug transporters, and protein binding. Markers are needed to document pharmacologic efficacy
- An additional source of variability is the way in which studies are conducted, including the geographic location of studies, the characteristics of the individuals who interact with study participants, and the mechanisms by which studies are supported

New strategies and approaches in HIV prevention research were called for during the meeting. A recommendation was made to rethink the way time, money, and resources are allocated.

- Multidisciplinary teams are needed to conduct studies
- OARAC participants recognized a particular imperative to decrease barriers to prevention for populations with the greatest need for reducing their risk of HIV including young African women and MSM in the United States
- Analyzing actionable data during the course of trials and acting on the data moving forward was discussed

- Acknowledging that people have different needs for prevention strategies (e.g., sustained release, topical vs. systemic, combinations with other drugs such as contraceptives) that will affect their choices is important
- Researchers should be attentive to the perspectives of end-users from the beginning of and throughout the development process
- For future research, strategies and interventions need to be potent and include a breadth of activity across different viral strains
- Practical issues such as manufacturing, biophysical and chemical properties of interventions and their practical use in the community, cost, and scaling up all need to be considered

New preventive approaches are in development.

- Non-ARVs are showing promise, particularly broadly neutralizing antibodies and protein HIV entry inhibitors, both of which are in clinical trials
- *Lactobacillus* is an example of a live microbicide being studied
- Two longer-acting injectable ARVs are in advanced clinical development: cabotegravir and rilpivirine, Novel implantable devices for ARVs for extended release are also being developed. Longer-acting agents offer the potential for increased adherence but also possible risks of adverse events and resistance
- New topical strategies via different formulations: gels, creams, rings with and without pods, inserts, suppositories, films, and enemas are being tested
- Effectiveness of products for different sites (i.e., vagina vs. rectum) is being assessed, as well as effectiveness at both sites
- Other innovations include combining topical agents with advances in nanotechnology including fibers, matrix composites, and polymer and lipid carrier systems, to allow delivery by biodegradable systems, high-level “bursts” of drug, sustained-release products, and different administration routes (injectable, oral, or topical)

Measurement of adherence was an important topic discussed. Measures can be subjective or objective, and each has its associated advantages and disadvantages. Pharmacokinetic measures include plasma, PBMCs, dried blood spots, and hair; again, each with associated pros and cons. Ideally, a complete picture of adherence would combine short- and long-acting measures.

Clinical trial design was covered, including superiority studies, non-inferiority studies, and so-called “me too” studies

- Determining the standard of care in a community is a complicated question, varying as it does by nation, state, and even local jurisdiction
- The effectiveness of the standard of care and HIV incidence rates in the community studied have implications for sample size, costs, and feasibility of studies
- Different designs for superiority studies were described. The results of previous studies can determine future approaches, which might differ for the same intervention in men versus women
- Non-inferiority trials can be justified in the context of what is known about HIV incidence in the community and what adherence might be. Interpreting successful non-inferiority trials is complicated, however, by the need to discriminate between risk and efficacy

- Pragmatic approaches to prevention trials include population-based, individual-based, and demonstration projects.

The meeting provided an assessment of the current status of research in microbicides and PrEP, including successes and variability in success. New technologies were described that will represent the future of HIV prevention. Throughout the meeting, remaining at the forefront was the motivation for prevention research: to benefit the participants who will use the new strategies, as well as to consider the priorities of end-users.

Concluding Comments

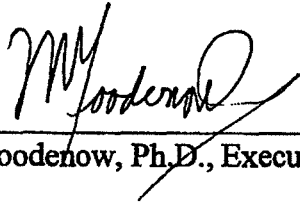
Robert W. Eisinger, Ph.D., OAR, NIH

Dr. Eisinger concluded the meeting by thanking all of the presenters, as well as the OARAC members, for highlighting the scientific opportunities, needs, and gaps in this area of research, which is one of the overarching priorities for the NIH AIDS research program. He pledged that the OAR will continue to work closely with the NIH ICs to ensure forward progress.

The meeting was adjourned

Roy M. Gulick, M.D., M.P.H., Weill Cornell Medicine

Dr. Gulick adjourned the 42nd meeting of the OARAC at 5:00 p.m. on April 7, 2016.



Maureen M. Goodenow, Ph.D., Executive Secretary



Roy M. Gulick, M.D., M.P.H., Chair