EXECUTIVE SUMMARY

ADHERENCE AND ITS MEASUREMENT IN MICROBICIDE CLINICAL TRIALS

A Workshop Project of the Quick Working Group

Jointly Sponsored by the
Alliance for Microbicide Development and Family Health International

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EXECUTIVE SUMMARY

This Executive Summary provides an overview of themes, pertinent conclusions, and key actions presented and discussed at a recent meeting on "Adherence and Its Measurement in Microbicide Clinical Trials". The meeting, held 18-19 December 2007, in Washington, DC, USA, was jointly sponsored by the Alliance for Microbicide Development and Family Health International (FHI) and was a project of the Quick Working Group (QWG). This Summary provides the gist of each presentation and closes with key findings emerging from those presentations and associated discussions. The Alliance and FHI are developing strategies for implementing those conclusions and welcome questions or comments on this Summary toward that objective.[1]

MEETING BACKGROUND

In two meetings of the QWG in 2007, its members discussed the recent terminations of the Carraguard®, cellulose sulphate, MIRA,[2] and Savvy (C31G) trials, and the opportunity they offered to examine and compare adherence-related data from different trials and to extract concrete lessons. As the QWG considered experience in the microbicide field and the literature on adherence in relevant fields, its members concluded that a meeting focused on the measurement of adherence could generate evidence-based insights into current trials as well as practical applications to incorporate into future trial design and implementation. The goals of such a meeting would be to provide guidance for: 1) the design and, possibly, re-design of clinical trial protocols to enhance adherence to protocol and product use; and 2) measurement of sexual and adherence behavior to facilitate determination of product effectiveness. Thus, on 18-19 December 2007, more than 50 primary investigators, researchers, behavioral scientists, statisticians, and advocates met to discuss these topics and seek consensus on next steps in this vital area of microbicide research and development.

INTRODUCTION

Orientation to Adherence Measurement Issues – *Nancy Padian:* In a microbicide trial, as is the case in any prevention trial that relies on individual behavior, the effect of the intervention is a combination of the biological efficacy of the study product combined with participants' adherence. Generally, adherence is measured using self-reported data that might be subject to recall and social desirability bias. Novel methods of measuring adherence include cell phones, electronic diaries, or directly observed procedures. Innovative biomarkers are also being explored. If adherence could be adequately measured, it might then be possible to identify factors that predict adherence (including motivation, context, and male partner involvement), which could subsequently be used to identify and enroll those women most likely to adhere to a future study protocol.

Baseline Participant Statistics – *Stephanie Tillman*: Recently terminated and ongoing microbicide effectiveness trials will have enrolled a total of more than 22,000 participants. There is noteworthy variation among these trials with respect to participant baseline characteristics (age, education, parity, and relationship status), inclusion criteria, and data on sexual partners and sexual activity. Some key terms, including "marriage" and "anal sex," have had to be refined since their meanings vary across sites. Highlighting data variations among trials has focused attention on the differences and similarities in the ways that each trial collects data and what this means for the potential for and utility of standardizing data collection within and across trials. Clearly, not all microbicide trials are measuring the same thing, nor is

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[2] MIRA -- Methods for Improving Reproductive Health in Africa

there clarity or consensus about what should be measured and why, although there is agreement on the need for more investment in methods for getting accurate data and how to adapt those methods for different populations.

MEASURING AND OPTIMIZING ADHERENCE BEFORE OR DURING A TRIAL

MIRA – *Ariane van der Straten*

- **Product Use and Adherence:** Product adherence in MIRA was lower than targeted. A variety of strategies were implemented to improve adherence, including retraining staff, a competition among staff for adherence improvement ideas, staff quizzes and values clarification, reminder memos and data reports, enhanced counseling and information sessions for participants, and enhanced attempts to involve male partners. Reported adherence increased slightly in the months following these activities, but then returned to previous rates. Data showed differential condom use in the control and intervention arms, suggesting that study arm assignment can influence behavior, possibly due to misconceptions about product effectiveness or to women's ability to negotiate condom use with partners. Trajectory analysis was conducted, and associations of baseline characteristics with adherence trajectories could be used to select high compliers in future studies or to identify women who need more product support or intensive counseling during future trials.
- **Adherence-related Challenges**: Some MIRA participants reported rushing through the ACASI, which increased reporting errors and led in some cases to participants in the control arm reporting diaphragm use. Some women also said they considered the diaphragm and condoms to be the same since both are barrier methods. To address these issues, the ACASI was shortened and pictures were added to clarify questions about methods. As a result, reported rates of diaphragm use in the control arm decreased. A second adherence-related challenge, possible underreporting of gel use, was traced to participant beliefs that the diaphragm and gel went hand in hand, so when asked what they had used at their last sex act, participants believed saying they used a diaphragm meant it was understood that they had also used the gel. These findings and an additional comparison of ACASI and face-to-face interviews demonstrate that ACASI is not immune to misreporting and that participant comprehension and attention are particular challenges to collecting data using this technique.

MDP301 – *Robert Pool, Sheena McCormack*: A random sub-sample of 100 women in each MDP301 site is being followed intensively three times during the study. Methods used include clinic case report form (CRF) interviews, applicator returns, coital diaries, in-depth interviews (IDIs), and memory aids. At each of these three visits, the social science team collects CRF interviews and coital diaries, fills in key data on a comparison form, and adds data for applicator returns. A few days later, each woman has an IDI to probe inconsistencies, explore reasons for inconsistency, and decide with the woman what data are most accurate. Most inconsistencies are resolved during the IDI, and women often have valid reasons for inconsistent data. An additional finding was that comparing reported use at the last sex act to use during previous acts indicated that asking about the last sex act provides a good estimate of product use over time.

HPTN 035 – *Anne Coletti:* Adherence rates are routinely monitored in HPTN 035. Early in the trial, researchers identified that below-target reported adherence levels were due in part to misunderstanding among site staff of key messages to be conveyed to study participants during adherence counseling. Through a collaborative process, researchers and site staff jointly modified key adherence messages into a simple but comprehensive statement suitable for use in all adherence counseling sessions. Implementation of the modified adherence message has been associated with increased adherence rates over time, such that current rates are now consistent with targeted rates.

CAPRISA 004 – *Leila Mansoor*: To individualize support for each trial participant's adherence capabilities and goal-setting, researchers in CAPRISA 004 are implementing a structured Adherence Support Program (ASP), which utilizes the information-motivation-behavioral (IMB) skills model and motivational interviewing, along with modified and innovative materials. ASP is re-enforced in three stages: pre-enrollment through a general information session and product introduction, during enrollment with a demonstration of gel use and regimen explanation, a customized motivational session to address individual participant's sexual experiences, a session on frequently asked questions, and "booster" sessions during trial participation, with continued motivational interviewing, goal-setting, and monthly product use measurement to determine timing and use of gel during the last coital act. Constant evaluation and monitoring of the ASP program allows all site staff and trial participants to give regular feedback about the program's effectiveness and ensures proper delivery of the ASP messages.

ATN-062/MTN-004 – *Alex Carballo-Diéguez***:** Interactive voice response (IVR), a method of data collection that allows clinical trial participants to submit responses to trial research questions through a phone call, will be used in the Adolescent Trials Network microbicide study "ATN-062–'Tell Juliana'", which will run parallel to MTN-004. Trial participants will meet "Juliana" (a staff person) via a web cast, use a phone diary for 14 days, send email messages detailing experiences with the microbicide, and have follow-up teleconferences with Juliana at the end of the trial to provide qualitative feedback and settle discrepancies in reported data.

ASSESSING AND ANALYZING ADHERENCE AFTER TRIAL COMPLETION

Savvy Ghana – *Betsy Tolley:* Trajectory analysis (a statistical method drawn from developmental psychology) was conducted, and suggested that associations of baseline characteristics with adherence trajectories could be used to select high compliers for future enrollment or to identify women needing more product support or intensive counseling during future trials. Analyses were conducted separately for participant condom and gel use during sex acts in the 7 days prior to interview. Both sets of data fit a trajectory that identified 3 user groups: high consistent use, increasing use over time, and decreasing use over time. For both condom use and gel use, a number of baseline characteristics were associated with a higher probability of being in 1 of the 3 trajectories. These differences between adherence trajectory groups suggest potential ways to monitor adherence in future trials.

CONRAD cellulose sulfate – *Mark Weaver*: Trajectory analysis of condom and gel use with all partners identified 3 groups: high consistent use, increasing gel use over time, and decreasing gel use over time. A number of baseline characteristics were associated with a higher probability of being in a particular trajectory. Trajectory analyses were also conducted for gel and condom use with primary and "other" partners. With "other" partners, the same 3 gel-use groups were evident, while self-reported condom use with "other" partners was virtually 100%. With primary partners, a fourth group of women who never use condoms or gel emerged. Women who use gel but are inconsistent condom users are the most informative group for establishing effectiveness. In this analysis, these women accounted for a small percentage of participants.

Carraguard®

- **Adherence –** *Barbara Friedland*: The Population Council uses face-to-face interviews to collect information on number of sex acts and gel/condom use at each act. An applicator assay has been developed to determine whether returned, opened applicators have been inserted into the vagina. A composite measure of adherence was developed using the results of the applicator assay and face-to-face interviews to determine "covered" sex acts. A number of baseline and follow-up characteristics were associated with applicator insertion rates and the composite "covered" sex acts.

- **Ancillary Study** – *Barbara Mensch, Johanna Rankin*: Following completion of the Phase 3 Carraguard® trial, an ancillary study is being conducted to: 1) assess whether ACASI produces more "accurate" reporting of gel use and sex without a condom; 2) validate self-reported data using the Population Council's applicator test and a rapid stain identification of human semen; and 3) evaluate the acceptability of ACASI-based data collection. Preliminary findings from the first month support the premise that ACASI produces significantly higher reporting than face-to-face interviews for sensitive behaviors. However, reporting of gel use and sex acts was still problematic, perhaps even more so for ACASI since recall bias for a one-month time period can be considerable and consistency checks were not incorporated into the computerized interview, a feature which has been integrated into the ACASI program for use in the HPTN 035b trial.
- **Exit Interviews –** *Barbara Friedland*: The impetus for conducting exit interviews was that during the trial the applicator test indicated low levels of adherence. At exit, a subset of women (N=1601) were asked about reasons for not using gel and acceptability (effect on sexual pleasure, lubrication, etc.) to get a better sense of why adherence rates were low. Reasons for not using gel included running out, forgetting, not having time to insert gel before sex, not having the applicators nearby, partner refusal, and having enough gel from the "last round."

HPTN 059 Sub-study – *Betsy Tolley*: An "Enhanced Acceptability" study was conducted in parallel with HPTN 059 to identify predictors of initiation and sustained use of vaginal microbicides. The study recruited 100 women enrolled in HPTN 059, 100 women recruited from the same communities who declined participation in HPTN 059, and 100 male partners. The study examined how reported consistency of gel and condom use change over the course of a trial and how trial participants' condom use patterns compare to condom use patterns for women not enrolled in a clinical trial. In addition, psychosocial factors were examined to determine whether they predict consistency of reported gel and/or condom use.

HPTN 035b – *Pamina Gorbach*: HPTN 035b is designed to assess the feasibility of ACASI on handheld computers as a method of collecting data on gel adherence and condom use in the Microbicide Trials Network clinical trials. The Population Council has developed for HPTN 035b a special program for self-administered adherence questionnaires for non-literate and non-numerically literate women, since current ACASI tools assume a basic comprehension of numbers that is not present at all trial sites. Colors understandable in every language, pictures modified and approved by participants as indicative of their intended meaning, and concise questions also used in HPTN 035, all help each participant understand and accurately answer each question. The study will begin March 2008.

Subgroup analyses – *Doug Taylor, Barbra Richardson***:** Subgroup analyses of data from randomized clinical trials are typically performed with hopes to identify evidence of effectiveness among subgroups of participants, to achieve a more accurate measure of efficacy among perfect or near-perfect users of a method, or to obtain a better general understanding of an overall null, harmful, or effectiveness finding. Two primary concerns dominate the use of such subgroup analyses in microbicide trials: selection bias and measurement error/misclassification. And since there is no way to rule out that any measure of adherence that occurs post-randomization is not influenced by the treatment itself, stratifying an analysis on that measure can lead to bias. Despite serious concerns for the validity of inferences drawn from adherence-based subgroup analyses, such procedures do have utility in microbicide trials; they can aid in explaining heterogeneity of treatment effects across sites, help to assess whether adherence was too low to identify an effective product, and generate new hypotheses from the trial data. Ultimately it is essential to maximize adherence to product, regardless of whether researchers intend to measure or perform subgroup analyses based on these data. Understanding barriers to adherence and pre-screening women to assess their potential acceptance of a potential microbicide could increase levels of adherence during the trial and thus improve the chance of successfully identifying an efficacious product.

OUTSIDE INPUT

Lessons from practice – Adherence to ART – *Leine Stuart***:** Management of patients on anti-retroviral therapy (ART) requires the dual processes of education and counseling on the prescribed drug regimen. It is the responsibility of the provider to prepare clients to start ART, a preparation which includes identifying the benefits of the treatment regimen and educating the patient on each drug and the importance of adhering to the medications and the clinic monitoring protocol. Mini versions of Directly Observed Therapy, or "Mini-DOTS" to ensure accurate pill-taking procedures throughout a trial or regimen, home visits by care workers, and adherence support workers provide ongoing education, counseling, and support both in the clinic setting and through home visits to focus on the individual needs and constraints faced by patients.

HSV-2 treatment and HIV prevention studies – *Connie Celum***:** High rates of adherence to study protocol in current HSV-2 studies, HPTN 039 and "Partners in Prevention," are the result of intense adherence counseling, supportive and non-judgmental staff, and multiple structures implemented throughout the trial. Researchers utilized pill reminders, tailored adherence strategies to optimize incorporation of twice-daily pills into a participant's daily routine, along with other counseling messages to enhance adherence capabilities. Additional efforts include dispensing an extra pill bottle in anticipation of a missed visit, updating adherence messages to keep them fresh, and reinforcing safety of the study drug in the context of illnesses, other medications, and alcohol.

Adherence to Antiretroviral Therapy in the *Adherence and Evaluation of Protease Therapy* (ADEPT) Study – *Carol Golin***:** The ADEPT study sought to determine how adherent participants would be when initiating HAART, the relationship between adherence and virologic outcomes, any psychological factors that might predict adherence, and how different adherence measures compare with each other and, possibly, predict virologic outcomes. While the study determined that no "gold standard" exists for the measurement of adherence to a pill regimen, this trial utilized a composite adherence score from the triangulation of electronic cap data supplemented by calibrated pill count and self-report data. Barriers and facilitators of adherence were defined by the four 'P's': patient, potion, provider, and place.

FDA Perspectives – *Jeff Murray***:** To date, adherence data to support drug development have not been used in primary analyses to support a product's efficacy, though such data and other exploratory analyses are helpful in supporting outcome data from an initial trial. Adherence in the "real world" is imperfect, as it is in a clinical trial setting, despite the fact that trial researchers are responsible for answering an investigative question and thereby tied to ensuring adherence as part of drug regimens to ensure product efficacy. However, intent-to-treat (ITT) analysis is a more realistic description of the impact of a new medicine, and thus should be the standard for evaluating the efficacy of the tested product's efficacy.

NOVEL METHODS OF MEASURING AND OPTIMIZING ADHERENCE

Biomarkers of Adherence – *Christine Mauck*: In prevention trials, biomarkers might provide objective evidence of behavior which could replace self-reported behavioral assessments. Useful biomarkers would assess semen exposure, product use, or condom use. By combining such biomarkers, it might be possible to determine which products were used when sex occurred, based upon the expected results of each assay. Biomarkers might also be used to compare behavioral assessment tools, under the assumption that the biomarker in question would be a "gold standard" for verifying self-reports. Development of various biomarkers can be prioritized based on the information that can be gathered from each marker.

The FHI Truvada Study – *Jen Deese*: Protocol and design for the FHI Truvada™ PrEP trial (now called FEM-PrEP) is underway. A multitude of options to support participant adherence to product

are planned. The study will conduct a short run-in period prior to enrollment, to allow participants to self-assess their capability for taking a pill (vitamin) daily, though the outcomes of this run-in are not intended to be used as inclusion or exclusion criteria. Weekly pill containers, tailored counseling based on rapid data analysis, a buddy system, and strategic clinic visit scheduling are other potential strategies being considered for the trial to maximize adherence. The study also aims to include participants as partners in the trial, which may potentially enhance their ability and desire to adhere.

IPM Dapivirine Studies – *Zeda Rosenberg, Annalene Nel*

- *Novel technologies:* A "smart" applicator and "Sexometer" are in development for use in safety and acceptability studies of dapivirine. The "smart" applicator would record time and temperature of the environment in which a product dose was dispensed, collect mucin to stain for presence of vaginal fluids, and contain a bar code for each applicator to be traced to a specific trial participant. The "Sexometer" would measure the use of a microbicide during coitus. Future prototypes could be designed with sensors to measure the presence of gel, semen, and virus so as to determine exposure to HIV.
- *Daily monitored adherence:* Daily monitored adherence—a modified version of the Directly Observed Therapy used in tuberculosis trials and treatment—would involve daily contact between microbicide trial staff and participants, with the regular collection of used applicators both as a support system and ancillary indicator of adherence rates. Site staff would either visit participants at their homes through daily scheduled visits, or participants would visit the clinic drop-off center; both designs would have to take into account participant safety, time schedules of participants and staff, and travel distances.

KEY FINDINGS

The following list consists of extracts from this Summary that point to areas where more work could be done to refine current approaches, build on key findings, and reconcile earlier understandings that have not passed the test of time. It is obviously not exhaustive and should be considered, at least for the time being, suggestive — a base on which to proceed pragmatically, which was the point of the workshop.

- The usefulness of reported use at the last sex act as an estimate of product use over time was mixed. While one study found this question to be a good indicator of product use over time, another found the question to overestimate product use.

- Reported consistency of gel and condom use change over the course of a trial.

- Low adherence levels are frequently due, at least in part, to misunderstanding among site staff of key messages conveyed to study participants during adherence counseling.

- Women who use gel but are inconsistent condom users are the most informative group for establishing effectiveness but, so far at least, these women appear to account for a small percentage of participants.

- In a trial in which the study arms were not blinded, data have showed differential condom use in the control and intervention arms, suggesting that study arm assignment can influence behavior, possibly due to prevention misconceptions or partner negotiation.

- Comparison of ACASI and face-to-face interviews demonstrate that ACASI is not immune to misreporting, and partner comprehension and attention are particular challenges to collecting data using this technology. However, ACASI may produce significantly higher reporting than face-to-face

interviews for sensitive behaviors, although reporting of gel use and sex acts in the month prior to interview remains problematic.

- Not all microbicide trials are measuring the same thing, nor is there clarity or consensus about what should be measured and why, though there is agreement on the need for more investment in methods for getting accurate data and how to adapt those methods for different populations.

- Trajectory analysis suggests that baseline characteristics may be associated with different patterns of adherence during a trial. Pooled analyses from current trials could provide future trials with indicators to select high compliers for future enrollment or to identify women needing more product support or intensive counseling. Differences among adherence trajectory groups suggest potential ways to monitor adherence in future trials.

- Adherence data have multiple uses in microbicide trials: aiding explanations of heterogeneity of effects across sites, making determinations about whether adherence was too low to identify an effective product, and generating new hypotheses from trial data. However, intent-to-treat analysis is a more realistic description of the impact of a new medicine, and thus should be the standard for evaluating the efficacy of the tested product.

- Factors that might predict adherence (including motivation, context, and partner involvement) could be used to identify and enroll participants most likely to adhere to a future study protocol. Standardizing adherence measurement across trials might also be helpful but is challenged by the complexities of inter- and intra-trial variations, contextual differences, and needs to fine-tune data collection methods for specific populations.

- Novel methods of self-report intended to minimize biases include cell phones, electronic diaries, interactive voice response, directly-observed procedures, innovative delivery systems, and "triangulation" of several recruitment and measurement strategies. Biomarkers to validate self-reported data are also being explored, since they might provide objective evidence of behavior which could replace, supplement, and/or validate self-reported behavioral assessments. Preliminary – sometimes very preliminary – data and early hypotheses recommend further exploration of all these approaches, even though some of them, for example, biomarkers, may be far from realization and validation.