Published in final edited form as:

AIDS Behav. 2008 March ; 12(2): 272–283. doi:10.1007/s10461-007-9266-z.

Assessing Microbicide Acceptability: A Comprehensive and Integrated Approach

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Abstract

A safe, effective, and acceptable microbicide is needed in order to decisively impact the global AIDS pandemic. As such, microbicide acceptability research is of paramount importance. In order to best utilize limited financial resources and save precious development time, acceptability studies should be fully integrated into preclinical and clinical trial contexts where candidate products are being developed and tested. An integrated approach for examining theoretically valid and relevant variables is needed so that data across studies and products can more effectively advance the field. We propose an approach for measuring factors related to microbicide acceptability in each phase of product development, and dependent on what product-specific knowledge is already established in the field. We discuss the roles that behavioral and social science methodologies should play in all phases of microbicide development, as well as the challenges faced when conducting acceptability research in the context of preclinical and clinical trial settings.

Keywords

Microbicides; Acceptability; Measurement; Clinical trials; Preclinical development

Each day, approximately 14,000 individuals globally are newly infected with HIV; of these, almost half are women (Boonstra, 2000; UNAIDS/WHO, 2005). Even as they face increased risk, many women have little control over HIV/STD prevention decisions. Currently, women must rely on HIV prevention methods that require the knowledge and consent of sex partners (i.e., male condom, female condom, and abstinence) (Bentley et al., 2000; Mason et al., 2003; Wulf, Frost, & Darroch, 1999).

Microbicides could change this reality. While the focus has primarily been on developing topical vaginal microbicides, rectal microbicides will likely also have a significant impact on HIV infection rates among both women and men. By developing a product that can be used overtly or covertly (i.e., with or without a partner's knowledge, awareness, or consent), individuals can control their own protection against HIV and, potentially, other STDs. Although not all individuals want or need to use a product covertly, researchers and advocates are particularly interested in the possibility that microbicides could place prevention control in the hands of those who need it. The possibility of covert use would be particularly valuable

in relationships and cultural systems where gender norms or social status limit one's ability to exert control over the timing or frequency of sexual acts. Microbicides containing contraceptive agents may also facilitate fertility regulation.

Currently, there are nearly three dozen microbicide candidates in active preclinical and approximately one dozen in clinical development, representing a wide array of potential HIV prevention strategies (Finley, Plescia, Harrison, & des Vignes, 2006). Various biologic strategies to block HIV infection in the context of sexual exposure and several different delivery systems to deploy the active ingredient are under study. Some are formulated as coitally dependent products (i.e., gels that require insertion within a brief window of time before sexual intercourse, potentially being inserted with an applicator or as part of a gel-diaphragm delivery system), while others are being developed that are coitally independent (e.g., daily use gels, intravaginal rings). If a microbicide were proven to be effective at interrupting HIV infection, the potential impact on the global HIV/AIDS pandemic would be enormous (The Rockefeller Foundation, 2002; Watts, Kumaranayake, Vickerman, & Terris-Prestholt, 2002).

However, this impact will not be achieved if effective microbicides are not used by at-risk individuals (Elias & Coggins, 2001; Mantell et al., 2005; Morrow et al., 2003b; The Rockefeller Foundation, 2002; Watts et al., 2002). The success of any microbicide, as measured by decreased HIV transmission rates, will be a function of its clinical efficacy in combination with its real world effectiveness (Severy & Newcomer, 2005). Achieving widespread, consistent, and correct use will partially rely on developing a microbicide that is accessible and acceptable to potential users. Since product acceptability is dependent on both user and product characteristics, clear consensus exist that acceptability studies are relevant in the context of clinical safety and efficacy trials (Tolley & Severy, 2006). However, a clear plan that incorporates both preclinical development and appropriate strategies within clinical trials has yet to be proposed. In this paper, we propose that a comprehensive and considered approach for studying microbicide acceptability be integrated and implemented with rigor throughout preclinical and clinical trials. By advocating for and achieving greater emphasis on theoretically relevant behavioral and social factors via consistent and well-constructed methodologies, microbicide use and non-use can be better understood both within and outside of the clinical trial context, and lead to more effective uptake when such products are ultimately approved for commercial use.

Measuring Acceptability

Evaluating product acceptability is a complex task that has changed as our understanding has evolved beyond the most basic concept of utilization (Mantell et al., 2005; Morrow et al., 2003b; Severy & Newcomer, 2005). In early microbicide safety trials, acceptability was seen almost exclusively as a function of the vehicle's physical qualities (e.g., formulation, scent, and color) and was typically measured by questions designed to elicit a woman's hypothesized intention to use a potentially available product. This basic conceptualization has expanded over time with the gradual acknowledgement that acceptability is neither static nor objective, but involves a combination of factors and interactions of the product with the user, the sex partner, the environment, and social and cultural norms. An evolving and more complex conceptualization of acceptability as a multifactorial construct has resulted in a more prominent and valued role for acceptability research within clinical trials, a change that is supported by the need for more comprehensive approaches to understanding product use in real world contexts (Elias & Coggins, 2001). Indeed, the recently released Microbicide Development Strategy (MDS Working Groups, 2006), a document developed in a collective process across multiple disciplines and stakeholders, notes throughout the imperative to better understand acceptability and incorporate behavioral and social research into the microbicide development process.

Acceptability research to date has utilized both quantitative and qualitative data collection strategies. However, since the utility of quantitative findings often has been limited by the small sample sizes of early stage clinical trials (Bentley et al., 2000; Morrow et al., 2003b; El-Sadr et al., 2006), it is often the qualitative methods that yield a greater depth of understanding of the many factors associated with acceptability, thereby complementing and enhancing the quantitative data (Morrow, Costello, & Rosen, 2003a). Data from focus groups and in-depth interviews conducted in conjunction with standard quantitative assessments, as opposed to purely in-depth qualitative designs, have confirmed the validity of clinical data (Denzin, 1978; Denzin & Lincoln, 1998), explained unexpected findings in quantitative analysis (Morrow, 2006; Morrow et al., 2003b), and helped microbicide developers understand the product-related factors that contribute to or detract from its acceptability and use (Bentley et al., 2000; Mantell et al., 2005; Morrow et al., 2003b; Rosen et al., 2006; Severy & Newcomer, 2005).

Both qualitative and quantitative data, collected during clinic visits, or in focus groups or interviews, provide specific answers to well-constructed research questions during clinical trials and avoid problems associated with pre-use and hypothetical studies (Elias & Coggins, 2001; Mason et al., 2003; Murphy, Miller, Moore, & Clark, 2000). However, many clinical trials have not been designed to incorporate comprehensive acceptability measures, and the utilization of these measures—particularly those requiring qualitative data collection methods—can increase trial cost and burden. Incorporation of appropriate acceptability assessment is dependent on trial phase and sample size, as well as product-specific knowledge already ascertained from previous studies. Although qualitative methods can prove more useful than quantitative approaches in the context of small-scale clinical trials, the limited number of participants can restrict both the nature and range of data, limiting generalizability and introducing potential bias and homogeneity of information if not done properly. For instance, questions related to a product's impact on sexual pleasure, partner reaction, and feasibility of use in various sexual contexts cannot be satisfactorily explored in sexually abstinent cohorts in Phase I and II clinical trials.

While some factors challenge inclusion of acceptability research in clinical trial contexts, they are not sufficient to lessen the importance of acceptability data and their potential value to product development and eventual widespread utilization. The incorporation of acceptability measures and protocols should be done simultaneous to main trial design and appropriate to trial phase, with qualitative measures being highly focused and linked to appropriate quantitative measures. For instance, quantitative items could ascertain whether the product was perceived to dry or lubricate the vagina following application. Subsequent qualitative inquiries could expand this information by determining when this occurred, whether it did so under all circumstances or just some, and whether such an experience had a specific impact on use during the trial or subsequent ratings of willingness to use the product in the future. As microbicide developers look toward future efficacy trials, with the recognition that use-associated factors critical to ultimate product acceptability remain largely unaddressed, consideration of best practices in acceptability data collection in the clinical trial context is necessary.

The Value of Studying Microbicide Acceptability During Development

Acceptability research has the potential to inform at the earliest stages of microbicide formulation and delivery device development, when changes are still relatively easy and inexpensive (Heise, 1997), and when a potential microbicide with proven *in vitro* (and, in some cases, *in vivo* animal models) ability to protect against virus is being assessed for compatibility with the basic excipients and vehicles needed to deliver the microbicide vaginally or rectally. Additionally, acceptability data can direct future research by assisting scientists in choosing product candidates that are best suited to the preferences and needs of a given user population

(The Rockefeller Foundation, 2002; WHO, 1997). Ramjee and colleagues conducted acceptability research with participants to address concerns related to the formulation of COL-1492 and implications for dry sex. These data were used to ascertain whether the product was initially acceptable and whether it compromised traditional sexual practices of the cohort being considered for large-scale efficacy trials (Ramjee et al., 1999). Given there will likely be different formulations and delivery systems in future clinical trials, it will be important for behavioral scientists to work with clinical trial scientists in ascertaining the unique needs of various research populations with specificity to the products being studied.

Early safety and toxicity trial participants (Phase I) are an invaluable source of information regarding acceptability. They constitute the handful of individuals with actual product use experience and, thus, are in the best position to provide feedback on actual product characteristics (e.g., formulation, application, and post-application leakage) and how these factors might influence individuals' willingness to initiate and maintain product use over time.

Acceptability studies nested within clinical trials can accumulate a great deal of data related to that particular product. It is also the case that acceptability data and conclusions from previous trials, as well as acceptability studies outside the scope of clinical trials, can facilitate development of future formulations, delivery devices, application materials, and procedures. Moreover, such data can elucidate other behavioral and social variables affecting an individual's willingness to use a microbicide. Working together, the various scientific disciplines involved in microbicide development will be able to increase the likelihood of producing microbicide candidates that, even before clinical trials, will have a greater likelihood of success in human use.

Incorporating Acceptability Research

A complete understanding of product acceptability involves studying all the factors that might influence user and partner acceptability. This necessitates the use of theoretically relevant constructs. Several health behavior theories, whether HIV-specific or not (e.g., IMB meta-model, social cognitive theory, health belief theory, etc.), as well as sociological theories (e.g., empowerment theory, socioecological theory, etc.) can be used to articulate the most valuable and relevant research questions. Assessments can be conducted at the most relevant phase of development for each construct. In order to produce the most relevant information and avoid redundancy, researchers should ensure that acceptability studies are product-specific and have an appropriate balance of quantitative and qualitative methods. If multiple product-specific studies are conducted using comparable methodologies, meta-analyses across products are possible.

The discussion below, in conjunction with Table 1, describes the role that acceptability research can play in all phases of microbicide research and development. Figure 1 provides a simplified exemplar of the added-value of incorporating mixed methods research to gain greater depth of understanding in acceptability.

It is important to note here that, for simplicity's sake, we will confine our presentation to *user* acceptability. To truly understand acceptability of microbicides, acceptability data from sexual partners, and an understanding of cultural and community norms and influences is required. In this sense, microbicide acceptability is not merely multifactorial, but multidimensional, and ultimately will need to be examined as such.

Preclinical Research

Along with the discovery of potent microbicidal compounds, preclinical research includes work by product developers on the "vehicles" (i.e., "formulations" such as gels, or devices

such as rings) that deliver microbicidal agents to target tissues, fluids, and/or organs. Proposed delivery systems play a crucial role, since the application process can affect, for example, the biophysical properties of gels or the placement of devices, and, therefore, user perceptions and experiences. First generation formulations/devices may be discarded for biophysical reasons (e.g., stability, compatibility with microbicidal agents). However, given a more thorough understanding of vehicle-associated factors (e.g., formulation biophysics) that impact acceptability, these preclinical studies could incorporate acceptability research. For instance, as formulation scientists begin to understand how various biophysical properties of formulations affect deployment (i.e., distribution and retention) characteristics (Barnhart et al., 2004; Fuchs et al., 2005; Geonotti & Katz, 2005; Kieweg, Geonnotti, & Katz, 2004; Kieweg & Katz, 2006), behavioral scientists can collect preliminary data pertaining to the acceptability of various formulations being developed. Choosing what elements are used to develop a stable formulation with a defined set of biophysical properties (pH, viscosity, spreading, shearing, etc.) can be directly influenced by the knowledge that specific formularies are inherently acceptable or unacceptable to women or men. By understanding the correspondence between formulations' biophysical properties and cognitive-behavioral perceptions and ratings of formulation characteristics, formulation scientists and their behavioral colleagues can rationally design candidate formulations best suited as microbicide vehicles. Early examples include the candidate microbicides C31G and λ -Carageenan-containing PC-503 gel, for which acceptability results led to the formulation of C31G product as a co-polymer gel (Bax et al., 2002) and a reformulation and dosage decrease for PC-503 (Coggins et al., 2000). Early experimentation with the physical elements of a formulary toward a paradigmatically acceptable formulation can be used not only to increase the chances of positive outcomes in terms of initiation and sustained usage, but also as a method to rationally design and accelerate microbicide development by focusing preclinical formulation efforts on a predetermined group of formulation characteristics. Consequently, it would be possible to rationally design acceptable formulations prior to incorporation of the active (anti-HIV) ingredient. Such knowledge would enable formulation scientists to design products that meet the requirements of both efficient and effective deployment *and* reasonable acceptability.

Pragmatically, it may be prudent to compile a compendium of formulation/device options based, in part, on user acceptability data. By conducting acceptability studies during preclinical development, formulation/device developers and behavioral scientists could together develop a "menu" of formulation and delivery device options that optimize both deployment *and* acceptability. These options could then be paired with appropriate anti-HIV agents, thus yielding greater confidence in the ability of these products to be used within the varying cultural contexts of perspective users.

At the same time, it will, of course, be important for formulators and behavioral scientists to consider application methods. Microbicidal agents must be compatible and stable in the applicator, as well as in the vehicle and the vaginal or rectal environment. In addition, the application process must not alter the formulation such that it changes its viability. Likewise, if a particular applicator or application process is not easy, comfortable, and, in some instances, private, for the user, efforts to use it will be unsuccessful. By providing developers with guidelines that indicate likely acceptability, the preclinical development framework can be optimized and resources saved.

Phase I

Given the design of Phase I trials (e.g., small sample size, limited, and brief exposure to the product) and the respective limitations of qualitative and quantitative research discussed previously, we propose the collection of product-specific initial acceptability outcomes focused on a limited number of discrete dimensions. Quantitative studies should examine vehicle- and

application-associated variables *specific* to the product being studied, including formulation (e.g., texture and viscosity, color, scent, as appropriate) and ease of application. Items would measure the relative perceived presence or absence of each variable, the rate at which problems with the product occurred (where applicable), and the degree to which trial participants report these factors—and the product as a whole—to be acceptable or unacceptable. These data could then be supplemented by brief qualitative assessments that allow for expansion on the dimensions measured by the quantitative items, such as elucidations of the contexts when product use was problematic (see Fig. 1 and Table 1). Additional qualitative questions could be administered for a limited set of daily use-associated factors (if the study product is intended for daily use), describing the impact of leakage during daily use, how lubricating or drying effects impact application, culturally specific issues with applicator and packaging disposal, and what changes were required in hygiene practices (and whether such changes could be permanent and acceptable routine hygiene changes).

In trials with sexually active cohorts, additional dimensions can be explored, including volume issues associated with penile penetration (e.g., displacement of gel, awareness of product in the vagina or rectum), leakage (e.g., color, odor, and consistency changes in sex-associated leakage), and dryness or stickiness with sex-associated use (and changes in these variables across the duration of the sexual act). Also included here would be user evaluation of product influence on sexual pleasure and hygiene. It is, of course, important to note that due to the primary aim of Phase I safety trials, condom use during sex is required until penile safety studies are completed. As such, acceptability data, including data on sexual pleasure and covert use, will be considered by the participants within that context.

In addition to gathering useful acceptability data with respect to the user perspective, it would also be important in Phase I trials that include sexually active cohorts to gather data on the partners' experiences of the product. These dimensions could include evaluations of the same variables assessed among the users (e.g., color, scent, consistency during sex, and leakage concerns). Product effects on sexual pleasure (as well as product awareness during sex) should be explored.

Phase II

Phase II studies expand sample sizes and often include increases in how long participants are exposed to the product. This enhances the utility of acceptability studies by expanding the range of responses and circumstances in which the product is experienced. With sexually active participants, quantitative acceptability studies can continue to focus on product-specific data related to vehicle- and application-associated factors, while enhancing selected questions pertaining to use-associated product characteristics (e.g., experiences during and after sex). Since participants are using the product daily as well as in conjunction with sexual intercourse, assessments can be made to compare coitally dependent and coitally independent use. Additionally, researchers could begin to delve into some of the crucial determinants of acceptability that remain largely unknown or uncertain, such as the potential for product use to be incorporated into, or interrupt, foreplay. Of particular relevance to long-term use, acceptability research conducted during Phase II trials with sexually active cohorts must take into account the importance of product impact upon sexual pleasure and covert use (Morrow et al., 2003b; Rosen et al., 2006; Severy & Newcomer, 2005). These data can provide knowledge that can be crucial to efficacy trial design, when opportunities to test products with exponentially larger populations and in different sexual contexts exist.

Overall, data from Phase I and II trials can be used to facilitate acceptability measurement development, and provider and patient product information development. In addition, these data can be useful to product developers, who may choose to reformulate future versions (i.e., second generation) of the product to enhance performance in sexual contexts. Data collected

from participants in these phases could also provide information that might refine the instruction that accompanies microbicide administration during trials and post-market use, such as developing strategies to address barriers to correct and consistent product use.

Since new and groundbreaking acceptability data for *gel* products may be somewhat redundant at this point in the developmental process, both Phase I and Phase II experimental gel studies can be limited to structured items paired with semi-structured short answer questions, allowing for greater ease of conduct and speed of analysis. Sample descriptives and acceptability data patterns could be easily completed and supplemented with qualitative narrative illustrations. Qualitative studies can be truncated to brief narratives that are highly specified to the product and dimensions being studied, but that offer the opportunity to reveal any previously undiscovered issues. Data most relevant to decisions to move a product forward—or to anticipate issues in subsequent studies—would be available in a timely fashion. This would be less true, at least initially, for new formulations or delivery devices (e.g., vaginal rings, suppositories), where full-scale qualitative studies vis-a-vis in-depth interviews or focus groups would be required in Phase I and Phase II trials.

Phase III

Phase III trials offer a wealth of opportunities to explore various complex issues associated with microbicide acceptability. While larger sample sizes make all-inclusive qualitative studies cost-prohibitive, quantitative acceptability assessments and analyses become more feasible and their outcomes more informative and generalizable. Since efficacy studies are, by necessity, conducted in a more real world context compared to Phase I and II studies, interpersonal, social, and cultural factors associated with “typical” use can begin to be explored. For example, variables associated with taste and color during sexual intercourse can be added to the list of vehicle-associated factors to be examined, while contextualized application privacy and disposal issues can be added to application-associated factors with respect to topical gels (Table 1). Phase III trials also provide an opportunity to increase understanding of coitally dependent dosing (i.e., product use closely associated in time to actual sexual intercourse), which will be critical to understanding real world use and will help explore hypotheses regarding the effect of penile penetration on spread, coating, and retention of microbicides in the vagina or rectum—all integral to deployment and drug delivery. This strategy allows microbicide science to develop within an iterative and self-correcting process, where Phase III trials can better inform preclinical development of subsequent products.

Another advantage of Phase III studies is that the larger sample sizes are likely to provide sufficient statistical power for theoretical model testing (i.e., health behavior models) related to behavior change and the individual, product-related, and contextual factors that could affect decision-making regarding microbicide use. The use of diaries or calendar-based recall methods, whether throughout a trial or in time-sampling designs, could provide explicit measurement of use patterns by context and partner type. Similarly, valuable insights and clarifications related to microbicide use contexts, use patterns, and product acceptability under varying circumstances (interpersonally and culturally) can be provided through qualitative examinations of particular cohort subsamples, such as particularly high risk women, drug users or their sexual partners, adolescents, or individuals who rate covert use as a primary reason for wanting to use a microbicide. Thus in Phase III trials, both large scale survey studies of factors related to microbicide acceptability and qualitative studies of particular subsamples can be completed with relative ease, given adequate planning and resources.

Condom-Only and Placebo Research Conditions

The issue of control arms in efficacy trials needs to be well understood before acceptability assessments can be considered and interpreted. As with all drug development studies, inert

products (e.g., inactive intravaginal rings; universal placebo gels) are, by regulation, employed as placebo comparisons. However, the degree to which an inactive product protects against HIV acquisition (e.g., acting as a non-specific barrier to virus-cell interaction) is unknown. Until this question is answered, any study using a placebo product as a comparison may be required to have a condom only arm in order to maintain the current standard of prevention among sexually active individuals. Ethically, all participants using trial products—either experimental candidates or placebos—are counseled to also use condoms. Whether one agrees with this design or not, until efficacy data and regulatory bodies allow alternative study designs, acceptability measures pertaining to sexual pleasure and covert product use will need to take into account the fact that individuals' ratings of these variables may be different than if they were able to make the same assessment without the recommended condom use. While some would consider condom use during clinical trials a necessary confound, in fact, condom use will likely be recommended when first generation microbicides are approved and enter the market. As such, acceptability using both the microbicide and the condom is not only applicable, but the most appropriate measure of microbicide acceptability when used as directed—at least for first generation microbicides.

On the other hand, there is the likelihood that, during Phases II and III trials, some sexual acts will not be condom-protected despite participants having received condom counseling as required by trial protocol. While condom non-use is not to be encouraged in microbicide product testing, obtaining data from participants who do not use condoms (whether at all or inconsistently) allows researchers to examine potential differences in product acceptability among condom users and non-users. Additionally, researchers could obtain both quantitative and qualitative data on the contexts in which condoms were not used, thereby shedding light on users' perceptions of product efficacy, influence on sexual pleasure, and/or potential for covert use. Indeed, it will be just as important to collect microbicide *plus* condom acceptability data, as microbicide alone acceptability data.

Phase IV

The post-marketing phase allows exploration of acceptability and use as a function of cost and access parameters in a real world context where health delivery systems may not be well structured or may be resource poor. For microbicides with the potential to curb the HIV/AIDS pandemic, data pertaining to actual usage is crucial. Acceptability research during this phase could not only continue to examine the various product- and use-related factors examined in clinical trials, but could also provide data on factors that mediate use (Severy, Tolley, Woodsong, & Guest, 2005b), as well as factors that influence product preference (in the case of multiple available products) and the diffusion of microbicides as a prevention innovation. Additionally, given the probability of a partially effective product being made available, acceptability data pertaining to microbicide use in combination with other prevention strategies (e.g., condoms, contraception) would be necessary for a more comprehensive understanding of how individuals choose prevention methodologies and make decisions about when, where, and with whom to use various prevention strategies.

Data from Trial Non-participants

To this point, we have explored the field's ability to collect significant and important data from preclinical and clinical trials of candidate microbicides. Also significant and important to microbicide acceptability is a better understanding of the same dimensions discussed above in those who cannot, or choose not to, enroll in clinical trials, or who are part of the larger community where trials are taking place. Ancillary studies should be considered, where these individuals are enrolled into studies designed to better understand the broader individual- and community-level influences on microbicide acceptability. For instance, sexual behavior studies among trial non-participants within the same cultural and geographic arenas can provide a more

in-depth understanding of HIV prevention needs and potential best practices for community preparedness, education, and intervention.

Challenges

Identifying the acceptability dimensions that should be addressed in each phase of inquiry is only one step in outlining the future path of microbicide acceptability research. The methodology employed in data collection, as well as the interpretation of results, must be carefully considered. Issues of small sample sizes, required/recommended condom use, and restrictions in some trials on oral and anal sex, as well as restrictions on certain hygiene practices, will continue to limit the full-scale applicability of early phase microbicide acceptability findings to real life. The context and experience of participants in efficacy trials also limit the applicability of findings, though less so than in earlier phases.

It is important to take into account individual- and community-level understandings of the risks and benefits associated with microbicide use. Researchers must examine and modify existing methodologies, and develop new methodologies and measures to more accurately assess an individual's comprehensive understanding of the risks and benefits of using a particular product. User perceptions of drawbacks, including a less than 100% efficacious product and various side effects, must be considered in tandem with advantages, such as disease prevention and positive changes in sexual experience. A thorough understanding of the advantages and disadvantages or challenges in microbicide use decision-making and sustained use will allow behavioral and social scientists to discern domains of cognition, behavior, and environment that could be amenable to intervention, and thus increase the likelihood of strong uptake and sustained use of microbicides where they are needed most.

An analysis of an individual's perceived need and desire to use the product must be accompanied by an assessment of their ability to use that product correctly. A user must know how, when, and how often to apply the product, appropriate dosing (e.g., whether or not a single application of a gel, for instance, would be effective for multiple sex acts or exposures), and be aware of any prohibitions or contraindications (e.g., product is not consumable, not for rectal use, etc). The evaluation of many of these factors will have begun in Phases I and II when vehicle and applicator characteristics are initially investigated, but they must be continuously revisited as real world use is more closely approximated. Similarly, while current trials of candidate products focus on use during vaginal sex, it is likely that, in the real world, individuals will have a much broader sexual repertoire and often engage in a variety of sexual behaviors, and in varying sequences, during the course of one sexual encounter. To that end, future studies must take into account the variation of activities in sexual encounters where microbicides might be used, as well as consider the implications of microbicide use for increased protection during oral and anal sex. Ultimately, behavioral and social scientists need to understand how best to convey microbicide knowledge, increase microbicide use motivations commensurate with an individual's risk, and teach behavioral skills (i.e., cognitive, emotional, and behavioral repertoires) that can address both a user's first time use and her/his sustained use of the product. These domains (knowledge, motivations, and skills) are best explored throughout microbicide development, such that assessment and intervention protocols can be developed and evaluated before the marketing phase. While some of these objectives can be achieved as a result of behavioral studies being fully integrated into clinical trials, some may also be amenable to ancillary studies or other independent research mechanisms.

In addition to these assessment and methodological issues, financial costs associated with conducting acceptability research, particularly in the context of clinical trials, must be considered. Traditional assessment formats (e.g., paper-and-pencil surveys) are useful for

collecting quantitative data, but alternate formats such as punchkey surveys using cell phone technology, web-based surveys, and CAPI or A-CASI formats should be considered where appropriate. Some of these may require adaptation to developing world contexts, but are already being employed in some settings and could be easily adapted. While upfront costs in equipment and software may be required, depending on the complexity of the instrument, currently available software can be obtained at little expense, and data entry costs, by definition, can be obviated. In addition, these same databases of instruments can be reused in subsequent trials, saving development costs, and contributing to the possibility of future meta-analyses.

The collection of qualitative data requires staff trained in the elicitation of rich qualitative data. To that end, projects would need to employ staff that are well trained in both quantitative survey administration *and* qualitative data collection and who possess skills necessary to conduct mixed-methods interviews. Again, while upfront training may be significant, the long-term advantages could serve the field for years to come, as subsequent trials using the same study teams or sites would save from previous training. Similarly, while the costs associated with coding and analyzing qualitative and mixed-methods data need to be considered (as these data cannot be fully analyzed by traditional statistical software programs) the richness and depth of the acceptability data acquired can be particularly helpful in early stages of development, especially for new delivery forms or systems. As these costs are not significant relative to the overall cost of clinical trials, they are worth considering given the added value that acceptability research can contribute to knowledge gained.

While less time-consuming data collection and analysis will clearly alleviate staff and subject burden, it is important to note that the sample size of Phase I and II trials will obviate the use of standard statistical inference procedures. Descriptive outcomes will benefit the particular product and trial, but will likely not make significant contributions to the overall field: this is currently the case for topical vaginal gels only, but, as other formulations and delivery devices and uses (e.g., rectal use) progress through the pipeline, this dynamic will also become true for them. As such, it will be important for early phase clinical trials to utilize comparable quantitative acceptability measures, so that meta-analyses can be conducted across products and time, ultimately leading to significant impact in the field.

Regulatory demands clearly have implications for conducting acceptability studies during clinical trials. By conducting acceptability studies secondary (or ancillary) to Phase III trials, investigators risk regulatory entities viewing those data as potentially confounding, especially if acceptability data contradict trial data, or appear to. Reconciling these can cost credibility and resources. However, if behavioral and social science methods and measures, acceptability-related and otherwise, were developed in a multidisciplinary framework, there would be little need to collect redundant data, thus avoiding irreconcilable variances. If integrated well, behavioral data can serve to explain or validate clinical outcomes.

Last, but certainly not least, is the consideration of participant and staff burden. This is especially problematic in larger-scale clinical trials where a plethora of clinical data is being collected and where standard participant visits can be time-consuming. If incorporated and implemented properly, the addition of an acceptability component to existing clinical research does not need to interrupt clinic flow or add undue burden to either the participants or research staff. Quantitative studies need not require large amounts of participant and staff time; yet they can yield important information that can shed light on study outcomes, whether positive or negative. The open-endedness of qualitative studies nested within the trial but completed at different points in time, for instance, may provide research participants with an opportunity to share their experiences with the investigational product and the research in a way that they may not feel comfortable doing with clinical staff. Offering participants the ability to relate non-

clinical data and experiences may have the added benefit of increasing motivation and commitment to the study, thereby, potentially increasing adherence and retention.

Investment in scientific infrastructure, whether through large clinical trials networks or multidisciplinary collaborations between institutions and countries, offers the opportunity to strategize across several years and multiple protocols. While all the efforts described here could never be accomplished in one clinical trial or formative study, a thoughtful strategic plan has the potential to significantly move behavioral and social science forward in its efforts to understand and ultimately impact microbicide acceptability and use.

Much of the research concerning the acceptability of any microbicide will be hypothetical until proof-of-concept is established and a product can be used under real world circumstances. However, concerns about these limitations should be put into perspective by considering that decision-making about trying any new product is always hypothetical for individuals who encounter that new product at a doctor's office, drug store, or apothecary. Microbicide researchers and developers can have the advantage of maximizing eventual product acceptability by gathering information and feedback *throughout* microbicide development. Improving the chances of product acceptability can also be accomplished by using acceptability data to inform formulation and delivery system development, and to create appropriate community education materials, package guidelines, and provider training, all of which will help individuals make informed decisions about using a product when it becomes available. By relying on an integrated multidisciplinary team of scientists, combining sound quantitative and qualitative acceptability studies in each phase of the microbicide development process, and by efficiently utilizing appropriate variables and methods in data collection at each phase (i.e., using methods and measuring variables intentionally given current product-specific knowledge), investigators can continue to make much-needed progress in microbicide acceptability research. Appropriate questions that *can* be answered at each phase must be targeted, and appropriate data collection methods *must* be employed. This necessitates the development of valid measures and the use of a more comprehensive and considered approach offered by a multidisciplinary effort. As much as qualitative data collection with each and every participant is unrealistic during large-scale Phase III clinical trials, quantitative data collection alone in small-sampled Phase I and II trials also has limited utility. Methodologies must utilize all relevant strategies throughout the developmental process, balancing the strengths of these with the appropriate study questions and budget solutions.

Acknowledgments

Dr Ruiz is now at the Foundation for AIDS Research (amfAR). Some of the conceptualizations by the first author (Morrow) are derived from work completed under grant number R01 MH064455, R21 MH080591 and CFAR P30 AI42853, and well as the culmination of lessons learned through her work on the following projects: HIVNET 009 N01-AI-35176 and N01-AI-45200, N01-AI-35176, 1RO1DA10871, HPTU U01 AI48040 (HPTN 020, HPTN 050 and HPTN 049). The authors would like to thank Dr David Katz for his thoughts on conceptualizing preclinical acceptability, as well as Drs Roberta Black and Jim Turpin for their editorial comments on early drafts of this manuscript.

The views expressed in this paper do not necessarily represent the views of the Department of Health and Human Services, the National Institutes of Health, or any of its constituent units.

Portions of this work were presented at Microbicides 2006, Cape Town, South Africa, April 2006. Some of the conceptualizations in this manuscript by the first author are derived from work completed under grant number R01 MH064455, R21 MH080591 and CFAR P30 AI42853

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Fig. 1.
Mixed Method Microbicide Acceptability Assessment Leverages Greater Understanding of
How Products Interact with Participants' Use Contexts

Table 1

Suggested Microbicide Acceptability Variables of Interest by Pre-Clinical and Clinical Trial Phase, Given Lack of Overwhelming Evidence from Previously Collected Data for the Specific Product Being Studied at a Particular Phase

Factors	Pre-Clinical [‡]	Phase I [§]	Phase II [§] /IIb	Phase III ^{**}	Phase IV
Vehicle-associated					
Formulation	✓	✓	✓	✓	✓
Texture and Viscosity	✓	✓	✓	✓	✓
Product Scent		✓	✓	✓	✓
Product Color		✓	✓	✓	✓
Product Taste				✓	✓
Desirable/Appealing Elements of Product Vehicle	✓	✓	✓	✓	✓
Application-associated					
Clarity of Instructions		✓	✓	✓	✓
Ability to Adhere to Instructions ^a		✓	✓	✓	✓
Ease of Product Preparation, e.g., filling applicator with product		✓	✓	✓	✓
Ease of Application		✓	✓	✓	✓
Desirable/Appealing Elements of Application ^a				✓	✓
Assessment of Correct Application	✓			✓	✓
Product interaction during foreplay				✓	✓
Privacy Issues				✓	✓
Portability				✓	✓
Disposal Issues				✓	✓
Use-associated^b					
Frequency and timing of product use, partner-specific		✓	✓	✓	✓
Odor		✓	✓	✓	✓
Post-application odor ^a		✓	✓	✓	✓
Odor during/after sex ^a		✓	✓	✓	✓
Leakage					
Post-application Product Leakage ^a	✓	✓	✓	✓	✓
Leakage during/after sex ^a	✓	✓	✓	✓	✓
Lubrication/Drying Effects					
Post-application Lubricating Effects ^a	✓	✓	✓	✓	✓
Post-application Drying Effects ^a	✓	✓	✓	✓	✓
Lubricating/Drying during/after sex ^a	✓	✓	✓	✓	✓
Product consistency post-use		✓	✓	✓	✓
Desirable/Appealing Elements of Use ^a		✓	✓	✓	✓
Use with/without Condom				✓	✓
Covert Use (possibility of; need for; attempts at): partner-specific	✓			✓	✓
Assessment of Correct Use (e.g., timing, waiting period)		✓	✓	✓	✓
Changes in Hygiene Practices secondary to use		✓	✓	✓	✓
Changes in Sexual Pleasure secondary to use				✓	✓
Related Covariates					
History of Vaginal/Anal Product Use			✓	✓	✓
Frequency of Vaginal/Anal Sex		✓	✓	✓	✓
Perceived Product Efficacy				✓	✓
Relationship "harmony"; relationship communication				✓	✓
Number of Male Sexual Partners				✓	✓
Type of Male Sexual Partners (monogamous, casual, commercial, forced/rape; duration of relationship)			✓	✓	✓
Perceived HIV/STD Risk				✓	✓

Factors	Pre-Clinical [‡]	Phase I [§]	Phase II [§] /IIB	Phase III ^{**}	Phase IV
History of STD Diagnoses (ever; last 12 months; during current relationship)				✓	✓
Desire/Need for Pregnancy				✓	✓
Condom Acceptability			✓	✓	✓
Psychosocial Variables: Condom Self-Efficacy, Microbicide Self-Efficacy, Perceived Norms (Sex; Product Use), HIV Knowledge, STD Knowledge, Sociotropic Cognitions, Importance of Product Characteristics, Willingness to Use Microbicides				✓	✓
Process Measures					
Comprehension of written application instructions	✓	✓	✓	✓	✓
Frequency of provider "booster" instructions		✓	✓	✓	
Frequency of which parameters of use need further clarification/instruction (e.g., timing of product application)		✓	✓	✓	
Eligible Non-Participants and Withdrawals/Non-Completers:					
Reasons for non-participation		✓	✓	✓	
Product perceptions (perceived efficacy (person and product); perceived product characteristic acceptability)		✓	✓	✓	

[‡]Pre-Clinical Studies to involve formulation/delivery device science, likely without active microbicidal agent(s)

[§]Phase I and Phase II: given smaller sample sizes, investigators could take this opportunity to develop measures (items and/or scales), as well as get more comprehensive understandings of the product use experience

^{*}in preclinical studies, these variables could be ascertained via simulated coitus

^{**}some qualitative or mixed method studies could be conducted with particular subsamples of interest or within less well-understood or new cultural settings

✓ data can be collected using both quantitative and qualitative methods (or mixed methods) depending on what is already known about a given product or formulation/device

✓✓ including concurrent use with traditional products

^Aif sexually active cohorts are utilized

^aSuggest correlating these variables with side-effect data

^bData to be collect on daily use versus coitally-dependent use, as applicable